SYNTHESIS AND STRUCTURE OF 3,4,5-TRIHYDROXY-5-(4-NITROPHENYL)IMIDAZOLIDIN-2-ONE

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4-Nitrophenylglyoxal reacts with *N*-hydroxyurea both in water and in acetic acid forming the mixture of diastereomers of 3,4,5-trihydroxy-5-(4-nitrophenyl)imidazolidin-2-one. The diastereomer with *cis*-orientation of OH-groups dominates. In the acetic acid medium, 4-nitrophenylglyoxal reacts with 2-methylfuran selectively yielding 2-hydroxy-2-(5-methylfuran-2-yl)-1-(4-nitrophenyl)ethanone.

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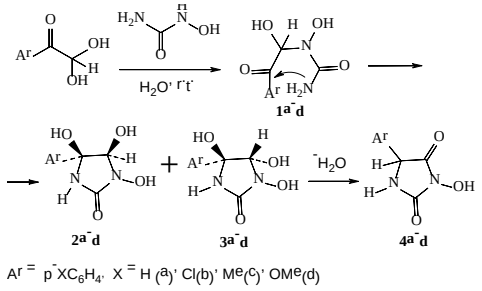
INTRODUCTION

Arylglyoxals are important precursors in the forming of some heterocyclic compounds[1-4] but the investigation of such interesting chemical properties of arylglyoxals, as their interaction with N-hydroxyurea[5] and with activated furans,[6] has just recently begun and needs to be continued.

Interaction of arylglyoxals with N-hydroxyurea in aqueous medium occurs in three stages and involves the formation of acyclic N-hydroxyureas (**1**) at the first stage, 5-aryl-3,4,5-trihydroxyimidazolidin-2-ones (**2** and **3**) at the second stage and 5-aryl-3-hydroxyimidazolidine-2,4-diones (5-aryl-3-hydroxyhydantoins) (**4**) at the third stage[5] (Scheme 1).

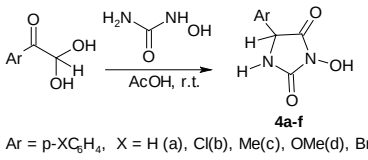


Scheme 1. Arylglyoxal's interaction with *N*-hydroxyurea in aqueous medium[5]

In this case, the product's identity depends on arylglyoxal's nature. 4-Tolylglyoxal and 4-anisylglyoxal form acyclic ureas **1c**, **1d**, and 5-aryl-3-hydroxyhydantoins **4c**, **4d**.[5] Phenylglyoxal usually gives 3-hydroxy-5-phenylhydantoin **4a**, but if this reaction occurs at 10–20°C without further heating, the mixture of 3,4,5-trihydroxy-5-phenylimidazolidines (**2a** and **3a**) and 3-hydroxy-5-phenylhydantoin (**4a**) is formed. Interaction of 4-chlorophenylglyoxal with N-hydroxyurea at the room temperature selectively yields the main diastereomer of 5-(4-chlorophenyl)-3,4,5-trihydroxyimidazolidin-2-one (**2b**) with the *cis* orientation of hydroxyl groups at C-4,5 carbon atoms.[5,7] Careful heating of the reaction mixture leads to the receiving of 5-(4-chlorophenyl)-3-hydroxyhydantoin (**4b**).

5-Aryl-3,4,5-trihydroxyimidazolidin-2-ones (**2a**,**3a**,**2b**,**3b**) are easily converted into 5-aryl-3-hydroxyhydantoins (**4a** and **4b**) under heating in water, acetonitrile or dichloromethane.

The interaction in the acetic acid medium during one day (as described in the referenced procedure[7]) of such arylglyoxals as phenyl-, 4-bromophenyl-, 4-chlorophenyl-, 4-fluorophenyl-, 4-methoxyphenyl- and 4-methylglyoxal with N-hydroxyurea gets 5-aryl-3-hydroxyhydantoins **4a-f** (Scheme 2) selectively.



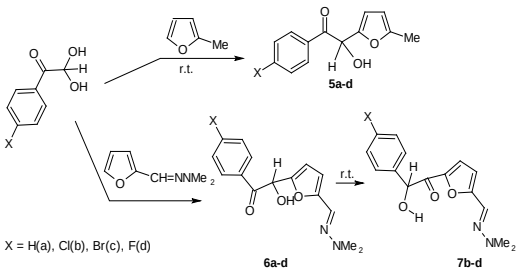
Scheme 2. Synthesis of 5-aryl-3-hydroxyhydantoins **4a-f** in acetic acid medium[7]

But the interaction of 4-nitrophenylglyoxal with N-hydroxyurea has not been investigated yet.

As it is known, arylglyoxals interaction with furan derivatives at the room temperature can proceed in two ways, which are a little bit different. Phenylglyoxal and 4-X-phenylglyoxals (X= F, Cl, Br) react with 2-methylfuran yielding only α-benzoins (**5a-d**) (Scheme 3).[6,8]

Similarly, phenylglyoxal and 4-fluorophenylglyoxal reacts with N,N-dimethylhydrazone of furan-2-carbaldehyde yielding α-benzoins (**6a,d**).[6,8] But it has been shown, that at

the room temperature 4-chlorophenylglyoxal and 4-bromophenylglyoxal forms β-benzoins (**7b,c**)[5,6] via primary formation α-benzoins (**6b,c**). α-Benzoins(**6d**) spontaneously isomerizes into β-benzoins (**7d**) at the room temperature during one month.[8]



Scheme 3. Synthesis of benzoins **5a-d**, **6a-d**,**7b-d**[6,8]

4-Nitrophenylglyoxal's interaction with both 2-methylfuran and N-hydroxyurea has remained not investigated. This arylglyoxal has a high activity due to the presence of 4-NO_2 moiety, a strong electronegative substituent. It might cause a different course of the described reaction.

As it was shown before, arylglyoxals' interaction with N-hydroxyurea[2] and furans[6,8-10] have some differences which depend on the nature of the substituting group in arylglyoxal. But it wasn't clear at all what products would be received if arylglyoxal had a strong electronegative substituting group, such as, for example, nitro group. That's why we decided to fill in this gap.

So, the first goal of our present research was to investigate both the interaction of 4-nitrophenylglyoxal with N-hydroxyurea in aqueous medium and acetic acid medium. The second goal was to investigate the interaction of 4-nitrophenylglyoxal with 2-methylfuran in the same mediums.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian VXP-300 spectrometer and Varian Jemini 400 spectrometer (300 and 400 MHz, respectively). ^{13}C NMR spectra were recorded on a Varian VXP-300 spectrometer (75 MHz). The solvents were DMSO-d6 (compounds **2g**, **3g**, **5e**) and $CDCl_3$ (compound **5e**).^{1}H NMR chemical shifts were reported relative to the residual solvent protons as an internal standard ($(CD_3)_2SO$: 2.50 ppm) or with TMS as an internal standard (in $CDCl_3$). Solvent carbon atoms served as an internal standard for ^{13}C NMR spectra ($(CD_3)_2SO$: 39.32 ppm; $CDCl_3$: 77.16 ppm). Mass spectra were recorded on a VG 70-70EQ mass spectrometer in fast atom bombardment mode (FAB). The solvents were purified and dried according to the standard procedures.

N-Hydroxyurea[11] was obtained according to published procedures.

4-Nitrophenylglyoxal hydrate was obtained according to the standard procedure by 4-nitroacetophenone oxidation by H_2SeO_3 in boiling AcOH for 2h, the removing of AcOH and the crystallization of the residue from boiling water, as a yellow powder, mp 87–89ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.66 (1H, t, J = 6.8 Hz, CH(OH)2); 7.03 (2H, d, J = 6.8 Hz, CH(OH)$_2$); 8.29 (2H, d, J = 9.2 Hz, H Ar); 8.34 (2H, d, J = 9.2 Hz, H Ar).

Preparation of cis- and trans-3,4,5-trihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones 2g, 3g in aqueous medium.

4-Nitrophenylglyoxal hydrate (217 mg, 1.101 mmol) was dissolved in boiling water (10 mL), after cooling to 14ºC a solution of N-hydroxyurea (93 mg, 1.223 mmol) in water (5 ml) was added at stirring. The reaction solution was maintained at 14ºC for 25h, then the obtained precipitate was filtered off, washed out with cold water (2 mL), dried at 14ºC under vacuum (3 mmHg), yielding 114 mg (38%) cis-diastereomer (4S,5S)-3,4,5-trihydroxy-5-(4-nitrophenyl)-imidazolidin-2-one hydrate (2g, purity 97%) as yellow crystals, m.p. 132–133 ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ= 4.55 (1H, d, J = 7.5 Hz, CHOH); 6.49 (1H, s, OH); 6.63 (1H, d, J = 7.5 Hz, CHOH); 7.75 (2H, d, J = 8.7 Hz, C(2)H, C(6)H Ar); 8.24 (1H, s, NH); 8.26 (2H, d, J = 8.7 Hz, C(3)H, C(5)H Ar); 9.13 (1H, s, NOH). ^{13}C NMR (75 MHz, DMSO-d_6) : δ = 82.6 (C-4 imidazolidine); 89.4 (C-5 imidazolidine); 123.4, 127.6 (C-2 ,C-6, C-3, C-5 Ar); 147.3 (C-1 Ar); 149.9 (C-4 Ar (C–NO2)); 159.5 (C=O). ^{13}C NMR (75 MHz, APT mode, DMSO-d_6): δ = a) CH: 82.6 (C-4 (CHOH) imidazolidine); 123.4 (C-2 ,C-6, Ar); 127.6 (C-3, C-5 Ar); b) Cq, C=O: 89.4 (C-5 imidazolidine); 147.2 (C-1 Ar); 149.8 (C-4 Ar (C–NO_2)); 159.5 (C=O). MS (FAB), m/z 256 $[M+H]^+$ (77); 210 (13); 195 (18); 106 (87); 88 (100). Anal. Calc. for $C_9H_9N_3O_6 \bullet H_2O$: C 39.57; H 4.06; N 15.38. Found: C 39.52; H 4.25; N 15.26.

The filtrate was concentrated under vacuum (2 mmHg) at 16ºC to the volume of 7 mL, the obtained precipitate was filtered off, dried under vacuum (2 mmHg), resulting 93 mg (31%) mixture diastereomers **2g** and **3g** in the molar ratio 61:39 (^{1}H NMR).

The second filtrate was concentrated under vacuum (2 mmHg) at 16ºC to volume 2.5 ml, the obtained precipitated was filtered off, dried under vacuum (2 mmHg), giving 40 mg (13%) mixture diastereomers 2g and 3g in molar ratio 59:41 (1H NMR).

(4*R*,5*S*)-3,4,5-Trihydroxy-5-(4-nitrophenyl)imidazolidin-2-one hydrate (3g), *trans*-diastereomer

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.91 (1H, d, *J* = 5.4 Hz, CHOH); 6.56 (1H, d, *J* = 5.4 Hz, CHOH); 6.85 (1H, s, OH); 7.63 (2H, d, J = 8.4 Hz, C(2)H, C(6)H Ar); 8.17 (1H, s, NH); 8.21 (2H, d, J = 8.4 Hz, C(3)H, C(5)H Ar); 9.16 (1H, s, NOH).

Crystals of the compound **2g** were grown from aqueous solution during the reaction. The studied crystal was monoclinic, $C_9H_{11}N_3O_7$, at 20 °C, *a* = 11.983(5), *b* = 6.988(4), *c* = 13.156(7) Å, β = 90.91(4)°, *V* = 1101.6(10) Å^3, M_r = 273.21, *Z* = 4, space group P2$_1$/c, $d_{calc.}$= 1.647 gcm^3, μ (MoK_α)=0.144 mm^{-1}, *F*(000) = 568. X-ray structural study of compound 2g was performed on an Xcalibur 3 automatic four-circle diffractometer (MoKα-radiation, graphite monochromator, Sapphire-3 CCD detector, ω-scanning, $2\theta_{max}$ = 50º). The structure was solved by the conjugate

gradient technique with the SHELXD12 software and refined by full matrix method of least squares in anisotropic approximation for non-hydrogen atoms, using the SHELXL12 software. Positions of hydrogen atoms were located from the difference electron density maps and further included into refinement in riding model approximation with $U_{iso}(H) = nU_{eq}$ with n =1.5 for methyl groups and n = 1.2 for remaining H-atoms. Refinement against F2 in an anisotropic approximation for non-hydrogen atoms by a full matrix least-squares method for 1939 reflections was carried out to wR2=0.147 (*R1*=0.092 for 635 reflections with $F>4\sigma(F)$, S = 0.911).

The atomic coordinates, molecular geometry parameters, and crystallographic data of compound **2g** were deposited at the Cambridge Crystallographic Data Center, 12 Union Road, CB2, 1EZ UK (fax:+44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk and is available on request quoting the deposit number CCDC 1894817).

Preparation of cis- and trans-3,4,5-trihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones (2g, 3g) in acetic acid medium.

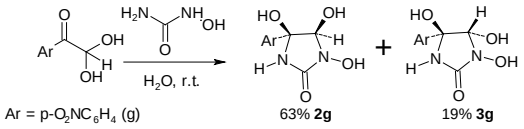
N-Hydroxyurea (139 mg, 1.828 mmol) was dissolved at stirring in a solution of 4-nitrophenylglyoxal hydrate (108 mg, 0.548 mmol) in AcOH (3 mL), the reaction solution was maintained at 17ºC for 25h, then AcOH was removed by evaporation under vacuum (2 mmHg) at 12ºC, the residue was extracted with water (15 mL). The aqueous extract was evaporated under vacuum (2 mmHg) at 12ºC. Yield 144 mg (96%) mixture of diastereomers **2g** and **3g** in molar ratio 74:26 (^{1}H NMR).

