2-MORPHOLINOETHANESULFONIC ACID CATALYZED ONE POT SYNTHESIS OF ISOINDOLO [2,1-a]QUINAZOLINE AT ROOM TEMPERATURE UNDER ULTRASONICATION

D. S. Bhagat[a], M. V. Katariya[a], R. D. Ingle[a], V. M. Joshi[b], M. R. Bachhav[b], R. N. Udavant[c] and R. P. Pawar [a]*

Keywords: 2-morpholinoethanesulfonic acid, ultrasound, multi-component reactions, 2-carboxybenzaldehyde, isatoic anhydride, aromatic amines, benzylamine.

An efficient and greener one pot method has been developed for the synthesis of isoindolo[2,1-*a*]quinazolines using 2-morpholinoethane sulfonic acid as a water soluble green catalyst at ambient temperature and excellent yield of product. The synergetic effect of 2-morpholineethane sulfonic acid and ultrasound irradiation process has been also discussed.

* Corresponding Authors
Fax: +91 0240 2334430
Tel.: +91 0240 2334577
E-Mail: rppawar@yahoo.com
[a] Department of Chemistry, Deogiri College, Station Road, Aurangabad 431 005, India
[b] Department of Chemistry, K.R.A. Arts, Science and Commerce College, Deola, Nasik, India
[c] Department of Chemistry, Dnyanopasak College, Parbhani 431 401, India

Introduction

Construction of complex molecules through multicomponent reactions (MCRs) under ultrasonication constitutes a very attractive strategy in organic synthesis. Sonochemistry is widely used in organic chemistry, offering a versatile and facile pathway for a large variety of syntheses. Ultrasound is the part of the sonic spectrum, which ranges about 20 to 100 MHz and can be roughly subdivided in three main regions: low frequency high power ultrasound (20–100 kHz), high frequency medium power ultrasound (100 kHz–1 MHz), and high frequency low power ultrasound (1– 10 MHz). Sonochemistry involves the use of ultrasound technique to promote the chemical reactions.[1] Ultrasonic irradiation has been introduced as an eco-environmental technology in green chemistry.[2] Ultrasonic energy provides an unusual mechanism to generate high-energy chemistry owing to the extraordinary temperature and pressure generated by the cavitations bubble collapse.[3]

Some compounds synthesized by using ultrasonication are pyrimidine,[4] 5-(pyrazol-4-yl)-4,5-dihydropyrazoles,[5] benzimidazoles, benzoxazoles and benzothiazoles,[6] amine-*N*-Oxides,[7] polyhydroquinolines[8] and Schiff's bases.[9] In MCRs three or more reactants are involved in a cascade of bond-forming individual steps to provide a complex molecule without isolation of intermediates or modification of the reaction conditions. Attractive features of MCRs are simplicity of operation, reduction in isolation and purification steps, and minimization of costs, time, energy, solvents, and waste production. 2-Morpholinoethanesulfonic acid (2-MESA) mediated reactions at room temperature in ultrasonication have been explored as a green approach for this purpose.

The quinazolinone moiety is a building block for approximately 150-200 natural important sub-structure of various biologically active natural products such as bhimamycin C, and bhimamycin D,[10] potent inhibitors of TNF-aw,[11] antifungal,[12] anti-tumour activity,[13,14] antibacterial,[15] anti-inflammatory,[16,17] anticonvulsant,[18] analgesic[19] and antitubercular.[20] Drugs containing quinazolinone moirty showed significant therapeutic efficiency against solid tumors,[21] antimalarial,[22] antivirals,[23] antimicrobial activities,[24,25] ovarian cancer cell lines and are also EP4 receptor agonists in the treatment of pain,[26] anticancer,[27] cytotoxicity and anti-HIV.[28]

The title synthesis has been carried out under different reactions conditions viz., without catalyst and solvent[29] and catalyzed by Pt-multi-walled carbon nanotubes (Pt-MWCNTs),[30] *Saccharomyces cerevisiae*,[31] montmorillonite K10 and (+)-camphor-10-sulfonic acid (CSA)[11] and DEAD[32], etc. A comparison of the yields is given in Table 1.

Experimental

General procedure for synthesis of 6-phenyl-6,6a-dihydroiso-indolo[2,1-a]quinazoline-5,11-dione (1)

To a mixture of isotonic anhydride (1 mmol), 2-formylbenzoic acid (1.1 mmol) and aniline (1.2 mmol) in ethanol (2.0 mL), 2-MESA (15 mol %) was added. The reaction vessel was irradiated in sonication bath for a period ranging from 1.8 to 2.8 h. The progress of reaction was monitored by TLC. After completion of reaction, the mixture was cooled to room temperature the reaction mixture was poured onto ice cold water and the crude product was recrystallized from ethanol. Some derivatives were purified by column chromatography technique. The general reaction is depicted in Scheme 1.

Structures of the synthesized products were confirmed by comparison of their melting points with authentic values reported in literature and spectral data like ^{1}H NMR, IR, and LRMS.

Table 1. Comparison of catalyst and solvent on yields under different reaction conditions.

S. No.	Catalysts	Time	Yield (%)	Temp. (°C)	Solvent	Ref.
1	Pt-MWCNTs	15	95	600	EtOH	[30]
2	S. cerevisiae	2 h	84	RT	THF	[31]
3	CSA	6 min	72	80–850	EtOH	[11]
4	DEAD	10-12 h	40	RT	EtOH	[32]
5	No catalyst	3 h	80	1500	-	[29]
6	2-MESA	2h	90-98	RT	EtOH	Present work

Spectral data of representative compounds

6,6a-Dihydro-6-m-tolylisoindolo[2,1-a]quinazoline-5,11-dione

This compound is a white solid, yield 95 %. M.p. 162-163 °C. IR (KBr) 3028, 2926, 1662, 1584, 1489, 1332, 1138 cm^{-1}. ^1H NMR 1.63 (s, 3H), 7.37-7.41 (t, 1H), 7.48-7.52 (t, 3H), 7.65-7.67 (d, 3H), 7.75-7.88 (m, 4H), 8.30 (s, 1H), 8.51-8.53 (d, 1H). LRMS m/z 333 $(M)^+$.

6-(2,4-Dichlorophenyl)-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione

This compound is a white solid, yield 75 %. M.p. 223-225 °C. IR (KBr) 3052, 1661, 1585, 1489, 1327, 1135 , 734 cm^{-1}. ^1H NMR 7.38-7.52 (m, 4H), 7.65-7.88 (m, 6H), 8.30 (s, 1H), 8.51-8.53 (d, 1H). LRMS m/z 413, 416$(M)^+$.

6,6a-Dihydro-6-phenylisoindolo[2,1-a]quinazoline-5,11-dione

This compound is a white solid, yield 78 %. M.p. 184-185 °C. IR (KBr) 3038, 2926, 1660, 1592, 1489, 1332, 1137 cm^{-1}. ^1H NMR 7.38-7.41 (t, 1H), 7.49-7.52 (m, 3H), 7.66-7.67 (m, 3H), 7.75-7.86 (m, 5H), 8.30 (s, 1H), 8.51-8.52 (d, 1H),). LRMS m/z 351$(M)^+$.

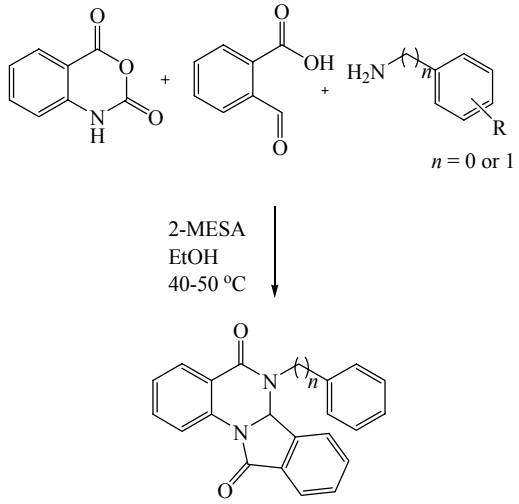
6-(4-chlorophenyl)-6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione

This compound is a white solid, yield 85 %. M.p. 207-209 ^{0}C. IR (KBr) 3063, 2924, 1662, 1584, 1489, 1332, 1138, 767 cm^{-1}. ^1H NMR 7.24-7.44 (m, 1H), 7.51-7.55 (m, 3H), 7.67-7.70 (m, 3H), 7.82-7.84 (m, 1H), 7.87-7.90 (m, 3H), 8.33 (s, 1H), 8.53-8.55 (d, 1H). LRMS m/z 385,386 $(M+Na)^+$.

Result and Discussion

In search of the best experimental reaction conditions, the reaction of isatoic anhydride, 2-formylbenzoic acid and aromatic amines or benzylamine in the presence of 2-MESA as a catalyst in ethanol was considered as a standard model reaction (Scheme 1). To evaluate the exact concentration of 2-MESA required for the reaction, we investigated the model reaction of aniline using different concentrations. The result revealed (Table 2) that when the reaction was carried out in the absence of catalyst, the product formed in a very trace amount (entry 1).

When the reaction was carried out in presence of 2, 5 and 8 mol % of catalyst, yields were lower even after prolonged duration. The reaction in the presence of 10, 12 and 15 mol % of catalyst gave excellent yields in shorter time. The optimal results were obtained with 15 mol % of catalyst and this concentration was ideal of carry out reaction smoothly (entry 7).



Scheme 1. Synthesis of title compounds.

Table 2. Effect of concentration of catalyst.

S. No.	2-MESA, mol %	Time, h	Yield, %
1	0	a	10
2	2	8	40
3	5	6	50
4	8	2	60
5	10	2	80
6	12	1.5	85
7	15	1	90
8	20	1	90

In order to evaluate the effect of solvent, reactions were carried out in various solvents. Dichloromethane, acetonitrile, THF and DMSO afforded moderate yield 50, 65, 55 and 40 %, respectively. Methanol and DMF resulted in good yields of 80 and 70 %, respectively. However, ethanol furnished the product in 90 % yield making it the most suitable solvent. To investigate the role of substituents on

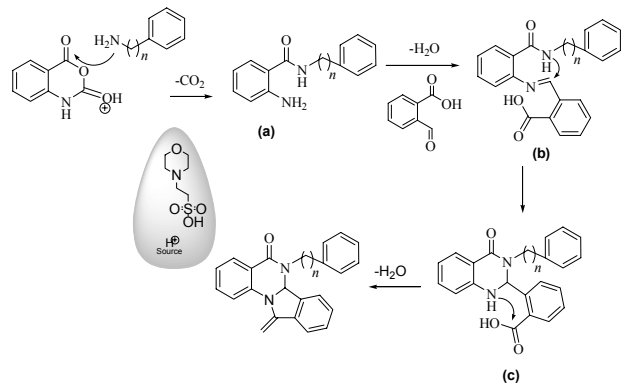
aniline on the reaction (*n*=0, Scheme 1) differently substituted anilines were treated with 2-formylbenzoic acid, isatoic anhydride in presence of 2-MESA using ethanol as a solvent to get desired product. The results found for benzylamine (entry h, *n*=1) is also mentioned in the Table 3. It was noticed that all the substrates are well tolerated under optimized conditions furnishing the product in good to excellent yields. The results are summarized in Table 3. Formation of the desired product was confirmed by comparing their physical constant, IR, 1H NMR and mass spectroscopic data with reported compounds.

Table 3. Synthesis of isoindolo[2,1-*a*]quinazolines derivatives

Entry	Amine moiety	Time, h	Yield, %	M.p. °C
a	3-Methylaniline	2	95	162-163
b	2,4-Dichloro-aniline	2.2	75	223-225
c	Aniline	2.8	78	184-185
d	4-Chloroaniline	2.4	85	207-209
e	4-Bromoaniline	2.2	82	111-112
f	4-Acetylaniline	2.6	77	158-161
g	3-Nitroaniline	2.8	83	235-237
h	Benzylamine	2	88	149-150
i	4-Methylaniline	2	82	195-196
j	4-Cyanoaniline	1.8	90	202-203
k	4-Hydroxyaniline	1.9	88	215-217

Reaction Mechanism

The nucleophic attack of the aromatic amine on isatoic anhydride gives an intermediate (**a**), the amino group of intermediate (**a**) attack on 2-formylbenzoic acid gives another intermediate (**b**), which on cyclization is converted to another intermediate (**c**). Finally intermediate (**c**) on dehydration gives isoindolo [2,1-*a*]quinazoline (Scheme 2).



Scheme 2. A probable mechanism of the sysnthesis.

Conclusion

Here we have demonstrated the use of 2-MESA as greener catalyst to accelerate the synthesis of isoindolo [2,1-*a*] quinazoline derivatives in ethanol. The role of ultrasonication in the use of greener organic acid catalyzed reaction has been highlighted. The methodology may prove useful for this transformation is high yield at room temperature under mild reaction conditions with fast, and easy isolation of the product under ultrasonic irradiation.

Acknowledgment

We are great thankful to the Department of Chemistry, Deogiri College, Aurangabad for providing laboratory facilities and the permission to use facility the Central Research Laboratories. Council of Science and Industrial Research (CSIR), New Delhi (110012) for financial support under Junior Research Fellowship.

References

[1]Patil, R., Bhoir, P., Deshpande, P., Wattamwar, T., Shirude, M., Chaskar, P., *Ultrason. Sonochem*., **2013,** *20*, 1327.

[2]Mason, T. J., Cintas, P., Clark, J., Macquarrie (Eds.), D., *Handbook of Green Chemistry and Technology*, Blackwell Science, Oxford, **2002**.

[3]Suslick, K. S., *Britannica Chicago*, **1994**, 138.

[4]Dabholkar, V. V., Ansari, F. Y., *Green Chem. Lett. Rev*., **2010**, *3*, 245.

[5]Trilleras, J., Polo, E., Quiroga, J., Cobo, J., Nogueras, M., *Appl. Sci.*, **2013**, *3*, 457.

[6]Pardeshi, S. D., Sonar, J. P., Pawar, S. S., Dekhane, D., Gupta, S., Zine, A. M. Thore, S. N., *J. Chil. Chem. Soc.*, 2014, *59*, 2335.

[7]Yoo, B. W., Hwang, S. K., Kim, D. Y., Choi, J. W., Kang, S. O., Yoo, B. S., Choi, K., Kim, J.H., *Bull. Korean Chem. Soc*., **2004** , *25*, 1633.

[8]Kaur, B., Parmar, A., Kumar, H., *Heterocyclic Letters*, **2011,** *1*, 55.

[9]Thalla, N., Devineni, S. R., Parimi, B. N., Chamarthia, N. R., *Chem. Sin.*, **2012**, *3*, 808.

[10]Maske, S. B., Argade, N. P., *Tetrahedron Lett*., **2006**, *62*, 9787.

[11]Kumar, K. S., Kumar, P. M., Kumar, K. A., Senivasulu, M., Jafar, A.A., Rambabu, D., Krishna, G. R., Reddy, C. M., Kapavarapu, R., Shivakumar, K., Priya, K. K., Parsac K. V. L., Pal, M., *Chem. Commun.*, **2011**, *47*. 5010.

[12]Tiwari, A. K., Singh V. K., Bajpai, A., Shukla, G., Singh, S., Mishra, A. K., *Eur. J. Med. Chem.*, **2007**, *42*, 1234.

[13]Cao, S. L., Feng, Y. P., Jiang, Y. Y., Liu, S. Y., Ding, G. Y., Li, R. T., *Bioorg. Med. Chem. Lettt.*, **2005**, *15*, 1915.

[14]Abbas, S. E., Barsoum, F. F., Georgey, H. H., Mohammed, E. R., *Bull. Fac. Sci. Cairo. Univ*., **2013**, *51*, 273.

[15]Grover, G., Kini, S.G., *Eur. J. Med. Chem*., **2006**, *41*, 256.

[16]Giri, R. S., Thaker H. M., , Giordano, T., Williams, J., Rogers, D., Sudersanam, V., Vasu, K. K., *Eur. J. Med. Chem*. **2009**, *44*, 2184.

[17]Giri, R. S., Thaker, H. M., Giordano, T., Williams, J., Rogers, D., Vasu, K. K., Sudarsanam, V., *Bioorg. Med. Chem*., **2010,** *18*, 2796.

[18]Adnan, A., Kadi, A. S., El-Azab, Ahmed. M., Alafeefy, Abdel-Hamide, S. G., *J. Pharm. Sci*., **2006**, *34*, 147.

[19]Kumar, A., Sharma, S., Bajaj, K., Archana, S., Sharma, S. H,. Panwar, T., Singh, V. K., *Bioorg. Med. Chem*., **2003**, *11*, 5293.

[20]Mohamed, M. S., Ibrahim, M. K., Alafeefy, A. M., Abdel-Hamide, S. G., *J. Appl. Sci*., **2004**, *4*, 302.

[21]Al-Rashood, S. T., Aboldahab, I. A., Nagi, M. N., Abouzeid, L. A., Abdel-Aziz, A. A., Abdel- Hamide, S. G., Youssef, K.M., Al-Obaid, A.M., El-Subbagh, H.I., *Bioorg. Med. Chem*.,**2006**, *14*, 8608.

[22]Gomes, P., Araujo, M. J., Rodrigues, M., Vale, N., Azevedo, Z., Iley, J., Chambel, P., Morais, J., Moreira, R., *Tetrahedron*, **2004**, *60*, 5551.

[23]Herget, T., Freitag, M., Morbitzer, M., Kupfer, R., Stamminger, T., Marschall, M., *Antimicrob. Agents. Chemother.*, **2004**, *48*, 4154.

[24]Mohamed, M. S., Ibrahim, M. K., Alafeefy, A. M., Abdel-Hamide, S. G., *Pak. J. Biol. Sci.*, **2004**, *7*, 1262.

25Khodarahmi, G., Jafari, E., Hakimelahi, G., Abedid, D., Khajouei, M.R., Hassanzadeh, F., *Iran. J. Pharm. Res*., **2012**, *11*, 789.

[26]Boven, E., Erkelens, C. A. M., Luning, M., Pinedo, H. M., *Br. J. Cancer*, **1990**, *61*, 709.

[27]Kovalenko, S. I., Antypenko, L. M., Bilyi, A. K., S Kholodnyak,.V., Karpenko, O.V., Antypenko, O. M., Mykhaylova, N. S., Los, T. I., Kolomoets, O. S., *Sci. Pharm*., **2013**, *81*, 359.

[28]Mohamed, Y. A., El-galil, A. B. D., Amr, E., Mohamed, S. F., Abdalla, M. M., Al-omar, M. A., Shfik, A.H., *J. Chem. Sci*., **2012**, *124*, 693.

[29]Mahdavi, M., Asadi, M., Saeedi, M., Tehrani, M. H., Mirfazli, S. S., Shafiee, A., Foroumadi, A., *Synth. Comm.,* **2013**, *43*, 2936.

[30]Safari, J., Gandomi-Ravandi, S., *J. Saudi Chem. Soc.,* **2014**.

[31]Avalani, J. R., Patel, D. S., Raval, D. K., *J. Mol. Catal B: Enzym*., **2013,** *90*, 70.

[32]Martinez-Viturro, C. M., Dominguez, D., *Tetrahedron Lett.,* **2007**, *48*, 1023.

Received: 22.08.2015.
Accepted: 15.09.2015.

INVESTIGATION ON ENHANCED MICROWAVE DEMULSIFICATION USING INORGANIC SALTS

Adango Miadonye[a]* and Shanshan Lin[b]

Keywords: crude oil, microwave process, demulsification process, inorganic salts, brine water, oil-water emulsions.

While the formation of water-in-crude oil (W/O) emulsion is identified to cause serious problems in petroleum industry such as decrease in the efficiency of oil recovery, increase in pumping cost, and pipeline corrosion its treatment has been based mostly on gravity separation by mechanical/chemical technology. As an integral part in the process of oil production and transportation, crude oil demulsification has received attention. In this work, microwave demulsification and the influence of a variety of inorganic salts to the microwave process has been studied. A comparative study on microwave demulsification of heavy oil and light oil has also been conducted. The obtained results showed water separation of 47 % between irradiated and non-irradiated emulsion for heavy crude oil compared to 13 % for light crude oil. The effect of different inorganic salts and the optimum amount of the electrolyte to promote demulsification were also determined.

* Corresponding Authors
Fax: 1(902) 563 1880
E-Mail: adango_miadonye@cbu.ca
[a] School of Science and Technology
Cape Breton University, Sydney, NS. Canada.
[b] Department of Process Engineering and Applied Sciences,
Dalhousie University, Halifax, NS. Canada.

Introduction

During the process of mining, processing and transportation, wet crude oil passes through pores of formation, pipelines and pumps where fierce disturbance occurs. Consequently, water in the crude oil is split into separate tiny droplets, at the same time the natural emulsifier content in crude oil forms a protective film at the interface of oil and water resulting in the formation of crude oil emulsions. Most crude oil emulsion is water-in-oil type (W/O), while oil-in-water type or a combination of both also exists.[1-4] Emulsion causes serious problems in petroleum industry such as decrease in the efficiency of oil recovery, increase in pumping cost, and pipeline corrosion, so appropriate treatment measures are necessary. The process of breaking down water-oil emulsions is called demulsification. As one of the important aspects in crude oil production, demulsification process has become a significant research direction.

With the decrease in light oil reserves, more focus and attempts are turned to the recovery of heavy crude oil and bitumen. Due to the high viscosity and more complex composition of heavy oil, the demulsification by conventional heating seems to be more time-consuming and inadequate to meet the industry need. The microwave irradiation has proved to be an effective method to separate the water and oil with the rapid heat conduction. Thus, it is of great significance to determine whether microwave demulsification has optimum process conditions when it comes to heavy oil.

Microwave irradiation has long been applied to crude oil demulsification based on the fact that microwave heating can dissipate heat inside the medium and raise the energy of the molecules quickly. Compared with conventional heating, materials in microwave irradiation can directly absorb the energy and transmit it into heat.[5] According to previous work,[6-8] the existence of ions leads to higher conductivity of emulsion and enables it to get more efficient heating. From the microcosmic perspective, large quantity of ions can reduce dielectric loss; besides, microwave coupling are able to produce superheating.

Tambe and Sharma[7] have conducted research on the effects of sodium chloride and calcium chloride solutions on emulsion stability. They showed that certain amount of inorganic salts can influence the stability of colloid emulsions in negative ways and enhance the demulsification.

A research on salt-assisted microwave demulsification has been conducted by Xia and Cao,[8] proving that demulsification efficiency is enhanced effectively and the light transmittance of the water separated from the emulsions is increased by the addition of a very small amount of inorganic salts. However, these researches mainly focused on the effect of sodium chlorate. To understand the utilization of inorganic-salts in crude oil demulsification, optimum choice of inorganic salts with effective concentration needs to be examined.

This work is focused on the effect of inorganic salts on microwave demulsification, comparing salt-assisted microwave demulsification of heavy oil and light oil and identifying the best inorganic salt required to promote the demulsification process and its optimum concentration. To simulate the emulsions formed under field conditions, the emulsions prepared with sea water and fresh water were also examined.

Experimental

Materials and Equipment

The experiment was carried out in a modified domestic microwave oven. The details of the modifications made on the microwave has been given in previous publications.[9,10] In order to impose restrictions on the evaporation, only high frequency microwave was applied in this experiment. The microwave equipment is Kenmore domestic microwave oven. The parameters are listed in Table 1. The temperature measurement is achieved with Diqi-Sense (Dual log RTM Thermocouple).

Table 1. Parameters of Microwave Equipment.

Parameter	Details
Model	Kenmore, Model No. 86706
Power	120 V A.c. 60 Hz, single phase, consumption : 0.91KW
Power Generator	Magnetron
Operating Frequency	2450 MHz
Maximum output	600 W, Water load: 275 mL
Operating voltage	4.0 KV

The chemicals viz. NaCl, KCl, $MgCl_2$, $CaCl_2$, KI, $NaNO_3$, Na_2CO_3, NaBr, NaI and SDS (sodium dodecyl sulfate, 95 %) were of analytical grade and were from Sigma-Aldrich, Canada. The crude oil samples used for this study are Arabia heavy oil and Bonny light crude, obtained from Saudi Aramco Ltd and SGS Canada, Port Tupper, NS, respectively. The properties of the crude oil samples are compared in table 2. Sea water (blackish water) from the Atlantic Ocean estuary and fresh water from Mackenzie River, both in Victoria Mines, Nova Scotia, were also used for preparation of emulsions.

Table 2. Properties of Arabian Heavy Crude Oil and Bonny Light Crude Oil.

Property	Arabian Crude	Bonny Light
Gravity, $API_\circ$	27.31	33.40
Gravity SG	0.89	0.84
Sulfur, wt%	3.066	0.16
Viscosity, cSt @ 40 °C	28.84	3.28

Both crude oils were used to prepare the water-in-oil (W/O) emulsions. A detailed procedure for the preparation of water-oil (W/O) emulsions has been given in our previous publication.[11] In this study, the salt solutions of 0.02 mol L^{-1} concentrations were prepared using distilled water and the pure solid salts (NaCl, KCl, $MgCl_2$, $CaCl_2$, KI, $NaNO_3$, Na_2CO_3, NaBr, NaI). To prepare the emulsions, 3 mL of the salt solution was added to a mixture of 6 mL crude oil and 0.2 wt% SDS surfactant. The mixture was agitated using a Heidolph RZR 2020 overhead 2-blades stirrer at a speed of 500 rpm for 1 min. Each emulsion sample was then exposed to microwave irradiation for 5 or 10 s, as necessary, and transferred into a 10 mL-graduated cylinder. The real time temperature of the mixture during irradiation was measured with a thermocouple and recorded on a desktop computer. The maximum irradiation time of 10 s was chosen in order to limit the emulsion temperature to 80 °C to control the vaporization of water and other volatile components. The volume of separated water is recorded every 2 min for an initial 120 min and then for every 5 min for a total of 5 h. The sample of distilled water emulsion is set as reference. For the experiments which require larger volume of emulsion, 15 mL of the salt solution and 30 mL crude oil were used. Then, the emulsion sample was divided into three equal portions and the procedure on irradiation and water separation discussed earlier are followed.

Results and Discussion

The temperature profile during 10 s irradiation of the crude oil emulsions formed from the solutions of various inorganic salts is illustrated in Figure 1. Unlike the gradual energy transmission in conventional heating, the energy is directly absorbed in microwave heating and the temperature is elevated locally.

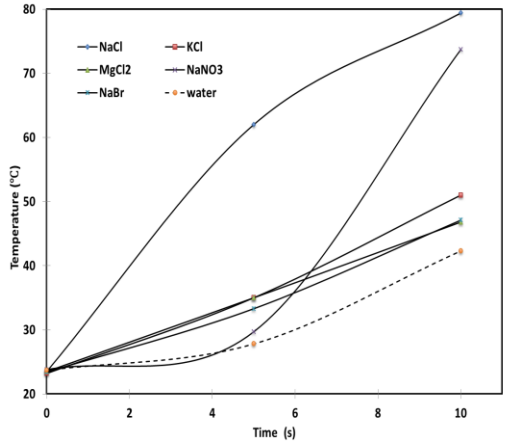


Figure 1. Temperature versus microwave heating time.

From the temperature profile in Figure 1, the impact of inorganic salts on the heating efficiency of microwave irradiation is evident, as the emulsions with inorganic salts exhibit higher temperatures compared to the emulsion with no salt. This is due to the presence of inorganic salts which causes additional superheating of the solution in a microwave field, increasing the temperature of the crude oil emulsions.[6]

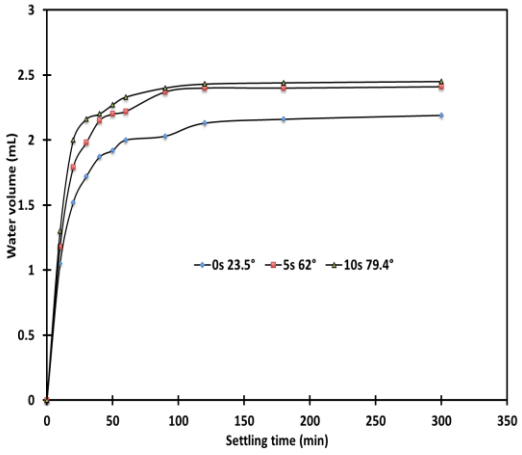


Figure 2. Separated water volume of NaCl emulsion

Effect of Inorganic Salts on Demulsification

The water-oil emulsions from Arabian heavy crude oil with 0.02 molar solutions of inorganic salts were evaluated for their effects on microwave demulsification. Figure 1 showed that inorganic salt generally enhances the heating process of the emulsions which can subsequently improve the demulsification process.

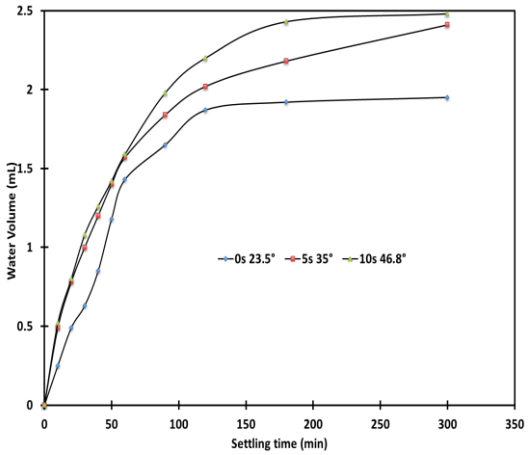


Figure 3. Separated water volume of KCl emulsion.

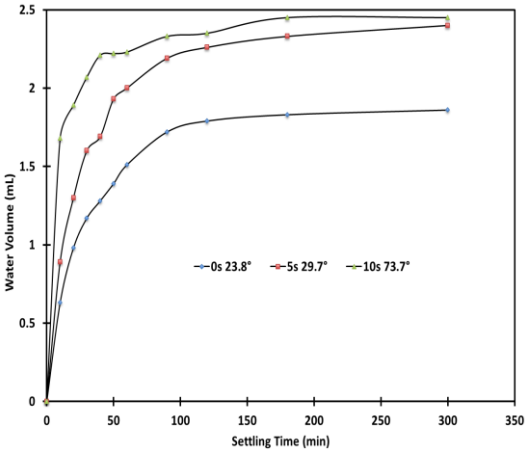


Figure 4. Separated water volume of $MgCl_2$ emulsion.

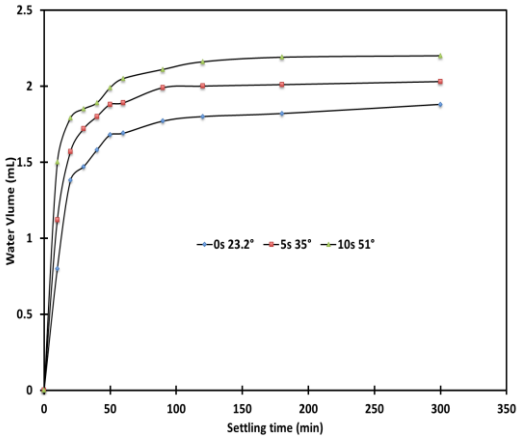


Figure 5. Separated water volume of $NaNO_3$ emulsion.

The room temperature was 23.5°C, and the prompt temperatures after microwave heating for 5 s and 10 s were 62 °C and 79.4 °C, respectively for emulsions with NaCl salt (Figure 2). The temperatures with other inorganic salts for the the same irradiation periods are lower as illustrated in Figure 1.

The volume of separated water increases with the settling time for the various salts as given in Figures 2 to 6. The amount of separated water for microwaved samples is higher than for non-irradiated emulsion samples. The final results of demulsification after 5 h also showed that more water is separated after microwave irradiation compared with gravity settling. Similar results were seen from the experiments with KCl, $MgCl_2$, $NaNO_3$ and NaBr (Figures 3-6).

From the Figures it is obvious that longer retention in microwave leads to higher demulsification rate, that is, larger volume of water is separated from the emulsions. Also, the process of demulsification is rapid for the first 2 hours after irradiation process, then, slows down with the drop in temperature and settling time. Similar trend is observed for non-irradiated samples but, with much lower demulsification rate.

The results are in agreement with the theory that the inorganic salts can cause further superheating of the solution in a microwave field, which subsequently enhance the process of demulsification.[6] It has been shown that the electromagnetic field formed by the microwave can neutralize the zeta potential by disturbing the ordered arrangement of the electrical charges surrounding the water droplets.[1,12] The presence of salts in the emulsions enhances the dielectric loss effect and microwave coupling which results in the absorption of more energy by the water droplets, thus, increasing the temperature of the emulsions (Figure 1). As a result, water droplets expand in the continuous phase, collide and coalesce into bigger droplets and separate from the emulsion.

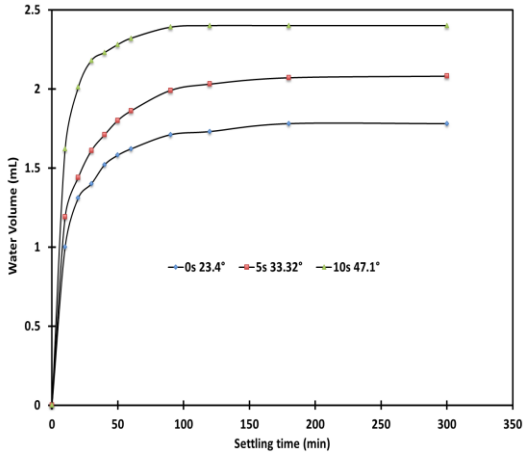


Figure 6. Separated water volume of NaBr emulsion.

Previous studies on the interactions between the ions in emulsion have been reported.[13,14] The interaction between calcium and SDS has been reported in the work of Iyota et.al,[13] that the critical mole fraction of SDS needed to form particles in a solution is much larger for the $CaCl_2$-SDS

mixture than for the NaCl-SDS mixture due to the electrostatic attraction between Ca^{2+} and DS^- ions in the aggregates being larger than that between Na^+ and DS^- ions

This, arguably, may account for the insignificant difference in volume of water separation between microwaved and non-microwaved emulsions from the solutions of $CaCl_2$, Na_2CO_3 and KI salts. Figure 7 showed an example of results obtained with these salts solutions. The poor water separation efficiency has also been attributed to the probability of the formation of azeotrope, which can inhibit the formation of emulsion.

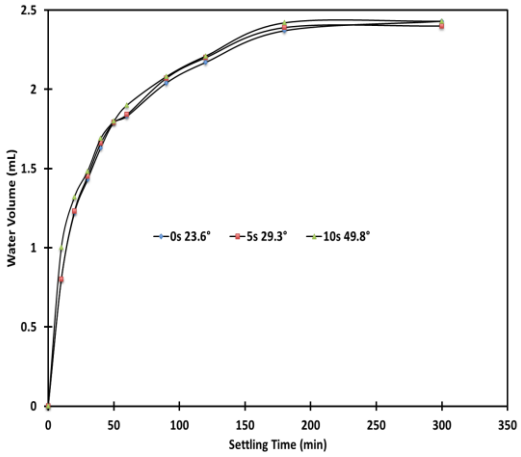


Figure 7. Separated water volume of $CaCl_2$ emulsion.

As a reference, emulsions prepared with only distilled water were also examined. As shown in Figure 8, microwave demulsification still has favourable effect over gravity settling (non-microwaved emulsion). Since the temperature of the emulsion after 10 s microwave irradiation was only 42.3 °C, much lower than the emulsion with NaCl (79.4 °C), the final volume of separated water was 2.23 mL. This is approximately 10 % less than the results obtained from emulsions with inorganic salts.

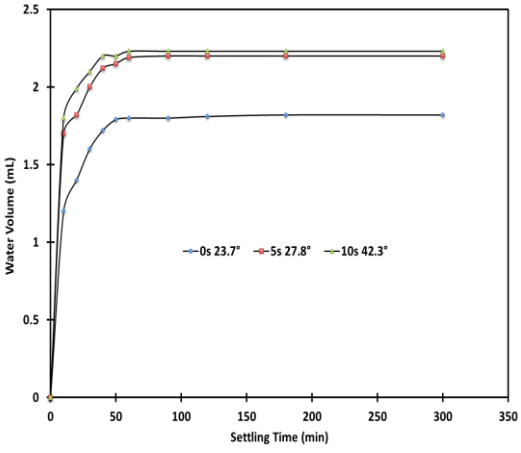


Figure 8. Separated water volume of distilled water emulsion.

Effect of Salt Concentrations on Demulsification

The results shown in Figures 2 to 5 indicate that different salts can enhance the microwave demulsification to different degrees. Since the emulsion with NaCl showed higher superheating property, NaCl was used in the study of effect of salt concentrations on demulsification. Emulsion of NaCl solutions of different concentrations and Arabian crude oil with SDS was prepared as described earlier in the experimental section. Each emulsion was irradiated in the microwave oven for 10 s with real time temperature measurement, and the volume of separated water recorded every 2 min.

The effects of different NaCl concentrations on microwave demulsification as illustrated by the volume of water separated and temperature is shown in Figure 9. The results of demulsification vary with the concentration of solution. However, the amount of separated water does not show a sustainable growth with the increase in salt concentration. As shown in the figure, the volume of separated water increases with the salt concentration until it reaches the highest value when the concentration is 0.04 mol L^{-1}, and then the amount of separated water begins to decrease. Compared to distilled water, NaCl solutions with concentrations less than 0.1 mol L^{-1} play a positive role in the microwave demulsification. But when the concentration is greater, the separation seems to be hindered, in other words, the volume of separated water is even less than that without NaCl. Another thing to be noted is that the temperature has a positive relation with the NaCl concentration, albeit, not with the volume of separated water. It is worthy to note that at the optimum NaCl concentration of 0.04 mol L^{-1}, the water separation is 34.5 % higher as compared to emulsion from distilled water.

It is logical, perhaps, to expect that the increasing concentration of inorganic salts will enhance the process of demulsification because more ions meant better electric effect and better superheating characteristic of the emulsion.

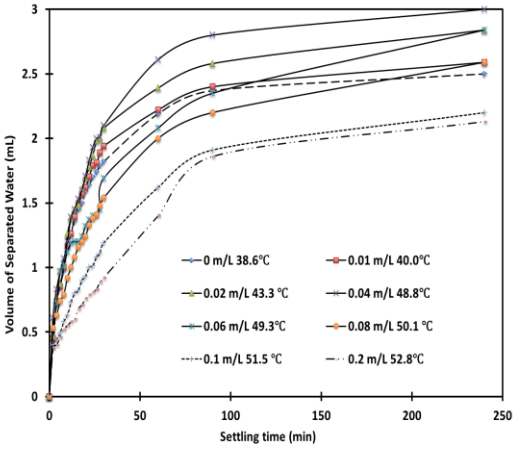


Figure 9. Effect of salt concentration on separation water.

But the results indicate that maximum water separation efficiency is obtained at an optimum NaCl concentration of 0.04 mol L^{-1}, followed by a decline in volume of water separated as concentration increases. This trend could be attributed to fact that demulsifcation is a combination of multiple influencing factors, salt concentration being one of them. On one hand, the increasing salinity may also have stabilizing effect on the W/O emulsion. Zylyftari et.al,[15] have reported that as salt concentration increases, the equilibrium temperature for hydrate stability is shifted to lower values as a result of chemical potential changes of water in the brine solution. It has also been reported that for

the emulsion stability of water-in-crude oil, the role of NaCl strongly enhances the stability performance of W/O emulsion and reaches to 100 % stability for 5% NaCl concentration.[16] Therefore, it is possible that the effect of superheating enhanced by NaCl is surpassed by its stabilization effect when the concentration reaches the optimum salt concentration of 0.04 mol L^{-1}.

Effects of Different Crude Oils and Production Water on Demulsification

The W/O emulsions were prepared with 0.02 mol L^{-1} solution of NaCl and Saudi Arabian heavy crude oil and Bonny light oil. Here, the emulsions were prepared with 15 mL water and 30 mL crude oil to meet the large sample volume needed for the study. The surfactant was 0.2 % (wt) concentration of SDS. To study the effects of production water only the Arabian heavy crude oil emulsion was used.

The method is described in the experimental section, except that the solution is replaced by distilled water, fresh water and salt water, respectively.

The comparison of the emulsions of the two crude oils, with large distinction in API gravity, is shown in Figure 10. It is worth mentioning that the emulsion prepared with heavier oil is much more stable. In the Figure, non-MW indicates that the demulsification is only achieved by gravitational force. The temperature of the emulsions measured during the microwave irradiation is shown in Figure 11.

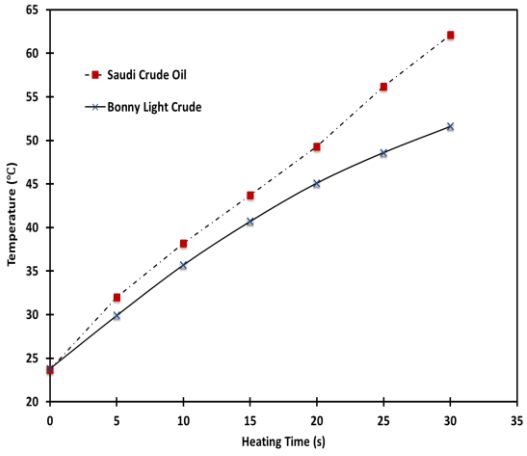


Figure 10. Comparison of microwave demulsification between Saudi Arabian Heavy Oil and Bonny Light Oil.

The results showed that more water was separated from Saudi Arabian heavy oil between microwaved and non-microwaved emulsions than from those of Bonny light crude oil. The separated water is 47 % for Arabian heavy crude while that for Bonny light is 13.8 % after microwave irradiation. The reason can be inferred from Figure 11, the heavy crude oil has a higher growth rate in temperature during microwave heating, which leads to larger reduction in viscosity, and hence, better water separation efficiency.

The result for production water under field condition simulation is illustrated in Figure 12. The separation efficiency of distilled water emulsion was lower than the ones for emulsions prepared with sea water and fresh water, confirming the significance of inorganic salts in microwave demulsification. Fresh water, which contains a small amount of inorganic salts, results in the most effective separation compared to sea water; in agreement that most effective separation is not obtained with the highest salt concentration.

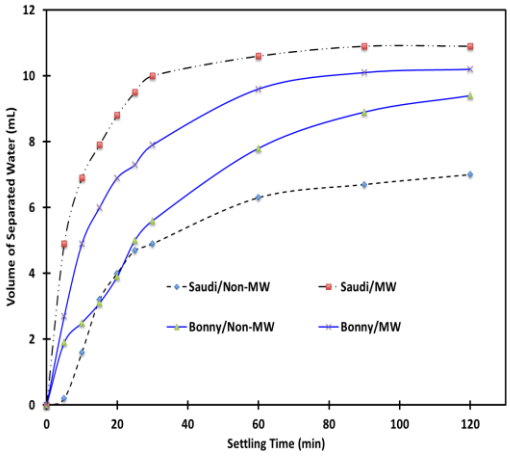


Figure 11. Temperature change of Arabian Heavy Oil and Bonny Light Crude Oil.

However, it was noted that the water separated from sea water emulsion has the highest transmittance to light, and the water obtained from fresh water emulsion was much more turbid. The reason is that, arguably, some mineral substances in fresh water trap the tiny oil droplets in water, thus making it less transmittance to light.

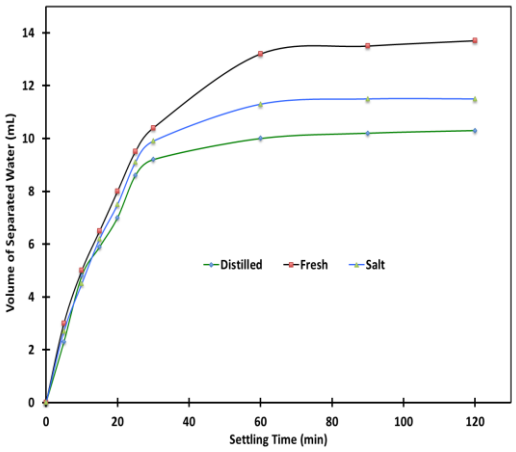


Figure 12. Effects of water source on microwave demulsification.

Conclusion

In this work, a broad range of inorganic salts and NaCl concentrations were investigated for microwave demulsification of two crude oils of large distinction in API gravity. The comparison between microwave heating and gravity settling elucidates the advantages and benefits of salts-assisted microwave demulsification process. The results showed that different salt solutions have distinct positive effects on the process of demulsification of crude oil emulsions.

The results obtained can thus be summarized as follows. The existence of inorganic salts in microwave demulsification accelerates the heating process and increases the amount of separated water. Different salts can enhance the microwave demulsification of crude oil emulsions to different degrees. The results of demulsification vary irrationally with the concentration of NaCl salts, with the highest water separation efficiency obtained at 0.04 mol L^{-1} concentration. Generally, a relatively small amount of salts enhance the demulsification. Among the salts examined, NaCl stands out in the separation of water and more pronounced with heavy crude (Saudi Arabian crude) oil emulsion. Salt-assisted microwave demulsification has better performance in dealing with heavier crude oil. The sources of water in emulsion influence the result of demulsification due to their distinct components and concentration of salts. The results shows that fresh water favours the demulsification more than sea water and distilled water, in agreement with the conclusion obtained previously, that a small amount of inorganic salts could enhance the separation to the greatest degree.

Acknowledgements

The authors are grateful for the financial support provided by the Office of Research, Teaching and Graduate Studies, Cape Breton University. We thank Saudi Aramco Ltd for supplying the heavy oil sample and Dr. David J.G. Irwin (Retired Physicist, Cape Breton University) for his help in the modification of the domestic microwave oven.

References

[1]Fang, C. S., Chang, B. K. L., Lai, P. M. C., Klaila, W. J., *Chem. Eng. Commun*., **1988**, *73*, 227-239.
[2]Chih-Chieh C., Yeong-Ching, C., *Sep. Sci. and Technol*., **2002**, *37*, 3407-3420.
[3]Pekdemir, T., Akay, G, Dogru, M., Merrells, R.E., Schleicher. B., *Sep. Sci. Technol*., 2003, 38, 1161-1183.
[4]Xia, L., Lu, S., Cao, G., *Sep. Sci. Technol.*, **2003**, *38*, 4079-4094.
[5]Martínez-Palo, R., Cerón-Camacho, R., Chávez, B., Vallejo, A. A., Villanueva-Negrete, D., Castellanos, J., Karamath, J., Reyes, J., Aburto J., *Fuel*, **2013**, *113*, 407–414.
[6]Xia, L., Lu, S., Cao, G., *Chem. Eng. Comm*., **2004**, *191*, 1053-1063.
[7]Tambe, D. E., Sharma, M.M., *J. Colloid Interface Sci.*, **1993**, *157*, 244-253.
[8]Xia, L., Cao, G., *J. Macromol. Sci*., **2006**, *43*, 71-81.
[9]Miadonye, A., Snow, S., Irwin, D. J. G., Khan, R. M., Britten, A., *WIT Trans. Eng .Sci.*, **2009**, *63*, 455-65.
[10]Miadonye, A., MacDonald, B., *J. Petrol. Sci. Res*., **2014**, *3(3)*, 130 – 135.
[11]Miadonye, A, Nwankwor, E., *J. Petrol. Sci. Res*., **2014**, 3(2), 68 – 72.
[12]Michael, D., Mingos, P., Baghurst, D.R., *Chem. Soc. Rev.*, **1991**, *20*, 1-47.
[13]Iyota, H., Tomimitsu, T., Aratono, M., *Colloid Polym. Sci.*, **2010**, *288*, 1313–1320.
[14]Yang, F., Liu, S., Xu, J., Lan, Q., Wei, F., Sun, D., *J. Colloid Interface Sci*., **2006**, *302*, 159–169.
[15]Zylyftari, G., Lee, J W., Morris, J.F., *Chem. Engr. Sci*., **2013**, *95*, 148-160.
[16]Ghannam, M.T., *Petrol. Sci. Technol*., **2005**, *23*, 649-667.

Received: 21.08.2015.
Accepted: 22.09.2015.

THREE-COMPONENT SYNTHESIS OF 1-ARYL-1,2,3,4-TETRAHYDROPYRIMIDO[1,2-*a*][1,3,5]TRIAZINE-6-ONES

A. Yu. Potapov[a], K. S. Shikhaliev[a] and A. V. Falaleev[a]

Keywords: 2-Arylamino-3H-pyrimidine-4-ones; three-component reaction; aliphatic amines; 1,2,3,4-tetrahydropyrimido[1,2-*a*][1,3,5]triazine-6-ones.

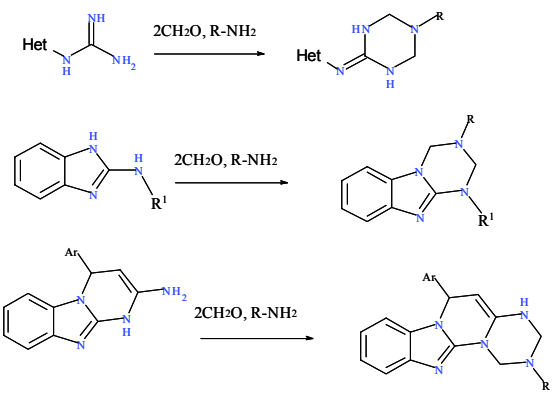
This study is concerned with a three-component method of synthesis of new 1,2,3,4-tetrahydro-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-ones based on 2-amino-3H-pyrimidine-4-ones, aliphatic amines and formaldehyde. Conditions of reaction were optimized.

* Corresponding Authors
Mobile No. : +79103464169
E-Mail: pistones@mail.ru
[a] Voronezh State University, Department of Organic Chemistry, Voronezh, Russian Federation. 394006 Voronezh Universitetskaya pl. 1.

Introduction

Over the last years condensed 1,3,5-triazines are found in the center of medicinal chemistry due to the opportunity of building structurally diverse compounds, exhibited various kinds of biological activity.[1] However, pyrimido[1,2-*a*]triazines were studied insufficiently and in the literature reported only a few number of methods of preparation.[2] For some compounds of this series, antibacterial and antifungal activities were found. Recently, the synthesis of partly hydrogenized pyrimido[1,2-*a*]triaxines[3] capable of inhibit cancer cell growth.[4]

We have previously reported[5,6] about the three-component methods of synthesis of 1,3,5-hexahydrotriazines from hetarylguanidines and its benzimodazo[1,2-*a*]condensed derivatives on the basis of N-alkyl(aryl)amino-benzimidazoles (scheme 1).



Scheme 1. Synthesis of triazines.

Development for annelation methods of triazine cycle to various heterocyclic substrate having 1,3-dinuclepphilic centers in their structure has been undoubted interest. The aim of this work is to develop a one-pot method of synthesis of tetrahydropyrimido[1,2-*a*][1,3,5]triazine system designed in the framework of a program for searching of new antibacterial, anti-inflammatory and antitumor medicines.

Experimental part

General

All commercial reagents were purchased from Bekton, Lancaster, Acros, Aldrich, and Sigma and were used as received without further purification. The course of the reactions and purities of the compounds were monitored by thin layer chromatography (TLC) on SILUFOL UV-254 plates, eluent: chloroform, methanol in different proportions and spots were visualized by exposure to iodine vapours. The ^{1}H-NMR spectra were recorded on a *Bruker AM-300* spectrometer operating at 300.13 MHz, using DMSO-d_6 as solvent and TMS as internal standard. Elemental analyses were determined by using a *Carlo Erba NA 1500* elemental analysis instrument. Melting points were recorded using *Stuart SMP30* melting point instrument.

General procedure for the synthesis of 1,2,3,4-tetrahydro-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-ones (3a-p)

To a suspension of 40 mmol of 2-aminopyrimidinone **1** in 3 ml of ethanol was added 40 mmol of aliphatic amine **2** and 80 mmol 37 % of aqueous formaldehyde solution. The mixture was refluxed until complete dissolving of pyrimidine compound (2-3 hours). When the reaction was completed, the reaction mixture was cooled to room temperature; the obtained precipitate was filtered off and recrystallized from isopropyl alcohol.

^{1}H-NMR spectra of tetrahydropyrimido[1,2-a][1,3,5]triazin-6-ones (**3a-p**), δ in ppm (J in Hz) are the followings:

3-(2-Methoxyethyl)-7,8-dimethyl-1-phenyl-1,2,3,4-tetrahydro-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (3a)

Yield = 64 %, M.p.= 95-97 °C. ^{1}H NMR (DMSO-d_6): δ = 1.87 (s., 3H, CH_3-C7); 2.02 (s., 3H, CH_3-C8); 2.99 (t., J=8.8, 2H, N(3)-CH_2); 3.32 (s, 3H, O-CH_3); 3.59 (t, J=8.8, 2H, O-CH_2);4.72 (s., 2H, CH_2-triazine); 4.98 (s, 2H, CH_2- triazine); 7.22-7.32 (m, 3H, arom.); 7.34-7.40 (m, 2H, arom.). Anal. Calcd. for $C_{17}H_{22}N_4O_2$: C, 64.95; H, 7.05; N, 17.82. Found: C, 65.11; H, 7.03; N, 17.85.

3-Benzyl-7,8-dimethy-1-phenyl-1,2,3,4-tetrahydro-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (3b)

Yield = 85 %, M.p. = 142-144 °C. ^{1}H NMR (DMSO-d_6): δ = 1.88 (s., 3H, CH_3-C7); 2.01 (s., 3H, CH_3-C8); 3.73 (s., 2H, CH_2-C7); 3.82 (s., 3H, O-CH_3); 4.03 (s., 2H, N(3)-CH_2); 4.73 (s., 2H, CH_2-triazine); 5.03 (s., 2H, CH_2-triazine); 6.88-6.97 (m., 2H, arom.); 7.06-7.19 (m., 4H, arom.); 7.20-7.28 (m, 4H, arom.). Anal. Calcd. for $C_{21}H_{22}N_4O$: C, 72.81; H, 6.40; N, 16.17. Found: C, 72.73; H, 6.37; N, 16.14.

3-(2-Furylmethyl)-7,8-dimethyl-1-phenyl-1,2,3,4-tetrahydro-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (3c)

Yield = 63 %, M.p. = 141-143 °C. ^{1}H NMR (DMSO-d_6): δ = 1.89 (s., 3H, CH_3-C7); 2.01 (s., 3H, CH_3-C8); 4.02 (s., 2H, N(3)-CH_2) 4.68 (s., 2H, CH_2-triazine); 5.02 (s., 2H, CH_2-triazine); 6.24 (d, J=3.2, 1H, H-furane); 6.36 (d.d., J=3.2, J=2.0, 1H, H-furane); 7.25-7.34 (m, 3H, arom.); 7.35-7.41 (m, 2H, arom.); 7.49 (d, J=1.7, 1H, H-furane). Anal. Calcd. for $C_{19}H_{20}N_4O_2$: C, 67.84; H, 5.99; N, 16.65. Found: C, 67.77; H, 6.00; N, 16.61.