2-Hydroxy-2-(5-methylfuran-2-yl)-1-(4-nitrophenyl)ethanone (5e)

The solution of 4-nitrophenylglyoxal hydrate (99 mg, 0.502 mmol) and 2-methylfuran (130 mg, 1.583 mmol) in AcOH (10 mL) was maintained at 18–19ºC for 170h, then AcOH was removed by evaporation under vacuum (3 mmHg), the residue was washed with cold (4ºC) water (3 mL), dried under vacuum (3 mmHg). Yield 105 mg (80%), yellow solid, mp. 85–86ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.16 (3H, s, Me); 5.99 (1H, br. s, CHOH); 6.10 (1H, d, J = 6.4 Hz, H Fur); 6.15 (1H, d, J = 6.4 Hz, H Fur); 6.27 (1H, d, J = 2.8 Hz, CHOH); 8.17 (2H, d, J = 8.0 Hz, H Ar); 8.28 (2H, d, J = 8.0 Hz, H Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6 (Me); 70.2 (CHOH); 107.3, 111.2 (C-3, C-4 furan); 124.0, 130.1 (C-2, C-6, C-3, C-5 Ar); 138.2 (C-1 Ar); 148.6 (C-4 Ar (C-NO_2)); 150.8 153.9 (C-2, C-5 furan); 195.1 (C=O). ^{13}C NMR (75 MHz, APT mode, $CDCl_3$): δ = a) CH, CH_3: 13.5 (Me); 70.1 (CHOH); 107.2, 111.0 (C-3, C-4 furan); 123.9, 130.0 (C-2,C-3,C-5,C-6 Ar); b) Cq, C=O: 138.2 (C-1 Ar); 148.6 [C-4 Ar (C-NO_2)]; 150.8, 153.9 (C-2, C-5 furan); 195.1 (C=O). MS (FAB), m/z 261 M^+ (8); 260 $[M-H]^+$ (10); 244 $[M+H-H_2O]^+$ (71); 150 (30); 111 (100). MS (FAB, KI) m/z 300 $[M+K]^+$ (35); 261 M^+ (7); 244 $[M+H-H_2O]^+$ (66); 150 (30); 111 (100). Anal. Calc. for $C_{13}H_{11}NO_5$: C 59.77; H 4.24; N 5.36. Found: C 59.65; H 4.42; N 5.17.

RESULTS AND DISCUSSION

We have found that 4-nitrofhenylglyoxal reacts with N-hydroxyurea in aqueous solution at 14°C yielding mixture of diastereomers of 3,4,5-trihydroxy-5-(4-nitrophenyl)-imidazolidin-2-one (**2g** and **3g**) (the overall yield of both compounds is 82%) (Scheme 4).



Scheme 4. Synthesis of diastereomeres of 3,4,5-trihydroxy-5-(4-nitrophenyl)imidazolidin-2-one (**2g** and **3g**)

Firstly, from the reaction solution crystals of almost pure cis diastereomer (**2g**) precipitate (according to ^{1}H NMR data molar ratio **2g**:**3g** is 97:3). The same phenomenon was established earlier for 5-(4-chlorophenyl)-3,4,5-trihydroxyimidazolidin-2-one (**2b**).[5,7] Additionally step-by-step evaporation of the aqueous filtrate without any heating gave two portions of the mixture of **2g** and **3g**. In this mixture, cis diastereomer **2g** was dominated (molar ration 61:39 and 59:41, respectively). The overall yield of compound **2g** was 63%, the overall yield of compound **3g** was 19%.

In the compound **2g** the cis orientations of 4-HO- and 5-HO-moieties were confirmed by X-ray structural analysis (Figure 1), as earlier in the compound **2b**.[5]

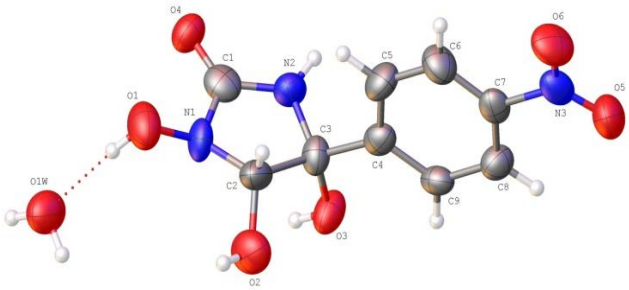


Figure 1. Molecular structure of monohydrate of *cis*-3,4,5-trihydroxy-5-(4-nitrophenyl)imidazolidin-2-one (**2g**) with atoms represented by thermal vibration ellipsoids of 50% probability

In the crystals, the compound **2g** exists as a monohydrate. The five-membered ring adopts an envelope conformation. The C(2) atom lies -0.40 Å off the plane of remaining ring atoms. The N(1) nitrogen atom has a pyramidal configuration. The sum of bond angles centered at the N(1) atom (∑β) is 342º. The N(2) nitrogen atom has a planar configuration (∑β is 360º). The lengths of the N(1)–C(1) bond (1.352(11) Å) and N(2)–C(1) bond (1.355(10) Å) are similar to the corresponding bonds' lengths in 5-(4-chlorophenyl)-3,4,5-trihydroxyimidazolidin-2-one (**2b**).[5,7] In the compound **2b** the substantial difference of those bonds was established [1.3822(16) Å and 1.1.3462(16) Å].[5]

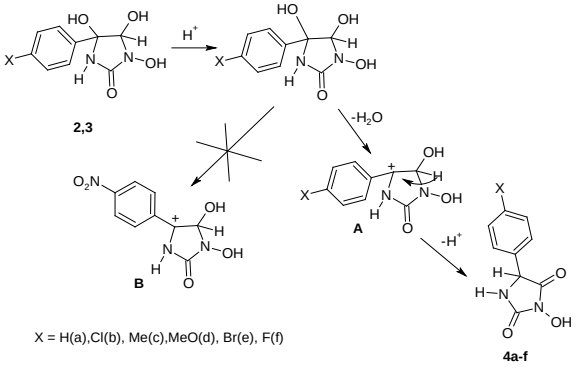
The C(1)=O(4) group is elongated to 1.251(9) Å as compared to the mean value of 1.210 Å. Similar elongation of this group has been found in the compound **2b** [1.2300(15) Å][5] and in N-methoxyurea [1.244(2) Å].[13]

In the compound **2g** the ordinary bonds O(2)–C(2) and O(3)–C(3) are somewhat different: the O(3)–C(3) bond [1.409(8) Å] is longer than the O(2)–C(2) bond [1.384(9) Å]. In the compound **2b** that bonds difference is some greater [1.4203(14) Å and 1.387(4) Å]5. The length of the O(1)–N(1) of the compound **2g** [1.398(7) Å] is similar to the same bond's length in 5-(4-chlorophenyl)-3,4,5-trihydroxyimidazolidin-2-one (**2b**) [1.4047(14) Å].[5]

In the compound **2g** HO-moiety at C(3) atom (5-HO-moiety of hydantoin's cycle) has the axial orientation relative to five-membered ring (the torsion angle N(1)–C(2)–C(3)–O(3) is -93.7(7)º). 4-Nitrophenyl moiety has the equatorial orientation to five-membered ring (the torsion angle N(1)–C(2)–C(3)–C(4) is 143.3(7)º). It is rotated relatively to the N(2)–C(3) endocyclic bond (the torsion angle N(2)–C(3)–C(4)–C(5) is 53.4º). The weak intramolecular hydrogen bond C(9)–H(9)…O(3) (H…O 2.32 Å, C–H…O 102º) takes place. The nitro group is slightly rotated towards the plane of the aromatic cycle (the torsion angle C(6)–C(7)–N(3)–O(6) is 13.1º, the torsion angle C(8)–C(7)–N(3)–O(5) is 7.4º).

In the crystal molecules of the compound **2g** linked by the intermolecular hydrogen bonds O(3)-H(3)…O(4)' (1-x,-0.5+y,1.5-z) (H…O1.92Å, O-H…O 174°), O(2)-H(2)…O(4)' (x,1.5-y,-0.5+z) (H…O2.02Å, O-H…O 156°), N(2)-H(2A)…O(5)' (2-x,-0.5+y,1.5-z) (H…O2.35Å, N-H…O 135°), O(1W)-H(1WA)…O(6)' (1+x,-1+y,z) (H…O2.12Å, O-H…O 171°), O(1W)-H(1WB)…O(2)' (1-x,2-y,1-z) (H…O2.37Å, O-H…O 129°), O(1W)-H(1WB)…O(3)' (1-x,2-y,1-z) (H…O2.17Å, O-H…O 157°).

Contrary to the other arylglyoxals, in acetic acid at the room temperature 4-nitrophenylgyoxal reacts with N-hydroxyurea giving only the mixture of 3,4,5-trihydroxyimidazolidin-2-ones (**2g** and **3g** in molar ratio near 3:1) (r.t., 25h). 3-Hydroxy-5-(4-nitrophenyl)hydantoin (**4g**) didn't form. But, earlier we supposed that the presence of acid (acetic acid or excess of N-hydroxyurea) make to be easy the transformation 5-aryl-3,4,5-trihydroxyimidazolidin-2-ones (**2** and **3**) into 5-aryl-3-hydroxyhydantoins (**4** and **7**) (Scheme 5).

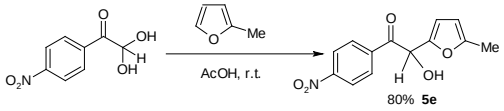


Scheme 5. The proposed mechanism of the conversion of 5-aryl-3,4,5-trihydroxyimidazolidin-2-ones (**2** and **3**) into 5-aryl-3-hydroxyhydantoins (**4**)

The protonation of 4-HO-group with the further elimination of molecule of water yields "benzylic" cation **A**, which transforms into 5-aryl-3-hydroxyhydantoin (**4**) by 1,2-shift and proton elimination from 4-HO-group. But the forming of destabilized cation **B** from 3,4,5-trihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones (**2g** and **3g**) seems to be more hindered.

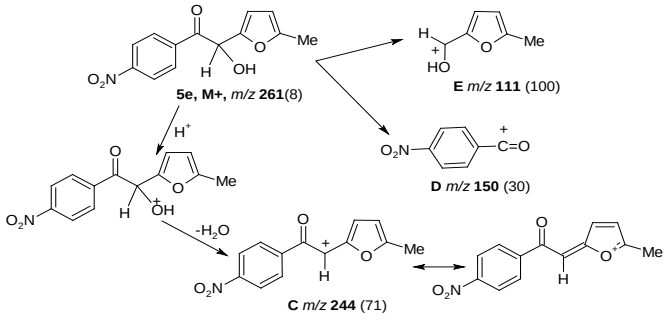
It is possible that such a strong electronegative substitute group in aryl's fragment, as the nitro group makes this transformation impossible.

4-Nitrophenylglyoxal reacts with 2-methylfuran only in acetic acid (r.t.) selectively yielding 2-hydroxy-2-(5-methylfuran-2-yl)-1-(4-nitrophenyl)ethanone (**5e**) (Scheme 6). Into inert solvents, such as CH_2Cl_2 or THF, we couldn't obtain the compound **5e**.



Scheme 6. Synthesis of 2-hydroxy-2-(5-methylfuran-2-yl)-1-(4-nitrophenyl)ethanone (**5e**)

In this case, any α→β benzoin isomerization[4,5] hasn't occurred. The structure of the compound **5e** is consistent with data of ^1H and ^{13}C NMR and MS spectra. In ^1H NMR spectrum of the compound **5e**, the doublets of H(3) and H(4) protons of furan ring are situated closely in the same field. That is a test on α-benzoin's structure.[6,8] The doublets of C(2,6)H and C(3,5)H protons are situated closely too. In mass spectrum cation C $[M+H-H_2O]^+$ (m/z 244), 4-nitrobenzoyl cation D (m/z 150) and "benzylic" furyl cation E (m/z 111) dominate (Scheme 7), which is typical for α-benzoins.[6,8,10,14,15]



Scheme 7. Fragmentation pattern of 2-hydroxy-2-(5-methylfuran-2-yl)-1-(4-nitrophenyl)ethanone (**5e**) (FAB)

Conclusions

The reaction of 4-nitrophenylglyoxal with N-hydroxyurea leads to the mixture of diastereomers of 3,4,5-trihydroxy-5-(4-nitrophenyl)imidazolidin-2-one.

The diastereomer with cis-orientation of OH-groups dominates. Its structure has been investigated by X-ray structural analysis.

The reaction of 4-nitrophenylglyoxal with 2-methylfuran is also possible, but only in the special conditions – in the acetic acid medium at the room temperature. The product of this reaction is α-benzoin, which did not isomerize into β-benzoin in these conditions last time.

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SYNTHESIS AND ANTIMICROBIAL SCREENING OF 5-(SUBSTITUTED PHENYL)-N-(2-OXO-2-(SUBSTITUTED PHENYL)ETHYL)-N-METHYLFURAN-2-SULFONAMIDE DERIVATIVES

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We synthesized substituted furansulfonamide compounds and developed reaction conditions for a series of 5-(substituted phenyl)-N-(2-oxo-2-(substituted phenyl)ethyl)-N-methylfuran-2-sulfonamide derivatives (**4a**-**4m**). We have optimized methodology for targets from milligram scale to multi gram scale. The structure of synthesized compounds were elucidated and confirmed by 1H NMR, 13C NMR, LCMS and purity was checked by HPLC. All the synthesized final compounds (4a-4m) are screened for antimicrobial activity (minimum inhibitory concentration) against a series of strains of Bacillus subtillis, Staphylococcus aureus and Escherichia coli for antibacterial activity and against the strains of Candida albicans, Aspergillus flavus and Aspergillus niger for antifungal activity. The results of antimicrobial screening data revealed most of compounds (4a-4m) showed moderate to promising microbial inhibitions.

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INTRODUCTION

Medicinal chemistry deals with discovery, development and identification of mechanism of action of different compounds at molecular levels. Discovery for new antimicrobial drugs are still remains a challenge, because of development of resistance to old antimicrobial drugs.[1,2]

Furan-ring is a constituent of many natural products and furan derivatives are an important class of heterocycles have various types of biological activities. Furan-ring coupled with different groups showed varied biological activities such as antioxidant,[3] antimicrobial,[4] anti-inflammatory,[5] antitumor and antiviral.[6] Furan-amidine series acts as inhibitors of the enzyme quinone oxidoreductase-2,[7] some furonaphthoquinones shows anti-cancer activity,[8] cyclopenta[*b*]furans acts as inhibitors of CCR-2 as it is a G-protein coupled receptor of the chemokinine family[9] and some furan-2-carbohydrazides acts as glucagon receptor antagonists.[10] Some derivatives comprising thiophene and sulfur containing groups attatched with different groups showed as variety of biological activities.[11-13]

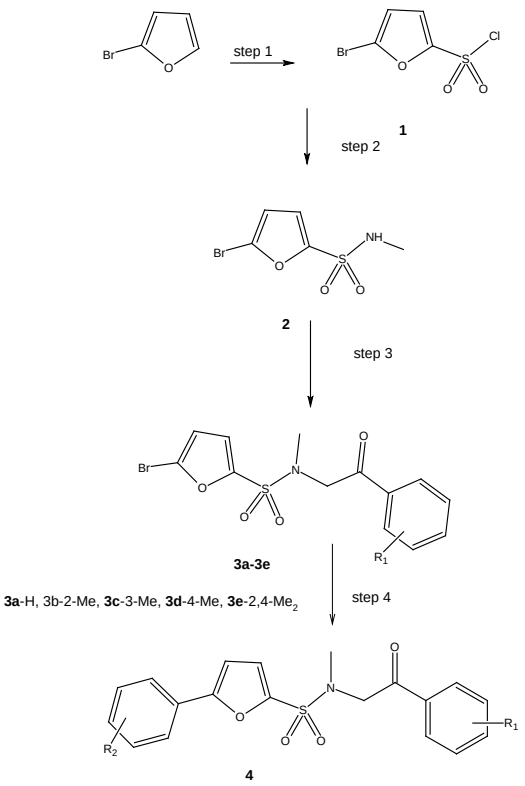
Some natural products with benzofuran scaffold display a variety of biological activities like anti-inflammatory, antibacterial, antitumor, antitubercular activities.[14-17] Some benzodifuran derivatives shows various biological activities like antimicrobial,[18] antifeedant[19] and anti-inflammatory.[20] Heterocyclic nuclei when coupled with different substituents in different reaction sequesces like Buchwald, Suzuki, peptide, oxidation or reduction reactions results novel heterocycles show variety of biological activities.[21-23] For example, benzodifuran scaffold can be easily utilized as dyes in solar cells,[24] building blocks for optoelectronic devices[25] and transistors.[26]

By considering the varied biological importance of furanes and sulfonamides and in continuation of research on heterocyclic compounds in our group for the development of antimicrobial and anticancer agent[27-29] we have synthesized a series of 5-(substituted phenyl)-N-(2-oxo-2-(substituted phenyl)ethyl)-N-methyl-furan-2-sulfonamide derivatives (**4a-4m**) depicted in Scheme 1 and tested their antimicrobial activity.

RESULT AND DISCUSSION

Synthesis of 5-(substituted phenyl)-N-(2-hydroxy-2-(phenyl)ethyl)-N-methylfuran-2-sulfonamide series starting from cheaply available 2-bromofuran through a series of reactions including aromatic sulfonation, sulfonamide formation, substitution and Suzuki reaction for the formation of C-C bond have been performed as depicted in Scheme 1. We have tried to optimize all the reaction steps for economy, safety, clean reaction conditions, yield, time and less harsh conditions.

In step 1 we have done aromatic chlorosulfonation by using chlorosulfonic acid. We have optimized the condition for aromatic chlorosulfonation of 2-bromofuran. The reactivity changes according to the equivalence of chlorosulfonic acid used.



R_1,R_2=H, 2-Me (**a**); H, 3-Me (**b**); H, 4-Me (**c**); H, H (**d**); 2-Me, H (**e**) , 3-Me, H (**f**); 4-Me, H (**g**); 2,4-Me_2, 2-Me (**h**); 2,4-Me_2, 3-Me (**i**); 2,4-Me_2, 4-Me (**j**); 2-Me, 2,4-Me_2 (**k**); 2-Me, 2,4-Me_2 (**l**); 2-Me, 2,4-Me_2 (**m**);

Scheme 1. Synthesis of 5-(substituted phenyl)-N-(2-oxo-2-substituted-phenylethyl)-N-methylfuran-2-sulfonamide derivatives **(4a-4m).** Reagents and conditions: Step 1- Chlorosulfonic acid, DCM, rt, 1 h; Step 2- $MeNH_2$, TEA, DCM, rt, 6 h; Step 3- substituted phencyl bromide, K_2CO_3, acetone, rt 2 h; Step 4- substituted boranic acid, $Pd(dppf)Cl_2$, Na_2CO_3, X-phos, Dioxane-H_2O.

We have carried out 7 different combinations and optimized the reaction condition which reduced the efforts of tedious work up and purifications of intermediate for the first time for 2-bromofuran. For all the reactions we have kept the time to be constant. It is confirmed that when we use neat excess of chlorosulfonic acid without solvent there is 20 % formation of required product, (entry 7) then we have used excess chlorosulfonic acid with dichloromethane (DCM) then yield was 30 % (entry 6). From above these two conditions it is clear that we have to use chlorosulfonic acid in equivalents along with in neat and in DCM solvent conditions. The results are shown in Table 1.

Table 1. Screening of sulfonyl chloride equivalent and solvent of compound (2)

Entry	$ClSO_3H$	Solvent	Yield[a] (%)
1	3 eq.	Neat	30
2	2 eq.	Neat	25
3	3 eq.	DCM	40
4	2 eq.	DCM	50
5	1.2 eq.	DCM	78
6	Excess	DCM	40
7	Excess	Neat	20

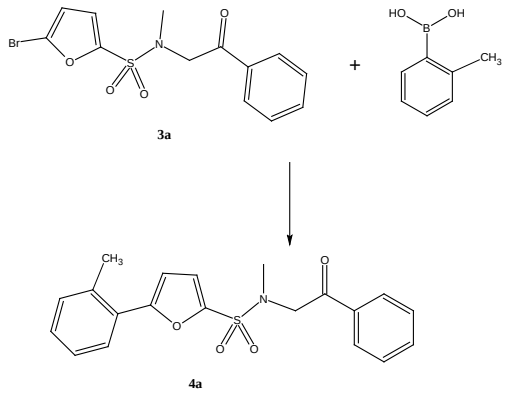
[a]Isolated yield, time 2 h

The entries (1, 2, 3 and 4) shows there is formation product along with side products, the yields are 25 % to 50 %. When we consider (entries 5) the yield is 78 % when we used equivalent amount of chlorosulfonic acid (1.1 eq.) and DCM as solvent. The yields are isolated yields after series of reactions optimization and the condition of (entry 5). By using this method the work up is easy, we have to evaporate the reaction mixture under reduced pressure and obtained gummy material, which is washed with excess of n-hexane and it is recrystallized from 10 % ethyl acetate: hexane mixture to obtain white solid which is used further for methylation reaction. In entries 1 to 4, the first three resulted in formation of polar junk material, which required purification by column chromatography, so the yields are less, but in the last case by washing with cold pentane and cold diethyl ether, pure compound 1 could be obtained.

In step 2 we have done sulfonamide preparation by using 2 molar solution of methyl amine in THF. We tried a reaction using compd. 1 and 3 eq. of methyl amine in acetonitrile from 0 °C to room temperature for 4 h but there was no formation of the desired product. Then we used 3 eq. of methyl amine in DCM along with 3 eq. of triethylamine as base when there was isolated 35 % of product with column chromatography after 4 h. Then we used 3 eq. of methyl amine in THF at 0 °C to room temperature for 6 h when there was 90 % formation of compound **2**. The reaction profile is very clean on TLC. We have modified the work up. Without evaporating the reaction mixture, that was diluted with 10 volumes of water and extracted twice with ethyl acetate to obtain the desired compound 2. The obtained solid compound washed with 10 ml of 20 % ethyl acetate : n-hexane, 10 ml of cold pentane and 10 ml cold diethyl ether to obtain compound **2**. Compound **2** is white solid with purity more than 90 %.

For step 3 we have treated compd. **2** (1 eq.) with substituted phenacyl bromide (1 eq.) by using inorganic base like K_2CO_3 (2 eq.) and Cs_2CO_3 (2 eq.) in acetone and THF, respectively, for 2 h at room temperature, to obtain 85 and 30 % isolated yields, respectively. The reaction with K_2CO_3 and acetone gave a simple work up procedure evaporating acetone under reduced pressure and adding water to the obtained gummy material with stirring the reaction mass for 1 h. A solid precipitates out was filtered off and washed with excess of water and dried properly to obtain compound **3a** as white solid which were used further for Suzuki-coupling reactions.

In step-4 we have done C-C bond formation by using Suzuki coupling reaction, we have done a series of optimization reactions to get better yield and less reaction time.



Scheme 2. Synthesis of compound **4a**.

Different catalysts, ligands, bases and solvents were screened. As model reaction we used the compound **3a** and 2-methylboronic acid. We used $Pd(PPh_3)_4$, $Pd(OAc)_2$, $Pd(dppf)Cl_2$ and $NiCl_2{\cdot}6H_2O$ as catalysts, X-phos, Xanthophos and BINAP as ligands. We used K_3PO_4, Na_2CO_3 and CS_2CO_3 as bases and dioxane-water, DMF-water and DME as solvents. For all the optimization reactions we used 2-methylboronic acid (1.5 eq.), catalyst (10 mol %), ligand (15 mol %) and base (2 eq.). All reactions were done at temperature 110 °C and for 6 h, the % yields are the isolated yields after purification, and the results of optimization reactions are tabulated in Table **2**.

Table 2. Screening of catalyst, bases and solvent for the synthesis of N-(2-oxo-2-(phenyl)ethyl)-N-methyl-5-(o-tolyl)-furan-2-sulfonamide 4a:

Catalyst	Ligand	Base	Solvent	Yield, %
$Pd(PPh_3)_4$	-	K_3PO_4	Dioxane:H_2O	40
$Pd(PPh_3)_4$	X-phos	K_3PO_4	DMF:H_2O	35
$Pd(OAc)_2$	X-phos	K_3PO_4	DMF:H_2O	50
$Pd(OAc)_2$	Xanth-ophos	K_3PO_4	DMF:H_2O	40
$Pd(dppf)Cl_2$	-	Na_2CO_3	Dioxane:H_2O	55
$Pd(dppf)Cl_2$	BINAP	Cs_2CO_3	Dioxane:H_2O	62
$Pd(dppf)Cl_2$	X-phos	Na_2CO_3	Dioxane:H_2O	85
$NiCl_2{\cdot}6H_2O$	BINAP	K_3PO_4	DME	40

In entries 1 and 2 we have used $Pd(PPh_3)_4$ as catalysts and K_3PO_4 as base we have used dioxane-water as solvent as no ligand we got 40 % yield of compound **4a**, in other case we used X-phos as ligand and DMF-H2O As solvent we for 35 % yield the yield is decreases. In entries 3 and 4 we have tried $Pd(OAc)_2$ as catalyst K_3PO_4 as base and DMF-H_2O as solvents we used X-phos and Xanthophos as ligands we got 50 % and 40 % yield, respectively. In entry 8 we have used $NiCl_2{\cdot}6H_2O$ as catalyst BINAP as ligand and K_3PO_4 as base and DME as solvent we got 40 % yield. In all these 5 optimization reactions we got yield in the range of 35 % to 50 %. In entry 5 we have used as $Pd(dppf)Cl_2$ catalyst and Na_2CO_3 as base, dioxane-H_2O as solvent we got 55 % yield which is higher than earlier 5 combinations. We have kept the same combination of catalyst solvents and varied the ligand and base in entries 6 and 7. In entry 6 we got 62 % yield and desired product and in entry 7 condition we got 85 % of desired product. The entry 7 reaction condition of $Pd(dppf)Cl_2$, X-phos, Na_2CO_3 dioxane-H_2O worked well in getting good yields. We have used the same set of condition for the synthesis of remaining derivatives **4b**-**4m**. The yields obtained are in the range of 75 to 85 %. The detailed experimental procedure and analytical data are given in experimental section.

Experimental procedure for synthesis of 5-(substituted phenyl)-N-(2-oxo-2-(substituted phenyl)ethyl)-N-methyl-furan-2-sulfonamides (**4a**-**4m**).

Step a: Synthesis of 5-bromofuran-2-sulfonyl chloride (1):

To a stirred solution of 2-bromofuran (10g, 68.03 mmol) in DCM (100 mL) chlorosulfonic acid (5.41 ml, 81.63 mmol) was added dropwise at 0 °C. Allowed the reaction mass to come to room temperature and stirred for 1 h. Progress of reaction and the consumption of starting material was monitored by TLC and LCMS, respectively. The reaction mixture was evaporated under reduced pressure to obtained a gummy material. The gummy material was washed with cold hexane (100 mL) and crystallized from EtOAc:hexane (10 %, 50 mL) mixture to obtain 5-bromofuran-2-sulfonyl chloride (1,14 g, 84 %) as an off-white solid.

Step b: Synthesis of 5- bromofuran-2-sulfonyl amide (2):

To a stirred solution of compound **1** (10 g, 40.73 mmol) methyl amine was added (61 mL, 122 mmol) in THF (100 mL) at 0 °C. The reaction mass was allowed to come to room temperature and stirred for 6 h. Progress of reaction and consumption of starting material were monitored by TLC and LCMS, respectively. After completion the reaction, the mixture was poured in H_2O (100 mL) and extracted with EtOAc (2 × 50 mL). The organic layer was collected, washed with brine (25 mL) and dried over anhydrous Na_2SO_4, and evaporated in vacuum. The obtained gummy material was washed with EtOAc:hexane (20 %, 50 mL), pentane (50 ml) and cold diethyl ether (50 ml) and dried it under vacuum to obtain compound **2** (8g, 82 %) as a white solid.

Step 3: General procedure for the synthesis of compounds 3a-3e:

To a stirred solution of compound 2 (1.0 mmol) in acetone (10 vol.) K_2CO_3 was added (2.0 mmol), the reaction mixture was stirred at room temperature for 30 min. Color change was observed from white to light pink. Substituted phenacyl bromide (a-H, b-2-Me, c-3-Me, d-4-Me, e-2,4-diMe) (1.0 mmol) was added and the mixture was stirred at room temperature for 2 h. Progress of reaction and the

consumption of starting material were monitored by TLC and LCMS, respectively. After completion the reaction, reaction mass was evaporated under reduced pressure to obtain a gummy material, which was poured into cold H_2O (10 vol.) and the mixture was stirred for 15 min. A solid was precipitated out from the reaction mass, that was filtered off and washed with H_2O, cold pentane and cold ether to obtain compounds **3a-3e** (60 to 87 %) as white solids.

Step 4: General procedure for the synthesis of compounds 4a-4m:

To a stirred solution of comp **3a-3e** (1.0 mmol) in dioxane:water was added substituted phenylboronic acid (**a**-2-Me, **b**-3-Me, **c**-4-Me, **d**-H, **e**-2,4diMe) (1.5 mmol). Na_2CO_3 (2.0 mmol), $Pd(dppf)Cl_2$ (10 mol %) and X-phos (15 mol%) were added, the reaction mass was inerzized with using argon for 10 min and the reaction mixture was heated until 100 °C for 6 h. Progress of reaction and consumption of starting material were monitored by TLC and LCMS. After completion the reaction, the reaction mixture was cooled to room temperature and filtered through a pad of celite to obtain a filtrate. The filtrate was evaporated under reduced pressure to obtain different crude compounds, **4a-4m**, these crude compounds were purified by flash column chromatography by using (silica gel 230-400 mesh; EtOAc:hexane 10-60:90-40) to obtain the desired compounds **4a-4m** (75% to 85%) as solids.

N-(2-Oxo-2-(phenyl)ethyl)-N-methyl-5-(o-tolyl)furan-2-sulfonamide (4a):

White solid; M.p. 163-164 °C; Yield: 78 %; IR (KBr) (ν_{max}, cm^{-1}): 1627 (C=O), 1580 and 1530 (Ar). Anal. calc. for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79; Found: C, 65.06; H, 5.11; N, 3.84. LC-MS m/z (%): 370 (M+H); HPLC-97.3 % RT 8.23 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, *J* = 4.4 Hz, 1H, ArH), 7.43 (d, *J* = 7.2 Hz, 1H, ArH), 7.35-7.32 (m, 5H, ArH), 7.31-7.26 (m, 4H, ArH), 3.08 (s, 2H, CO-CH_2), 2.79 (s, 3H, N-CH_3), 2.39 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$,100 MHz): 169.6, 140.43, 138.64, 136.33,133.45, 131.14, 128.95, 128.18, 127.35, 127.34, 126.24, 126.23, 125.5, 125.54, 124.68, 124.32, 124.22, 57.38, 36.35, 24.45.