7-Benzyl-3-(2-methoxyethyl)-8-methyl-1-phenyl-1,2,3,4-tetrahydro-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (3d)

Yield = 64 %, M.p. = 122-124 °C. ^{1}H NMR (DMSO-d_6): δ = 1.99 (s., 3H, CH_3-C8); 3.00 (t., J=8.8, 2H, N(3)-CH_2); 3.32 (s, 3H, O-CH_3); 3.58 (t, J=8.8, 2H, O-CH_2); 3.71 (s., 2H, CH_2-C7); 4.60 (s., 2H, CH_2-triazine); 5.03 (s, 2H, CH_2-triazine); 7.09-7.16 (m, 2H, arom.); 7.35-7.48 (m, 8H, arom.). Anal. Calcd. for $C_{23}H_{26}N_4O_2$: C, 70.75; H, 6.71; N, 14.35. Found: C, 70.27; H, 6.73; N, 14.31.

1-(4-Fluorophenyl)-3-(2-methoxyethyl)-7,8-dimethyl-1,2,3,4-tetrahydro-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (3e)

Yield = 72 %, M.p. = 92-94 °C. ^{1}H NMR (DMSO-d_6): δ = 1.88 (s., 3H, CH_3-C7); 2.09 (s., 3H, CH_3-C8); 3.02 (t., J=8.8, 2H, N(3)-CH_2); 3.32 (s, 3H, O-CH_3); 3.59 (t, J=8.8, 2H, O-CH_2);4.71 (s., 2H, CH_2-triazine); 4.97 (s, 2H, CH_2-triazine); 7.09-7.16 (m, 2H, arom.); 7.28-7.35 (m, 2H, arom.). Anal. Calcd. for $C_{17}H_{21}FN_4O_2$: C, 61.43; H, 6.37; N, 16.86. Found: C, 61.56; H, 6.39; N, 16.91.

1-(4-Fluorophenyl)-3-(2-furylmethyl)-7,8-dimethyl-1,2,3,4-tetrahydro-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (3f)

Yield = 79 %, M.p. = 133-135 °C. ^{1}H NMR (DMSO-d_6): δ = 1.89 (s., 3H, CH_3-C7); 2.10 (s., 3H, CH_3-C8); 4.04 (s., 2H, N(3)-CH_2); 4.70 (s., 2H, CH_2-triazine); 4.96 (s, 2H, CH_2- triazine); 6.25 (d, J=3.2, 1H, H-furane); 6.35 (d.d., J=3.2, J=2.0, 1H, H-furane); 7.10-7.15 (m, 2H, arom.); 7.27-7.34 (m, 2H, arom.); 7.48 (d, J=1.7, 1H, H-furane). Anal. Calcd. for $C_{19}H_{19}FN_4O_2$: C, 64.40; H, 5.40; N, 15.81. Found: C, 64.54; H, 5.40; N, 15.78.

7-Benzyl-1-(4-fluorophenyl)-8-methyl-3-(3-pyridinylmethyl)-1,2,3,4-tetrahydro-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (3g)

Yield = 75 %, M.p. = 143-145 °C. ^{1}H NMR (DMSO-d_6): δ = 2.02 (s., 3H, CH_3-C8); 3.72 (s., 2H, CH_2-C7); 4.07 (s., 2H, N(3)-CH_2); 4.73 (s., 2H, CH_2-triazine); 4.95 (s, 2H, CH_2- triazine); 6.95-7.07 (m, 2H, arom.); 7.11-7.19 (m., 2H, arom.); 7.20-7.29 (m, 5H, arom.); 7.42 (t., J=7.8, CH-pyridine); 7.75 (d., J=7.8, CH-pyridine); 8.49 (d., J=7.4, CH-pyridine); 8.54 (s., CH-pyridine). Anal. Calcd. for $C_{26}H_{24}FN_5O$: C, 70.73; H, 5.48; N, 15.86. Found: C, 70.67; H, 5.50; N, 15.82.

7-Benzyl-1-(4-fluorophenyl)-3-(2-furylmethyl)-8-methyl-1,2,3,4-tetrahydro-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (3h)

Yield = 70 %, M.p. = 140-142 °C. ^{1}H NMR (DMSO-d_6): δ = 2.03 (s., 3H, CH_3-C8); 3.72 (s., 2H, CH_2-C7); 4.03 (s., 2H, N(3)-CH_2); 4.72 (s., 2H, CH_2-triazine); 4.96 (s, 2H, CH_2- triazine); 6.26 (d, J=3.2, 1H, H-furane); 6.34 (d.d., J=3.2, J=2.0, 1H, H-furane); 6.94-7.06 (m, 2H, arom.); 7.10-7.18 (m., 2H, arom.); 7.21-7.30 (m, 5H, arom.); 7.47 (d, J=1.7, 1H, H-furane). Anal. Calcd. for $C_{25}H_{23}FN_4O_2$: C, 69.75; H, 5.39; N, 13.01. Found: C, 70.02; H, 5.41; N, 12.98.

3-(2-Methoxyethyl)-1-(2-methoxyphenyl)-7,8-dimethyl-1,2,3,4-tetrahydro-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (3i)

Yield = 68 %, M.p. = 94-96 °C. ^{1}H NMR (DMSO-d_6): δ = 1.86 (s., 3H, CH_3-C7); 1.97 (s., 3H, CH_3-C8); 2.98 (t., J=8.8, 2H, N(3)-CH_2); 3.32 (s, 3H, O-CH_3); 3.59 (t, J=8.8, 2H, O-CH_2); 3.80 (s., 3H, O-CH_3); 4.47 (s., 2H, CH_2-triazine); 5.03 (s., 2H, CH_2-triazine); 6.95 (t, J=8.3, 1H, arom.); 7.06 (d., J=7.9 1H, arom.); 7.22-7.31 (m, 2H, arom.). Anal. Calcd. for $C_{18}H_{24}N_4O_3$: C, 62.77; H, 7.02; N, 16.27. Found: C, 62.58; H, 7.04; N, 16.23.

1-(2-Methoxyphenyl)-7,8-dimethyl-3-(3-pyridinylmethyl)-1,2,3,4-tetrahydro-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (3j)

Yield = 81 %, M.p. = 154-156 °C. ^{1}H NMR (DMSO-d_6): δ = 1.87 (s., 3H, CH_3-C7); 1.98 (s., 3H, CH_3-C8); 3.81 (s., 3H, O-CH_3); 4.09 (s., 2H, N(3)-CH_2) 4.48 (s., 2H, CH_2-triazine); 5.04 (s., 2H, CH_2-triazine); 6.97 (t, J=8.3, 1H,

arom.); 7.07 (d., J=7.9 1H, arom.); 7.24-7.37 (m, 3H, arom.+CH-pyridine); 7.76 (d., J=7.8, CH-pyridine); 8.48 (d., J=7.4, CH-pyridine); 8.54 (s., CH-pyridine). Anal. Calcd. for $C_{21}H_{23}N_5O_2$: C, 66.83; H, 6.14; N, 18.55. Found: C, 66.75; H, 6.16; N, 18.58.

7-Benzyl-1-(2-methoxyphenyl)-3-(3-methoxypropyl)-8-methyl-1,2,3,4-tetrahydro-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (3k)

Yield = 61 %, M.p. = 93-95 °C. ^{1}H NMR (DMSO-d_6): δ = 1.61-1.68 (m., 2H, CH_2-$\underline{CH_2}$-CH_2); 2.02 (s., 3H, CH_3-C8); 2.95 (t., J=8.9, 2H, N(3)-CH_2); 3.30 (s, 3H, O-CH_3); 3.44 (t., J=8.9, 2H, O-CH_2); 3.70 (s., 2H, CH_2-C7); 3.81 (s., 3H, O-CH_3); 4.50 (s., 2H, CH_2-triazine); 5.02 (s., 2H, CH_2-triazine); 6.96 (t, J=8.3, 1H, arom.); 7.08-7.15 (m., 3H, arom.); 7.20-7.35 (m, 5H, arom.). Anal. Calcd. for $C_{25}H_{30}N_4O_3$: C, 69.10; H, 6.96; N, 12.89. Found: C, 68.87; H, 6.98; N, 12.93.

7-Benzyl-3-(2-furylmethyl)-1-(2-methoxyphenyl)-8-methyl-1,2,3,4-tetrahydro-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (3l)

Yield = 77 %, M.p. = 144-146 °C. ^{1}H NMR (DMSO-d_6): δ = 2.04 (s., 3H, CH_3-C8); 3.70 (s., 2H, CH_2-C7); 3.81 (s., 3H, O-CH_3); 4.04 (s., 2H, N(3)-CH_2); 4.49 (s., 2H, CH_2-triazine); 5.03 (s., 2H, CH_2-triazine); 6.25 (d, J=3.2, 1H, H-furane); 6.35 (d.d., J=3.2, J=2.0, 1H, H-furane); 6.97 (t, J=8.3, 1H, arom.); 7.07-7.14 (m., 3H, arom.); 7.19-7.33 (m, 5H, arom.); 7.46 (d, J=1.7, 1H, H-furane). Anal. Calcd. for $C_{26}H_{26}N_4O_3$: C, 70.57; H, 5.92; N, 12.66. Found: C, 70.68; H, 5.93; N, 12.63.

3-(2-Hydroxyethyl)-1-(4-methoxyphenyl)-7,8-dimethy-1,2,3,4-tetrahydro-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (3m)

Yield = 84 %, M.Pt = 161-163 °C. ^{1}H NMR (DMSO-d_6): δ = 1.89 (s., 3H, CH_3-C7); 1.98 (s., 3H, CH_3-C8); 2.96 (t., J=8.8, 2H, N(3)-CH_2); 3.58 (t, J=8.8, 2H, O-CH_2); 3.81 (s., 3H, O-CH_3); 4.61 (bro. m., 1H, OH); 4.69 (s., 2H, CH_2-triazine); 5.07 (s., 2H, CH_2-triazine); 6.90 (d, J=7.9, 2H, arom.); 7.16 (d., J=7.9, 2H, arom.). Anal. Calcd. for $C_{17}H_{22}N_4O_3$: C, 61.80; H, 6.71; N, 16.96. Found: C, 61.69; H, 6.72; N, 16.91.

1-(4-Methoxyphenyl)-7,8-dimethy-3-[2-(4-morpholinyl)ethyl]-1,2,3,4-tetrahydro-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (3n)

Yield = 60 %, M.p. = 112-114 °C. ^{1}H NMR (DMSO-d_6): δ = 1.89 (s., 3H, CH_3-C7); 1.97 (s., 3H, CH_3-C8); 2.48 (t., J=8.9, 4H, $(CH_2)_2$N); 2.67 (t., J=8.8, 2H, CH_2-N); 2.98 (t., J=8.8, 2H, N(3)-CH_2); 3.51 (t., J=8.9, 4H, $(CH_2)_2$O); 3.80 (s., 3H, O-CH_3); 4.69 (s., 2H, CH_2-triazine); 5.08 (s., 2H, CH_2-triazine); 6.91 (d, J=7.9, 2H, arom.); 7.15 (d., J=7.9, 2H, arom.). Anal. Calcd. for $C_{21}H_{29}N_5O_3$: C, 63.14; H, 7.32; N, 17.53. Found: C, 63.38; H, 7.35; N, 17.49.

7-Benzyl-3-(2-furylmethyl)-1-(4-methoxyphenyl)-8-methy-3-(3-pyridinylmethyl)-1,2,3,4-tetrahydro-6H-pyrimido[1,2-*a*][1,3,5]-triazin-6-one (3o)

Yield = 85 %, M.p. = 147-149 °C. ^{1}H NMR (DMSO-d_6): δ = 2.02 (s., 3H, CH_3-C8); 3.72 (s., 2H, CH_2-C7); 3.83 (s., 3H, O-CH_3); 4.02 (s., 2H, N-CH_2); 4.58 (s., 2H, CH_2-triazine); 5.06 (s., 2H, CH_2-triazine); 6.29 (d, J=3.2, 1H, H-furane); 6.38 (d.d., J=3.2, J=2.0, 1H, H-furane);6.90 (d, J=7.9, 2H, arom.); 7.10-7.18 (m., 2H, arom.); 7.17-7.26 (m, 5H, arom.); 7.47 (d, J=1.7, 1H, H-furane). Anal. Calcd. for $C_{26}H_{26}N_4O_3$: C, 70.57; H, 5.92; N, 12.66. Found: C, 70.69; H, 5.94; N, 12.70.

7-Benzyl-1-(4-methoxyphenyl)-8-methy-3-(3-pyridinylmethyl)-1,2,3,4-tetrahydro-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (3p)

Yield = 88 %, M.p. = 153-155 °C. ^{1}H NMR (DMSO-d_6): δ = 2.01 (s., 3H, CH_3-C8); 3.73 (s., 2H, CH_2-C7); 3.82 (s., 3H, O-CH_3); 4.09 (s., 2H, N-CH_2); 4.57 (s., 2H, CH_2-triazine); 5.08 (s., 2H, CH_2-triazine); 6.90 (d, J=7.9, 2H, arom.); 7.10-7.18 (m., 2H, arom.); 7.19-7.28 (m, 5H, arom.); 7.43 (t., J=7.8, CH-pyridine); 7.76 (d., J=7.8, CH-pyridine); 8.49 (d., J=7.4, CH-pyridine); 8.54 (s., CH-pyridine). Anal. Calcd. for $C_{27}H_{27}N_5O_2$: C, 71.50; H, 6.00; N, 15.44. Found: C, 71.39; H, 6.02; N, 15.41.

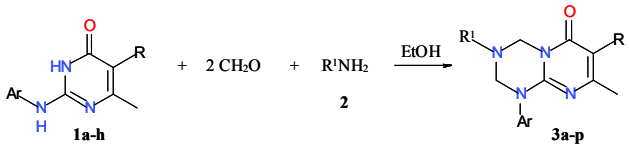
Results and discussions

2-Arylaminopyrimidine-4-ones derivatives **1**, can easily be prepared by the condensation reaction of arylguanidines with 2-alkylacetoacetic esters consists of 1,3-N-C-N binucleophilic fragment in their structure that allows to consider them as promising building blocks for various condensed systems.

Previously we reported a method for annelation of 1,3,5-triazine cycle to 2-aminobenzimidazoles or 2-amino-1,4-dihydro[1,3,5]triazino[1,2-*a*]benzimidazoles with formaldehyde and primary amines.[6] This method is successfully extended to series of 2-arylaminoperimidine-4-ones **1a-h**. It was found that three-component interaction allows to obtain a series of new 7-R-3-R^1-1-aryl-1,2,3,4-tetrahydropyrimido[1,2-*a*][1,3,5]triazine-6-ones **3a-p** in one synthetic step. Although the reaction is more smoothly than in case of the previously studied systems, this reaction can be proceeded under refluxing of equimolar mixture of reagents in ethanol (Scheme 2). Perimido[1,2-*a*][1,3,5]triazine-6-ones **3a-p** obtained were isolated in 60-88 % yield from reaction mass under cooling.

In the NMR ^{1}H spectra of **3a-p** compounds there are no signals of exo- and endocyclic amino groups. Two singlets of methylene group as well as proton signals of corresponded aliphatic amines moieties could unambiguously assigned. Characteristic signals of two methylene groups of tetrahydrotriazines cycle could be observed as two singlets at 4.48-4.73 and 4.91-5.08 ppm.

The compounds **3a-p** are colorless crystalline substances with district melting points.

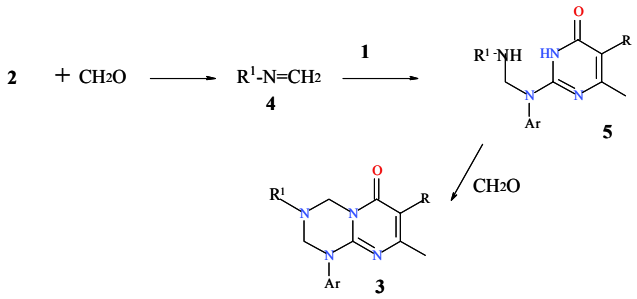


Ar=Ph, R=CH3 (**1a, 3a-c**); Ar=Ph, R=C6H5CH2 (**1b, 3d**); Ar=4-FC6H4, R=CH3 (**1c, 3e,f**); Ar=4-FC6H4, R=C6H5CH2 (**1d, 3g,h**); Ar=2-CH3OC6H4, R=CH3 (**1e, 3i,j**); Ar=2-CH3OC6H4, R=C6H6CH2 (**1f, 3k,l**); Ar=4-CH3OC6H4, R=CH3 (**1g, 3m,n**); Ar=CH3OC6H4, R=C6H5CH2 (**1h,3o,p**).

R1=CH3OCH2CH2 (**2a, 3a,d,e,i**), R1=C6H5CH2 (**2b, 3b**), R1=2-FurCH2 (**2c,3c,f,h,l,o**), R1=3-PyrCH2 (**2d, 3g,j,p**), R1=CH3OCH2CH2CH2 (**2e, 3k**), R1=HOCH2CH2 (**2f, 3m**), R1=MorphCH2CH2 (**2, 3n**).

Scheme 2. Synthesis of tetrahydropyrimidotriazinones **3a-p**

A possible reaction mechanism is a route with stepwise reactions involving formation of various reactive intermediates. The first step is supposed to be a Schiff base formation (**4**) in the condensation reaction of formaldehyde and the primary amines. Addition of this intermediate to the aminopyrimidone (**1**) may give an intermediate aminomethylene derivative (**5**) which further condensation with a second formaldehyde molecule leads to ring closure into product **3** (Scheme 3).



Scheme 3. Plausible reaction mechanism for the synthesis of **3**.

Conclusions

Three-component annelation method of tetrahydrotriazine cycle to aminopyrmidone derivatives was developed. Series of new 7-R-3-R[1]-1-aryl-1,2,3,4-tetrahydropyrimido[1,2-a][1,3,5]triazine-6-ones synthesized will be investigated for their biological activity.

Acknowledgments

The results obtained in the framework of the work on the RF Government Resolution № 218 contract N 02.G25.31.0007 supported by the Ministry of Education and Science of the Russian Federation.

References

[1](a)Waly, M. A., Abou Dobara, M. I., *Pol. J. Chem.*, **2009**, *83*, 1601. (b) Shah, D. R., Mohd, R. P., Chikhalia, K. H., *Future Med. Chem.*, **2014**, *6*, 463. (c) Lim, F. P. L., Dolzhenko, A. V., *Eur. J. Med. Chem.*, **2014**, *85*, 371.

[2]Lucry, L., Enoma, F, Estour, F., Oulyadi, H., Menager, S., Lafont, O., *J. Heterocycl. Chem.,* **2002**, *39*, 663.

[3](a) Dolzhenko, A. V., Chui, W. K., *J. Heterocycl. Chem.*, **2006**, *43*, 1513. (b) Dolzhenko, A. V., Chui, W. K., *J. Heterocycl. Chem.*, **2008**, 45, 173.

[4]Sachdeva, N., Dolzhenko, A. V., Chui, W. K., *Org. Biomol.Chem.,* **2012**, *10*, 4586.

[5]Potapov, A. Yu., Shikhaliev, Kh. S., Kryl'ski D,V., Peshkov M.D. *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.*, **2004**, *47*, 151 [*Izv. Vuzov. Khim. Khim. Tekhnol.,* **2004**, *47* (Engl. Transl.)].

[6](a) Shikhaliev, Kh. S., [1]Potapov, A. Yu., Kryl'ski D,V. *Russ. Chem. Bull., Int. Ed.,* **2007**, ***56,*** 367. (b) Potapov, A. Yu., Shestakov, A. S., Verezhnikov, V.N., Shikhaliev, Kh. S., *Russ. J. Org. Chem.,* **2011**, *47*, 1074.

Received: 15.09.2015.
Accepted: 10.10.2015.

INTERACTION OF 1,2-DIAMINOBENZIMIDAZOLE WITH N-ARYLIMIDES

D. Yu .Vandyshev[a] *, Kh. S. Shikhaliev[a] and A. Yu. Potapov[a]

Keywords: N-arylmaleimides, 1,2-diaminobenzimidazole, polynucleophiles, 10-amino-2,3,4,10-tetrahydro-4-oxo-N-aryl-pyrimido[1,2-*a*]benzimidazol-2-carboxyamides.

Substituted 10-amino-2,3,4,10-tetrahydro-4-oxo-N-arylpyrimido[1,2-*a*]benzimidazole-2-carboxamides are formed by condensation of 1,2-diaminobenzimidazole with N-arylmaleimides in isopropyl alcohol in the presence of catalytic amount of acetic acid.

* Corresponding Authors
Mobile No. : +79601093856
E-Mail: francy_2007@mail.ru
[a] Voronezh State University, Department of Organic Chemistry, Voronezh; Russian Federation. 394006 Voronezh Universitetskaya pl., 1.

Introduction

Aminobenzimidazole and its derivatives increasingly attract scientists' attention due to theirs multiscale biological activities such as antibacterial, antifungal, antihistaminic, cytostatic and hypotensive actions. Particular attention is paid to their use as medicines preparation to treat HIV infections.[1-2]

Benzimidazolepyrimidines[2] have special interest among the benzimidazole derivatives and a great number of works dedicated to prepare compounds consist this ring system starting from 2-aminobenzimidazole.[3] However, there is no data about synthesis of imidazopyrimidines from 1,2-diaminobenzimidazole as starting material.

In order to continue our studies on building of aza-heterocyclic compounds with imidazole moieties, the aim of present work is a study on the synthesis of substituted tetrahydrobenzimidazolepyrimidines in the reaction between 1,2-diaminobenzimidazole and N-maleimides as potential reactants to form various penta- and hexaatomic cycles in nucleophilic attacks.[4]

Experimental Part

General

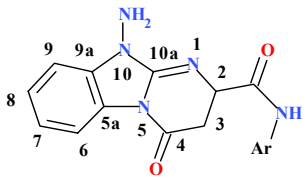
NMR Spectra of all new compounds were registered on Bruker DRX, 500 ^{1}H spectrometer at 500 MHz and ^{13}C at 125.76 MHz in DMSO-d_6, internal standard was TMS. Mass-spectra recorder on FINNIGAN MAT.INCOS 50 spectrometer (EI ionization, 70 eV). Elemental analyses was performed on Carlo Erba NA 1500.

Melting points was determined on Stuart SMP30. Identity of the reagents and synthesized compounds, quality of reaction mass were controlled out by TLC on Merck TLC Silica gel 60 F_{254} plate (eluents: methanol, chloroform and theirs mixture in the different ratios). Chromatograms were developed in the UV light and with iodine vapour.

1,2-Diaminobenzimidazole **1** was synthesized according to reported method[5]. The compounds **2a-e** were purchased from Acros Organics.

Preparation of 10-amino-2,3,4,10-tetrahydro-4-oxo-N-arylpyrimido[1,2-*a*]benzimidazole-2-carboxamides 5a-e.

A mixture of 0.74 g (5 mmol) of diaminobenzimidazole **1**, 5 mmol of N-arylmaleimide **2a-e**, 5 ml of isopropyl alcohol and 1-2 drops of acetic acid were heated under reflux for 1-2 h in a flax. The precipitate formed was filtered and recrystallized from the mixture of i-PrOH–DMFA 2:1 mixture. White powder compounds were obtained.



10-amino-2,3,4,10-tetrahydro-4-oxo-N-phenylpyrimido[1,2-*a*]benzimidazole-2-carboxamides, 5a.

Yield: 85 %. M.p. 214-215 °C. NMP ^{1}H (DMSO-d6): δ = 2.76 (dd, *J*=1.9, *J*=14.5 ,1H, H-3); 3.17 (dd, *J*=8.8, *J*=9.7, 1H, H-3); 5.34 (dd, *J*=1.8, *J*=6.9, 1H, H-2); 5.69 (s, 2H, NH_2); 7.03 (t, *J*=7.4, 1H, H-Ar); 7.18 (t, *J*=7.4, 1H, H-Bz); 7.23 (t, *J*=7.5, 1H, H-Bz); 7.31 (qu, *J*=7.8, 3H, H-Ar); 7.38 (d, *J*=7.7, 1H, H-Ar); 7.57 (d, *J*=7.8, 2H, H-Bz); 10.49 (s, 1H, CONH). NMR ^{13}C (DMSO-d6): δ = 33.5 (C-3); 53.5 (C-2); 108.7, 109.3 (C-7 and C-8); 119.5 (C Ph); 122.4,

123.7 (C-6 and C-9); 124.0, 127.4, 128.9, 131.7 (C Ph); 138.4 (C-5a and C-9a); 155.1 (C-10a); 167.1 (NHCO); 173.3 (C-4). Mass-spectra, *m/z* (I_{rel}, %): 201 $[M-120]^+$. $C_{17}H_{15}N_5O_2$ Found, %: C 63.16; H 4.70; N 21.73. Calculatēd, %: C 63.54; H 4.71; N 21.79.

10-amino-2,3,4,10-tetrahydro-N-(2-methylphenyl)-4-oxopyrimido[1,2-*a*]benzimidazole-2-carboxamides (5b).

Yield: 90 %. M.p. 240-241 °C. NMR ^{1}H (DMSO-d6): δ = 2.06 (s, 3H, CH_3); 2.80 (dd, *J*=1.8, *J*=14.9, 1H, H-3); 3.18 (dd, *J*=8.7, *J*=7.6, 1H, H-3) 5.45 (dd, *J*=1.8, *J*=7.3, 1H, H-2); 5.69 (s, 2H, NH_2); 7.00 – 7.17 (m, 2H, H-Bz); 7.19 – 7.26 (m, 3H, H-Ar); 7.28 – 7.40 (m, 3H, H-Bz + H-Ar); 9.90 (s, 1H, CONH). NMR ^{13}C (DMSO-d6): δ = 17.8 (CH_3); 33.6 (C-3); 53.0 (C-4); 108.7, 109.3 (C-7 and C-8); 114.8, 117.9, 120.2 (C Ar); 122.3, 122.8 (C-6 and C-9); 125.4, 126.0, 130.5 (C Ar); 135.0, 135.4 (C-5a and C-9a); 155.3 (C-10a); 167.4 (NHCO); 173.3 (C-4). Mass-spectra, *m/z* (I_{rel}, %): 201 $[M-134]^+$. $C_{18}H_{17}N_5O_2$ Found, %: C 64.09; H 5.09; N 20.88. Calcd, %: C 64.47; H 5.11; N 20.84.

10-amino-2,3,4,10-tetrahydro-N-(4-isopropylphenyl)-4-oxopyrimido[1,2-*a*]benzimidazole-2-carboxamide (5c).

Yeild 87 %. M.p. 245-246 °C. NMR ^{1}H (DMSO-d6): δ = 1.16 (d, *J*=6.9, 6H, 2CH_3-*i*Pr); 2.76 (dd, *J*=1.9, *J*=14.4, 1H, H-3); 2.83 (pent, *J*=6.8, 1H, CH-*i*Pr); 3.17 (dd, *J*=8.6, *J*=7.7, 1H, H-3); 5.34 (dd, *J*=2.2, *J*=6.6, 1H, H-2); 5.72 (s, 2H, NH_2); 7.15 – 7.20 (m, 2H, H-Bz); 7.23 (t, *J*=7.5, 2H, H-Ar); 7.29 (d, *J*=7.7, 1H, H-Ar); 7.39 (d, *J*=7.7, 1H, H-Ar); 7.48 (d, *J*=8.5, 2H, H-Bz); 10.45 (s, 1H, CONH). NMR ^{13}C (DMSO-d6): δ = 23.8, 23.9 (2CH_3-*i*Pr); 32.9 (CH-*i*Pr); 33.5 (C-3); 53.5 (C-2); 108.7, 109.3 (C-7 and C-8); 119.5 (C Ar); 122.3, 122.8 (C-6 and C-9); 126.6, 126.8, 127.4 (C Ar); 136.1 (C-5a and C-9a); 144.2 (C Ar); 155.1 (C-10a); 166.9 (NHCO); 173.3 (C-4). Mass-spectra, *m/z* (I_{rel}, %): 201 $[M-162]^+$. $C_{20}H_{21}N_5O_2$ Found, %: C 65.71; H 5.80; N 19.23. Calcd, %: C 66.10; H 5.82; N 19.27.