N-(2-Oxo-2-(phenyl)ethyl)-N-methyl-5-(m-tolyl)furan-2-sulfonamide (4b):

Off white solid; M.p. 169-170 °C; Yield: 77 %; IR (KBr) (ν_{max}, cm^{-1}): 1628 (C=O), 1584 and 1520 (Ar). Anal. calc. for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79; Found: C, 65.22; H, 5.22; N, 3.84. LC-MS m/z (%): 370 (M+H); HPLC 99.3 %, RT 8.13min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62–7.58 (m, 2H, ArH), 7.55-7.51 (m, 3H, ArH), 7.35-7.32 (m, 4H, ArH), 7.29-7.25 (m, 1H, ArH), 7.22 (d, *J* = 8.0 Hz, 1H, ArH), 3.11 (s, 2H, CO-CH_2), 2.78 (s, 3H, N-CH_3), 2.33 (s, 3H Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 169.4, 140.59, 138.74, 136.39, 133.25, 131.14, 128.85, 128.14, 127.35, 127.34, 126.14, 126.13, 125.5, 125.44, 124.68, 124.32, 124.22, 57.4, 36.37, 24.5.

N-(2-Oxo-2-(phenyl)ethyl)-N-methyl-5-(p-tolyl)furan-2-sulfonamide (4c):

Off white solid; M.p. 178-179 °C; Yield: 81 %; IR (KBr) (ν_{max}, cm^{-1}): 1628 (C=O), 1586 and 1524 (Ar). Anal. calc. for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79; Found: C, 64.97; H, 5.15; N, 3.75. LC-MS m/z (%): 370 (M+H); HPLC-98.9 %, RT 6.07 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63-7.6 (m, 3H, ArH), 7.56 (d, *J* = 4.4 Hz, 1H, ArH), 7.35-7.34 (m, 4H, ArH), 7.27-7.25 (m, 3H, ArH), 3.17 (s, 2H, CO-CH_2), 2.8 (s, 3H, N-CH_3), 2.39 (s, 3H Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 169.3, 140.41, 138.34, 136.19, 133.15, 131.14, 128.85, 128.44, 127.35, 127.24, 126.14, 126.13, 125.5, 125.64, 124.68, 124.22, 124.21, 57.41, 36.37, 24.52.

N-(2-Oxo-2-(phenyl)ethyl)-N-methyl-5-(phenyl)furan-2-sulfonamide (4d):

White solid; M.p. 153-154 °C; Yield: 84 %; IR (KBr) (ν_{max}, cm^{-1}): 1628 (C=O), 1576 and 1516 (Ar). Anal. calc. for $C_{19}H_{17}NO_4S$: C, 64.21; H, 4.82; N, 3.94; Found: C, 64.17; H, 4.77; N, 3.91. LC-MS m/z (%): 356 (M+H); HPLC-97.3 %, RT 8.16 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, *J* = 4.4 Hz, 1H, ArH), 7.43 (d, *J* = 7.2 Hz, 1H, ArH), 7.35-7.32 (m, 5H, ArH), 7.31-7.26 (m, 5H, ArH), 3.15 (s, 2H, CO-CH_2), 2.79 (s, 3H, N-CH_3). ^{13}C NMR ($CDCl_3$,100 MHz): 171.4, 140.43, 138.64, 136.33,133.45, 131.14, 128.95, 128.18, 127.35, 127.34, 126.24, 126.23, 125.5, 125.54, 124.68, 124.32, 124.22, 57.38, 36.35.

N-(2-Oxo-2-(o-tolyl)ethyl)-N-methyl-5-phenylfuran-2-sulfonamide (4e):

Off white solid; M.p. 162-163 °C; Yield: 76 %; IR (KBr) (ν_{max}, cm^{-1}): 1630 (C=O), 1586 and 1530 (Ar). Anal. calc. for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79; Found: C, 65.03; H, 5.19; N, 3.78. LC-MS m/z (%): 370 (M+H); HPLC-97.3 %, RT 8.14 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, *J* = 4.4 Hz, 1H, ArH), 7.43 (d, *J* = 7.6 Hz, 1H, ArH), 7.35-7.32 (m, 5H, ArH), 7.31-7.26 (m, 4H, ArH), 3.15 (s, 2H, CO-CH_2), 2.79 (s, 3H, N-CH_3), 2.39 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$,100 MHz): 171.2, 140.43, 138.64, 136.33,133.45, 131.14, 128.95, 128.18, 127.35, 127.34, 126.24, 126.23, 125.5, 125.54, 124.68, 124.32, 124.22, 57.38, 36.35, 24.45.

N-(2-Oxo-2-(m-tolyl)ethyl)-N-methyl-5-phenylfuran-2-sulfonamide (4f):

Off white solid; m.p. 171-172 °C; Yield: 82 %; IR (KBr) (ν_{max}, cm^{-1}): 1620 (C=O), 1570 and 1528 (Ar). Anal. calc. for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79; Found: C, 65.03; H, 5.10; N, 3.85.LC-MS m/z (%): 370 (M+H); HPLC 99.3 %, RT 8.22 min; ^{1}H NMR (400 MHz, DMSO-d_6), δ 7.62–7.58 (m, 2H, ArH), 7.55-7.51 (m, 3H, ArH), 7.35-7.32 (m, 4H, ArH), 7.29-7.25 (m, 1H, ArH), 7.22 (d, *J* = 8.0 Hz, 1H, ArH), 3.11 (m, 2H, CO-CH_2), 2.78 (s, 3H, N-CH_3), 2.33 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 170.2, 140.59, 138.74, 136.39, 133.25, 131.14, 128.85, 128.14, 127.35, 127.34, 126.14,

126.13, 125.5, 125.44, 124.68, 124.32, 124.22, 57.4, 36.37, 24.5, 18.4.

N-(2-Oxo-2-(p-tolyl)ethyl)-N-methyl-5-phenylfuran-2-sulfonamide (4g):

Off white solid; M.p. 169-170 °C; Yield: 75 %; IR (KBr) (ν_{max}, cm^{-1}): 1628 (C=O), 1574 and 1526 (Ar). Anal. calc. for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79; Found: C, 65.04; H, 5.15; N, 3.81. LC-MS m/z (%): 370 (M+H); HPLC-98.9 %, RT 8.18 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63-7.6 (m, 3H, Ar-H), 7.56 (d, *J* = 4.4 Hz, 1H, Ar-H), 7.35-7.34 (m, 4H, Ar-H), 7.27-7.25 (m, 3H, Ar-H), 3.17 (s, 2H, CO-CH_2), 2.8 (s, 3H, N-CH_3), 2.39 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 168.9, 140.41, 138.34, 136.19, 133.15, 131.14, 128.85, 128.44, 127.35, 127.24, 126.14, 126.13, 125.5, 125.64, 124.68, 124.22, 124.21, 57.41, 36.37, 24.52.

N-(2-(2,4-Dimethylphenyl)-2-oxoethyl)-N-methyl-5-(o-tolyl)furan-2-sulfonamide (4h):

White solid; M.p. 193-194 °C; Yield: 82 %; IR (KBr) (ν_{max}, cm^{-1}): 1634 (C=O), 1586 and 1528 (Ar). Anal. calc. for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.51; Found: C, 66.52 H, 5.81; N, 3.54. LC-MS m/z (%): 398 (M+H); HPLC-97.3 %, RT 8.13 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, *J* = 4.4 Hz, 1H, Ar-H), 7.43 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.35-7.32 (m, 4H, Ar-H), 7.31-7.26 (m, 4H, Ar-H), 3.15 (s, 2H, CO-CH_2), 2.79 (s, 3H, N-CH_3), 2.39 (s, 3H, Ar-CH_3), 2.33 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 169.8, 140.43, 138.64, 136.33,133.45, 131.14, 128.95, 128.18, 127.35, 127.34, 126.24, 126.23, 125.5, 125.54, 124.68, 124.32, 124.22, 57.38, 36.35, 24.45, 18.4.

N-(2-(2,4-Dimethylphenyl)-2-oxoethyl)-N-methyl-5-(m-tolyl)furan-2-sulfonamide (4i):

Off white solid; M.p. 201-202 °C; Yield: 79 %; IR (KBr) (ν_{max}, cm^{-1}): 1636 (C=O), 1576 and 1518 (Ar). Anal. calc. for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.51; Found: C, 66.46 H, 5.85; N, 3.47. LC-MS m/z (%): 398 (M+H); HPLC 99.3 %, RT 8.20 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62–7.58 (m, 2H, Ar-H), 7.55-7.51 (m, 3H, Ar-H), 7.35-7.32 (m, 3H, Ar-H), 7.29-7.25 (m, 1H, Ar-H), 7.22 (d, *J* = 8.4 Hz, 1H, Ar-H), 3.11 (s, 2H, CO-CH_2), 2.78 (s, 3H, N-CH_3), 2.33 (s, 3H, Ar-CH_3), 2.33 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 170.2, 140.59, 138.74, 136.39, 133.25, 131.14, 128.85, 128.14, 127.35, 127.34, 126.14, 126.13, 125.5, 125.44, 124.68, 124.32, 124.22, 57.4, 36.37, 24.5, 17.8.

N-(2-(2,4-Dimethylphenyl)-2-oxoethyl)-N-methyl-5-(p-tolyl)furan-2-sulfonamide (4j):

White solid; M.p. 198-199 °C; Yield: 84 %; IR (KBr) (ν_{max}, cm^{-1}): 1628 (C=O), 1586 and 1520 (Ar). Anal. calc. for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.51; Found: C, 66.44 H, 5.79; N, 3.46. LC-MS m/z (%): 398 (M+H); HPLC-98.9 %, RT 8.18 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63-7.6 (m, 3H, Ar-H), 7.56 (d, *J* = 4.4 Hz, 1H, Ar-CH_3), 7.35-7.34 (m, 3H, Ar-CH_3), 7.27-7.25 (m, 3H, Ar-CH_3), 3.17 (s, 2H, CO-CH_2), 2.8 (s, 3H, N-CH_3), 2.39 (s, 3H, Ar-CH_3), 2.33 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 169.52, 140.41, 138.34, 136.19, 133.16, 131.14, 128.84, 128.44, 127.35, 127.24, 126.14, 126.13, 125.5, 125.64, 124.68, 124.23, 124.21, 57.41, 36.37, 24.51, 18.2.

5-(2,4-Dimethylphenyl)-N-methyl-N-(2-oxo-2-(o-tolyl)-ethyl)furan-2-sulfonamide (4k):

Off white solid; M.p. 193-194 °C; Yield: 76 %; IR (KBr) (ν_{max}, cm^{-1}): 1628 (C=O), 1580 and 1520 (Ar). Anal. calc. for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.51; Found: C, 66.54 H, 5.87; N, 3.56. LC-MS m/z (%): 398 (M+H); HPLC-97.3 %, RT 8.13 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, *J* = 4.6 Hz, 1H, Ar-H), 7.43 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.35-7.32 (m, 4H, Ar-H), 7.31-7.26 (m, 4H, Ar-H), 3.15 (s, 2H, CO-CH_2), 2.79 (s, 3H, N-CH_3), 2.39 (s, 3H, Ar-CH_3), 2.33 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 168.77, 140.43, 138.64, 136.33,133.45, 131.14, 128.95, 128.18, 127.35, 127.34, 126.24, 126.23, 125.5, 125.54, 124.68, 124.32, 124.22, 57.38, 36.35, 24.45, 18.6.

5-(2,4-Dimethylphenyl)-N-methyl-N-(2-oxo-2-(m-tolyl)-ethyl)furan-2-sulfonamide (4l):

Off white solid; M.p. 207-208 °C; Yield: 79 %; IR (KBr) (ν_{max}, cm^{-1}): 1624 (C=O), 1584 and 1528 (Ar). Anal. calc. for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.51; Found: C, 66.50 H, 5.79; N, 3.45. LC-MS m/z (%): 398 (M+H); HPLC 99.3 %, RT 8.21min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62–7.58 (m, 2H, Ar-H), 7.55-7.51 (m, 3H, Ar-H), 7.35-7.32 (m, 3H, Ar-H), 7.29-7.25 (m, 1H, Ar-H), 7.22 (d, *J* = 8.8 Hz, 1H, Ar-H), 3.11 (s, 2H, CO-CH_2), 2.78 (s, 3H, N-CH_3), 2.33 (s, 3H, Ar-CH_3), 2.33 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 169.4, 140.59, 138.74, 136.39, 133.25, 131.14, 128.85, 128.14, 127.35, 127.34, 126.14, 126.13, 125.5, 125.44, 124.68, 124.32, 124.22, 57.4, 36.37, 24.5, 18.4.

5-(2,4-Dimethylphenyl)-N-methyl-N-(2-oxo-2-(p-tolyl)-ethyl)furan-2-sulfonamide (4m):

Off white solid; M.p. 195-196 °C; Yield: 76 %; IR (KBr) (ν_{max}, cm^{-1}): 1627 (C=O), 1582 and 1520 (Ar). Anal. calc. for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.51; Found: C, 66.53 H, 5.86; N, 3.57. LC-MS m/z (%): 398 (M+H); HPLC-98.9 %, RT 8.16 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63-7.6 (m, 3H, Ar-H), 7.58 (d, *J* = 4.6 Hz, 1H, Ar-H), 7.35-7.32 (m, 3H, Ar-H), 7.27-7.21 (m, 3H, Ar-H), 3.17 (s, 2H, CO-CH_3), 2.8 (s, 3H, N-CH_3), 2.39 (s, 3H, Ar-CH_3), 2.33 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 169.4, 140.41, 138.33, 136.17, 133.15, 131.14, 128.85, 128.44, 127.35, 127.24, 126.14, 126.13, 125.75, 125.64, 124.68, 124.21, 124.21, 57.41, 36.37, 24.52, 18.6.

Table 3. Antimicrobial activity data for compounds **4a-4m**

Compounds	MIC values[a], μg mL^{-1}					
	B. subtilis	***E. coli***	***S. aureus***	***C. Albicans***	***A. Flavus***	***A. Niger***
4a	30	51	26	54	51	56
4b	29	29	36	26	14.5	14.5
4c	48	90	95	65	80	80
4d	38	63	58	80	60	40
4e	35	32	29	29	32	15.5
4f	42	29	33	48	29	26
4g	35	60	37	90	60	50
4h	45	90	90	75	90	80
4i	55	56	56	90	56	50
4j	56	67	100	75	59	80
4k	37	46	70	75	46	25
4l	48	78	100	75	78	90
4m	28	89	70	75	89	54
Ciprofloxacin	26	26	25	-	-	-
Fluconazole	-	-	-	36	23	23
Miconazole	-	-	-	13.5	13.5	13.5

[a]Values are the average of three readings.