10-amino-2,3,4,10-tetrahydro-N-(2,4-dimethylphenyl)-4-oxopyrimido[1,2-*a*]benzimidazole-2-carboxamide (5d).

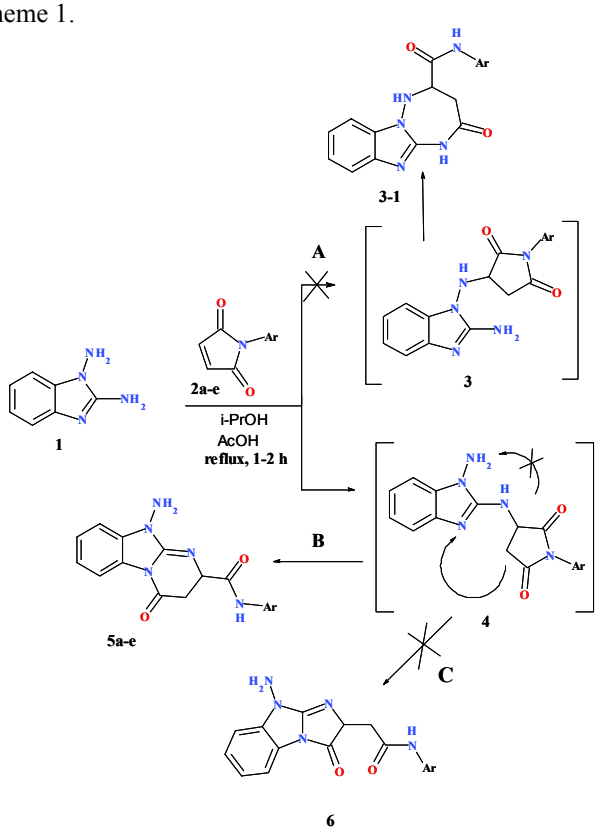
Yield 92 %. M.p. 238-239 °C. NMR ^{1}H (DMSO-d6): δ = 2.11 (s, 6H, 2CH_3); 2.77 (dd, *J*=1.9, *J*=14.4, 1H, H-3); 3.17 (dd, *J*=8.6, *J*=7.6, 1H, H-3); 5.41 (dd, *J*=2.0, *J*=6.8, 1H, H-2); 5.68 (s, 2H, NH_2); 6.95 (d, *J*=7.9, 1H, H-Ar); 7.02 (s, 1H, H-Ar); 7.14 (d, *J*=8.0, 1H, H-Ar); 7.19 – 7.25 (m, 2H, H-Bz); 7.32 (dd, *J*=1.7, *J*=5.0, 1H, H-Bz); 7.37 (dd, *J*=2.2, *J*=5.0, 1H, H-Bz); 9.80 (s, 1H, CONH). ЯМР ^{13}C (DMSO-d6): δ = 17.7, 20.6 (CH_3); 33.6 (C-3); 53.0 (C-2); 108.6, 109.3, 122.3, 122.6 (C-7, C-8, C-6, C-9); 125.4, 126.6, 127.4, 131.0, 131.7, 132.4 (C Ar); 135.2 (C-5a и C-9a); 155.1 (C-10a); 167.3 (NHCO); 173.3 (C-4). Mass-spectra, *m/z* (I_{rel}, %): 201 $[M-148]^+$. $C_{19}H_{19}N_5O_2$ Found, %: C 64.93; H 5.46; N 20.01. Calcd, %: C 65.32; H 5.48; N 20.04.

10-amino-2,3,4,10-tetrahydro-N-(5-chlorine-methylphenyl)-4-oxo-pyrimido[1,2-*a*]benzimidazole-2-carboxamide (5e).

Yield: 83 %. M.p. 228-229 °C. NMR ^{1}H (DMSO-d6): δ = 2.18 (s, 3H, CH_3); 2.81 (dd, *J*=1.8, *J*=14.6, 1H, H-3); 3.19 (dd, *J*=8.8, *J*=7.5, 1H, H-3); 5.48 (dd, *J*=2.0, *J*=6.9, 1H, H-2); 5.54 (s, 2H, NH_2); 7.09 (dd, *J*=1.4, *J*=6.1, 1H, H-Ar); 7.15 – 7.26 (m, 3H, H-Bz + H-Ar); 7.33 (dd, *J*=1.4, *J*=7.3, 1H, H-Ar); 7.37 – 7.47 (m, 2H, H-Bz); 9.98 (s, 1H, CONH). NMR ^{13}C (DMSO-d6): δ = 17.3 (CH_3); 33.5 (C-3); 53.0 (C-2); 108.7, 109.4 (C-7 and C-8); 117.9, 120.2 (C Ar); 122.4, 122.7 (C-6 and C-9); 124.4, 125.5, 130.0 (C Ar); 134.9, 135.0 (C-5a and C-9a); 136.8 (C Ar); 155.1 (C-10a); 167.7 (NHCO); 173.3 (C-4). Mass-spectra, *m/z* (I_{rel}, %): 201 $[M-168.5]^+$. $C_{18}H_{16}ClN_5O_2$ Found, %: C 58.11; H 4.35; N 18.91. Calcd, %: C 58.46; H 4.36; N 18.94.

RESULTS AND DISCUSSIONS

Polynucleophilic character of 1,2-diaminobenzimidazole (1,3-N-C-N[6a-b] and 1,4-N-C-N-N[6c-d]) ensures various types of interactions with electrophilic reagents. There are two possible reaction ways with maleimides as it shown on the Scheme 1.



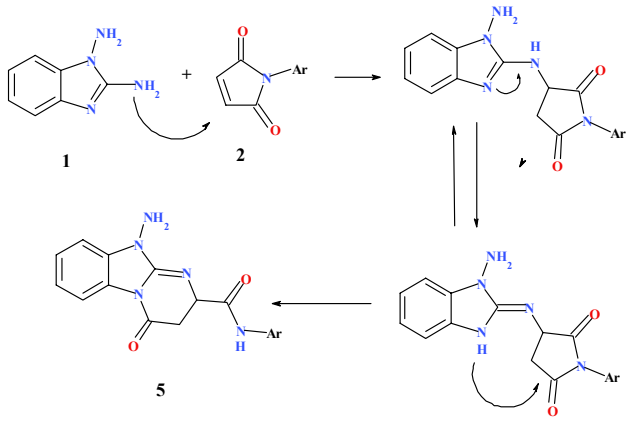
Scheme 1. Possible reaction routes in the interaction of 1,2-diaminobenzimidazole and N-arylmaleimides. **Ar:** Ph **(a);** 2-MePh **(b);** 4-*i*PrPh **(c);** 3, 4-diMePh **(d);** 2-Me-5-ClPh **(e)**

Heterocyclization of 1,2-diaminobenzimidazole **1** with N-arylmaleimides **2a-e** was performed in isopropyl alcohol under reflux for 1-2 h in the presence of catalytic amount of acetic acid. The reaction led to a white single product formation.

On the basis of NMR ^{1}H and ^{13}C spectra the products formed were assigned as 10-amino-2,3,4,10-tetrahydro-4-oxo-N-arylpirimido[1,2-*a*]benzimidazole-2-carboxamides (**5a-e**).

The all proton signals of aryl and CH_3 groups for the compounds **5** could be assigned in the NMR spectra of the isolated products. The proton signals of free NH_2 group linked to the imidazole ring was found at 5.69 ppm. The signals of methylene protons emerge as a doublet of doublet at 2.76-2.81 and 3.17-3.19 ppm (C-3) and the signals of amide protons are located in a stronger field (9.80-10.50 ppm). Based on the analysis of literature data[3] the methine proton of the hexaatomic cycle in structure **5** shows a doublet of doublet signal (C-2) at 5.34-5.48 ppm resonating with the protons of the methylene fragment (C-3)**.**

^{13}C NMR spectra of the compounds **5a-e** contain the characteristic signals of benzene moiety C-5a, C-6, C-7, C-8, C-9, C-9a and the signal of C10 at 108, 109, 122, 123, 135-138 ppm and at 155 ppm, respectively. Carbon atom signals of pyrimidine cycle are located at 33, 53 and 173 ppm, assigned to C-3, C-2 and C-4 atoms, respectively. Appearance of the singlet of NH_2 group (2H) in the 1H NMR spectra of reaction products unambiguously excludes the formation of heptaatomic rings **3-1** (reaction route A).

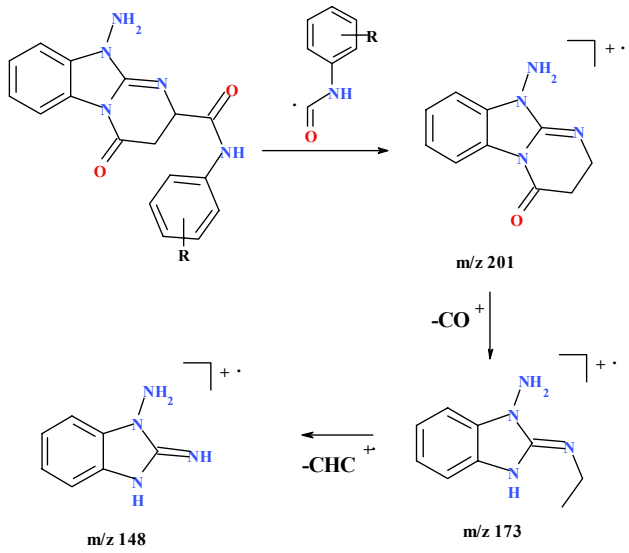


Scheme 2. A possible reaction mechanism leads to formation of compounds **5**

A possible reaction mechanism leads to formation of compounds **5** is assumed on the basis of work dedicated to interaction of N-arylmaleimides[3a] and maleic anhydride[3b] with aminoazoles (Scheme 2) when both five and six-membered ring systems can be formed depending on the cyclization conditions. Based on the polynucleophilic nature of 1,2-diaminobenzimidazole **(1),** the interaction with maleimides **(2a-e)** might be started with addition of the first or the second NH_2 group of diaminoimidazole to the double bound of aryl maleimide moiety with formation of intermediate products **3** or **4**, respectively. Since intermediate **3** would be cyclized to seven or six-membered rings without free NH_2 group based on the presence of NH_2 signals in NMR spectra of the products **5**, the exclusive formation of intrermediate **4** can be assumed.

Among the two possible route of intramolecular cyclization of the intermediate **4** the direction "B" leads the found tetrahydropyrimido[1,2-*a*]benzimidazoles **5**, whereas the path "C" would result dihydroimidazoles **6**.

In the mass spectra analysis of reaction products the molecular ion could not be fixed. For similar structures, it was noted forming fragments with m/z 201.[3,4] The probable fragmentation route is represented on the Scheme 3. It is assumed that on the first step there is a bond splitting with following elimination of arylamide's moiety leading to relatively stable tetrahydrobenzimidazopyrimidine ion (m/z 201) and 1-amino-2-imino-benzimidazole-ion (m/z 148). This last one is subjected to further fragmentation.



Scheme 3. Fragmentation pathway of the compounds **5**.

Conclusions

Thus, determined new heterocyclization of 1,2-diaminobenzimidazole with N-arylmaliemides have completely proceeded regionselectively with formation of 10-amino-2,3,4,10-tetrahydro-4-oxo-N-arylpyrimido[1,2-a]-benzimidazole-4-oxo-2-carboxoamides.

Acknowledgements

The results obtained in the framework of the work on the RF Government Resolution № 218 contract N 02.G25.31.0007 supported by the Ministry of Education and Science of the Russian Federation.

References

[1](a) Betti, L., Botta, M., Corelli, F., Floridi, M., Giannaccini, G., Maccari, L., ... & Corsano, S., *J. Med. Chem.,* **2002**, *45(17)*, 3603. (b) Lopez-Rodriguez, M. L., Benhamu, B., Morcillo,

M. J., Tejada, I., Avila, D., Marco, I., ... & Del Río, J., *Bioorg. Med. Chem*., **2004**, *12(19)*, 5181. (c) Borza, K. S., Gere, A., Kolok, S., Nagy, J., Fodor, L., Galgóczy, K., ... & Domány, G., *Bioorg. Med. Chem. Lett.,* **2006**, *16(17)*, 4638. (d) Beaulieu, C., Wang, Z., Denis, D., Greig, G., Lamontagne, S., O'Neill, G., ... & Wang, J., *Bioorg. Med. Chem. Lett.*, **2004**, *14(12),* 3195. (e) Ayhan-Kilcigil, G., Kuş, C. T., Cobanb, T., Can-Ekeb, B., Iscanb, M., *J. Enzym. Inhib. Med. Chem*., **2004**, *19*; 129. (f) Kamal, A., Subba Rao, A. V., Lakshma Nayak, V., Subba Reddy, N. V., Konderu S., Ramakrishna, G., Mallika, A., *Org. Biomol. Chem.*, **2014,** *12*, 9864. (g) Romero, D. H., Torres Heredia, V. E., García-Barradas, O., López, M. E. M., Pavón, E. S., *J. Chem. Biochem.*, **2014**, *2(2)*, 45.

[2](a) Alper, S., Temiz-Arpaci, O., Aki-Sener, E., I. Yalcin, *Il Farmaco,* **2003**, *58(7)*, 497-507. (b) Gata, L., Perna, F., Figura, N., Ricci, C., Holton, J., D′Anna, L., Miglioli, M., D. Vaira, *J. Antimicrob. Chemother.* **2003**, *51,* 439. (c) Kucukbay, H., Durmaz, R., Orhan, E., S. Gunal, *Il Farmaco.* **2003**, 58, 431. (d) Kazimierczuk, Z., J.A. Upcroft, J.A., Upcroft, P., Gorska, A., Starosciak, B., A. Laudy, *Acta Biochim. Polon*., **2002**, *49*, I, 185. (e) Garuti, L., Roberti, M., C. Cermelli, *Bioorg. Medicinal Chem. Letter,* **1999**, *9*, 2525. (f) Akbay, A., Oren, I., Temiz-Arpaci, O., Aki-Sener, E., I. Yalcin, *Arzneim.-Forcsh./Drug Res.* **2003**, *53,* 266. (g) Casse, C., Giannoni, f., Nguyen, V.T., Dubois, M.F., O. Bensaude, *J. Biol. Chem.*, **1999**, *274*, 16097.

[3](a) Shikhaliev, Kh. S., Potapov, A. Yu., Kryl'skii, D. V., *Russ. Chem. Bull., Int. Ed*., **2007**, *56*, 367. (b) Romano, C., Cuesta, E., Avendaño, C., *Heterocycles*, **1990**, *31*, 267. (c) Shikhaliyev, H. S., Kryl'skii, D. V., Potapov, A. Yu., Krysin, M. Yu., Trefilova, J. H., *Math. Univ. Chem. Chem. Eng. Technol.*, **2004**, *47(*3), 149 [in Rus.]. (d) Kovigin, Y. A., Shikhaliyev, H. S., Potapov, A., Krylsky, D. V., *Math. Univs. Chem. Chem. Eng. Technol.*, **2005**, *48(1)*, 59 [in Rus.].

[4](a) Rudenko, R. V., Komykhov, S. A., Desenko, S. M., Musatov, V. I., Shishkin, O. V., Konovalova, I. A., Vashchenko, E. V., Chebanov, V. A., *Synthesis,* **2011**, *5*, 783. (b) Filimonov, S. I., Korsakov, M. K., Chirkova, Zh. V., Abramov, I. G., Stashina, G. A., Firgang, S. I., Kovygin, Yu. A., Shikhaliev, Kh. S., *Chem. Heterocycl. Compd.*, **2013**, *49*, 993.

[5]Pozharsky, A. F., Anisimov, V. A., Tsupak, E. B., *Practical works on heterocyclic chemistry,* Publishing house of Rostov University, **1988**, 106.

[6](a) Morkovnik, A. S., Divaeva, L: N., Kuz'Menko, T. A., Borodkin, G. S., *Russ. J. Org. Chem.*, **2013**, *49(6)*, 895. (b) Kuz'menko, T. A., Kuz'menko, V. V., Pozharskii, A. F., Anisimova, V.A., *Chem. Heterocycl. Compd.*, **1990**, *26(11),* 1264. (c) Povstyanoi, M. V., Kruglenko, V. P., Gnidets, V. P., *Chem. Heterocycl. Compd.*, **1984**, *20(5)*, 568. (d) Gnidets, V. P., Kruglenko, V. P., Povstyanoi, M. V., Klyuev, N. A., *Chem. Heterocycl. Compd*., **2002**, *38(5)*, 598.

Received: 10.09.2015.
Accepted: 15.10.2015.

SYNTHESIS AND REACTIONS OF SOME NEW BENZIMIDAZOLE DERIVATIVES

Reda M. Fikry[a]*, Nabila A. Ismail[a], Said A. Said[a] and Mohammed E. Hafez[a]

Keywords: benzimidazole, 4-aminopyridine-carbonitrile, pyridopyrimidine, naphthyridine, pyridotriazine.

4-Amino-5-(1*H*-benzimidazol-2-yl)-6-(4-chlorophenyl)pyridine-3-carbonitrile (**3**) was obtained from reaction of 2-cyanomethyl-1*H*-benzimidazole **1** with chlorobenzaldehyde followed by reaction with malononitrile. Reaction of (**3**) with cyclohexanone, formic acid and hydrazine hydrate afforded tetrahydrobenzonaphthyridine amine, pyrido[4,3-*d*]pyrimidin-4(3*H*)one and pyrazolo[4,3-*c*]pyridine-3-amine, respectively. Heterocyclization of (**3**) with carbon disulfide and benzoyl isothiocyante gave the corresponding pyrido[3,4-*d*]pyrimidindithione and thioxopyrido[4,3-*d*]pyrimidine methanone. While, the reaction of (**3**) with ethyl cyanoacetate, diethyl malonate and nitrous acid afforded oxo-1,6-naphthyridin-3-carbonitrile, carboxylate and pyrido[4,3-*d*][1,2,3]triazine, respectively. Dihydroimidazol pyridin-4-amine was obtained from reaction of (**3**) with ethylendiamine and carbon disulfide. Finally, cyclization of (**3**) with triethyl orthoformate, in the presence of hydrazine hydrate, afforded pyrido[4,3-*d*]pyrimidin-3-ylamine.

* Corresponding Authors
E-Mail: redmof56@yahoo.com
[a] Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt

Introduction

Benzimidazole and its condensed system compounds serve as important ligands e.g. with cobalt as in vitamine B_{12} and with many other transition metal.[1,2,3] Benzimidazole and its derivatives have important pharmacological activities as antifungals, antitumorals and antivirals[4]. Most common antifungal agents containing imidazole nucleus are Clotriamazole, Miconazole and Ketoconazole [5,6].

Experimental

Melting points were recorded using SMP30 Melting Point Apparatus (Stuart) and are uncorrected. The IR spectra were record on KBr discs using a FTIR 600 Series spectrophotometer (JASCO) and ^{1}H NMR spectra (δ ppm) were recorded on a Varian 300 MHz spectrometer using $CDCl_3$ as solvent. Elemental analyses were carried out on Micro Analytical Center at Cairo University.

2-(1*H*-Benzimidazol-2-yl)-3-(4-chlorophenyl) acrylonitrile (2)

To a solution of 2-cyanomethyl-1*H*-benzimidazole (**1**) (0.1 mol) in 30 mL ethanol, 4-chlorobenzaldehyde (0.1 mol) was added with few drops of pyridine then refluxed for 2 h. The solution was poured on crush ice and stirred until solid products appeared. The solid products was filtrated off, washed with water several times, dried and recrystallized from ethanol, yield 90 %. m.p. 235-237 °C. IR (KBr): 1640 (C=C), 2240 (C-N), 3260 cm^{-1} (N-H) cm^{-1}. ^{1}HNMR ($CDCl_3$): 3.6 (s, 1H, C=CH-Ar), 7.0-7.8 (m, 8H, Ar-H) 8.6 (s, 1H, NH). Anal Calcd. for $C_{16}H_{10}ClN_3$: C, 68.70; H, 3.60; N, 15.02 %; Found: C, 68.79; H, 3.61; N, 14.99 %.

4-Amino-5-(1*H*-benzimidazol-2-yl)-6-(4-chlorophenyl)pyridine-3-carbonitrile (3)

To a solution of (**2**) (0.1 mol) in ethanol (40 mL), malononitrile (0.1 mol) was added with few drop of pyridine and refluxed for 5 h. The solution was poured on crush ice and stirred until solid products appeared. It was filtrated off and recrystallized from ethanol, yield 88 %. m.p 308-310 °C. IR (KBr): 2240 (CN) and 3260, 3390 (NH_2) cm^{-1}. ^{1}HNMR ($CDCl_3$): 4.3 (s, 2H, NH_2), 7, 7.8 (m, 9H, Ar-H and pyridine protons), 8.2 (s, 1H, NH). Anal Calcd. for $C_{19}H_{12}ClN_5$: C, 66.00; H, 3.50; N, 20.25 %; Found: C, 65.98; H, 3.52; N, 20.22 %.

4-(1*H*-Benzimidazol-2-yl)-3-(4-chlorophenyl)-6,7,8,9-tetrahydrobenzo[*b*][1,6]naphthyridin-10-amine (4)

Compound (**3**) (0.01 mol) was added to cyclohexanone (15 mL) containing anhydrous zinc chloride (0.01 mol) and the reaction mixture was refluxed for 30 min. The complex with zinc chloride was separated from solution and dissolved in 40% sodium hydroxide (10 mL), and extracted with benzene. The benzene layer was evaporated to give solid product (**4**), which was dried and recrystallized from benzene, yield 73 %. m.p 328-330 °C. IR (KBr): 3000 (C-H aliphatic), 3320, 3220 (NH_2), 1560 (C=N) cm^{-1}. ^{1}HNMR ($CDCl_3$): 1.5 (s, br, 4H, C-7 and C-8), δ 2.2 (s, br, 2H, C-9), 6.0 (s, 2H, NH_2), 7.4-7.8 (m, 9H, Ar-H and pyridine protons), 8.6 (s, 1H, NH). Anal Cacld. For $C_{25}H_{20}ClN_5$: C, 70.50; H, 4.73; N, 16.44 %; Found: C, 70.53, H, 4.72; N, 16.42 %.

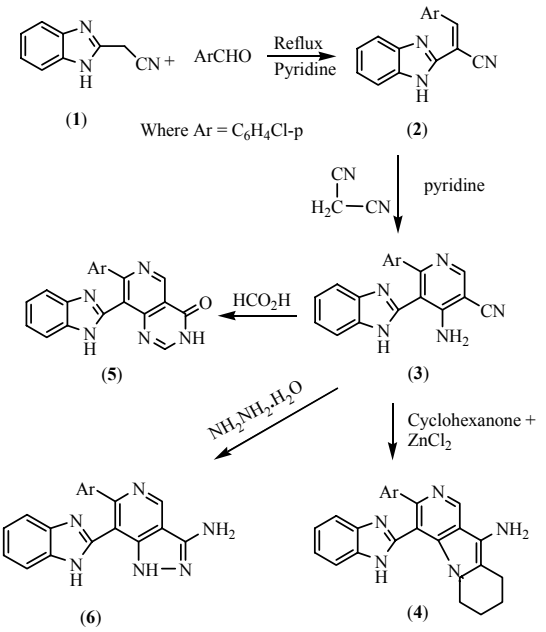
8-(1*H*-Benzimidazol-2-yl)-7-(4-chlorophenyl)pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (5)

A solution of compound (**3**) (0.01 mol) in formic acid (15 mL) was refluxed for 6 h. The excess of formic acid was removed by vacuum evaporator. The residue was dried and recrystallized from ethanol, yield 54 %. m.p. 324-327 °C. IR

(KBr): 3430 (OH), 3130 (NH group), 1740 (C=O) cm^{-1}. ^{1}HNMR ($CDCl_3$): 6.8, 8.2 (m, 9H, Ar-H and pyridine protons), 12 (s, br, 1H, OH). Anal Cacld. For $C_{20}H_{12}ClN_5O$: C, 64.26; H, 3.24; N, 18.74 %; Found: C, 64.24; H, 3.23; N, 18.75 %.

7-(1*H*-Benzimidazol-2-yl)-6-(4-chlorophenyl)-1*H*-pyrazolo[4,3-*c*]pyridin-3-amine (6)

To a solution of compound (**3**) (0.01 mol) in ethanol (30 mL) hydrazine hydrate (0.03 mol) was added. Then the reaction mixture refluxed for 3 h. After cooling mixture, the solid precipitate was filtered off, dried and crystallized from ethanol, yield 61%. m.p 225-227 ^oC. IR (KBr): 3260, 3330 (NH_2), 1540 (C=N) cm^{-1}. ^{1}HNMR ($CDCl_3$): 4.1 (s, br, 2H, NH_2), 6.9-8.4 (m, 9H, Ar-H and pyridine protons), 12.1 (s, br, 1H, NH). Anal Calcd. For $C_{19}H_{13}ClN_6$: C, 63.25; H, 3.63; N, 23.29 %; Found: C, 63.18; H, 3.69; N, 23.27 %.



Scheme 1. Synthesis of compounds (**2**) – (**6**).

8-(1*H*-Benzimidazol-2-yl)-7-(4-chlorophenyl)pyrido[4,3-*d*]pyrimidin-2,4-(1*H*,3*H*)-dithione (7)

To a solution of compound (**3**) (0.01 mol) in DMF (30 mL) carbon disulfide (20 mL) was added. Then reaction mixture heated on a water bath for 10 h. After cooling mixture, the solid precipitate was collected by vacuum filtration, dried and crystallized from ethanol, yield 61 %. m.p 321-324 ^oC. IR (KBr): 3200 (NH), 2550 (SH), 1340 (C=S) cm^{-1}. ^{1}HNMR ($CDCl_3$): 8.3 (s, 1H, NH), 7.4-7.8 (m, 9H, Ar-H and pyridine protons). Anal Calcd. For $C_{20}H_{12}ClN_5S_2$: C, 56.93; H, 2.87; N, 16.60; S, 15.20 %; Found: C, 56.97; H, 2.79; N, 16.68; S, 15.18 %.

(8-(1*H*-Benzimidazol-2-yl)-7-(4-chlorophenyl)-1,2-dihydro-4-imino-2-thioxopyrido[4,3-*d*]pyrimidin-3(4*H*)-yl)(phenyl)methanone (8)

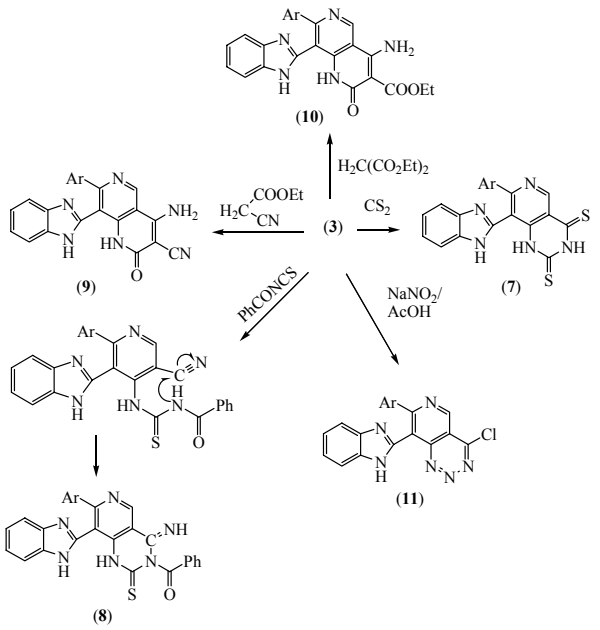
A mixture of benzoyl isothiocyanate [prepared by refluxing a mixture of ammonium thiocynate (0.012 mol) and benzoyl chloride (0.01 mol) in dioxane (20 mL) for 20 min] and (**3**) (0.01mol) in dioxane (20 mL) refluxed for 5 h. After cooling, the solid precipitate was filtrated off, dried and crystallized from ethanol, yield 55%. m.p 318-320 ^oC. IR (KBr): 3200 (NH), 1760 (C=O), 1340 (C=S) cm^{-1}. ^{1}HNMR ($CDCl_3$) 3.3 (s, 1H, NH), 7.1, 7.8 (m, 14H, Ar-H and pyridine protons). Anla. Calcd. For $C_{27}H_{17}ClN_6OS$: C, 63.71; H, 3.37; N, 16.51; S, 6.30 %; Found: C, 63.78; H, 3.37; N, 16.57; S, 6.28 %.