Antimicrobial activity

All the synthesized compounds **(4a-4m)** were screened for *in vitro* antimicrobial activity. The antibacterial activity was evaluated against two Gram positive bacteria *Staphylococcus aureus* (NCIM-2901), *Bacillus subtilus* (NCIM-2063), Gram negative bacteriaum, *Escherichia coli* (NCIM-2256), and four fungal strains *Candida albicans* (NCIM-3471), *Aspergillus flavus* (NCIM-539) and *Aspergillus niger* (NCIM-1196). For studying antimicrobial properties of compounds, Minimum Inhibitory Concentration (MIC, μg mL^{-1}), Minimum Bacterial Concentration (MBC) and Minimum Fungicidal Concentration (MFC) were studied by modified macrodilution technique. For bacterial strains MIC determination were done by a serial of microdilution technique using 96-well microtiter plate reader.

Compounds **4a-4m** are prepared in saline (0.8 % NaCl) solution containing 5 % dimethyl sulfoxide (DMSO) for dissolution. All microbial strains were incubated with different concentration of each compound in 96-well microtiter plate for 20 h at 37 °C on rotary shaker (160 rpm). After incubation the lowest concentration value without growth were defined as MICs. For Fungal strains agar dilution technique, on potato dextrose agar (PDA) medium were used for MIC determination. The MBC and MFC of compounds were determined by serial sub cultivation after inoculated for 72 h with tested compounds dissolved in saline containing 5 % DMSO. The lowest concentration with no visible growth was defined as MBC/MFC indicating 99.5 % killing of the original inoculums. All the experiments performed in triplicates and mean reading is taken as final reading. 5 % DMSO was used as a negative control along with Ciprofloxacin as the standard antibacterial drugs and Fluconazole and Miconazole as the standard antifungal drugs.[30] The antimicrobial activity results were given in Table 3.

From the antimicrobial data, it is observed that all the newly synthesized compounds showed good to moderate level of antibacterial and antifungal activity. The antimicrobial activity data reveals that compounds **4a, 4b, 4e, 4f, 4k** and **4m** are found to be active and potent as antimicrobial agents among the series. The antimicrobial activity data reveals that among the synthesized compounds **4b, 4e** and **4f** are very active compared with the standard.

For antibacterial activity evaluated for Gram positive bacteria the compounds **4a, 4b, 4e, 4f** and **4m** are most active and that of compounds **4d, 4g** and **4k** are moderately active the remaining compounds are mostly inactive. For Gram negative bacteria the compounds **4b, 4e** and **4f** are most active and remaining compounds are moderately active or mostly inactive. For antifungal activity the compounds **4b, 4e** and **4f** are very active compared with standard the compound **4k** is moderately active the remaining compounds are moistly inactive. The furan sulfonamide compounds are active mostly on antifungal stains when compared with antibacterial stains.

The SAR can be drawn like that when aromatic ring was coupled with methyl group it shows good activity and among then the substitution on meta position is the favorable one compared with ortho and para substitution. When we increased this electron donating tendency then the activity decreases, due to steric hindrance and more crowing of groups. When unsubstituted compounds are there then the activity decreases also. The small electron donating group plays a key role in the antimicrobial activity in this series.

CONCLUSIONS

In the present paper we have synthesized 5-(substituted phenyl)-N-(2-oxo-2-(substituted phenyl)ethyl)-N-methylfuran-2-sulfonamides (**4a-4m**).

A total 13 derivatives were synthesized starting from 2-bromofuran, we have used substituted phenacyl bromides and substituted aromatic boronic acids, through series of coupling reactions. We have optimized the sulfonation reaction and Suzuki reaction for getting good yields and clean reaction profiles. The synthesized compounds were characterized by analytical data. All the synthesized derivatives further tested for antimicrobial activity. Most compounds showed moderate to good antimicrobial activity but the compounds having substitution on meta position of benzene ring increases the activity compared with other compounds, as the substitution increases there is decrease in the activity.

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THIONYL CHLORIDE INDUCED CONVENIENT SYNTHESIS OF BENZAMIDES FROM 3-BROMO-5-NITROBENZOIC ACID AND AMINES UNDER SOLVENT FREE CONDITIONS

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Keywords:thionyl chloride;coupling reaction;benzamides;benzoic acid; solvent free.

A new method of thionyl chloride induced convenient synthesis of novel benzamides under solvent free conditions has been developed using benzoic acid and amines. The benzamides were synthesized through a coupling reaction of benzoic acid and different amines using thionyl chloride at room temperature. The abovementioned technique assists in the preparation of substituted benzamides which were obtained in good yields within 2-4 h using conventional heating. The developed method is flexible, economic, environment friendly; also is catalyst, ligand and solvent free and has major importance in industry and laboratory.

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INTRODUCTION

Preparation of bromo and nitro-substituted benzoic acids as precursors for preparation of pharmaceutically active benzamides is an important challenge of organic chemistry. The nitration of aromatic compounds may be achieved with many nitrating reagents but the conditions are incompatible with a range of compounds which are sensitive to oxidizing or strongly acidic conditions.[1,2] Nitration of benzoic acid 62% nitric acid is successfully carried out under solvent-free condition in a biphasic mode in the presence of the Bronsted acidic ionic liquids; the only by-product is water and ionic liquids are capable of being reused without any separation.[3]In this paper we give information about optimization of the initial reported method.

The classical bromination reactions involve the use of hazardous elemental bromine.[4] That's why bromination reaction has been still attracting attention to develop the more practical method without the use of hazardous and highly toxic elemental bromine.[5] Several acid-catalyzed N-bromosuccinimide (NBS) ring brominations have been reported and continue to be of interest, mainly in connection with the bromination of polyalkyl benzenes.[5,6] In terms of ease of handling and availability, N-bromosuccinimide (NBS) is a superior brominating reagent.[7] In this paper we give information about optimization the previously reported method to brominate 3-nitrobenzoic acid with NBS and sulfuric acid.

Benzamides are an important class of chemicals that have been widely used as chemical intermediates in organic synthesis, raw materials for engineering plastics, detergents, and lubricants.[8] The conversion of carboxylic acids to amides is one of the most important transformations in organic synthesis. In general, the conversion of carboxylic acids to carboxamides requires an activation of the carboxyl group. The solvents in most organic reactions increase the reaction yield, stereoselectivity and chemoselectivity.[9] The violent exothermic reactions are also controlled by the solvent which involves quick electron transfer from metal and that with a highly reactive species.[10] On the other hand, the use of a solvent may decrease the reaction rate, produces waste solvent, enhances the production cost, and make a chemical operation risky when a flammable solvent is used.[11-12] Solvent-free reactions are therefore becoming important from the viewpoint of green chemistry.[13]

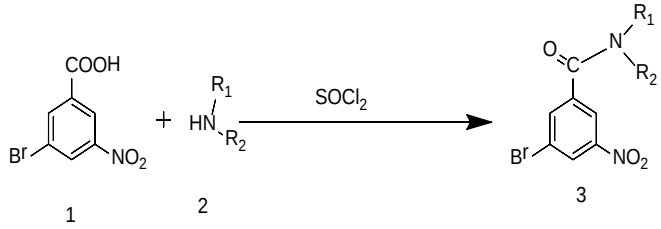
We have been engaged in the development of aromatic compounds as anti-cancer agents and have shown structure–activity relationships with several substituted benzoic acids (containing NO_2 and Br group) to which a heterocyclic aromatic amide group containing ring bound,[14] therefore the amidation reactions of 3-bromo-5-nitro benzoic acid was performed in the presence of $SOCl_2$ as promoter in a solvent and catalyst free conditions.[15]

In continuation of our work,[16-33] we have developed the new protocol synthesis of benzamides from 3-bromo-5-nitrobenzoic acid and amines.

MATERIALS AND METHOD

All chemicals, unless otherwise specified, were purchased from commercial sources and were used without further purification. The major chemicals were purchased from Sigma Aldrich and Avra labs. The development of reactions was monitored by thin layer chromatography (TLC) analysis on Merck pre-coated silica gel 60 F254 aluminum sheets, visualized by UV light. Melting points were recorded on SRS Optimelt. Melting points are uncorrected. The ^{1}H NMR

spectra were recorded on a 400 MHz Varian NMR spectrometer. The ^{13}C were recorded on a 100 MHz Varian NMR spectrometer. Mass spectra were taken with Micromass-QUATTRO-II of WATER mass spectrometer.



Scheme 1. Synthesis of 3-bromo-5-nitrobenzamides

General procedure for the synthesis of 3-bromo-5-nitro-benzamides

Nitration of benzoic acid

Benzoic acid (10 g, 0.0406 mmol) and cc. sulfuric acid (25ml) were added to a reaction vessel and nitrating mixture (H_2SO_4+HNO_3) (H_2SO_4:HNO_3= 1:1.5, 16.5 ml) was added drop wise at 0-5°C temperature for 45 minutes and further the reaction was stirred for 1 h. Then the reaction mixture was quenched with the addition of cracked ice (precipitate formation was observed) and the product was obtained by vacuum filtration. Further the product was recrystallized with methanol. Melting point observed was 139-141°C.

Bromination of 3-nitrobenzoic acid

3-Nitrobenzoic acid (10 g, 0.0598 mmol), NBS (N-bromo succinamide, (11.66 g, 0.05979 mmol), and conc. H_2SO_4 (20ml) were added to a reaction vessel. The mixture was then heated to 80°C temperature for 2 h. Then the reaction was quenched with the addition of cracked ice (precipitate formation was observed) and the product was obtained by vacuum filtration. The reaction product was recrystallized from methanol. Melting point was found to be 159-161°C.

Coupling reaction

3-Bromo-5-nitro benzoic acid **1** (1 g, 0.0406 mmol), amines (primary or secondary) **2** (1eq.) and thionyl chloride (5 ml) were put into a reaction vessel. The mixture was then stirred at room temperature for 2-4 h. It was then extracted with ethyl acetate; the solvents were removed under vacuum and the obtained product was recrystallized from ethanol to yield the corresponding substituted benzamides. The ^1H and ^{13}C NMR spectra are given in the Electronic Supplementary Information (ESI).

The following are the spectral analysis of the synthesized compounds:

Synthesis of 3-bromo-N-methyl-5-nitrobenzamide (3a)

^1H NMR (400 MHz, DMSO-d_6) &8.67 (m, 1H), 8.48 (s, 1H), 8.26 (s, 1H), 7.96 (s, 1H), 2.89 (d. 3H, J=5 Hz). ^{13}C NMR 167.9, 148.3, 136.0, 134.7, 129.2, 124.5, 121.57, 26.67

Synthesis of 3-bromo-N-(2-hydroxyethyl)-5-nitrobenzamide (3b)

^1H NMR (400 MHz, DMSO-d_6) & 8.70(s, 1H), 8.42(s, 1H), 8.24 (s, 1H), 8.16(t, 1H), 4.50 (t, 1H), 3.55 (d, 1H) (d. 3H, J=5 Hz). ^{13}C NMR 166.2, 148.7, 135.2, 134.4, 128.3, 124.5, 121.5, 60.12, 42.43

Synthesis of 3-bromo-N-butyl-5-nitrobenzamide (3c)

1H NMR (400 MHz, DMSO-d_6) 8.69 (s, 1H), 8.49 (s, 1H), 8.27 (s, 1H), 8.05 (td, 1H), 3.30 (t, 2H), 1.54 (t, 2H), 1.34 (t, 1H), 0.91 (d. 3H, J=5 Hz). ^{13}C NMR 166.2, 148.7, 135.3 , 134.2, 127.9, 121.5, 39.6, 31.2, 20.4, 13.7

3-bromo-N,N-dimethyl-5-nitrobenzamide (3d)

^1H NMR (400 MHz, DMSO-d_6) 8.59 (s, 1H), 8.44 (s, 1H), 8.13 (s, 1H), 3.01 (s, 6H). ^{13}C NMR 170.2, 148.1, 136.5, 134.5, 120.9, 36.47

(3-Bromo-5-nitrophenyl)(piperazin-1-yl)methanone (3e)

^1H NMR (400 MHz, DMSO-d_6) 8.60 (s, 1H), 8.44(s, 1H), 8.14 (s, 1H), 3.56 (t, 3H), 3.48 (d, 2H), 2.81 (t, 3H), 2.16 (d, 1H). ^{13}C NMR 169.0, 148.2, 135.9, 135.1, 127.6, 123.4, 121.3, 47.3, 45.9

3-Bromo-N-(4-methoxybenzyl)-5-nitrobenzamide (3f)

^1H NMR (400 MHz, DMSO-d_6) 8.70 (d, 1H), 8.48 (s, 1H), 8.19 (s, 1H), 7.25(d, 2H), 6.86 (d, 3H), 4.44 (s, 1H), 3.79 (s, 6H). ^{13}C NMR 166.2, 158.9, 149.2, 135.7, 135.1, 133.2, 129.1, 128.4, 124.9, 121.7, 113.8, 55.3, 44.4

(3-Bromo-5-nitrophenyl)(2-methylpiperazin-1-yl)methanone (3g)

^1H NMR (400 MHz, DMSO-d_6) 8.63 (s, 3H), 8.46 (s, 3H), 8.17 (s, 3H), 4.46 (t, 1H), 3.69 (d, 3H), 3.66 (d, 3H),3.06 (t, 2H), 2.99(d, 4H), 2.93(d, 2H), 2.10(t, 2H), 1.25(t, 8H). ^{13}C NMR 168.9, 148.5, 136.9, 135.0, 127.9, 123.3, 121.4, 51.4, 45.5, 44.4, 16.12

N-Benzyl-3-bromo-5-nitrobenzamide (3h)

^1H NMR (400 MHz, DMSO-d_6) 8.69(t, 5H), 8.67(s), 8.65 (s, 2H), 8.45(s, 1H), 7.34(d, 3H), 7.24 (t, 1H), 4.54 (d, 3H)
^{13}C NMR 166.1, 149.1, 138.6, 135.7, 134.4, 128.3, 128.1, 124.9, 121.7, 43.2

3-Bromo-5-nitro-N-(o-tolyl)benzamide (3i)

^1H NMR (400 MHz, DMSO-d_6) 9.68(s, 1H), 8.73(s, 1H), 8.45 (s, 1H), 8.20(s, 1H), 7.18 (t, 2H), 2.31(s, 3H). ^{13}C NMR 165.3, 149.1, 138.9, 135.6, 134.9, 133.2, 129.1, 128.5, 127.2, 125.5, 124.2, 121.6, 119.0, 17.7

3-Bromo-N-(furan-2-ylmethyl)-5-nitrobenzamide (3j)

^1H NMR (400 MHz, DMSO-d_6) 8.70(s, 1H), 8.58(t, 2H), 8.45 (s, 1H), 8.20(s, 1H), 7.34(d, 1H), 6.28 (d, 3H), 4.50 (d, 4H). ^{13}C NMR 166.4, 151.8, 149.1, 142.4, 135.6,134.9, 128.1, 134.8, 122.1, 110.4, 107.8, 37.3,

RESULTS AND DISCUSSION

The substituted benzamides are synthesized as per the established route of synthesis. The thionyl chloride was used as promoter in the synthesis (Scheme 1). We have optimized the condition for the preparation of our substituted products. Some solvents and solvent free conditions were also tested. We have presented the optimization conditions in Table 1.