4-Amino-8-(1*H*-benzimidazol-2-yl)-7-(4-chlorophenyl)-1,2-dihydro-2-oxo-1,6-naphthyridin-3-carbonitrile (9)

To a solution of compound (**3**) (0.01 mol) in acetic acid (20 mL) ethyl cyanoacetate and ammonium acetate (6 g) were added, The reaction mixture was heated with stirring for 3 h. After cooling, the mixture was diluted with ethanol, the solid precipitate filtered off, dried and crystallized from ethanol, yield 70%. m.p 286-287 ^oC. IR (KBr): 2220 (CN), 3230, 3320 (NH_2), 1630 (C=O) cm^{-1}. Anal. Calcd. For $C_{22}H_{13}ClN_6O$: C, 64.01; H, 3.17; N, 20.36 %; Found: C, 64.06; H, 3.22; N, 20.33 %.

Ethyl 4-amino-8-(1*H*-benzimidazol-2-yl)-7-(4-chlorophenyl)-1,2-dihydro-2-oxo-1,6-naphthyridine-3-carboxylate (10)

To a solution of compound (**3**) (0.01 mol) in acetic acid (20 mL) diethyl malonate and ammonium acetate (6 g) were added and heated with stirring for 3 h.



Scheme 2. Synthesis of compounds (7) – (**11**).

After cooling, the mixture diluted with ethanol, the solid precipitate was collected by vacuum filtration, dried and crystallized from ethanol, yield 73%. m.p 270-271^{o}C. IR (KBr): 1670 (C=O), 3230, 3330 (NH_2) cm^{-1}. ^{1}HNMR ($CDCl_3$): 3.8 (t, 3H, CH_3), δ 7.4-7.8 (m, 9H, Ar-H and pyridine protons), 12.0 (s, br, 1H, OH).

8-(1*H*-Benzimidazol-2-yl)-4-chloro-7-(4-chlorophenyl)pyrido[4,3-*d*][1,2,3] triazine (11)

A solution of sodium nitrite (0.01 mol) in water (10 mL) was added to cold solution of (**3**) (0.005 mol) in acetic acid (30 mL). Then concentrated hydrochloric acid (15 mL) added. After completing of addition, the ice path removed and the mixture stirred for 2 h. Solid product collected by filtration, crystallized from ethanol, yield 70%. m.p 257-259 ^{o}C. IR (KBr): 1530 (C=N), 3060 (Ar-H) cm^{-1}. ^{1}HNMR ($CDCl_3$): 4.8 (s, br, 1H, NH), 7.1-7.8 (m, 9H, Ar-H and pyridine protons). Anal. Calcd. For $C_{19}H_{10}Cl_2N_6$: C, 58.03; H, 2.56; N, 21.37 %; Found: C, 58.06; H, 2.57; N, 21.36 %.

3-(1*H*-Benzimidazol-2-yl)-2-(4-chlorophenyl)-5-(4,5-dihydro-1*H*-imidazol-2-yl)pyridin-4-amine (12)

To a suspension of compound (**3**) (0.02 mol) in benzene (20 mL) ethylenediamine (3 mL) and carbon disulfide (1 mL) were added drop wise. Then reaction mixture heated on a water bath for 3 h. Then the solution was diluted with ethanol (30 mL), the solid precipitate was collected by filtration, dried and crystallized from ethanol, yield 61%. m.p 276-277 ^{o}C. IR (KBr): 1560 (C=N), 3220, 3360 (NH_2) cm^{-1}. ^{1}HNMR ($CDCl_3$): 4.1 (s, 2H, NH_2), 8.8 (s, br, 1H, NH), 7.1-7.8 (m, 9H, Ar-H and pyridine protons). Anal. Cacld. For $C_{21}H_{17}ClN_6$: C, 64.86; H, 4.41; N, 21.61 %; Found: C, 64.88; H, 4.44; N, 21.66 %.

Ethyl-*N*-(3-cyano-5-(1*H*-benzimidazol-2-yl)-6-(4-chlorophenyl)-pyridin-4-yl) formimidate (13)

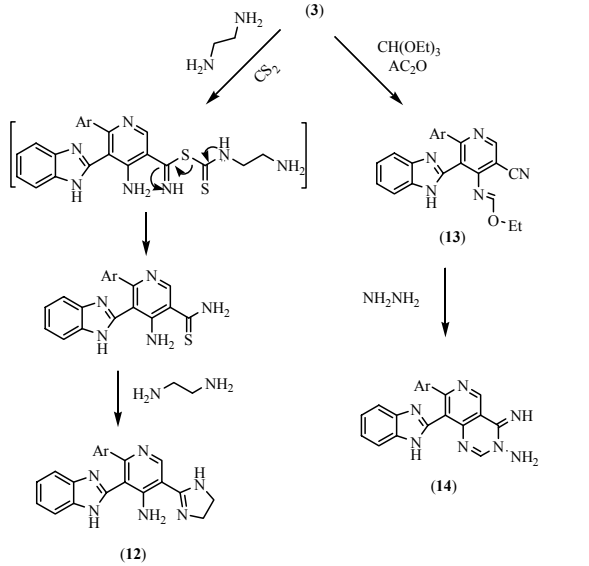
To a solution of compound (**3**) (0.02 mol) in acetic anhydrous (20 mL), triethyl orthoformate (3 mL) was added and reaction mixture refluxed for 5 h. Solid precipitate was collected, dried and crystallized from ethanol, yield 83%,. m.p 258-259 ^{o}C. IR (KBr): 1540 (C=N), 3240 (NH), 1120 (C-O-C) 2220 (CN) cm^{-1}. Anal Calcd. for $C_{22}H_{16}ClN_5O$: C, 65.76; H, 4.01; N, 17.43 %; Found: C, 65.78; H, 4.06; N, 17.42 %.

8-(1*H*-benzo[*d*]imidazol-2-yl)-7-(4-chlorophenyl)-4-iminopyrido[4,3-*d*]pyrimidin-3(4*H*)-amine (14)

To a suspension of compound (**13**) in benzene (20 mL), hydrazine hydrate (4 mL) was added and stirred for 2 h. The solid precipitate was collected by filtration, dried and crystallized from ethanol, yield 59%. m.p 281-282 ^{o}C. IR (KBr) 1540 (C=N), 3250, 3340 (NH_2) cm^{-1}. ^{1}HNMR ($CDCl_3$) 3.4 (s, 1H, NH), 7.3-8.0 (m, 9H, Ar-H and pyridine protons), 8.9 (s, 2H, NH_2). Anal. Calcd. For $C_{20}H_{14}ClN_7$: C, 61.94; H, 3.64; N, 25.28 %; Found: C, 61.98; H, 3.64; N, 25.25 %.

Results and discussion

2-(1*H*-Benzimidazol-2-yl)-3-(4-chlorophenyl)acrylonitrile (**2**) has been prepared by reaction of 2-(cyanomethyl)benzimidazole (**1**) and 4-chlorobenzaldehyde and then allowed to react with malononitrile to give 4-amino-5-(1*H*-benzimidazol-2-yl)-6-(4-chlorophenyl)pyridine-3-carbonitrile (**3**) The structure of compound (**3**) was confirmed by spectral and analytical data as given above in the experimental section.



Scheme 3. Synthesis of compounds (**12**) – (**14**).

As a continuation of our program for the synthesis of new condensed heterocyclic rings,[7,8] herein we wish to report the condensation of compound (**3**) with cyclohexanone in presence of anhydrous zinc chloride yielded 4-(1*H*-benzimidazol-2-yl)-3-(4-chlorophenyl)-6,7,8,9-tetrahydro-benzo[*b*][1,6] naphthyridin-10-amine (**4**). While the reaction of compound (**3**) with formic acid yielded 8-(*1H*-benzimidazol-2-yl)-7-(4-chlorophenyl)pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**5**). Cyclization of compound (**3**) was achieved by treatment with hydrazine hydrate to give 7-(*1H*-benzimidazol-2-yl)-6-(4-chlorophenyl)-1*H*-pyrazolo[4,3-*c*]-pyridin-3-amine (**6**) (Scheme 1). The structure of all these compounds has been assigned on basis of spectroscopic and analytical data.

Condensation of compound (**3**) with carbon disulfide to yielded 8-(1*H*-benzimidazol-2-yl)-7-(4-chlorophenyl)pyrido[4,3-*d*]pyrimidin-2,4(1*H*,3*H*)-dithione (**7**). Reaction of compound (**3**) with benzoyl isothiocyanate gives (8-(1*H*-benzimidazol-2-yl)-7-(4-chlorophenyl)-1,2-dihydro-4-imino-2-thioxopyrido[4,3-d]pyrimidin-3(4H)-yl)(phenyl)methanone (**8**). Treatment of compound (**3**) with ethyl cyanoacetate in ethanol in presence of ammonium acetate[9] resulted in the formation of 4-amino-8-(1*H*-benzimidazol-2-yl)-7-(4-chlorophenyl)-1,2-dihydro-2-oxo-1,6-naphthyridin-3-carbonitrile (**9**). Similarly, treatment of compound (**3**) with diethyl malonate give ethyl 4-amino-8-(1*H*-benzimidazol-2-yl)-7-(4-chlorophenyl)-1,2-dihydro-2-oxo-1,6-naphthyridine-3-carboxylate (**10**). Diazotization of compound (**3**) using nitrous lead to formation of 8-(1*H*-benzimidazol-2-yl)-4-chloro-7-(4-chlorophenyl)pyrido[4,3-*d*][1,2,3]triazine (**11**) (Scheme 2).

Compound (**3**) was reacted with excess of ethylenediamine in presence of carbon disulfide[10] to afford 3-(*1H*-benzimidazol-2-yl)-2-(4-chlorophenyl)-5-(4,5-dihydro-*1H*-imidazol-2-yl)pyridin-4-amine (**12**). The structure of compound (**12**) has assigned on basis of its spectroscopic data. The IR spectra revealed the presence of (NH_2) at 3220, 3360 cm^{-1}, there is no absorption band for (CN) and (C=S). Compound (**3**) react with triethyl orthoformate yielded ethyl-N-(3-cyano-5-(1*H*-benzimidazol-2-yl)-6-(4-chlorophenyl)pyridin-4-yl)formimidate (**13**) which underwent further cyclization in presence of hydrazine hydrate at room temperature affording to produce 8-(1*H*-benzo[*d*]imidazol-2-yl)-7-(4-chlorophenyl)-4-iminopyrido[4,3-*d*]pyrimidin-3(4*H*)-amine(**14**) (Scheme 3). The structures of all these compounds were elucidated from its spectral and elemental analysis data.

References

[1]Barker, H. A., Smith, R. D., Weissbach, H., Toohey, J. I., Ladd, J. N., Volcani, B. E., *J. Biol. Chem*., **1960**, *235*, 480–488.

[2]Jackstell, R., Frisch, A., Beller, Rottger, M. D., Malaun, M., Bildstein, B., *J. Mol. Catal. A: Chem.*, **2002**, *185*, 105–112.

[3]Huynh, H. V., Ho, J. H. H., Neo, T. C., Koh, L. L., *J. Organomet. Chem*., **2005**, *690*, 3854–3860.

[4]Tonelli, M., Simone, M., Asso, B. T., Novelli, F., Boido, V., *Chem. Biodiver*., **2008**, *5*, 2386.

[5]Tripathi, K. D., *Essentials of Medical Pharmacology*, 5th Ed., Jaypee Brother's Medical Publisher, Delhi, **1981**, 562-566.

[6]Harsch, C., Sammes, P. G., Taylor, J. B., *Comprehensive Medicinal Chemistry*, 1st Ed., Pergamon Press, Oxford, **1990**, 528.

[7]Fikry, R. M.. Ismael. N. A.. EL-Bahanaswav. A. A., EL-Ahl. A. A. S., *Phosphorus, Sulfur Silicon Relat. Elem*., **2004**, *179*, 1227-1236.

[8]Fikry, R. M., *Indian J. Heterocycl. Chem*., **1995**, *4*, 652-658.

[9]Checchi, S., Ridi, M., *Gazz. Chim. Ital*., **1957**, *87*, 597.

[10]El-Saghier, A. M. M., *Molecules*, **2002**, *7*,767-776.

Received: 08.09.2015
Accepted: 15.10.2015.

TOTAL LIPIDS, PROTEINS, MINERALS, ESSENTIAL OILS AND ANTIOXIDANT ACTIVITY OF THE ORGANIC EXTRACTS OF *MENTHA LONGIFOLIA* (L.) GROWING WILD IN KOSOVO

Fatmir Faiku[a] and Arben Haziri[a]

Keywords: *Mentha longifolia* (L.), essential oil, proteins, lipids, antioxidant activity, DPPH.

The soil and climatic conditions are conducive for the growth of a lot of medical herbs in Kosovo. *Mentha longifolia* (L.) is native to Europe, Central Asia and Australia. Lipids, proteins, minerals and essential oils were quantitatively determined from the *Mentha longifolia* (L.) growing wild in Germia Park (located in the northeast of Pristina). Total proteins were analyzed, by Kjeldahl method. The total amount of proteins in the *Mentha longifolia* (L.) is 8.227 %. Lipids are analyzed by Soxhlet extraction. The total amount of lipids in the *Mentha longifolia* (L.) are 5.804 %. Essential oils were isolated using steam distillation. The total amount of essential oils in the *Mentha longifolia* (L.) are 0.589 %. The mineral content was studied and analyzed by flame atomic absorption spectrometry. Six elements, sodium, potassium, calcium, zinc, iron and copper were determined in the *Mentha longifolia* (L.). The mean levels of sodium, potassium, calcium, zinc, iron and copper are 509.7 mg kg^{-1}, 4055 mg kg^{-1}, 9097 mg kg^{-1}, 256.7 mg kg^{-1}, 11841 mg kg^{-1}, 82.83 mg kg^{-1} in the *Mentha longifolia* (L.), respectively. Iron and calcium are present in large amounts in the *Mentha longifolia* (L.). The antioxidant activity of essential oil was evaluated by means of the 2,2-diphenyl-1-picrylhydrazil (DPPH) radical scavenging method. During the analysis of antioxidant activity of the extracts of *Mentha longifolia* (L) it has been observed that only H_2O extract shows strong antioxidant activity than BHT and BHA.

*Corresponding Authors
E-Mail: f_faiku@hotmail.com; arbeni77chem@hotmail.com
[a] Department of Chemistry, Faculty of Natural Sciences, University of Prishtina, Kosovo

Introduction

For primary health care needs, 80% of world population relies mainly on plant based traditional medicines because according to them, medicinal plants are natural or near to nature and are always safe. The important utilities of many plants have long been published but a large number of them remain unexplored up to now. So there is a necessity to explore their uses and to conduct pharmacognostic and pharmacological studies to ascertain their therapeutic properties.[1-3] Plants' diversity has a considerable importance as a source of pharmaceutically active substances.[4-7]

Mentha longifolia (L.) is perennial herb 40-120 cm high with musty scent. Stem white or grey-villous, sometimes sparsely hairy. Leaves are sessile or shortly petiolate usually oblong elliptical, hairs simple. Extremely variable in height, leaf size and shape, indumentum and inflorescence and complicated by the occurrence of hybrids.[8] *Mentha* species are widely used in conventional medicine, for their antispasmodic, antiseptic and emmenagogue effects. Moreover, their essential oils are used in chewing gums, alcoholic beverages, cosmetics, perfumes, toothpastes and mouthwashes.[9] The plant is mainly used as salad, spice and for tea besides mint herbage used for wool dyeing.[10]

Various biological activities have been reported for some species of *Mentha*, as antibacterial,[11-13] antifungal,[6] and antioxidant activity.[14-16]

Our research group is interested to analyze the chemical profile of different medicinal plants which are growing wild in the region of Kosova and Albania.[17-24] The aim of this research was to determine the quantity of proteins, lipids, minerals, essential oil and antioxidant activity in the *Mentha longifolia* (L.), growing in Germia Park. Germia is a regional Park located in the north-east of Pristina, capital city of Kosovo, and it covers an area of 62 km^2.

Experimental

Plant materials

The leaves of *Mentha longifolia* (L.), growing wild in Germia Park (located in the north-east of Pristina), was collected in July 2013. We took four samples from *Mentha longifolia* (L.). Voucher specimens were deposited in the Herbarium of the Department of Veterinary, University of Prishtina. The plants were dried at room temperature (22 °C).

Extraction of essential oils

Hydrodistillation was conducted by a standard procedure[25] (Clevenger apparatus) with dried *Mentha longifolia* (L.) leaves which had previously been chopped in a domestic blender. The isolation experiment was carried out continuously on a heating mantle at 60-80 ^{0}C until no further oil was extracted. The essential oil was dried over anhydrous Na_2SO_4 and after filtration stored in a dark bottle at 4 ^{0}C until tested and analyzed.

Determination of Mineral Content

An analysis of the collected leaves samples, by the method of Taleisnik et al,[26] showed the presence of sodium, potassium, calcium, zinc, iron and copper. Therefore, the leaves were washed with distillated water to remove any dust and were dried in an oven at 105 °C for 48 h. The dried

samples were pounded in a porcelain mortar until they formed a powder. Then, a 2 g sample was calcified in an oven at 300-400 °C. The ashes were placed into 100 cm^3 of normal flask. Next, 10 mL of 1 mol dm^{-3} nitric acid was added to each flask, homogenized, and then shaken for 20 min in a shaker. The homogenized samples were filtered and filled till 100 mL with 1 mol dm^{-3} HNO_3. Minerals like sodium, potassium, calcium, zinc, iron and copper were analyzed Atomic Absorption Spectrometry (Buc Scientific Model 200A).

Determination of protein content

The Kjeldahl method[27] was used for determination of proteins in which digestions, distillation and titration of the sample was done. The value of nitrogen was converted to protein by multiplying to a factor of 6.25.

Determination of lipid content

The solvent extraction method[28,29] was used for the determination of thelipid content of the samples. Diethyl ether was used as a solvent.

Antioxidant activity- DPPH assay

The hydrogen atom or electron donation abilities of the corresponding extracts and some pure compounds were measured from the bleaching of the purple-colored methanol solution of 2,2-diphenyl-1-picrylhydrazyl (DPPH). This spectrophotometric assay was done using the stable radical DPPH as a reagent according to the method of Burits and Bucar.[30] Briefly, 50 µL of the extracts (various concentrations) were added to 5 ml of the DPPH solution (0.004% methanol solution). After 30 min incubation at room temperature, the absorbance was read against pure methanol at 517 nm. The radical scavenging activities of the samples were calculated as percentages of inhibition according to the following equation:

$$I(\%) = 100 \frac{A_{\text{blank}} - A_{\text{sample}}}{A_{\text{blank}}} \qquad (1)$$

where

A_{blank} is the absorbance of the control (containing all reagents except the test compound), and

A_{sample} is the absorbance of the test compound.

Extract concentration providing 50% inhibition (IC_{50}) was calculated from the plot of inhibition percentages against extract concentration using PHARM/ PCS-version 4. All tests were done in triplicate.

Results and Discussion

The chemical aspects of *Mentha longifolia* (L.) were analyzed with the goal to determine the chemical nature. We have quantitatively analyzed the primary and secondary metabolites. The amount of lipids, proteins and essential oil of *Mentha longifolia* (L.) is given in Table 1.

From experimental data (Table 1) we can see that the amounts of lipids were 5.804 %, proteins 8.227 % and essential oil 0.589 % in the *Mentha longifolia* (L.). Figure 1 show the diagrams for the lipids, proteins and essential oil amounts to *Mentha longifolia* (L.) giving in percentage. On Figure 1 we can see that the amounts of proteins, lipids and essential oils in *Mentha longifolia* (L.) are as follows: proteins > lipids > essential oil.

Table 1. The amounts of lipids, proteins and essential oil of the *Mentha longifolia* (L.).

Components	Mean value (%)	Standard deviation
Lipids	5.804	0.21
Proteins	8.227	0.17
Essential oil	0.589	0.01

The amount of essential oil (0.589 %) of *Mentha longifolia* (L.) growing in Kosovo is almost same as that of *Mentha piperita* growing in Libya[15] (0.64 %). However, it is lower than the amount of essential oil of *Mentha longifolia* (L.) growing in Serbia[31] (0.9 %). The amount of proteins (8.227 %) of *Mentha longifolia* (L.) growing in Kosovo is comparable to that of *Mentha longifolia* (L.) growing in Pakistan[32] (7.491 %). The amount of lipids (5.804%) in *Mentha longifolia* (L.) growing in Kosovo is higher than that in *Mentha longifolia* (L.) growing in Pakistan[32] (2.34 %).

We determined the quantity of the minerals like sodium, potassium, calcium, zinc, iron and copper. The amount of minerals of *Mentha longifolia* (L.) are given in Table 2.

Table 2 shows that the average values in mg kg^{-1} of sodium, potassium, calcium, zinc, iron and copper in the sample are 509.7, 4055, 9097, 256.7, 11841 and 82.83 mg kg^{-1}. The plant contains large amounts of calcium (9097 mg kg^{-1}) and iron (11841 mg kg^{-1}).

Table 2. Quantity of minerals of the *Mentha longifolia* (L.) giving in mg kg^{-1}.

Elements	Mean value (%)	Standard deviation
Sodium	509.7	0.55
Potassium	4055	0.19
Calcium	9097	0.035
Zinc	256.7	0.21
Iron	11841	0.032
Copper	82.83	0.029

The result of the following study agrees with earlier study of elemental distribution in medicinal plant species as reported by Kim et al.[33] The result of the present study shows a high level of macro elements accumulation in the sampled plants. It is important to note that benefits accorded to human health by some plants, used in homeopathic system, have been traced to presence of Ca, Cr, Fe, Mn, Ca, K and Zn in those plants.[34] These elements equally contribute to neurochemical transmission and are food constituents of biological molecules. The mineral composition results of the *Mentha longifolia* (L.) show that this plant contains rich source of mineral elements, this result assumes importance. when the usefulness of mineral like Ca, Mg, K and Na in the body are considered.

The amount of sodium (509.7 mg kg^{-1}), iron (11841 mg kg^{-1}) and copper (82.83 mg kg^{-1}) in *Mentha longifolia* (L.) growing in Kosovo is higher than those in *Mentha longifolia* (L.) growing in Pakistan (sodium 29.9 mg kg^{-1}, iron 53.4 mg kg^{-1} and copper 6 mg kg^{-1}). [32]

The amount of iron (11841 mg kg^{-1}), zinc (256.7 mg kg^{-1}) and copper (82.83 mg kg^{-1}) in *Mentha longifolia* (L.) growing in Kosovo is higher than those in of *Mentha piperita* (iron 531.5 mg kg^{-1}, zinc 12.64 mg kg^{-1} and copper 11.52 mg kg^{-1}) and *Mentha spicata* (iron trace, zinc 4.654 mg kg^{-1} and copper 1.757 mg kg^{-1}) growing in Turkey.[16] The amount of calcium (4055 mg kg^{-1}) in *Mentha longifolia* (L.) growing in Kosovo is lower than that in *Mentha piperita* (12150 mg kg^{-1}) and *Mentha spicata* (4396 mg kg^{-1}) growing in Turkey.[16]

The DPPH radical scavenging method was used to evaluate the antioxidant properties of *Mentha longifolia* (L.) in comparison with those BHT and BHA. Table 3 shows antioxidant activity of extracted oil of *Mentha longifolia* (L.).

Table 3. Antioxidant activity of extracted oil of *Mentha longifolia* (L.).

Samples	IC_{50} (μg mL^{-1})
Diethyl ether	29.10
Chloroform	28.86
Ethyl acetate	18.98
1-Butanol	17.81
Water	7.89
Butylatedhydroxytoluene (BHT)	13.43
Butylatedhydroxyanisole (BHA)	11.55

All extracts of *Mentha longifolia* (L.) (water, n-butanol, ethyl acetate, chloroform and diethyl ether) have been able to reduce DPPH stable radical from DPPH-H violet color to DPPH-H with yellow color. Comparison of the neutralizing activity of the extracts of *Mentha longifolia* (L.) with that of BHT (13.43 μg mL^{-1}) and BHA (11.55 μg mL^{-1}) shows that only the aqueous extract shows stronger antioxidant activity. Hence, one can conclude that only the aqueous extract has a stronger antioxidant activity as compared those of BHT and BHA. According to the results recorded in Table 3, the highest radical scavenging activity was observed in the extracts of solvents in the following order: H_2O > BHA > BHT > n-BuOH >EtOAc > $CHCl_3$ > Et_2O.

Conclusion

In recent years, use of medicinal plants and their conservation has been accorded great importance. They are used globally by the indigenous and marginal communities for curing various diseases. These medicinal plant species are mostly used as food supplement along with their oral decoctions.

Mint species are used widely throughout the world as an important medicinal plant. The aim of this research was to determine the quantity of primary metabolites (lipids and proteins) and to analyze minerals as sodium, potassium, calcium, zinc, iron and copper. The important results of this study can be summarized as follows.

The total amount of proteins, lipids and essential oils in the *Mentha longifolia* (L.) is 8.227 %, 0.804 % and 0.589 %, respectively. The macro-elements present in *Mentha longifolia* (L.) occur in the order Fe > Ca > K > Na > Zn > Cu. Our current study on nutritional evaluation of *Mentha longifolia* (L.) has revealed that this plant is a good source of nutrients (proteins, lipids and minerals) and can be used as substitutes for food deficient in any of these nutrients. Further, the aqueous extract of the plant possessed a strong antioxidant activity. Antioxidant properties of the essential oils and various extracts from plants are of great interest in both fundamental science and the food industry, since their possible use as natural additives emerged from a growing tendency to replace synthetic antioxidants by natural ones.

References

[1]Soomro, T., Zahir, E., Mohiuddin, S., Khan, N., Naqvi, Ll., *Pak. J. Biol. Sci.,* **2008**, *11*, 285-289.

[2]Karak, T., Bhagat, R., *Food Res. Int.*, **2010**, *43*, 2234-2252.

[3]Diacony, D., Diacony, R., Navrotescu, T., *Ovidius Univ. Ann.Chem.,* **2012**, *23*, 115-120.

[4]Newman, J., Cragg, M., *J. Nat. Prod*., **2012**, *75*, 311-335.

[5]Cragg, M., Newman, J., *Biochim. Biophys. Acta*, **2013**, *1830*, 3670-3695.

[6]Ruikar, D., Kamble, S., Puranik, G., Deshpande, R., *Int. J. Pharm. Tech. Res*., **2009**, *1*, 1164-1166.

[7]Abreu, C., McBain, J., Simões, M., *Nat. Prod. Rep*., **2012**, *29*, 1007-1021.

[8]Džamić, A., Soković, M., Ristić, M., Novaković, M., Grujić-Jovanović, S., Tešević, V., Marin, P., *Bot. Serb.,* **2010**, *34*, 57-61.

[9]Edris, E., Shalaby, S., Fadel, M., Abdel-Wahab, A., *Eur. Food Res. Tech.*, **2003**, *218*, 74–78.