Table 1. Effect of solvents in the preparation of **3a**

Entry	Solvents	Time, h	Yield,[a] %
1	Toluene	20	58
2	DMF	18	31
3	Methanol	12	32
4	Dichloromethane	9	85
5	Solvent free	2	94

[a]Isolated yield

As can be seen from the above data, the reaction goes well in the absence of any solvent and the reaction time as well as the percentage yield of the synthesized compounds better than in the presence of solvents. Using toluene as the solvent the time required for completion was 20 h with only 58% yield (Table 1, Entry 1). Using N,N-dimethylformamide (DMF) the yield drastically decreased to 31% with 18 h of reaction time (Table 1, Entry 2). Methanol was also tried but the obtained yield was again very low (Table 1, Entry 3). Dichloromethane (DCM) was used which to our surprise gave 85% yield in 9 h but the product obtained was somewhat sticky which required further purification (Table 1, Entry 4). Lastly the reaction was carried out in the solvent free condition which not only increased the yield to 94% but also decreased the reaction time to 2 h (Table 1, Entry 5). Hence further derivatization was carried out in a solvent free condition to obtain the required products. The possible reaction mechanism is explained in Figure 1.

The first step is that 3-bromo-5-nitro benzoic acid reacts with the thionyl chloride species to form a 3-bromo-5-nitrobenzoyl chloride complex which acts as an intermediate for the coupling reaction. Due to high electronegativity of benzoyl chloride group, coordination is orientated by the partial charges on NH^+ and on the electronegative 3-bromo-5-nitrobenzoyl chloride group which assists the substitution by the amines to get desired product.

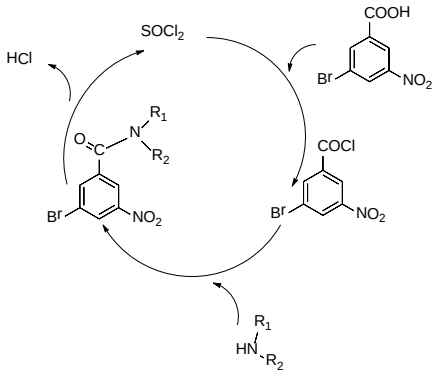
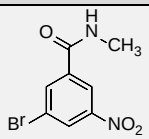
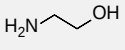
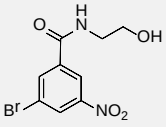
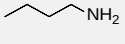
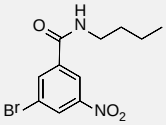
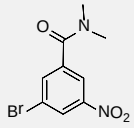


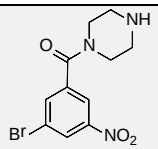
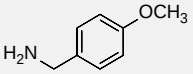
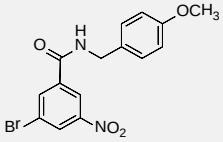
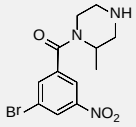
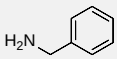
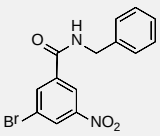
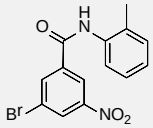
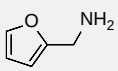
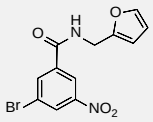
Figure 2. The plausible reaction mechanism

CONCLUSION

We have prepared novel benzamides using thionyl chloride to perform thecoupling reaction of 3-bromo-5-nitrobenzic acid and amines. Our method has minimum environmental impact, is flexible and economic. The reaction is done without using any transition metal catalyst, ligand, base, toxic or hazardous reagent, additives, promoters and organic solvent (i.e. solvent free). We believe that this substituted benzamide compound protocol has major importance in industry, laboratory as well as a drug intermediate due to all its advantages.

Table 2. Synthetic details of the prepared 3-bromo-5-nitrobenzamides

Entry	Amines	Prepared compound	Time, h	%Yield	Melting or boiling point, °C
3a			2	94	143
3b			2	90	136.8
3c			2	91.5	141
3d			3	85	298 (BP)

3e			3	80	142.9
3f			4	91	210 (BP)
3g			3	85	260 (BP)
3h			4	90	240 (BP)
3i			2	90	250 (BP)
3j			3	80	400 (BP)

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INFLUENCE OF SODIUM ON ASSIMILATION PROCESS OF Cr(VI) AND Cu BY *ARTHROBACTER* GLOBIFORMIS 151B CHROMIUM-RESISTANT BACTERIUM

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Keywords: bacteria; *Arthrobacter globiformis* 151B; biomass; metals; concentration.

The process of assimilation of Cr(VI) and Cu by chromium-resistant bacteria (*Arthrobacter globiformis* 151B) and the influence of high-concentration Na ions on this process have been studied. The bacteria are known for their property to assimilate the hexavalent chromium ions from the environment intensively, to convert them into trivalent form and to accumulate it in the cell. Thanks to these properties, it is possible to use them for detoxification of the environment, polluted by highly toxic Cr(VI). The strain of bacteria under investigation was isolated from basalt samples taken from the places highly contaminated by Cr(VI) in Kazreti. The solutions of the studied elements (Cr and Cu) and Na were introduced simultaneously into the nutrient medium. We studied the influence of different concentrations of Na ions during a different period of time of bacteria cultivation (17h, 24 h, 48 h, 96 h and 144 hours) on the process of assimilation of Cr and Cu by bacteria. The concentration of Na in the nutrient medium was 2, 3.5, 6.5 and 9.5 g mL^{-1}. For determination of the content of metals (Cr, Cu, and Na) in the cell, after the cultivation of bacteria, the precipitation of cells by centrifuge and the preparation of the obtained bacterial pellet for the analysis were carried out. The content of metals was measured by atom-absorption spectrometry.

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Introduction

Metals at the excess concentrations have toxic and carcinogenic properties. It is very important to develop the technologies by means of which it is possible to remove the toxic metals from the environment. Among the most prospective methods of remediation of the polluted environment are the biological technologies based on the use of different microorganisms.[1,2]

The pollution of the environment by the materials containing Cr(VI) is an urgent problem for many countries.[3] In Georgia, the places which are most contaminated by heavy metals, are Kazreti and Zestaphoni,[4] where the concentration of Cr in the soil and water reaches several hundreds of mg L^{-1} (the permissible concentration of Cr(VI) in surface waters is less than 0.05 mg L^{-1}.[3]

Chromium can be extremely toxic or non-toxic depending on its concentration and valence state.[5] In nature usually, it is met in trivalent and hexavalent forms, which have different transport properties. Cr(VI)- compounds are well water-soluble and toxic, while Cr(III)-compounds are less water-soluble and relatively harmless. The genotoxic and carcinogenic action of Cr(VI)-contained material is caused by their ability to penetrate rapidly into the cell, as well as by activation of this ability as a result of the intercellular reduction process.[6]

Detoxification of Cr(VI) that appeared in the environment can be made by its conversion into trivalent chromium, mainly, in the form of $Cr(OH)_3$ or makes a complex with surrounding ligands.[7] Various bacterial species (e.g., *Escherichia*, *Pseudomonas*, *Shewanella*, *Desulfovibrio*, *Bacillus sp.*)[8] are able to reduce Cr(VI). The recent researches proved that most of the studied bacterial strains are not metal resistant/tolerant. They lose their viability in co-existence of high concentration of heavy metals. Thus, it is reasonable to isolate the bacteria under investigation directly from the soil, mineral strata and water contaminated by metals.[9–15] At present, the testing of technologies based on endogenic microorganisms is carried out intensively,[16–18] providing that recently the application of biotechnologies is of high priority in the process of environment reduction in many countries.[19] The efficiency of biotransformation depends on the mechanism of bacteria–metal interaction, thus, for bacteria of any specific species, it is necessary to study this mechanism preliminarily in detail.

A significant part of experiments was concentrated on Gram-negative bacteria – a number of experiments concerning Gram-positive bacteria are comparably less. Not much is the number of experiments concerning the interaction of Gram-positive bacteria with heavy metals. According to new data,[11] Gram-positive bacteria appeared to be tolerant to higher doses of Cr(VI), as compared to gram-negative bacteria. Few are the information about the reaction

of bacteria to high doses of chromium. The mechanism of origination of chemically active intermediate (Cr(V)/Cr(IV)) products in the process of reducing Cr(VI) by bacteria, practically, is not studied. In this context, the pioneering research was carried out by Georgian investigators (N. Tsibakhashvili et al.).[20]

The vital natural medium of bacteria, which we are interested in contains, alongside with the elements under investigation (Cr and Cu), the (macro) elements that are widely spread in nature (Na, K, Si, …). These elements have an influence on the growth–evolution of bacteria, including the process of assimilation of elements (Cr and Cu) by bacteria and the biochemical process proceeding in bacteria. It is interesting to study the influence of macroelements on the process of assimilation and distribution of Cr(VI) and other elements in bacteria. The experimental material obtained as a result of the proposed and the similar investigation makes it possible to draw a certain conclusion about the biochemical processes taking place in bacteria and about the mechanisms, by which the assimilation of metals and the conversion of their compounds are made.

Experimentals

For the object of investigation, we chose the bacteria of *Arthrobcter globiformis* 151B. As is known,[21] the bacteria of Arthrobacter family are aerobic gram-positive bacteria living in the soil. They belong to Arthrobacteria class, type – Actinomycetales. According to the existing data,[22,23] they have a high potential of remediation of the chromium-contaminated environment. The selected bacteria were removed from basalt rocks**,** taken from ecologically the most contaminated regions of Georgia (Kazreti, Zestaphoni).[24] From the chosen basalts 157 endolithic bacteria resistant to Cr(VI) were singled out, among which 33 appeared to have the ability to remediated high concentrations of Cr(VI) (about 1000 mg L^{-2}). The objects of this investigation are bacterial strains isolated from Kazreti basalts.

For studying the influence of Na on the process of assimilation of Cr(VI), Cu and other elements by *Arthrobcter globiformis* 151B, we cultivated bacteria in 500 mL Erlenmaier flasks in 100 mL TSB broth. We additionally introduced Na solution in the form of NaCl into some samples (flasks), thus, the concentration of Na in the nutrient medium was 2, 3.5, 6.5 and 9.5 g mL^{-1}. In addition, the Cr(VI) solution was added in the same samples with concentrations of 40 μg mL^{-1}. The nutrient medium contained the studied elements in the following concentrations: Cr – 7 and Cu – 0.06 μg mL^{-1}.

The cultivation of bacteria proceeded during 17 and 24 h, and 2, 4 and 6 days. After cultivation we carried out the precipitation by centrifuge (3000 rpm, 10 min, 0 °C), we poured out supernatants and the remained bacterial pellet washed in sterile distilled water. We dried the obtained biomasses by low-temperature lyophilizer and weighted them (the whole masses). From the total quantity of bacterial pellet, we took the amount necessary for analyses, weighted it (~30 mg) and put it into test tubes. In order to convert the samples into a liquid state, we added the concentrated nitric acid (1 mL) into the test tubes, heated it and after complete ashing dissolved it. The analysis of the obtained samples on the content of metals was made by an atom-absorption spectrometer (Analyst 800, acetylene-air flame).

Results and discussion

We studied the process of assimilation of Cr(VI) and Cu by bacteria and the influence of Na ions of this process. The process of Na absorption by the bacteria *Arthrobacter globiformis* 151B was also studied. The results of measurement are given in Figures 1 – 4.

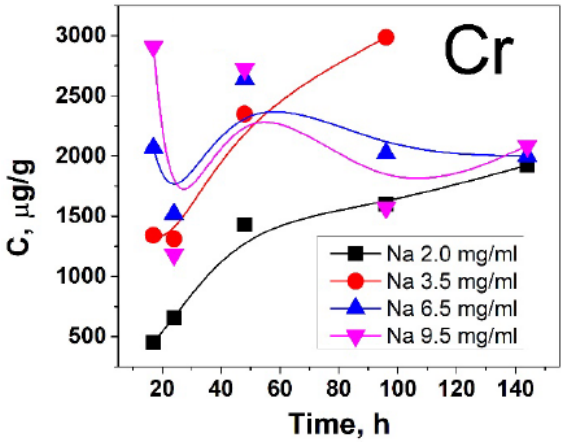

Figure 1. Dependence of Cr concentration (*C*, μg g^{-1}) in bacteria on time of growth–evolution of bacteria *t*(*h*). Concentration of Na in nutrient medium was 2.0, 3.5, 6.5, and 9.5 mg mL^{-1}.

As it is seen from the obtained results (Figure 1), Cr(VI) (40 μg mL^{-1}) added into the nutrient medium causes an abrupt increase of the content of Cr in bacteria during 4 days of their growth–evolution. In the nutrient medium with 7 and 40 μg mL^{-1} contents of Cr, on the 6th day of cultivation, an equalization of Cr content takes place. In the samples taken after 17 h cultivation, together with the increase of the concentration of added Na, the content of Cr is increasing as well. In the medium containing Na, after 24-hour cultivation the content of Cr in bacteria decreases and makes about one and the same value

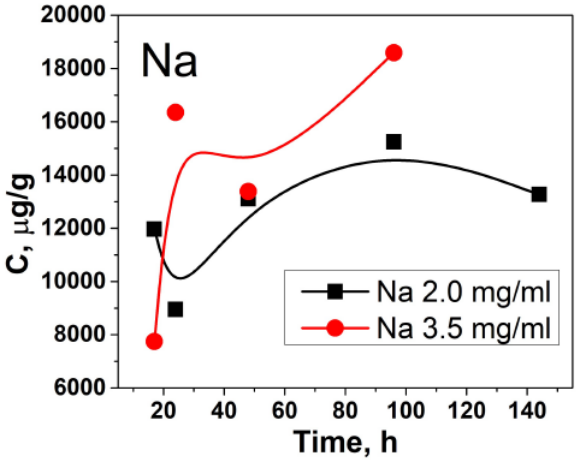

Figure 2. Dependence of Na concentration in bacteria (C, μg g^{-1}) on time of growth–evolution of bacteria *t* (*h*). The concentration of Na in the nutrient medium was 2 and 3.5 mg mL^{-1}.