[10]Leung, Y., Foster, S., *Encyclopaedia of common natural ingredients used in food, drugs and cosmetics*, New York, John Wiley & Sons, **2003**.

[11]Pramila, M., Xavier, R., Marimuthu, K., Kathiresan, S., Khoo, L., Senthilkumar, M., *J. Med. Plants. Res*., **2012**, *6*, 331-335.

[12]Hajlaoui, H., Snoussi, M., Ben Jannet, H., Mighri, Z., Bakhrouf, A., *Ann. Microbiol*., **2008**, *58*, 513-520.

[13]Pavela, R., *Fitoterapia*, **2005**, *76*, 691- 696.

[14]Saeide, S., Kazem, H., Mehdi,G., Mohammad, H., Ramezan, T., Ali, M., Gholamreza, F., *Asian Pac. J. Trop. Med*., **2014**, *7*, 186-189.

[15]Rajinder, S., Muftah, M., Shushni, B., *Arabian J. Chem.*, **2015**, *8*, 322–328.

[16]Süleyman, K., Nesrin, H., Veysel, T., Ersin, K., Uyan, Y., *Turk. J. Field Crops*, **2010**, *15*, 148-153.

[17]Faiku, F., Haziri, A., Domozeti, B., Mehmeti, A., *Eur. J. Exp. Biol.,* **2012**, *2*, 1273-1277.

[18]Faiku, F., Haziri, A., *Int. J. Pharm. Phytopharmacol. Res*., **2013**, *3*, 254-257.

[19]Haziri, A., Aliaga, N., Ismaili, M., Govori, S., Leci, O., Faiku, F., Arapi, V., Haziri, I., *Am. J. Biochem. Biotechnol.,* **2010**, *6*, 32-34.

[20]Haziri, A., Faiku, F., Mehmeti, A., Govori, S., Abazi, S., Daci, M., Haziri, I., Bytyqi-Damoni, A., Mele, A., *Am. J. Pharmacol. Toxicol.,* **2013**, *8*, 128-133.

[21]Haziri, A., Govori, S., Ismaili, M., Faiku, F., Haziri, I., *Am. J. Biochem. Biotechnol.,* **2009**, *5*, 226-228.

[22]Hajdari, A., Novak, J., Mustafa, B., Franz, C., *Nat. Prod. Res.,* **2012**, *26*, 1676-1681.

[23]Hajdari, A., Mustafa, B., Franz, C., Novak, J., *Nat. Prod. Commun.,* **2011**, *6*, 1343-1346.

[24]Faiku, F., Haziri, A., Gashi, F., Troni, N., Faiku, H., *Eur. Chem. Bull.,* **2015**, *4*,331-334.

[25]Hafedh, H., Najla, T., Emira, N., Mejdi, S., Hanen, F., Riadh, K., Amina, B., *World J. Microbiol. Biotechnol*., **2009**, *25*, 2227-2238.

[26]Taleisnik, E., Peyrano, G., Arias, C., *Trop. Grasslands*, **1997**, *31*, 232-240.

[27]Kjeldahl, J., *Z. Anal. Chem.,* **1883**, *22,* 366-383.

[28]Soxhlet, F., *Dingler's Polytechn. J.* (in German), **1879**, *232*, 461–465.

[29]Jensen, B., *J. Chem. Educ.,* (ACS), **2007**, *84*, 1913–1914.

[30]Burits, M., Bucar, F.*, Phytother. Res*., **2000**, *14*, 323-328.

[31]Stanisavljević, D., Đorđević, S., Ristić, M., Veličković D., Randelović, N., *Biologica Nyssana*, **2010**, *1*, 89-93.

[32]Ghani, A., Zulfiqar, A., Tahir, I., Samreen, S., Sadia, S., *Pak. J. Pharm. Sci*., **2014**, *27*, 597-600.

[33]Kim, Y., Kim, S., Lee, S., Yoo, H., *Agric. Sci. Soil Fen*., **1994**, *36*, 310-320.

[34]Perman, S., Gupita, K., Jhan, N., *Pharm. Biol.*, **1993**, *39*, 384-387.

Received: 16.09.2015.
Accepted: 15.10.2015.

SYNTHESIS OF NEW MERCAPTOPYRIMIDINES AND THIENOPYRIMIDINES

Abdelreheem A. Saddik[a]*, Khairy M. Hassan[a], Adel M. Kamal El-Dean[a] and Mohamed S. Abbady[a]

Keywords: benzaldehyde, thiourea, ethyl cyanoacetate, α-halo carbonyl compounds.

2-Alkylmercapto- 4-Chloro-6-phenyl-pyrimidine-5-carbonitrile (**4a-c**) were synthesized and converted into 2-alkylmercapto 4-mercapto-6-phenyl-pyrimidine-5-carbonitriles (**7a-c**). Compounds (**7a-b**) were alkylated with halogenated compounds to afford compounds (**8a-g**). Compounds (**8a-g**) underwent Thorpe-Ziegler Cyclization to give thienopyrimidines (**9a-g**). 5-Amino-2-alkylmercapto-4-phenyl-thieno-[2,3-*d*]pyrimidine-6-carboxamide derivatives (**9a-f**) underwent cyclization reaction using triethyl orthoformate to afford pyrimido-thienopyrimidines (**10a-e**).

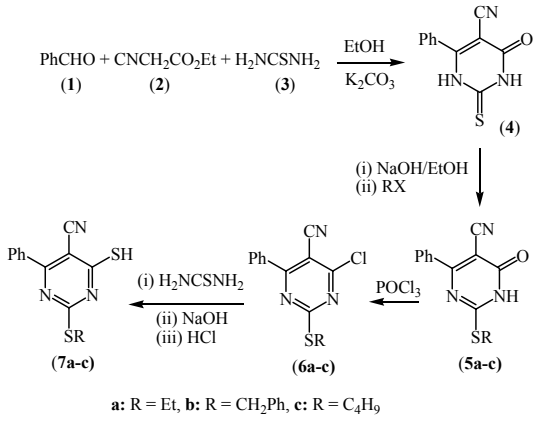
* Corresponding Authors
E-Mail: abdelraheemseddik@gmail.com
[a] Chemistry Department, Faculty of Science, Assiut University, Assiut 71516, Egypt

Introduction

The pyrimidine and thienopyrimidine derivatives have many biological activities, such as anticancer,[1] antiviral,[2] antitumor,[3] anti-inflammatory,[4] antimicrobial[5] and antimalarial.[6] Thieno[2,3-*d*]pyrimidine was first synthesized by Baker et al,[7] who reported that the action of methanolic ammonia on 2-formamido-3-carbomethoxythiophene gave a low yield (4%) of thieno[2,3-*d*]pyrimidin-4-one. Most of the methods for the preparation of this ring system have been achieved by ring closure of thiophene derivatives. In continuation of our program for the synthesis of heterocyclic compounds containing thienopyrimidine moiety,[8-17] in this paper we report the synthesis of new mercaptopyrimidine and thieno[2,3-*d*]pyrimidine derivatives from pyrimidine ring.

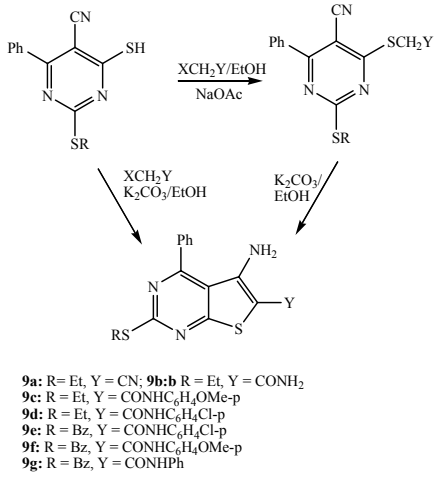
Result and Discussion

5-Cyano-4-oxo-6-phenyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine (**4**) was synthesized via multi components reaction (MCR) by one pot condensation reaction[18] of benzaldehyde (**1**), ethyl cyanoacetate (**2**) and thiourea (**3**) in refluxing ethanol in the presence of potassium carbonate. Refluxing (**4**) with sodium acetate in ethanol gave the sodium salt of (**4**) which reacts with alkyl halides to give 2-alkylmercapto-4-oxo-6-phenyl-pyrimidine-5-carbonitriles (**5a-c**). The carbonyl group in compound (**5a-c**) enolizes to hydroxyl group which it was displaced with a chlorine atom by reacting compound (**5**) with phosphorus oxychloride to give 2-alkylmercapto-4-chloro-6-phenyl-pyrimidine-5-carbonitriles (**6a-c**). Chlorine atom in compound (**6a-c**) is replaced by mercapto group on reacting it with thiourea in ethanol. Following it by treatment with sodium hydroxide solution and then acidification with dilute HCl gave 2-alkylmercapto-4-mercapto-6-phenyl-pyrimidine-5-carbonitriles (**7a-c**) (Scheme 1).



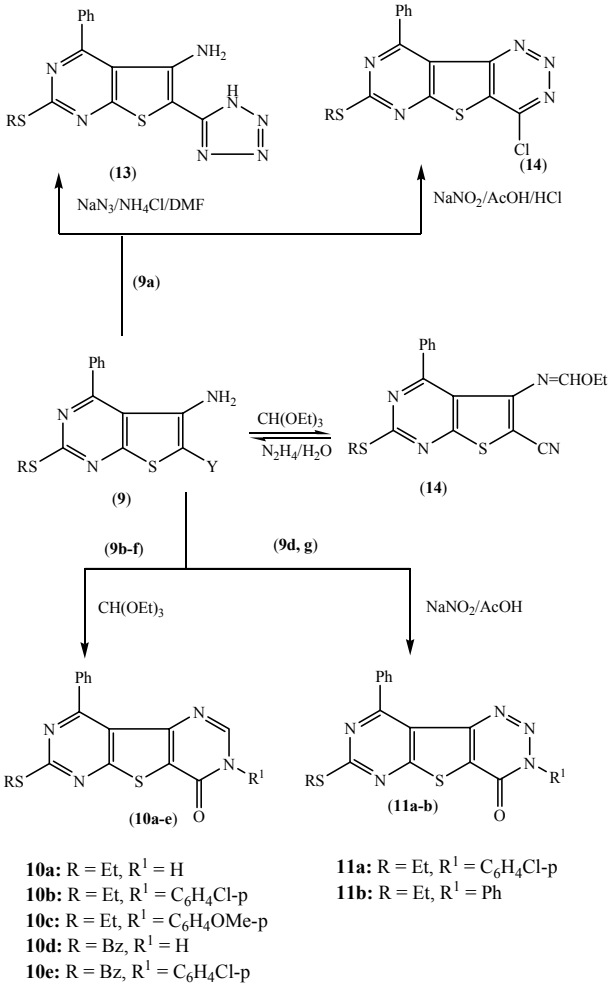
Scheme 1. Synthesis of 2-alkylmercapto-4-mercapto-6-phenyl-pyrimidine-5-carbonitriles.

Compound (**7a-b**) can be alkylated with α-halocarbonyl compounds in refluxed ethanol in the presence of sodium acetate to give alkylated mercaptopyrimidine derivatives (**8a-h**).



Scheme 2. Synthesis of thieno[2,3-*d*]pyrimidines.

Compounds (**8a-h**) upon refluxing with potassium carbonate in ethanol affording thieno[2,3-*d*]pyrimidine derivatives (**9a-h**). Compound (**9a-h**) can be prepared directly also from compound (**7a-b**) by refluxing it with α-halocarbonyl compounds in ethanol in the presence of potassium carbonate (Scheme 2).



Scheme 3. Synthesis of pyrimidothieno[2,3-*d*]pyrimidine derivatives.

Compounds (**9b-f**) were cyclized using triethyl orthoformate in the presence of catalytic amount of acetic acid affording pyrimidothieno[2,3-*d*]pyrimidine derivatives (**10a-e**). When compounds (**9d,g**) were treated with sodium nitrite in acetic acid, pyrimidothienotriazines (**11a,b**) were obtained. On the other hand, when compound (**9a**) was treated with sodium nitrite in acetic acid-HCl mixture, chloropyrimidothienotriazine (**12**) was obtained. Tetrazolyl thienopyrimidine (**13**) was obtained by treating compound (**9a**) with sodium azide in the presence of ammonium chloride in DMF. When compound (**9**) was refluxed with triethyl orthoformate in the presence of catalytic amount of acetic acid, 5-ethoxymethyleneamino-2-ethylmercapto-4-phenylthieno[2,3-*d*]pyrimidine-6-carbonitrile (**14**) was obtained which when treated with hydrazine hydrate in ethanol at refluxing temperature or even at room temperature, the C=N- underwent fission to afford compound (**9**) again (Scheme 3).

Experimental

All melting points are uncorrected. IR spectra were recorded (KBr discs) with a Perkin-Elmer 1430 Spectrophotometer. ^{1}H NMR spectra were obtained on a BRUKER (400 MHz) spectrometer in $CDCl_3$ and DMSO-d_6 using TMS as an internal standard, and chemical shifts are expressed as δ ppm. Mass spectra were obtained on a Jeol-JMS 600 spectrometer. Analytical data were obtained on Elementar Analyse system GmbH-VarioEL V.3 microanalyzer in the central lab of Assiut University. Compounds (**4,5a-c**) were prepared according to the literature procedure.[18,19]

2-(Alkylmercapto)-4-chloro-6-phenyl-5-pyrimidinecarbonitriles (6): General procedure

20 g of compound (**5b**) and 30 mL of $POCl_3$ was refluxed for 3 h. After cooling the solution was poured into a beaker containing 600 g of ice and was then neutralized using sodium carbonate. On stirring the solution for 30 min, a precipitate is formed. The crude precipitate was collected by filtration, washed several time with water, dried in air and recrystallized from ethanol.

2-(Ethylmercapto)-4-chloro-6-phenyl-5-pyrimidinecarbonitrile (6a)

This compound was obtained as white crystals (75 %). m.p. 64-66 ^{o}C. IR (KBr): 3047 (C-H aromatic), 2925 (C-H aliphatic), 2227 (C-N), 1640 (C=O), 694 (C–Cl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (t 3H, CH_3), 3.39 (q, 2H, CH_2), 7.45, 7.89 (2m, 5H, ArH). MS *m\z* 275.6. Anal. Calcd. for $C_{13}H_{10}ClN_3S$; C, 56.62; H, 3.66; Cl, 12.86; N, 15.24; S, 11.63 %; Found: C, 56.44; H, 3.44; Cl, 13.05; N, 15.06; S, 11.80 %.

2-(Benzylmercapto)-4-chloro-6-phenyl-5-pyrimidine-carbonitrile (6b)

This compound was obtained as white crystals (75 %). m.p. 78-80 ^{o}C. IR (KBr): 3047 (C-H aromatic), 2954 (C-H aliphatic), 2223 (C-N), 820 (C–Cl) cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ = 4.48, (s, 2H, CH_2), 7.25-7.9 (m, 5H, Ar-H). Anal. Calcd. for $C_{18}H_{12}ClN_3S$: C, 64.00; H, 3.58; Cl, 10.49; N, 12.44; S 9.49 %; Found: C, 63.82; H, 3.70; Cl, 10.64; N, 12.28; S 9.29 %.

2-(Butylmercapto)-4-chloro-6-phenyl-5-pyrimidinecarbonitrile (6c)

This compound was obtained as white crystals (83 %). m.p. 58-60 ^{o}C. IR (KBr) 3069 (C-H aromatic), 2956 (C-H aliphatic), 2223 (C-N), 816 (C–Cl) cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.95 (t, 3H, CH_3), 1.45, 1.8 (2m, 4H, $2CH_2$), 3.5 (t, 2H, CH_2), 7.45, 7.9 (2m, 5H, Ar-H). Anal. Calcd. for: $C_{15}H_{14}ClN_3S$: C, 59.30; H, 4.64; Cl, 11.67; N, 13.83; S, 10.55 %; Found: C, 59.18; H, 4.50; Cl, 11.80; N, 14.03; S, 10.70 %.

2-(Alkylmercapto)-4-mercapto-6-phenyl-5-pyrimidinecarbonitriles (7): General procedure

0.01 Mole of compound (**6**) and 0.02 mole of thiourea was refluxed in 100 mL ethanol for 6 h. On cooling, a yellow precipitate is formed. It was filtered, washed with ethanol, dissolved in 10 % NaOH solution and reprecipitated with dilute HCl. The crude precipitate is collected by filtration, washed several time with water, dried in air and recrystalized from ethanol\dioxane mixture.

2-(Ethylmercapto)-4-mercapto-6-phenyl-5-pyrimidinecarbonitrile (7a)

This compound was obtained as yellow crystals (63 %). m.p. 178-180 ^{o}C. IR (KBr): 3047 (C-H aromatic), 2984 (C-H aliphatic), 2216 (C-N), 1255(C=S) cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.3(t, 3H, CH_3), 3.1 (q, 2H, CH_2), 7.7 (s, 1H, NH), 8.3-7.9 (s, 5H, ArH). Anal. Calcd. for $C_{13}H_{11}N_3S_2$: C, 57.12; H, 4.06; N, 15.37; S 23.46 %; Found: C, 57.00; H, 3.98; N, 15.52; S 23.61 %.

2-(Benzylmercapto)-4-mercapto-6-phenyl-5-pyrimidinecarbonitrile (7b)

The crude product was recrystalized from ethanol as yellow crystals (65 %). m.p. 184-186 ^{o}C. IR (KBr): 3114 (C-H aromatic), 2969 (C-H aliphatic), 2223 (C-N) cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ = 2.7 (s, 1H, SH), 4.0 (s, 2H, CH_2, 7, 25, 7.42, 7.7, 8.3 (4m, 10H, Ar-H). MS *m\z* 335.6. Anal. Calcd. for $C_{18}H_{13}N_3S_2$: C 64.45; H; 3.91; N, 12.53; S, 19.12 %; Found: C 64.45; H; 3.91; N, 12.53; S, 19.12 %.

2-(Butylmercapto)-4-mercapto-6-phenyl-5-pyrimidinecarbonitrile (7c)

The crude product recrystalized from ethanol as yellow crystals (66 %). m.p. 182-184 ^{o}C. IR (KBr): 3115 (C-H aromatic), 2953 (C-H aliphatic), 2220 (C-N), 1250 (C=S) cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.93 (t, 3H, CH_3), 1.46-1.60 (m, 4H, $2CH_2$), 2.83-2.95 (m, 2H, CH_2), 2.75 (s, 1H, SH, 7, 25, 8.33 (2m, 5H, Ar-H). Anal. Calcd. for $C_{15}H_{15}N_3S_2$: C, 59.77; H, 5.02; N, 13.94; S, 21.27 %; Found: C, 59.92; H, 4.88; N, 14.10; S, 21.08 %.

2,4-Alkylmercapto-6-phenyl-pyrimidine-5-carbonitriles (8a-g): General procedure

Compound (**5**) (0.01 mole), sodium acetate (0.02 mole) and appropriate α-halogenated compound (0.01 mole) in 50 mL ethanol was refluxed for 1 h and allowed to cool. The solid product was filtered off, washed with water and ethanol, dried in air and recrystallized from ethanol.

4-(Cyanomethylthio)-2-(ethylthio)-6-phenylpyrimidine-5-carbonitrile (8a)

Yield 88.5 %. m.p. 136-138 ^{o}C. IR (KBr): 3037 (C-H aromatic), 2983 (C-H aliphatic), 2244 (C-N), 2215 (C-N) cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.38 (t, 3H, CH_3), 3.3 (q, 2H, CH_2), 4.3, (s, 2H, CH_2) and 7.5, 7.9 (2m, 5H, ArH). Anal. Calcd. for $C_{15}H_{12}N_4S_2$: C, 57.67; H, 3.87; N, 17.93; S, 20.53 %; Found: C, 57.83; H, 3.71; N, 17.73; S, 20.64 %.

2-(5-Cyano-2-(ethylthio)-6-phenylpyrimidin-4-ylthio)acetamide (8b)

Yield 66.5 %. m.p. 170-172 ^{o}C. IR (KBr): 3377, 3195 (NH_2), 3043 (C-H aromatic), 2967(C-H aliphatic), 2215 (C-N), 1645 (C=O) cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.38 (t, 3H, CH_3), 3.25 (q, 2H, CH_2), 4.1, (s, 2H, CH_2), 6.95 (s, 2H, NH_2) and 7.5, 7.9 (2m, 5H, ArH). Anal. Calcd. for $C_{15}H_{14}N_4OS_2$: C, 54.52; H, 4.27; N, 16.96; S, 19.41 %; Found: C, 54.37; H, 4.09; N, 16.74; S, 19.29 %.

2-(5-Cyano-2-(ethylmercapto)-6-phenylpyrimidin-4-ylthio)-N-(4-methoxy phenyl)acetamide (8c)

Yield 62 %. m.p. 148-150 ^{o}C. IR (KBr): 3279(N-H), 3047 (C-H aromatic), 2957 (C-H aliphatic), 2215 (C-N), 1659 (C=O) cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.38 (t, 3H, CH_3), 3.28 (q, 2H, CH_2), 3.72 (s, 3H, CH_3), 4.2(s, 2H, CH_2), 6.9-7.9 (m, 9H, Ar-H) and 9.1 (s, 1H, NH). MS *m\z* 436.22. Anal. Calcd. for $C_{22}H_{20}N_4O_2S_2$: C, 60.53; H, 4.62; N, 12.83; S, 14.69 %; Found: C, 60.68; H, 4.82; N, 13.00; S, 14.54 %.

N-(4-chlorophenyl)-2-(5-cyano-2-(ethylmercapto)-6-phenylpyrimidin-4-ylthio)acetamide (8d)

Yield 47 %. m.p. 158-160 ^{o}C. IR (KBr): 3297(N-H), 3058 (C-H aromatic), 2985 (C-H aliphatic), 2214 (C-N), 1662 (C=O) cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ= 1.38 (t, 3H, CH_3), 3.05(q, 2H, CH_2), 4.23(s, 2H, CH_2), 7.23-8.34 (m, 9H, Ar-H) and 9.50 (s, 1H, NH). MS *m\z* 440.26. Anal. Calcd. for $C_{21}H_{17}ClN_4OS_2$: C 57.20; H, 3.89; Cl, 8.04; N, 12.71; S, 14.54 %; Found: C, 57.02; H, 4.02; Cl, 7.86; N, 12.91; S, 14.44 %.

2-(2-(Benzylmercapto)-5-cyano-6-phenylpyrimidin-4-ylthio)-N-(4-chloro phenyl)acetamide (8e)

Yield 63 %. m.p. 182-184 ^{o}C. IR (KBr): 3296(N-H), 3061 (C-H aromatic), 2924 (C-H aliphatic), 2215 (C-N), 1661 (C=O) cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ = 4.00 (s, 2H, CH_2), 4.23 (s, 2H, CH_2), 7.25-8.36 (m, 14H, Ar-H) and 9.50 (s, 1H, NH); MS *m\z* 502. Anal. Calcd. for $C_{26}H_{19}ClN_4OS_2$: C, 62.08; H, 3.81; Cl, 7.05; N, 11.14; S, 12.75 %; Found: C, 61.92; H, 4.00; Cl, 6.90; N, 10.98; S, 12.92 %.

2-(2-(Benzylmercapto)-5-cyano-6-phenylpyrimidin-4-ylthio)-N-(4-methoxy phenyl)acetamide (8f)

Yield 67 %. m.p. 172-174 ^{o}C. IR (KBr): 3288 (N-H), 3061 (C-H aromatic), 2924 (C-H aliphatic), 2212 (C-N), 1662 (C=O) cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ = 3.6 (s, 3H, CH_3) 4.00 (s, 2H, CH_2), 4.23 (s, 2H, CH_2), 6.9-8.36 (m, 14H, Ar-H) and 9.50 (s, 1H, NH). MS *m\z* 498.29. Anal. Calcd. for $C_{27}H_{22}N_4O_2S_2$: C, 65.04; H, 4.45; N, 11.24; S, 12.86 %; Found: C, 64.88; H, 4.60; N, 11.02; S, 13.02 %.

2-(5-Cyano-2-(ethylmercapto)-6-phenylpyrimidin-4-ylthio)-N-phenylacetamide (8g)

Yield 62 %. m.p. 160-162 ^{o}C. IR(KBr): 3276 (N-H), 3037 (C-H aromatic), 2943 (C-H aliphatic), 2214 (C-N), 1664 (C=O). Anal. Calcd. for $C_{21}H_{18}N_4OS_2$: C, 62.05; H, 4.46; N, 13.78; S, 15.77 %; Found: C, 62.18; H, 4.27; N, 13.57; S, 15.51 %.

5-Amino-2-ethylmercapto-4-phenyl-6-subistituted thieno[2,3-d]pyrimidines (9a-g): General procedure

Compound (**7**) (0.01 mole), potassium carbonate (0.02 mole) and α-halocarbonyl compounds like chloroacetamide, chloloacetonitrile, ethyl chloroacetate, and p-chloro chloroacetanilide (0.011 mole) in 50 mL ethanol was refluxed for 3 h. The solid product was filtered off, washed with water and ethanol and dried in air.

5-Amino-2-ethylmercapto-4-phenyl-thieno[2,3-*d*]pyrimidine-6-carbonitrile (9a)

The compound was obtained as pale yellow crystals (65 %). m.p. 198-200 ^{o}C. IR (KBr): 3464, 3331 (NH_2), 3227 (N-H tautomer), 3047 (C-H aromatic), 2978 (C-H aliphatic), 2202 (C-N). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.4 (t, 3H, CH_3), 3.2 (q, 2H, CH_2), 4.58 (s, 2H, NH_2), 7.52 (s, 5H, Ar-H). ^{13}C NMR ($CDCl_3$) δ = 171.16, 169.82, 162.75, 148.5, 136, 130.9, 129.17, 128.72, 114.93, 114.74, 25.7, 14.36. MS *m\z* 312. Anal. Alcd. for $C_{15}H_{12}N_4S_2$: C, 57.67; H, 3.87; N, 17.93; S, 20.52 %; Found: C, 57.82; H, 4.06; N, 18.08; S, 19.32 %.

5-Amino-2-ethylmercapto-4-phenyl-thieno[2,3-*d*]pyrimidine-6-carbamide (9b)

The compound was obtained as pale yellow crystals (62 %). m.p. 174-176 ^{o}C. IR (KBr): 3475, 3429 (NH_2), 3327, 3208 (NH_2), 3047 (C-H aromatic), 2965 (C-H aliphatic), 1667 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.4 (t, 3H, CH_3), 3.2(q, 2H, CH_2), 5.35 (s, 2H, NH_2), 6 (s, 2H, NH_2), 7.4-7.6 (m, 5H aromatic). ^{13}C NMR ($CDCl_3$) δ = 170.19, 168, 167.13, 163.07, 146.46, 136.36, 130.58, 128.98, 128.76, 117.31, 94.32, 25.66, 14.44; MS *m\z* 329.8. Anal. Calcd. for $C_{15}H_{14}N_4OS_2$: C, 54.53; H, 4.27; N, 16.96; S 19.41 %; Found: C, 54.70; H, 4.19; N, 17.14; S 19.50 %.

5-Amino-2-ethylmercapto-4-phenyl-N-(p-methoxy-phenyl)-thieno[2,3-*d*]pyrimidine-6-carbamide (9c)

The compound is obtained as yellow crystals (40 %). m.p. 158-160 ^{o}C. IR (KBr): 3472, 3409 (NH_2), 3303 (N-H), 3046 (C-H aromatic), 2969 (C-H aliphatic), 1635 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.4 (t, 3H, CH_3), 3.25 (q, 2H, CH_2), 3.7 (s, 3H, CH_3), 6.3 (s, 2H, NH_2), 6.9, 7.6 (2d, 4H, Ar-H), 7.5, 8.2 (2m, 5H, ArH) 8.9 (s, 1H, NH); MS *m\z* 436.18. Anal. Calcd. for $C_{22}H_{20}N_4O_2S_2$: C, 60.53; H, 4.62; N, 12.83; S, 14.69 %; Found: C, 60.19; H, 4.21; N, 12.65; S, 14.52 %.

5-Amino-N-(4-chlorophenyl)-2-(ethylmercapto)-4-phenyl-thieno[2,3-*d*]pyrimidine-6-carboxamide (9d)

The compound is obtained as orange crystals (50 %). m.p. 188-190 ^{o}C. IR (KBr): 3485,3460 (NH_2), 3292 (N-H), 3046 (C-H aromatic), 2924 (C-H aliphatic), 1636 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, 3H, CH_3), 1.5 (s, 1H, NH), 3.2 (q, 2H, CH_2), 6 (s, 2H, NH_2), 7.2-7.5 (m, 9H, ArH). ^{13}C NMR ($CDCl_3$) δ = 170.46, 163.52, 163.09, 146.8, 136.2, 130.69, 129.54, 129.07, 128.76, 121.86, 117.4, 94.76, 25.71, 14.43. MS *m\z* 440. Anal. Calcd. for $C_{21}H_{17}ClN_4OS_2$: C, 57.20; H, 3.89; Cl, 8.04; N 12.71; S, 14.54 %; Foubd: C, 56.98; H, 4.10; Cl, 7.90; N 12.58; S, 14.70 %.

5-Amino-2-benzylmercapto–4-phenyl-N-(p-chlorophenyl)-thieno[2,3-*d*]pyrimidine-6-carbamide (9e)

The compound is obtained as orange crystals (53 %). m.p. 176-178 ^{o}C. IR (KBr): 3475, 3406 (NH_2), 3313 (N-H), 3046 (C-H aromatic), 2994 (C-H aliphatic), 1643 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.2 (s, 2H, CH_2), 6.5 (s, 2H, NH_2), 7.2-7.7 (m, 14H, ArH), 10.9 (s, 1H, NH). MS *m\z* 502. Anal. Calcd. for $C_{26}H_{19}ClN_4OS_2$: C, 62.08; H, 3.81; Cl, 7.05; N, 11.14; S, 12.75 %; Found: C, 61.90; H, 4.02; Cl, 6.88; N, 10.96; S, 12.92 %.

5-Amino-2-benzylmercapto–4-phenyl-N-(p-methoxyphenyl)-thieno-[2,3-*d*]pyrimidine-6-carbamide (9f)

The compound is obtained as orange crystals (53 %). m.p. 164-166 ^{o}C; IR (KBr): 3466, 3410 (NH_2), 3309 (N-H), 3030 (C-H aromatic), 2945 (C-H aliphatic), 1638 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.6 (s, 3H, CH_3), 4.1 (s, 2H, CH_2), 6.45 (s, 2H, NH_2), 6.8-7.7 (m, 14H, ArH), 11.0 (s, 1H, NH). MS *m\z* 436.18. Anal. Calcd. for $C_{27}H_{22}N_4O_2S_2$: C, 65.04; H, 4.45; N, 11.24; S, 12.86 %; Found: C, 64.88; H, 4.65; N, 11.04; S, 13.02 %.

5-Amino-2-(ethylmercapto)-N,4-diphenylthieno[2,3-*d*]pyrimidine-6-carboxamide (9g)

The crude product was recrystalized from acetic acid to yield yellow crystals (53 %). m.p. 88-90 ^{o}C. IR (KBr): 3603, 3479 (NH_2), 3321 (N-H), 3035 (C-H aromatic), 2955 (C-H aliphatic), 1636 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.45 (t, 3H, CH_3), 3.3 (q, 2H, CH_2), 7.15 (d, 2H, NH_2), 7.35 (m, 10H, 2ArH) and 7.55 (d, 1H, NH). MS *m\z* 405.75. Anal. Calcd. for $C_{21}H_{18}N_4OS_2$: C, 62.05; H, 4.46; N, 13.78; S, 15.77 %; Found: C, 61.83; H, 4.13; N, 13.53; S, 15.58 %.

2-Alkylmercapto-8-oxo-4-phenyl-7-subistitutedpyrimido [4',5':4,5]- thieno[2,3-*d*]pyrimidines (10a-d): General procedure:

Compound (**9**) (0.01 mole), 20 mL of triethyl orthoformate and few drops of glacial acetic acid was refluxed for 2 h. White crystals were formed during the reflux. After cooling the crystals were filtered, washed with ethanol and then dried in air.

2-Ethylmercapto-8-oxo-4-phenyl-(7H)-pyrimido[4',5':4,5]thieno[2,3-*d*]pyrimidine (10a)

The compound was obtained as white crystals (77 %). m.p. 278-280 ^{o}C. IR (KBr): 3431(N-H), 3030 (C-H aromatic), 2967 (C-H aliphatic), 1679 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (t, 3H, CH_3), 3.0 (q, 2H, CH_2), 7.3, 7.5 (2m, 5H, Ar-H), , 7.65 (s, 1H, CH pyrimidine), 9.5 (s, 1H, NH). MS *m\z* 339.5. Anal. Calcd. for $C_{16}H_{12}N_4OS_2$: C, 56.45; H, 3.55; N, 16.46; S, 18.84 %; Found: C, 56.60; H, 3.74; N, 16.62; S, 19.04 %.

2-Ethylmercapto-8-oxo-4-phenyl-7(p-chlorophenyl)pyrimido[4',5':4,5]thieno[2,3-*d*]pyrimidine (10b)

The compound was obtained as white crystals (68 %). m.p. 220-222 ^{o}C. IR (KBr): 3075 (C-H aromatic), 2929 (C-H aliphatic), 1689 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (t, 3H, CH_3), 3.0 (q, 2H, CH_2), 7.3, 7.5, 7.65 (3m, 9H, Ar-H), 8.9 (s, 1H, CH pyrimidine). MS *m\z* 450. Anal. Calcd. for $C_{22}H_{15}ClN_4OS_2$: C, 58.60; H, 3.35; Cl, 7.86; N, 12.42; S, 14.22 %; Found: C, 58.38; H, 3. 05; Cl, 8.04; N, 12.60; S, 14.00 %.

2-Ethylmercapto-8-oxo-4-phenyl-7(methoxyphenyl)pyrimido[4',5':4,5]-thieno[2,3-*d*]pyrimidine (10c)

The compound was obtained as white crystals (68 %). m.p. 164-166 ^{o}C; IR (KBr): 3035 (C-H aromatic), 2976 (C-H aliphatic), 1682 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (t, 3H, CH_3), 3.0 (q, 2H, CH_2), 3.7 (s, 3H, O-CH_3), 6.8, 7.2, 7.5, 7.65 (3m, 9H, Ar-H), 8.8 (s, 1H, CH pyrimidine). MS *m\z* 446. Anal. Calcd. for $C_{23}H_{18}N_4O_2S_2$: C 61.87, H; 4.06; N, 12.55; S, 14.36 %; Found: C 62.04, H; 3.90; N, 12.70; S, 14.50 %.

2-Benzylmercapto-8-oxo-4-phenyl-(7H)-pyrimido[4',5':4,5]-thieno[2,3-*d*]pyrimidine (10d)

The compound was obtained as white crystals (77 %). m.p. 244-246 ^{o}C. IR: 3136 (N-H), 3024 (C-H aromatic), 2953 (C-H aliphatic) and 1671 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.6 (s, 2H, CH_2), 7.3-7.95 (m, 10H, 2ArH), 7.9 (d, 1H, CH pyrimidine) and 8.1 (s, 1H, NH). Anal. Calcd. for $C_{21}H_{14}N_4OS_2$ (402.50): C, 62.67; H, 3.51; N, 13.92; S, 15.93 %; Found: C, 62.48; H, 3.19; N, 13.67; S, 15.67 %.

2-Benzylmercapto-8-oxo-4-phenyl-7(p-chlorophenyl)pyrimido[4',5':-4,5]thieno[2,3-*d*]pyrimidine (10e)

The compound was obtained as white crystals (95 %). m.p. 168-170 ^{o}C; IR (KBr): 3075 (C-H aromatic), 2929 (C-H aliphatic) and 1689 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.05 (s, 2H, CH_2), 7.3-7.7 (m, 14H, Ar-H), 9.2 (s, 1H, CH pyrimidine); MS *m\z* 511.9. Anal. Calcd. for $C_{27}H_{17}ClN_4OS_2$: C, 63.21; H, 3.34; Cl, 6.91; N, 10.92; S, 12.50 %; Found: C, 63.08; H, 3.02; Cl, 6.75; N, 10.74; S, 12.32%.

7-Ethylmercapto-9-phenyl-4-oxo-3-substituted pyrimido[5',4':4,5]thieno[3,2-d]triazines (11a,b): General procedure

Sodium nitrite solution (7 g, 0.1 mol) in water (10 mL) was added drop wise to a solution of (**9d,g**) (0.01 mol) in ice cooled acetic acid with stirring in five min. Then the solution was allowed to stand for 10 h. The solid product was filtered off, dried and recrystalized from ethanol.

7-Ethylmercapto-3,9-diphenyl-4-oxopyrimido[5',4':4,5]thieno[3,2-*d*]triazine (11a)

The compound was obtained as white crystals (95 %). m.p. 190-192 ^{o}C. IR (KBr): 3053 (C-H aromatic), 2968 (C-H aliphatic) and 1693 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55 (t, 3H, CH_3), 3.4 (q, 2H, CH_2) and 7.55-7.7 (m, 10H, 2ArH). Anal. Calcd. for $C_{21}H_{15}N_5OS_2$: C, 60.41; H, 3.62; N, 16.77; S, 15.36 %; Found: C, 60.17; H, 3.34; N, 16.53; S, 15.18 %.

7-Ethylmercapto-9-phenyl-3(4-chlorophenyl)-4-oxopyrimido-[5',4':4,5]thieno[3,2-*d*]triazine (11b)

The compound was obtained as white crystals (77 %). m.p. 218-220 ^{o}C. IR (KBr): 3092 (C-H aromatic), 2952 (C-H aliphatic) and 1691 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (t, 3H, CH_3), 3.3 (q, 2H, CH_2) and 7.35-8.05 (m, 9H, ArH). Anal. Calcd. for $C_{21}H_{14}ClN_5OS_2$: C, 55.81; H, 3.12; Cl, 7.84; N, 15.50; S, 14.19 %, Found: C, 55.68; H, 2.98; Cl, 7.53; N, 15.23; S, 14.07 %.

4-Chloro-7-ethylmercapto-9-phenylpyrimido [5',4':4,5]thieno[3,2-*d*]triazine (12)

To compound (**9a**) (1.3 g, 0.005 mol), dissolved in a mixture of acetic acid (10 mL) and concentrated HCl (7 mL), a 10 % sodium nitrite solution (4 mL, 0.006 mol) was added with stirring during 5 min. The stirring was continued at 5 ^{o}C for 3 h. The precipitate was collected and crystallized from ethanol to yield white plates of (**12**) (62.5 %). m.p. 180–181^{o}C. IR (KBr): 3093 (C-H aromatic), 2950 (C-H aliphatic) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.45(t, 3H ,CH_3), 3.3(q,2H,CH_2), 7.5-8(m, 5H-ArH). ^{13}C NMR ($CDCl_3$) δ = 175.26, 172, 165.87, 153.05, 151.48, 135.27, 132, 130.51, 128.78, 128.31, 115.56, 26.12, 14.27. MS *m/z* 359.5. Anal. Calcd. for $C_{15}H_{10}ClN_5S_2$: C, 50.07; H, 2.80; Cl, 9.85; N 19.46; S, 17.82 %; Found: C, 49.90; H, 3.00; Cl, 10.04; N 19.62; S, 19.02%.

5-Amino-2-ethylmercapto-4-phenyl-6-(1H-tetrazol-5-yl)thieno-[2,3-*d*]pyrimidine (13)

A mixture of compound (**9a**) (1.25 g, 0.004 mol), sodium azide (0.4 g, 0.006 mol), and ammonium chloride (0.32 g, 0.006 mol) in DMF (15 mL) was heated on a water bath for 5 h. The reaction was allowed to cool, diluted with water, and acidified with dilute acetic acid. The solid product was collected and crystallized from ethanol to yield yellow crystals (65 %). m.p. 236–240 ^{o}C. IR (KBr): 3469, 3352 (NH_2), 3142 (N-H), 3063 (C-H aromatic) and 2984 (C-H aliphatic) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.4 (t, 3H, CH_3), 3.2 (q, 2H, CH_2), 6.0 (s, 3H, NH, NH_2) and 7.6-7.7 (m, 5H, ArH). MS *m/z* 353.5. Anal. Calcd. for $C_{15}H_{13}N_7S_2$: C, 50.69; H, 3.69; N, 27.58; S, 18.04 %; Found: C, 50.49; H, 3.52; N, 27.57; S, 17.94 %.

5-Ethoxymethyleneamino-2-ethylmercapto-4-phenylthieno[2,3-*d*]pyrimidine-6-carbonitrile (14)

Compound (**9a**) (1 g, 0.004 mol) in triethyl orthoformate (10 mL) was heated under reflux for 3 h in the presence of acetic acid and then left to cool. The solid product was collected and crystallized from ethanol to yield yellow crystals (67 %). m.p. 112 – 114 ^{o}C. IR (KBr): 3073 (C-H aromatic), 2978 (C-H aliphatic) and 2207 (C-N) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.25, 1.45 (2t, 6H, $2CH_3$), 3.3, 4.25 (2q, 4H, $2CH_2$), 7.5-7.6 (m, 5H, ArH) and 8.1 (s, 1H, CH); MS *m/z* 368. Anal. Calcd. for $C_{18}H_{16}N_4OS_2$: C, 58.67; H, 4.38; N, 15.20; S, 17.40 %; Found: C, 58.54; H, 4.19; N, 14.96; S, 17.27 %.

Acknowledgements

We thank Prof. Dr. Ahmed Abdo Geies Vice-President and Professor of Organic Chemistry Assiut University.

References

[1]Petrie, C. R., Cottam, H. B., Mckernan, P. A., Robins, R. K., Revankar, G. R., *J. Med. Chem*., **1985**, *28,* 1010–1016.

[2]Nasr, M. N., Gineinah, M. M., *Arch. Pharm.,* **2002**, *335,* 289–295.

[3]Baraldi, P. G., Pavani, M. G., Nunez, M., Brigidi, P., Vitali, B., Gambari, R., Romagnoli, R., *Bioorg. Med. Chem.,* **2002**, *10,* 449–456.

[4]Sondhi, S. M., Johar, M., Rajvanshi, S., Dastidar, S. G., Shukla, R., Raghubir, R., Lown, J. W., *Aust. J. Chem.,* **2001**, *54,*69–74.

[5]Chowdhury, A. Z. M. S., Matin, M. M., Anwar, M. N., *Chittagong Univ. Stud. Part II.,* **1997**, *21,*79–83; *Chem. Abstr.,* **1999**, *130,* 237530p.

[6]Schroeder, M. C., Hamby, J. M., Connolly, C. J., Grohar, P. J., Winters, R. T., Barvian, M. R., Moore, C. W., Boushelle, S. L., Crean, S. M., Kraker, A. J., Driscoll, D. L., Vincent, P. W., Elliott, W. L., Lu, G. H., Batley, B. L., Dahring, T. K., Major, T. C., Panek, R. L., Doherty, A. M., Showalter, H. D., *J. Med. Chem.,* **2001**, *44,* 1915.

[7]Baker, B. R., Schaub, R. E., Joseph, J. P., Mc Eroy, F. J., Wiims, J. H., *J. Org. Chem*, **1953**, *18,* 138.

[8]Kamal El-Dean, A. M., *Monatsh. Chem.,* **1998**, *129,* 5, 523-533.

[9]Hassan, Kh. M., Kamal El-Dean, A. M., Youssef, M. S. K., Atta, F. M., Abbady, M. S., *Phosphorus, Sulfur and Silicon,* **1990**, *47,* pp. 283-289.

[10]Hassan, Kh. M., Kamal El-Dean, A. M., Youssef, M. S. K., Atta, F. M., Abbady, M. S., *Phosphorus, Sulfur and Silicon,* **1990**, *47,* 181.

[11]El-Kashef, H. S., Geies, A. A., Kamal El-Dean, A. M., Abdel-Hafez, A. A., *J. Chem. Tech. Biotechnol.,* **1993**, *57,* 15-19.

[12]Abdel-Hafez, A. A., Kamal El-Dean, A. M., Hassan, A. A., El-Kashef, H. S., *Bul. Fac. Sci., Assiut Univ.,* **1993**, *23(1-b),* 93.

[13]Kamal El-Dean, A. M., *Phosphorus, Sulfur and Silicon,* **1994**, *90,* 85.

[14]Abdel Hafez, A. A., Kamal El-Dean, A. M., Hassan, A. A., El-Kashef, H. S., Rault, S., Robba, M., *J. Heterocyclic Chemistry,* **1996**, *33,* 431.

[15]Geies, A. A., Kamal El-Dean, A. M., *Bull. Pol. Acad. Sci., Chem.,* **1997**, *45,* 831.

[16]Kamal El-Dean, A. M., Shaker, R., Abo El-Hassan, A. A., Abdel Latif, F. F., *J. Chin. Chem. Soc.*, **2004**, *51,* 335-345.

[17]Kamal El-Dean, A. M., Radwan, S. M., Zaki, R. M., *Eur. J. Med. Chem.,* **2011**, *46,* 567-578.

[18]Kambe, S., Saito, K., Kishi, H., *Synthesis*, **1979**, *4,* 287.

[19]Khalil, Z. H., Abdel Hafez, A. A., Ahmed, A. A., *Phosphorus, Sulfur and Silicon,* **1989**, *45,* pp. 81-93.

Received: 01.09.2015
Accepted: 18.10.2015.

CORRELATION ANALYSIS OF REACTIVITY IN THE OXIDATION OF SUBSTITUTED BENZALDEHYDES BY BIS[DIPYRIDINESILVER(I)] DICHROMATE

U. Soni[a], D. Yajurvedi[b], S. Vyas[c], O. Prakash[a] and Pradeep K. Sharma[a]*

Keywords: Correlation analysis; chromium(VI); kinetics; mechanism; oxidation; bis[dipyridinesilver(I)] dichromate.

Oxidation of thirty six monosubstituted benzaldehydes by bis[dipyridinesilver(I)] dichromate (BDSD) in dimethylsulphoxide (DMSO), leads to the formation of corresponding benzoic acids. The reaction is of first order with respect to BDSD. A Michaelis-Menten type kinetics was observed with respect to the reactants. The reaction is promoted by hydrogen ions; the hydrogen-ion dependence has the form $k_{obs} = a + b\,[H^+]$. The oxidation of [^{2}H]benzaldehyde (PhCDO) exhibited a substantial primary kinetic isotope effect. The reaction was studied in nineteen different organic solvents and the effect of solvent was analysed using Taft's and Swain's multi-parametric equations. The rates of the oxidation of para- and meta-substituted benzaldehydes showed excellent correlation in terms of Charton's triparametric LDR equation, whereas the oxidation of ortho-substituted benzaldehydes were correlated well with tetraparametric LDRS equation. The oxidation of para-substituted benzaldehydes is more susceptible to the delocalized effect than is the oxidation of ortho- and meta- substituted compounds, which display a greater dependence on the field effect. The positive value of η suggests the presence of an electron-deficient reaction centre in the rate-determining step. The reaction is subjected to steric acceleration by the ortho-substituents. A suitable mechanism has been proposed.

* Corresponding Authors
E-Mail: drpkvs27@yahoo.com
[a] Department of Chemistry, J.N.V. University, Jodhpur, 342 005, India
[b] Department of Chemistry, Raghunath Girls College, Meerut, India
[c] Department of Chemistry, University of Kota, Kota, India

Introduction

Halochromates and dichromates have been used as mild and selective oxidizing reagents in synthetic organic chemistry.[1] Bis[dipyridinesilver (I)] dichromate(BDSD) is also one of such compounds used as mild and selective oxidizing agent in synthetic organic chemistry.[2] We have been interested in kinetics of oxidations by dichromates and have already published a few reports on oxidation by BDSD.[3-6] In continuation of our earlier work, we report in the present article the kinetics of oxidation of some monosubstituted benzaldehydes by BDSD in DMSO as solvent. The major objective of this investigation was to study the structure-reactivity correlation for the substrate undergoing oxidation.

Experimental

Materials

BDSD was prepared by reported method[2] and its purity was checked by an iodometric method. The aldehydes were commercial products. The liquid aldehydes were purified through their bisulfite addition compounds and distilling them, under nitrogen, just before use.[7] The solid aldehydes were recrystallized from ethanol. Deuteriated benzaldehyde (PhCDO) was also prepared by the reported method.[8] Its isotopic purity, as ascertained by its NMR spectrum, was 96±5 %. Due to non-aqueous nature of the solvent, toluene-*p*-sulphonic acid (TsOH) was used as a source of hydrogen ions. Solvents were purified by the usual methods.

Product analysis

The product analysis was carried out under kinetic conditions. In a typical experiment, benzaldehyde (5.25 g, 0.05 mol) and BDSD (7.48 g, 0.01 mol) were made up to 50 mL in DMSO and kept in the dark for *ca*. 15 h to ensure completion of the reaction. The solution was then treated with an excess (200 mL) of a saturated solution of 2,4-dinitrophenylhydrazine in 2 mol dm^{-3} HCl and kept overnight in a refrigerator. The precipitated 2,4-dinitrophenylhydrazone (DNP) was filtered off, dried, weighed, recrystallized from ethanol, and weighed again. The yields of DNP before and after recrystallization were 2.55 g (89 %) and 2.38 g (83 %) respectively. The DNP was found identical (m.p. and mixed m.p.) with the DNP of benzaldehyde. Similar experiments were performed with other alcohols also. The oxidation state of chromium in completely reduced reaction mixtures, determined by an iodometric method was 3.90±0.10.

Kinetic Measurements

The pseudo-first order conditions were attained by maintaining a large excess (× 15 or more) of the alcohol over BDSD. The solvent was DMSO, unless specified otherwise. The reactions were followed, at constant temperatures (±0.1K), by monitoring the decrease in [BDSD] spectrophotometrically at 354 nm. No other reactant or product has any significant absorption at this wavelength. The pseudo-first order rate constant, k_{obs}, was evaluated from the linear (r = 0.990-0.999) plots of

log [BDSD] against time for up to 80 % reaction. Duplicate kinetic runs showed that the rate constants were reproducible to within ±3 %. The second order rate constant, k_2, was obtained from the relation: $k_2 = k_{obs}$ / [aldehyde]. All experiments, other than those for studying the effect of hydrogen ions, were carried out in the absence of TsOH.

Results and discussion

The rates and other experimental data were obtained for all the alcohols. Since the results are similar, only representative data are reproduced here.

Stoichiometry

Oxidation of benzaldehydes by BDSD results in the oxidation of corresponding benzaldehydes. Analysis of products and the stoichiometric determinations indicate the following overall reaction (1).

$$2ArCHO + Cr_2O_7^{2-} + 10H^+ \longrightarrow 2\ ArCOOH + 5H_2O + 2Cr^{3+} \qquad (1)$$

Test for free radicals

The oxidation of benzaldehyde by BDSD, in an atmosphere of nitrogen failed to induce the polymerisation of acrylonitrile. Further, an addition of a radical scavenger, acrylonitrile, had no effect on the rate (Table 1). To further confirm the absence of free radicals in the reaction pathway, the reaction was carried out in the presence of 0.05 mol dm^{-3} of 2,6-di-t-butyl-4-methylphenol (butylated hydroxy-toluene or BHT). It was observed that BHT was recovered unchanged, almost quantitatively.

Rate laws

The reactions are of first order with respect to BDSD. Figure 1 depicts a typical kinetic run. Further, the pseudo-first order rate constant, k_{obs} is independent of the initial concentration of BDSD. The reaction rate increases with increase in the concentration of the aldehydes but not linearly (Table 1).

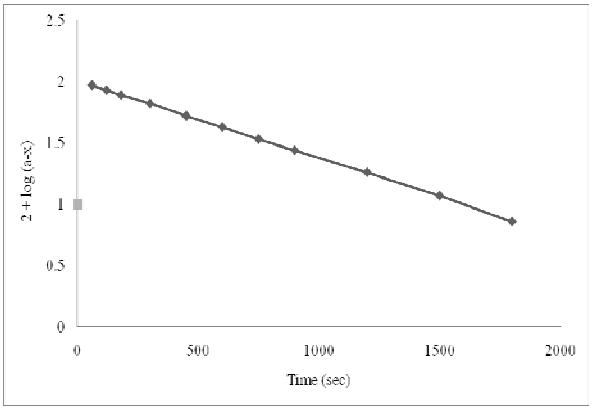


Figure 1. Oxidation of Benzaldehydes by BDSD: A typical kinetic run.

A plot of $1/k_{obs}$ against 1/[Aldehydes] is linear ($r > 0.995$) with an intercept on the rate-ordinate (Figure 2). Thus, Michaelis-Menten type kinetics is observed with respect to the aldehydes. This leads to the postulation of following overall mechanism (2) and (3) and rate law (4).

$$\text{Aldehyde} + \text{BDSD} \overset{K}{\rightleftharpoons} [\text{Complex}] \qquad (2)$$

$$[\text{Complex}] \xrightarrow{k_2} \text{Products} \qquad (3)$$

$$\text{Rate} = \frac{k_2 K [\text{Aldehyde}][\text{BDSD}]}{1 + K[\text{Aldehyde}]} \qquad (4)$$

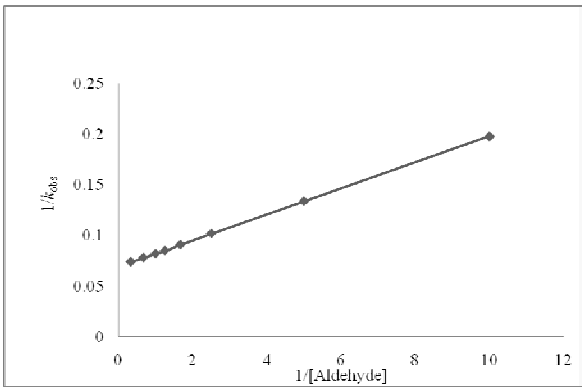


Figure 2. Oxidation of Benzaldehydes by BDSD: A double reciprocal plot.

Table 1. Rate constants for the oxidation of benzaldehyde by BDSD at 298 K.

10^3[BDSD], mol dm^{-3}	[Aldehyde], mol dm^{-3}	[TsOH], mol dm^{-3}	10^4 k_{obs}, s^{-1}
1.0	0.10	0.00	5.06
1.0	0.20	0.00	7.49
1.0	0.40	0.00	9.85
1.0	0.60	0.00	11.0
1.0	0.80	0.00	11.7
1.0	1.00	0.00	12.2
1.0	1.50	0.00	12.8
1.0	3.00	0.00	13.6
2.0	0.40	0.00	9.72
4.0	0.40	0.00	9.20
6.0	0.40	0.00	9.45
8.0	0.40	0.00	9.63
1.0	0.20	0.00	7.74*

*contained 0.001 mol dm^{-3} acrylonitrile

The dependence of reaction rate on the reductant concentration was studied at different temperatures and the values of K and k_2 were evaluated from the double reciprocal plots. The thermodynamic parameters of the complex formation and activation parameters of the decomposition of the complexes were calculated from the values of K and k_2 respectively at different temperatures (Tables 2 and 3).

Table 2. Formation constants for the decomposition of BDSD–Aldehyde complexes and thermodynamic parameters.