The decrease of Cr content coincides with the increase of bacteria biomass (see below). In bacteria grown in 2 days, the rise of Cr is observed, coinciding with the decrease of bacterial biomass.

As shown in Figure 2, the Na content in bacteria drops sharply at 24 h like Cr, when the Na content in the food medium is 2 mg mL^{-1}. When the Na content in the food medium is 3.5 mg mL^{-1}, the Na content increases dramatically at 24 h.

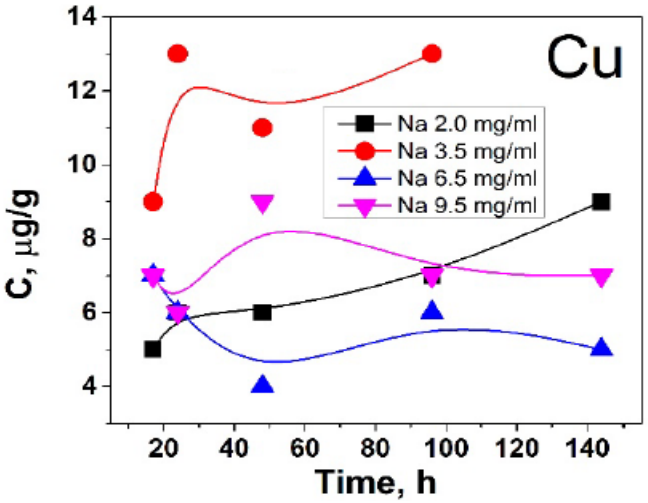

Figure 3. Dependence of Cu concentration (*C*) in bacteria on time of growth–evolution of bacteria *t*(*h*).

After 17 h of cultivation, the Cu content in bacterial cells increases, when Na is added to the nutrient medium. When the cultivation time is 24 hours, in the bacterial cells the Cu content is reduced, when in the nutrient medium the Na content is 6.5 mg/ml and 9.5 mg /ml. (Figure 3).

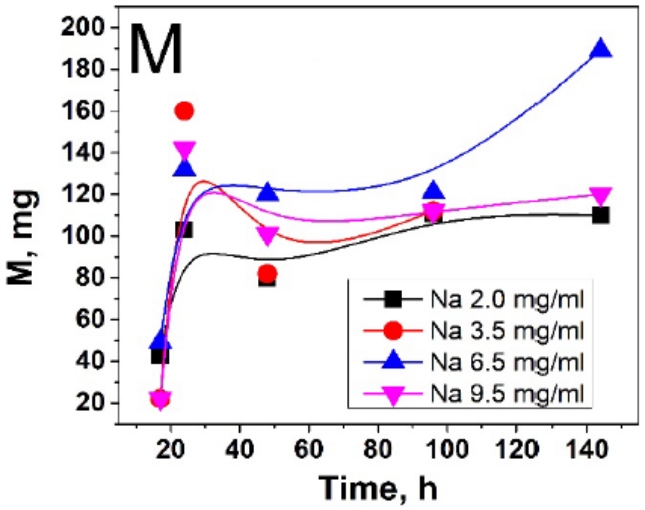

Figure 4. Dependence of bacteria masses *M* (mg) on time of growth–the evolution of bacteria *T*(*h*).

As it is seen from the results obtained (Figure 4), bacteria is evaluating rapidly during 17–24 h. Na added into nutrient medium favors the growth-development of bacteria.

Therefore, Na, added to the nutrient medium, contributes to the growth and development of bacteria during this period. After 48 h cultivation, in case of existence of different concentrations of Na in the nutrient medium, the bacterial biomass is decreased. For a further period (4 and 6 days) a gradual increase of the bacterial biomass is observed. It can be said that Na added into the nutrient medium slightly favors the growth of bacteria during the whole period of its growth–evolution.

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UTILIZATION OF SLUDGE RESULTED FROM CHLORINE INDUSTRY IN WASTEWATER TREATMENT

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Keywords: Chlorine industry sludge; heavy metals; wastewater treatment; activated brine sludge; non-activated brine sludge.

The chlorine industry sludge (CLS), which is a solid by-product resulted from the chlorine industry plants, is successfully applied as an effective adsorbent for removal of the heavy metal ions. CLS was activated by grinding to about 10 μm particle size and burned to 700 ºC for 3 h (ACLS) The physicochemical characteristics of CLS and ACLS were investigated using X-ray diffraction (XRD), scanning electron microscope (SEM) coupled with energy dispersed X-ray analysis (EDX) unit and texture propertied using N_2 adsorption-desorption isotherms. CLS and ACLS are tested for removal of Cu(II), Cd(II) and Pb(II) from the wastewater solutions under various factors such as contact time, pH and adsorbent dose. Results showed that CLS as well as ACLS exhibit high removal efficiency of the studied heavy metal ions. These nominate them as low-cost adsorbent for Cu(II), Cd(II), and Pb(II) ions.

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INTRODUCTION

Water resources and water supplies are a critical task which appeared recently. Only about 3 % of the water on Earth is fresh water while about 97% is salty water. Besides, more than two-thirds of the fresh water is frozen in the polar ice caps and glaciers.

Drinking water sources are contaminated by various contaminates due to the rapid industrial and civil development makes it unfit for its natural or intended uses. Contamination of drinking water sources by the heavy metals species may cause many severe health problems, diseases and in some may be fatal.[1,2]

The WHO gave standard regulation which specifies the limits of Total Dissolved salts (TDS), pH, metals, and other limits. Supply of clean and safe drinking water is the most crucial thing to the human life, and safe drinking water should not impose a considerable risk to humans.[3]

Brine Sludge is a solid by-product resulted from the chlorine industry. This solid by-products results as a precipitate from the coagulation-flocculation process from the treatment of the brine solution in the chlorine industry. The chemical composition of chlorine-sludge (CLS) have small changes depending on the source of salt which is used in the preparation of the brine solution under treatment as well as the types of chemical used in the chemical treatment, PH, temperature of the solution and the coagulant agent used.[4-7]

Due to the high rate and massive production of this waste many researchers tried to reuse of this solid waste material or treated it before reuse it in different applications. However, the key to reuse of these solid wastes or cycle them is the knowledge of their composition and characterization of their properties. Many researchers introduce brine sludge in the wastewater treatment as effective removal of heavy metal species from their wastewater solutions.[8-10]

The aim of this study is the reuse of CLS and activated CLS (ACLS) as a low-cost adsorbent for the removal of copper, cadmium and lead metal ions from the wastewater solutions.

Experimentals

The solid waste material:

Brine chlorine sludge (CLS) was produced during the standard chemical treatment of the brine solution in the chlorine-alkali plant (Egypt). CLS was treated as a solid residue by collecting the precipitate resulted from the coagulation-flocculation process, drying for 6 h at 110 °C then compresses at 300 bar. Activation of CLS done by grinding it to particle size 10 μm and heating at 700 °C for 2 h.

$Cu(NO_3)_2{\cdot}3H_2O$ (MW: 241.6, purity: 99 % and produced by Central Drug House LTD laboratory reagent), $Cd(NO_3)_2{\cdot}4H_2O$ (MW: 308.48 and purity: 99% and produced by Central Drug House LTD laboratory reagent) and $Pb(NO_3)_2{\cdot}6H_2O$ (MW: 331.21 and purity: 99% and produced by Alpha Chemika laboratory reagent) were used for the preparation of synthetic wastewater solutions used in the present study. Solutions of (0.1 M) of each nitric acid and sodium hydroxide were used to adjust pH.

Adsorption experiments

Batch adsorption experiments are carried out to examine the efficiency of brine sludge (activated, non-activated) for removing heavy metals ions from wastewater.[11] This includes the study the effect of contact time, initial solution pH, adsorbent dosage, initial metals concentration, and the

competitive metal ions were studied on the removal efficiency. The various experiments were carried out as follow:

Effect of contact time

0.5 g of CLS and activated CLS shacked with 50 mL of individual solutions of Pb, Cd or Cu nitrates (100 mg L^{-1}) in glass stopper conical flask for different time intervals; 2, 4, 6, 8, 12 and 24 hours at initial pH 5. At each time interval; filtration was carried out and the remaining concentration of each heavy metal by using inductively coupled plasma spectrometer ICP-OES Perkin Elmer Optima 8300 DV, equipped with a S10 Auto sampler and a Cetac 5000 Ultrasonic nebulizer. The removal (*R*) efficiency was calculated according to the following equation.

$$R(\%) = \frac{C_i - C_f}{C_f} \qquad (1)$$

where *R* is the of the removal efficiency and C_i and C_f are the concentration of the heavy metal ion in solution before and solution after removing process(mg L^{-1}).

Effect of adsorbent mass

50 mL of individual solutions of Pb, Cd or Cu nitrates (100 mg L^{-1}) are stirred with different dose of CLS or ACLS for 2 h at an initial solution pH 5. After 2 h, filtration was carried out, and the remaining concentration of each heavy metal was tested as mentioned above. The removal efficiency (*R*) was calculated by Eq .1.

Effect of solution pH

0.5 g of CLS or ACLS shacked with 50 mL individual solutions of Pb, Cd or Cu nitrates (100 mg L^{-1}) for contact time 2 h, and initial pH of the solution was adjusted at 3, 5, 7, 9 and 11) using HCl or NaOH. Solutions pH was measured using a HACH portable pH Meter model Sens ion 156 (malty parameters). After 2 h, filtration was carried out, and the remaining concentration of each heavy metal was tested by inductively coupled plasma spectrometer. The removal efficiency (*R*) was calculated by Eq .1.

Methods of physicochemical measurements

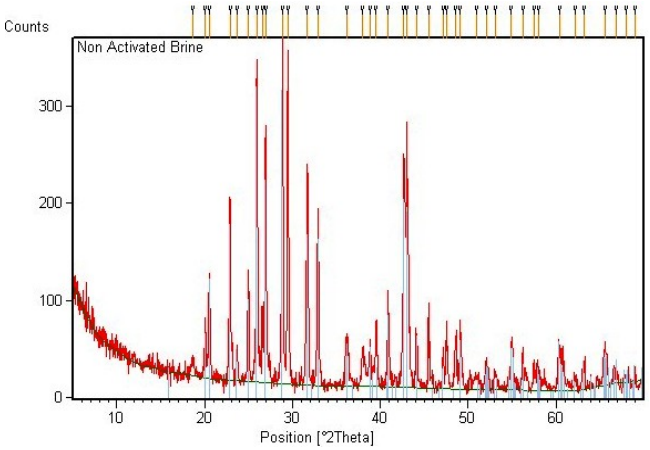
Phase compositions of each solid wastes used were examined using X-ray diffraction (XRD) analysis. For X-ray examination, a stabilized X-ray generator fitted with a copper target X-ray tube was used. The tube was run at 30 kV with 15 mA divergence.

Microstructure and surface morphology verified using scanning electron microscope (SEM). This done using SEM Model Quanta 250 FEG (Field Emission Gun) attached with EDX Unit (Energy Dispersive X-ray Analysis) with accelerating voltage 30 kV, magnification up to 1000000. The samples were covered by a thin filament of gold to improve conductivity during the examination.

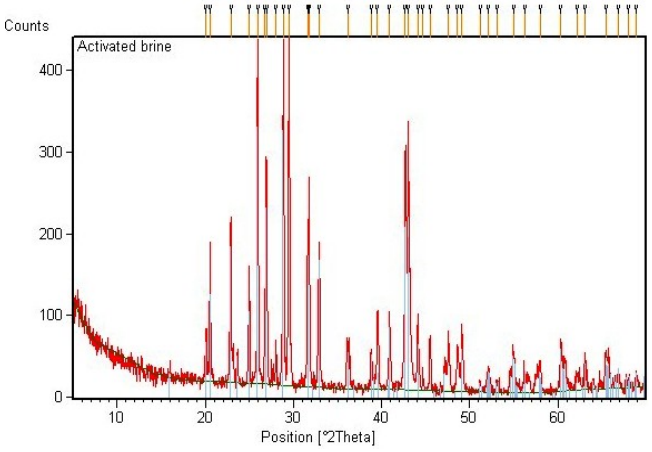
RESULTS AND DISCUSSION

Characterization of solid sludge

XRD charts of both CLS and CLS burned at 700 °C are shown in Figs. 1a and 1b. According to Fig. 1a and b; the main phases identified are illite and quartz in ACLS sample while albite phase appears only for CLS sample. Using quartz, illite and albite as an adsorbent for the removals of heavy metal ions are well known.[12,13]



a)



b)

Figure 1. XRD analysis for CLS (a) and ACLS (b)

SEM micrograph of CLS and ACLS and EDAX are shown in Figures 2a and 2b. CLS shows a loose structure composed mainly of oxides of Si, Ca and Mg. Traces of Cl and Ba are identified in EDAX of CLS. After activation at 700 ^{0}C, ACLS shows a more compact structure of similar oxides with an increased crystallinity and reduced chloride content.