Substituent	K dm^3 mol^{-1}				$-\Delta H$	$-\Delta S$	$-\Delta G$
	288 K	298 K	308 K	318 K	kJ mol^{-1}	J mol^{-1} K^{-1}	kJ mol^{-1}
H	6.23	5.42	4.57	3.72	15.5±0.7	30±2	6.63±0.6
p-Me	5.90	5.07	4.30	3.45	16.0±0.8	32±2	6.48±0.6
p-OMe	5.45	4.62	3.85	3.06	17.0±0.7	37±2	6.24±0.6
p-F	5.85	5.02	4.25	3.40	16.1±0.8	33±3	6.45±0.6
p-Cl	6.18	5.38	4.54	3.73	15.3±0.6	30±2	6.61±0.5
p-NO_2	5.92	5.10	4.32	3.51	15.7±0.7	31±2	6.49±0.5
p-CF_3	5.56	4.73	3.92	3.11	17.1±0.8	37±3	6.29±0.6
p-COOMe	5.35	4.55	3.75	2.96	17.4±0.8	38±3	6.19±0.6
p-Br	5.65	4.85	4.05	3.25	16.5±0.7	34±2	6.36±0.6
p-NHAc	6.15	5.31	4.55	3.70	15.2±0.7	29±2	6.60±0.5
p-CN	5.89	5.07	4.30	3.48	15.7±0.7	32±2	6.48±0.5
p-SMe	6.05	5.22	4.41	360	15.6±0.6	31±2	6.55±0.5
p-NMe_2	5.98	5.17	4.38	3.52	15.8±0.8	32±2	6.52±0.6
m-Me	6.12	5.33	4.52	3.65	15.5±0.8	30±3	6.59±0.6
m-OMe	5.58	4.70	3.95	3.10	17.2±0.8	37±3	6.30±0.6
m-Cl	5.67	4.83	4.08	3.20	16.8±0.9	36±3	3.63±0.7
m-Br	5.99	5.20	4.40	3.51	15.9±0.9	32±3	6.53±0.7
m-F	5.94	5.10	4.35	3.48	15.9±0.8	32±2	6.49±0.6
m-NO_2	6.18	5.35	4.55	3.78	14.9±0.5	28±2	6.62±0.4
m-CO_2Me	5.55	4.75	3.90	3.12	17.1±0.7	37±2	6.29±0.6
m-CF_3	5.90	5.10	4.30	3.45	16.0±0.8	32±3	6.48±0.6
m-CN	6.21	5.42	4.55	3.80	15.0±0.5	29±2	6.63±0.4
m-SMe	6.03	5.25	4.45	3.63	15.3±0.7	30±2	6.56±0.6
m-NHAc	5.50	4.71	3.85	3.06	17.4±0.8	38±3	6.27±0.6
o-Me	5.85	5.03	4.20	3.45	15.9±0.6	32±2	6.45±0.4
o-OMe	5.40	4.55	3.80	3.00	17.2±0.7	38±2	6.21±0.6
o-NO_2	5.80	4.95	4.20	3.34	16.3±0.8	34±3	6.42±0.3
o-COOMe	6.20	5.36	4.55	3.75	15.2±0.6	29±2	6.62±0.4
o-NHAc	5.90	5.10	4.26	3.45	16.1±0.7	33±2	6.48±0.6
o-Cl	6.30	5.45	4.68	3.85	14.9±0.6	28±2	6.67±0.5
o-Br	5.36	4.52	3.70	2.95	17.6±0.7	39±2	6.18±0.5
o-I	5.89	5.05	4.30	3.45	15.9±0.7	32±2	6.47±0.6
o-CN	5.68	4.90	4.05	3.28	16.4±0.7	34±2	6.37±0.6
o-SMe	6.08	5.25	4.45	3.60	15.7±0.7	31±2	6.56±0.6
o-F	5.76	4.93	4.15	3.36	16.1±0.6	33±2	6.41±0.5
o-CF_3	5.15	4.36	3.55	2.75	18.3±0.9	42±3	6.07±0.7
PhCDO	5.82	5.01	4.21	3.42	15.9±0.7	32±2	6.44±0.5

Effect of acidity

The reaction is catalysed by hydrogen ions. The hydrogen-ion dependence taking the form: $k_{obs} = a + b\,[H^+]$ (Table 4). The values for a and b for benzaldehyde are $4.94\pm0.31\times10^{-4}$ s^{-1} and $9.30\pm0.51\times10^{-4}$ mol^{-1} dm^3 s^{-1} respectively (r^2 = 0.9883). This suggests that BDSD is protonated is a fast pre-equilibrium and both the protonated and unprotonated forms are reactive oxidizing species.

Kinetic isotope effect

To ascertain the importance of the cleavage of the aldehydic C–H bond in the rate–determining step, oxidation of α,α-dideuterio-benzaldehyde (PhCDO) was studied. Results showed the presence of a substantial primary kinetic isotope effect (Table 3).

Effect of solvents

The oxidation of benzaldehyde was studied in 19 different organic solvents. The choice of solvents was limited by the solubility of BDSD and its reaction with primary and secondary alcohols. There was no reaction with the solvents chosen. Kinetics is similar in all the solvents. The values of k_2 are recorded in Table 5.

The correlation between activation enthalpies and entropies of the oxidation of the thirty- six banzaldehydes is linear (r^2 = 0.9150), indicating the operation of a compensation effect.[9] The value of the isokinetic temperature is 641±33 K. However, according to Exner,[10] an isokinetic relationship between the calculated values of activation enthalpies and entropies is often vitiated by random experimental errors.

Table 3. Rate constants and activation parameters for the decomposition of BDSD-Aldehyde complexes.

Substituents	$10^4 k_2$, dm^3 mol^{-1} s^{-1}				ΔH^*	$-\Delta S^*$	ΔG^*
	288 K	298 K	308 K	318 K	kJ mol^{-1}	J mol^{-1} K^{-1}	kJ mol^{-1}
H	5.58	14.4	36.0	86.4	67.0±0.3	75±1	89.2±0.3
p-Me	12.6	30.6	74.7	171	63.8±0.5	79±2	87.3±0.4
p-OMe	28.8	69.3	162	360	61.6±0.3	80±1	85.3±0.2
p-F	5.76	15.3	38.7	95.4	68.6±0.4	69±1	89.1±0.3
p-Cl	3.42	9.27	23.9	59.4	69.9±0.8	69±1	90.3±0.2
p-NO_2	0.22	0.65	1.89	5.31	78.3±0.7	63±2	96.8±0.6
p-CF_3	0.67	1.98	5.31	14.4	75.0±0.6	65±2	94.2±0.4
p-COOMe	0.92	2.52	7.02	18.0	73.2±0.6	69±2	93.5±0.5
p-Br	3.36	9.00	23.4	58.4	70.0±0.5	69±2	90.4±0.4
p-NHAc	12.9	32.4	78.3	180	64.4±0.2	77±1	87.2±0.2
p-CN	0.39	1.17	3.33	9.00	77.1±0.3	62±1	95.4±0.2
p-SMe	15.3	38.7	92.7	207	63.6±0.1	78±1	86.8±0.1
p-NMe_2	144	306	666	1350	54.5±0.5	91±2	81.6±0.4
m-Me	10.8	26.1	63.9	144	63.4±0.5	82±2	87.7±0.4
m-OMe	12.6	29.7	70.2	153	61.0±0.4	89±1	87.4±0.3
m-Cl	1.71	4.68	12.6	29.7	70.2±0.5	73±2	91.9±0.4
m-Br	1.70	4.59	11.7	28.8	69.8±0.6	75±2	92.0±0.4
m-F	2.25	6.03	15.3	37.8	69.0±0.3	76±1	91.4±0.3
m-NO_2	0.14	0.45	1.26	3.60	79.5±0.5	62±2	97.8±0.4
m-CO_2Me	0.81	2.25	6.21	16.2	73.6±0.6	68±2	93.8±0.5
m-CF_3	0.54	1.53	4.32	11.7	75.6±0.7	65±2	94.7±0.6
m-CN	0.27	0.81	2.25	6.30	77.2±0.6	65±2	96.3±0.5
m-SMe	7.83	18.9	46.8	99.9	62.6±0.6	88±2	88.5±0.5
m-NHAc	6.84	17.1	41.4	96.3	64.6±0.4	82±1	88.8±0.3
o-Me	57.6	126	279	567	55.7±0.4	95±1	83.8±0.3
o-OMe	73.8	162	360	747	56.4±0.5	90±2	83.2±0.4
o-NO_2	0.45	1.35	3.51	9.36	74.1±0.5	71±2	95.1±0.5
o-COOMe	3.51	8.91	21.6	51.3	65.5±0.4	84±1	91.4±0.3
o-NHAc	93.6	198	422	846	53.5±0.4	98±1	82.7±0.3
o-Cl	14.4	33.3	77.4	171	60.4±0.5	90±2	87.1±0.4
o-Br	18.0	43.2	97.2	207	59.5±0.1	91±1	86.5±0.3
o-I	29.7	67.5	144	306	56.5±0.4	97±1	85.4±0.3
o-CN	1.02	2.79	7.29	18.0	70.4±0.2	77±1	93.3±0.2
o-SMe	92.7	202	425	855	53.9±0.1	97±1	82.7±0.1
o-F	9.90	24.3	59.4	135	64.0±0.4	81±1	87.9±0.3
o-CF_3	7.83	18.9	43.2	95.4	60.9±0.2	93±1	88.6±0.2
PhCDO	0.92	2.52	6.70	16.8	71.3±0.4	75±1	93.5±0.3
k_H/k_D	6.07	5.71	5.37	5.14			

Exner suggested an alternative method for establishing the isokinetic relationship. Exner's plot between log k_2 at 288 K and at 318 K was linear (r = 0.9992). The value of isokinetic temperature evaluated from the Exner's plot is 731±41 K. The linear isokinetic correlation implies that all the alcohols are oxidized by the same mechanism and the changes in the rate are governed by changes in both the enthalpy and entropy of activation.

Table 4. Dependence of the reaction rate on hydrogen–ion concentration.

[TsOH], mol dm^{-3}	0.10	0.20	0.40	0.60	0.80	1.00
$10^4 k_{obs}$/s^{-1}	5.29	6.93	8.82	9.81	12.6	14.4

[Benzaldehyde] 0.10 mol dm^{-3} ; [BDSD] 0.001 mol dm^{-3} ; Temp. 298 K.

The rate constants k_2, in eighteen solvents (CS_2 was not considered as the complete range of solvent parameters was not available) were correlated in terms of linear solvation energy relationship (6) of Kamlet et al.[11]

$$\log k_2 = A_0 + p\pi^* + b\beta + a\alpha \quad (6)$$

In this equation, π^* represents the solvent polarity, β the hydrogen bond acceptor basicities and α is the hydrogen bond donor acidity. A_0 is the intercept term. It may be mentioned here that out of the 18 solvents, 13 has a value of zero for α. The results of correlation analyses terms of equation (6), a biparametric equation involving π^* and β, and separately with π^* and β are given below (7) - (10).

$$\log k_2 = -3.69 + 1.60\ (\pm 0.20)\pi^* + 0.20(\pm 0.17)\beta + 0.14(\pm 0.15)\alpha \quad (7)$$

$R^2 = 0.8610$; $sd = 0.19$; $n = 18$; $\psi = 0.42$

$$\log k_2 = -3.72 + 1.65(\pm 0.19)\pi^* + 0.16(\pm 0.15)\beta \quad (8)$$

$R^2 = 0.8434$; $sd = 0.19$; $n = 18$; $\psi = 0.42$

$$\log k_2 = -3.69 + 1.69(\pm 0.19)\pi^* \quad (9)$$

$r^2 = 0.8334$; $sd = 0.19$; $n = 18$; $\psi = 0.42$

$$\log k_2 = -2.76 + 0.45(\pm 0.36)\beta \quad (10)$$

$r^2 = 0.0880$; $sd = 0.44$; $n = 18$; $\psi = 0.98$

Kamlet's[11] triparametric equation explain *ca*. 86% of the effect of solvent on the oxidation. However, by Exner's criterion the correlation is not even satisfactory [cf.(7)]. The major contribution is of solvent polarity. It alone accounted for *ca*. 83 % of the data. Both β and α play relatively minor roles.

The data on the solvent effect were also analysed in terms of Swain's equation[13] of cation- and anion-solvating concept of the solvents (11).

$$\log k_2 = aA + bB + C \quad (11)$$

Here A represents the anion-solvating power of the solvent and B the cation-solvating power. C is the intercept term. ($A + B$) is postulated to represent the solvent polarity. The rates in different solvents were analysed in terms of equation (8), separately with A and B and with ($A + B$).

$$\log k_2 = 0.64 + (\pm 0.05)A + 1.73\ (\pm 0.03)B - 3.92 \quad (12)$$

$R^2 = 0.9938$; $sd = 0.04$; $n = 19$; $\psi = 0.08$

$$\log k_2 = 0.40\ (\pm 0.57)\ A - 2.73 \quad (13)$$

$r^2 = 0.0274$; $sd = 0.46$; $n = 19$; $\psi = 1.01$

$$\log k_2 = 1.68\ (\pm 0.12)\ B - 3.71 \quad (14)$$

$r^2 = 0.9225$; $sd = 0.13$; $n = 19$; $\psi = 0.29$

$$\log k_2 = 1.37 \pm 0.14(A+B) - 3.88 \quad (15)$$

$r^2 = 0.8456$; $sd = 0.18$; $n = 19$; $\psi = 0.40$

The rates of oxidation of benzaldehyde in different solvents showed an excellent correlation in Swain's equation (cf. equation 12) with the cation-solvating power playing the major role. In fact, the cation-solvation alone account for *ca*. 92 % of the data. The correlation with the anion-solvating power was very poor. The solvent polarity, represented by ($A + B$), also accounted for *ca*. 85 % of the data. In view of the fact that solvent polarity is able to account for *ca*. 89 % of the data, an attempt was made to correlate the rate with the relative permittivity of the solvent. However, a plot of log k_2 against the inverse of the relative permittivity is not linear ($r^2 = 0.5453$; $sd = 0.32$; $\psi = 0.69$).

Correlation analysis of reactivity

The effect of structure on reactivity has long been correlated in terms of the Hammett equation[14] or with dual substituent-parameter equations.[15,16] In the late 1980s, Charton[17] introduced a triparametric LDR equation for the quantitative description of structural effects on chemical reactivities. This triparametric equation results from the fact that substituent types differ in their mode of electron delocalization.

$$\log k_2 = L\sigma_l + D\ \sigma_d + R\ \sigma_e + h \quad (16)$$

Here, σ_l is a localized (field and/or inductive) effect parameter, σ_d is the intrinsic delocalized electrical effect parameter when active site electronic demand is minimal and σ_e represents the sensitivity of the substituent to changes in electronic demand by the active site. The latter two substituent parameters are related by equation (17).

$$\sigma_D = \eta\sigma_e + \sigma_d \quad (17)$$

Here η represents the electronic demand of the reaction site and is given by $\eta = R/D$, and σ_D represents the delocalized electrical parameter of the diparametric LD equation.

Table 5. Solvent effect on the oxidation of benzaldehyde by BDSD at 298 K.

Solvents	*K*	k_{obs}, s^{-1}
Chloroform	5.45	44.3
$ClCH_2CH_2Cl$	6.35	53.7
CH_2Cl_2	5.58	41.7
DMSO	5.42	144
Acetone	5.54	43.7
DMF	5.63	83.2
Butanone	4.92	29.5
Nitrobenzene	4.23	60.3
Benzene	5.56	14.8
Cyclohexane	5.50	1.78
Toluene	5.33	11.5
Acetophenone	5.12	66.1
THF	5.33	20.4
t-Butylalcohol	5.90	18.6
1,4-Dioxane	5.15	21.9
1,2-Dimethoxyethane	4.83	13.5
CS_2	5.16	5.89
Acetic acid	5.05	7.59
Ethyl acetate	5.11	17.0

Table 6. Temperature dependence for the reaction constants for the oxidation of substituted benzaldehydes by BDSD.

T/K	$-L$	$-D$	$-R$	S	η	R^2	sd	ψ	P_D	P_S
para substituted										
288	1.71	2.07	1.38	-	0.67	0.9999	0.007	0.01	54.8	-
298	1.61	1.98	1.23	-	0.62	0.9998	0.005	0.02	55.2	-
308	1.53	1.89	1.17	-	55.3	0.9989	0.002	0.04	55.3	-
318	1.44	4.80	1.02	-	0.57	0.9999	0.004	0.09	55.6	-
meta substituted										
288	2.09	1.63	1.20	-	0.74	0.9997	0.004	0.02	43.8	-
298	1.96	1.53	1.06	-	0.69	0.9998	0.006	0.02	43.8	-
308	1.90	1.45	0.99	-	0.68	0.9998	0.008	0.02	44.3	-
318	1.79	1.33	0.80	-	0.60	0.9998	0.007	0.02	42.6	-
ortho substituted										
288	1.90	2.07	1.48	1.27	0.71	0.9999	0.006	0.01	52.1	24.2
298	1.79	1.96	1.45	1.17	0.74	0.9998	0.004	0.02	52.3	23.8
308	1.72	1.89	1.34	1.08	0.73	0.9989	0.005	0.04	52.4	23.0
318	1.63	1.79	1.31	0.99	0.73	0.9999	0.004	0.01	52.3	22.4

For *ortho*-substituted compounds, it is necessary to account for the possibility of steric effects and Charton,[17] therefore, modified the LDR equation to generate the LDRS equation (17).

$$\log k_2 = L\sigma_I + D\sigma_d + R\sigma_e + S\upsilon + h \qquad (18)$$

where υ is the well known Charton's steric parameter based on Van der Waals radii.[18]

The rates of oxidation of ortho-, mata-, and para-substituted benzaldehydes show an excellent correlation in terms of the LDR/LDRS equations (Table 6). We have used the standard deviation (sd), the coefficient of multiple determination (R^2), and Exner's[15] parameter, ψ, as the measures of goodness of fit.

The comparison of the L and D values for the substituted benzaldehydes showed that the oxidation of para-substitued is more susceptible to the delocalization effect than to the localized effect. However, the oxidation of ortho- and meta-substituted compounds exhibited a greater dependence on the field effect. In all cases, the magnitude of the reaction constants decreases with an increase in the temperature, pointing to a decrease in selectivity with an increase in temperature.

All three regression coefficients, L, D and R, are negative indicating an electron-deficient carbon centre in the activated complex for the rate-determining step. The positive value of η adds a negative increment to σ_d, reflecting the electron-donating power of the substituent and its capacity to stabilize a cationic species. The positive value of S indicates that the reaction is subject to steric acceleration by an *ortho*-substituent.

To test the significance of localized, delocalized and steric effects in the ortho-substituted benzaldehydes, multiple regression analyses were carried out with (i) σ_I, σ_d and σ_e (ii) σ_d, σ_e and υ and (iii) σ_I , σ_e and υ. The absence of significant correlations showed that all the four substituent constants are significant.

$$\log k_2 = -1.55\ (\pm 0.43)\ \sigma_I - 2.03\ (\pm 0.29)\sigma_d - 3.72\ 1.94)\ \sigma_e - 2.45 \qquad (19)$$
$$R^2 = 0.7437;\ sd = 0.40;\ n = 12;\ \psi = 0.58$$

$$\log k_2 = -2.13\ (\pm 0.46)\ \sigma_d - 20.3\ (\pm 2.84)\sigma_e + 0.88\ (\pm 0.52)\upsilon - 3.39 \qquad (20)$$
$$R^2 = 0.8630;\ sd = 0.30;\ n = 12;\ \psi = 0.42$$

$$\log k_2 = -2.08\ (\pm 0.83)\ \sigma_I - 0.43\ (\pm 3.99)\ \sigma_e + 1.33(\pm 0.75)\upsilon - 2.43 \qquad (21)$$
$$R^2 = 0.4924;\ sd = 0.57;\ n = 12;\ \psi = 0.81$$

Similarly in the cases of the oxidation of para- and meta-subsituted benzaldehydes, multiple regression analyses indicated that both localization and delocalization effects are significant. There is no significant collinearity between the various substituents constants for the three series.

The percent contribution[18] of the delocalized effect, P_D, is given by following equation (22).

$$P_D = (|D| \times 100)/(|L| + |D|) \qquad (22)$$

Similarly, the percent contribution of the steric parameter[25] to the total effect of the substituent, P_S, was determined by using equation (23).

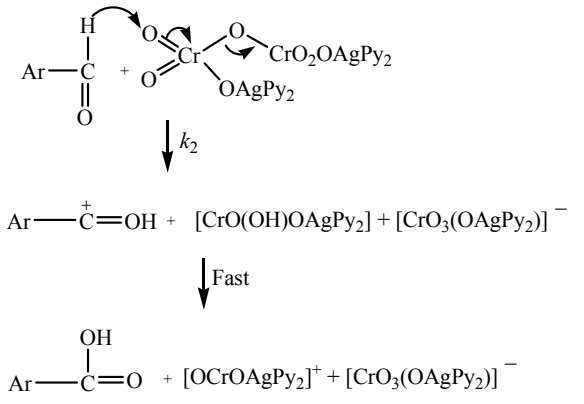
$$P_S = (|S| \times 100)/(|L| + |D| + |S|) \qquad (23)$$

The values of P_D and P_S are also recorded in Table 6. The value of P_D for the oxidation of *para*-substituted benzaldehydes is *ca.* 55 % whereas the corresponding values for the *meta*- and *ortho*-sobstituted aldehydes are *ca.* 43 and 52 %, respectively. This shows that the balance of localization and delocalization effects is different for differently substituted benzaldehydes. The less pronounced resonance effect from the *ortho*- position than from the *para*-position may be due to the twisting away of the alcoholic group from the plane of the benzene ring. The magnitude of the P_S value shows that the steric effect is significant in this reaction.

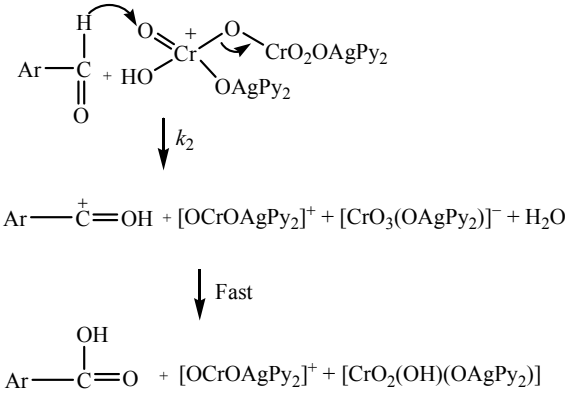
The positive value of *S* showed a steric acceleration of the reaction. This may be explained on the basis high ground state energy of the sterically crowded alcohols. Since the crowding is relieved in the in the product aldehyde as well as the transition state leading to it, the transition state energy of the crowded and un-crowded alcohols do not differ much and steric acceleration, therefore results.

Mechanism

A hydrogen abstraction mechanism leading to the formation of the free radicals is unlikely in view of the failure to induce polymerization of acrylonitrile and no effect of the radical scavenger on the reaction rate. The presence of a substantial kinetic isotope effect confirms the cleavage of an aldehydic –C-H bond in the rate-determining step. The negative values of the localization and delocalization electrical effects i.e. of *L*, *D* and *R* points to an electron-deficient reaction centre in the rate-determining step. It is further supported by the positive value of η, which indicates that the substituent is better able to stabilize a cationic or electron- deficient reactive site. Therefore, a hydride-ion transfer in the rate-determining step is suggested. The hydride-ion transfer mechanism is also supported by the major role of cation-solvating power of the solvents. (Schemes 1 and 2).



Scheme 1. Acid-independent pathway.



Scheme 2. Acid-dependent pathway.

The observed negative value of entropy of activation also supports the proposed mechanism. As the charge separation takes place in the transition state, the charged ends become highly solvated. This results in an immobilization of a large number of solvent molecules, reflected in the loss of entropy.[19]

Initially Cr(VI) is reduced to Cr(IV). It is likely to react with another Cr(VI) to generate Cr(V) which is then reduced in a fast step to the ultimate product Cr(III). Such a sequence of reactions in Cr(VI) oxidations is well known.[20]

Conclusion

The reaction is proposed to proceed through a hydride-ion transfer from aldehyde to the oxidant in the rate-determining step. It has also been observed that an α-C-H bond is cleaved in the rate-determining step. Both unprotonated and protonated forms of BDSD are the reactive oxidising species.

Acknowledgements

Thanks are due to UGC, New Delhi for financial support in the form of BSR One Time Grant (to PKS) CSIR, New Delhi for awarding SRF (to US) and to Professor Kalyan K. Banerji for constructive criticism.

References

[1]Corey, E. J., Suggs, W. J. *Tetrahedron Lett.*, **1975**, 2647; Guziec, F. S., Luzio, F. A. *Synthesis*, **1980,** 691; Bhattacharjee, M. N., Choudhuri , M. K., Dasgupta, H. S., Roy, N., Khathing, D. T. *Synthesis*, **1982**, 588; Balasubramanian, K., Prathiba, V. *Indian J. Chem.*, **1986**, *25B*, 326; Pandurangan, A., Murugesan, V., Palamichamy, P. *J. Indian Chem. Soc.*, **1995**, *72*, 479.

[2]Firouzabadi, H., Sardarian, A., Giaribi, H., *Synth. Commun.*, **1984**, *14*, 89.

[3]Meena, A. K., Daiya, A., Banerji, J., Sajo, I. E., Kotai, L., Sharma, V., *J. Indian Chem. Soc.*, **2011**, *88*, 1893.

[4]Meena, A. K., Khatri, J., Banerji, J., Bhagmar, M., Sharma, I. K., Sharma, V., *J. Chem. Asia*, **2011**, *2(4)* 258.

[5]Sharma, P. K. *Int. J. Chem.*, **2013**, *2(3)* 294.

[6]Mathur, L., Ranga, V., Goswami, G., Agarwal, S., Sharma, P. K., *Eur. Chem. Bull.*, **2014**, *3(8),* 823.

[7]Kalpan, J., *J. Am. Chem. Soc.*, **1958**, *80*, 2639.

[8]Wiberg, *K. B*., *J. Am. Chem. Soc.*, **1954**, *76*, 5871.

[9]Liu, L., Q-X Guo, *Chem. Rev.*, **2001**, *101*, 673

[10]Exner, O., *Collect. Chem. Czech. Commun.*, **1977**, *38*, 411.

[11]Kamlet, M. J., Abboud, J. L..M., Abraham, M. H. Taft, R.W., *J. Org. Chem.*, **1983**, *48*, 2877.

[12]Exner, O., *Collect. Chem. Czech. Commun.*, **1966**, *31*, 3222.

[13]Swain, C. G., Swain, M. S., Powel, A. L., Alunni, S., *J. Am. Chem. Soc.*, **1983**, *105*, 502.

[14]Johnson, C. D. *The Hammett equation*, University Press, Cambridge, **1973**, 78.

[15]Dayal, S. K., Ehrenson, S., Taft, R. W., *J. Am. Chem. Soc.*, **1974**, *94*, 9113.

[16]Swain, C. G., Unger, S. H., Rosenquest, N. R. Swain, M. S., *J. Am. Chem. Soc.*, **1983**, *105*, 492.

[17]Charton, M., Charton, B., *Bull. Soc. Chim. Fr.*, **1988**, 199 references cited therein.

[18]Charton, M., *J. Org. Chem.*, **1975**, *40*, 407.

[19]Gould, E. S., *Mechanism & structure in organic chemistry*, Holt, Rinehart & Winston Inc., New York, **1964**.

[20]Wiberg, K. B., Richardson, W. H., *Oxidation in organic chemistry*, Vol. *5A*, Academic Press, New York, **1965**.

Received: 01.10.2015.
Accepted: 24.10.2015.