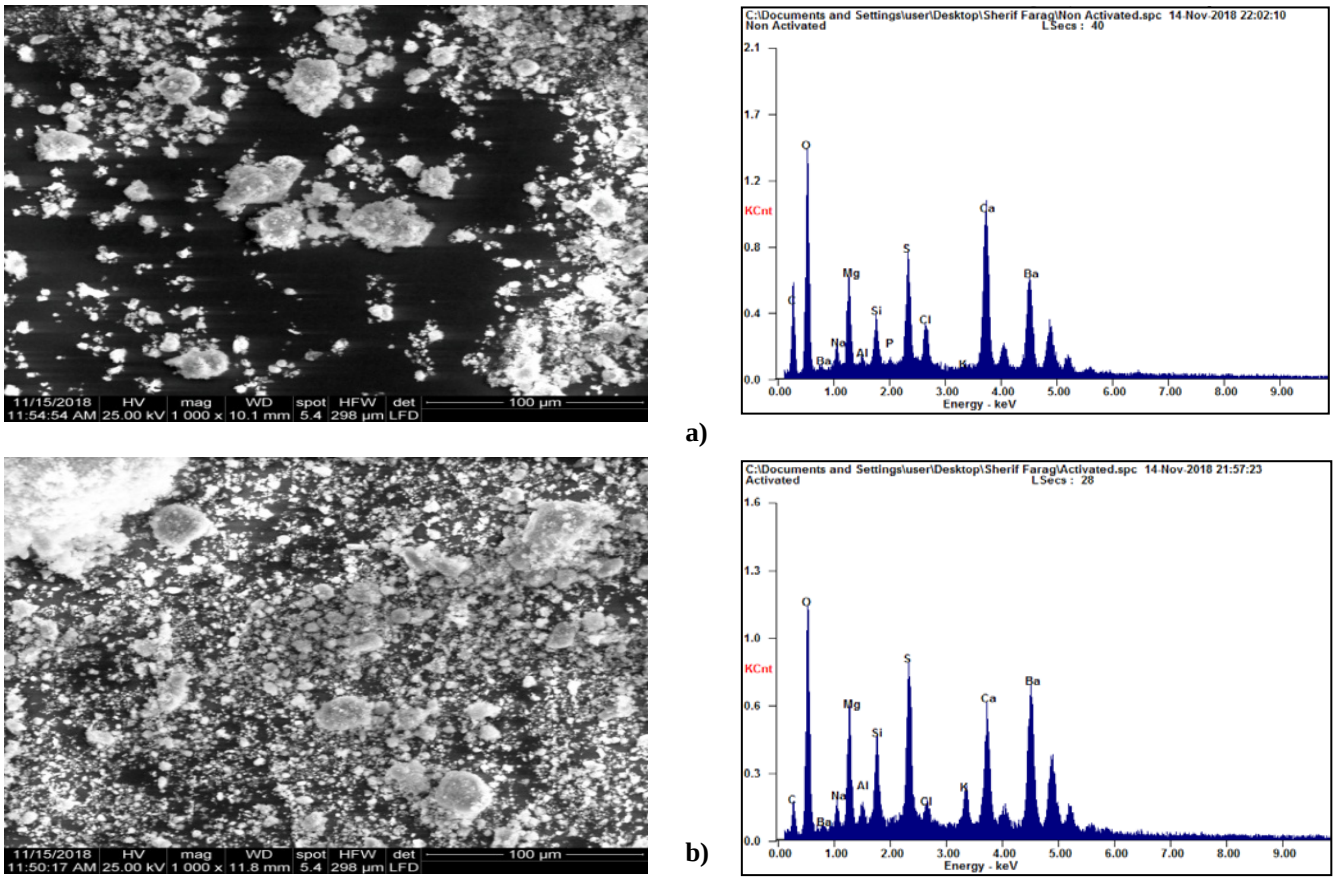


Figure 2. SEM and EDAX analysis for a) CLS and b) ACLS

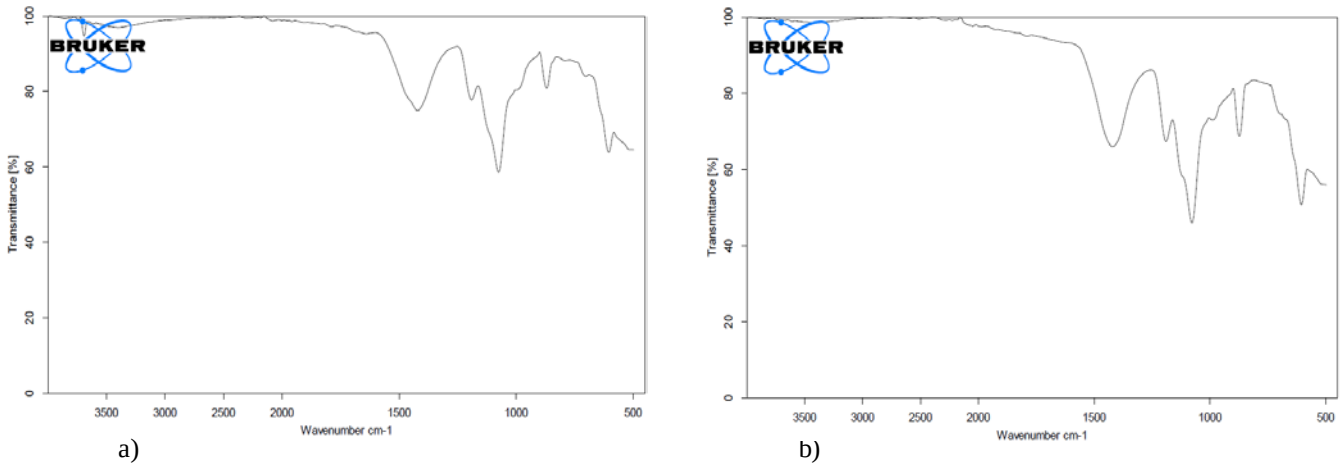


Figure 3. FTIR spectrum for a) CLS and b) ACLS

The IR spectra of CLS and ACLS samples are shown in Figs. 3a and b. The main function groups identified in FT-IR of CLS are the stretching vibration of Si=O band at 1450, and Si-O-Si at 980 cm^{-1}. Thermal activation did not change these function groups as indicated by the similarities in the FT-IR spectrum of CLS and ACLS.

Adsorption experiments

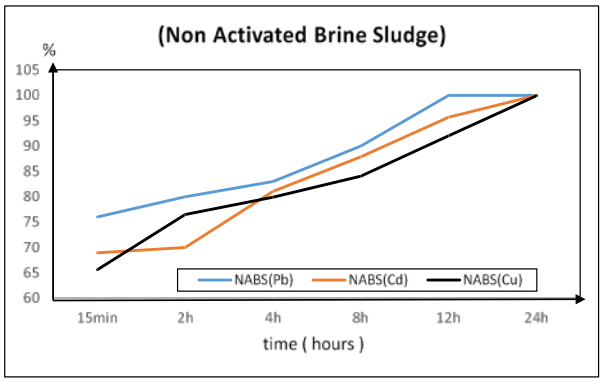
Effect of contact time

Figs. 3a and 3b show the effect of time on the removal efficiency (*R*%) of brine sludge (activated and non-activated) for Pb^{2+}, Cd^{2+} and Cu^{2+} ions from wastewater. The removal efficiency for CLS and ACLS increases with the soaking time for the three studied heavy metals ions. About 65% of the heavy metal ions are removed during the first 15 minutes and the equilibrium state reached after 24 h. Non activated brine sludge (CLS) shows removal efficiencies higher than those for activated brine sludge (ACLS) especially in case of Cd^{2+} ions.

Effect of adsorbent mass

Effect of adsorbent mass is an important parameter which indicates the active site in the adsorbent texture. Fig 5 shows the effect of increasing the mass of brine sludge on the removal efficiency. Generally increasing the sludge mass increases the *R* % value.

a)



b)

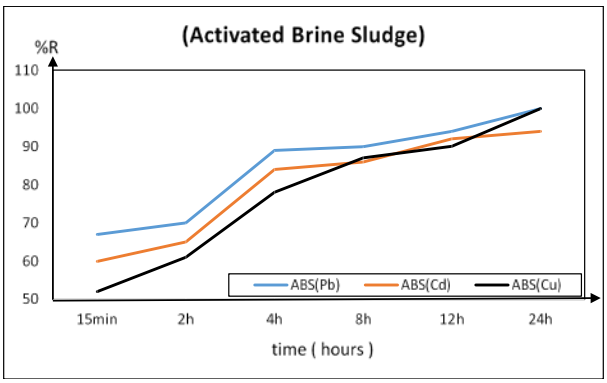
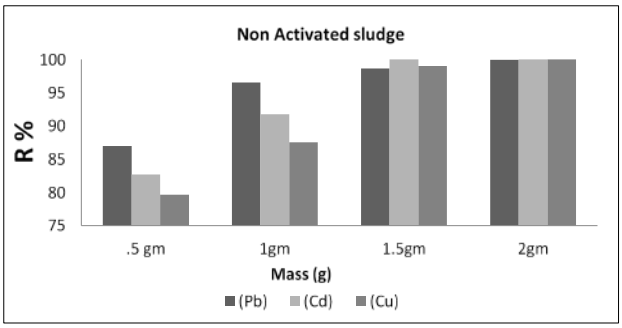


Figure 4. Effect of soaking time on removal efficiency for a) CLS and b) ACLS

a)



b)

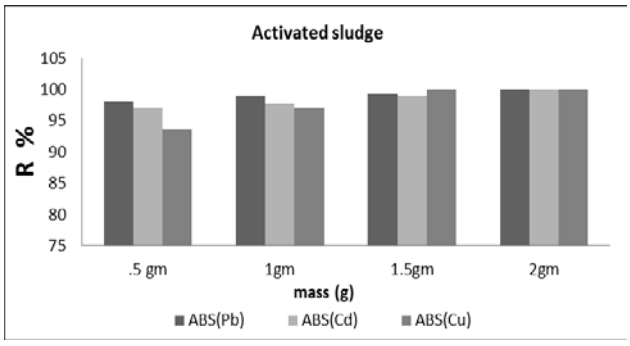


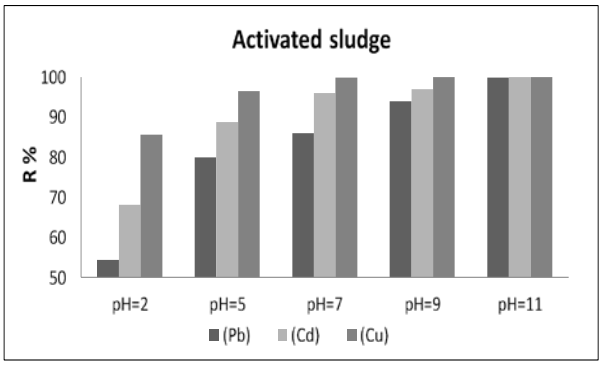
Figure 5. Effect of soaking time on Removal Efficiency for a) CLS and b)ACLS

Activated sludge (ACLS) shows higher *R*% at low absorbent mass 0.5 and 1 g than non-activated (CLS), especially for Cd $^{+2}$and Cu $^{+2}$ ions. However, at higher mass, the removal efficiency is similar for both CLS and ACLS.

Effect of solution pH

Figure 6 shows the effect of solution pH on *R* %. At low pH, *R*% for the three studied heavy metal decreases which can be attributed to the competition between H^+ and positive heavy metal ions to adsorbed in the active site on the brine sludge. Increasing the pH values to become near the neutral or alkaline values will lead to deprotonation of the acid sites on the CLS or ACLS surface and the surface becoming negatively charged with highly attractive properties.[14] This leads to an increase in the surface diffusion of M^{2+} ions into the adsorbent surface which highly increased the percentage of removal.

a)



b)

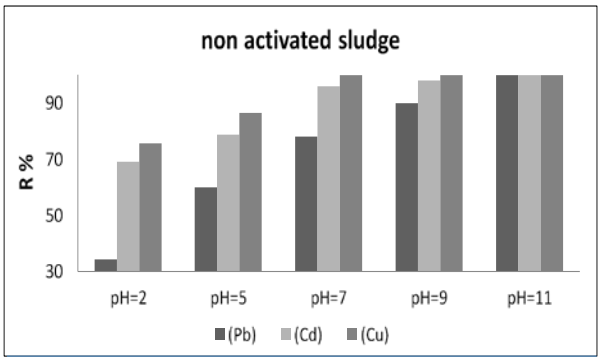


Figure 6. Effect of solution pH on removal efficiency for a) CLS and b) ACLS

Besides at alkaline pH, M^{2+} ions undergoes hydrolysis to MOH^+ and $M(OH)_2$ and these species have higher removal efficiency than that of M^{2+}.[15] Pb^{+2} ions undergo hydrolysis to $Pb(OH)_2$ between pH 6-10 while Cd^{+2} ions precipitate as $Cd(OH)_2$ only at pH > 7.

Conclusion

A sludge which is a by-product resulted from the chlorine industry plants during wastewater treatments was a useful absorbent or precursor of an absorbent for removal of the heavy metal ions such as Cu(II), Cd(II) and Pb(II) from the water. The high adsorption capacity of activated and non-activated brine sludge towards these ions ensures that they were proved to be low-cost adsorbent for these heavy metals.

There is no leaching effect after the adsorption which makes using the activated and non-activated brine sludge are more valuable in the wastewater treatment processes.

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SILICA SUPPORTED POLYPHOSPHORIC ACID CATALYZED SYNTHESIS OF SUBSTITUTED INDAZOLES

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Keywords: silica supported polyphosphoric acid; hydrazine hydrate; phenyl hydrazine; o-hydroxyacetophenones; indazole.

A clean and straightforward methodology developed for the synthesis of substituted indazoles using silica supported polyphosphoric acid (PPA-SiO_2) catalyzed condensation reaction between substituted 2-hydroxybenzaldehydes or acetophenones and hydrazine hydrate or phenylhydrazine. The reaction conditions are optimized for different solvents at different temperatures. The yield of the products improved to 88 to 90 % using silica supported polyphosphoric acid as a catalyst, which is reusable, cost-effective and straightforward to synthesize.

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Introduction

Indazole and its derivatives were important pharmacological compounds as benzene attached five-membered heterocyclic ring containing two nitrogen atom at 1,2-position forms a large number of drug moieties like HIV protease inhibition, anti-inflammatory, inhibition of protein kinase, high binding affinity for estrogen receptor,[1] 5-HT2 and HT3 receptor antagonism.[2] In literature precedent various methods have been reported by different researchers for the synthesis of indazoles and substituted indazoles. Main procedures involve cyclization of 2,6-dihydroxyacetophenone hydrazones in the presence of polyphosphoric acid,[3] using $NaHSO_3$/DMF,[4] chromium tricarbonyl complex,[5] trimethylsilylindazole/CSF,[6] 3-carboxyindazole,[7] palladium-catalyzed intramolecular amination reaction of N-tosylhydrazones trimethyl-silylindazole[8] as well as aryl halides[9] and copper-catalyzed synthesis of indazole.[10] Indazole N-oxide are also reported through 1,7-electrocyclization of azomethine ylides.[11] Condensation of o-fluorobenzaldehydes and their oximes with hydrazine[12] also yield indazoles, literature survey reveals that cyclization of o-substituted aryl hydrazones with halogens, nitro and methoxy[13] group as a substituent, 3-substituted indazole and benzoisoxazoles synthesis via palladium catalyzed cyclization reactions.[14]

Hangirgekar reported the synthesis of indazoles from 2-alkoxy-acetophenone, hydrazine hydrate and a catalytic amount of Montmorillonite K-10 in different solvents ethanol, methanol, toluene, acetonitrile, DMF, THF and DMSO.[7]

In this paper, we have reported reusable solid supported acid catalyst (PPA-SiO_2) as an efficient and mild protocol for the synthesis of indazoles. We have also optimized the reaction temperature to get maximum yield (Table 1 and 2) in ethanol and DMSO as solvents.

Experimental

General

All chemical used were AR grade and without further purification. All the products are known and their physical parameters are confirmed by comparison with the reported literature data. The catalyst was prepared according to the literature.[15] Melting points were determined in open capillaries and reported uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on at 400 MHz instruments in $CDCl_3$ using TMS as an internal standard.

Preparation of catalyst (PPA-SiO_2)

PPA (2.1 g) was taken in 100 ml round bottom flask and $CHCl_3$ (50 ml) was added. Then the reaction mixture was stirred well at room temperature and then heated 50 ^{o}C for 1 h. SiO_2 (400 mesh, 4.9 g) was added in portions to the solution. The mixture was stirred for further 1 hr. The solvent $CHCl_3$ was distilled off under vacuum and resulting solid was dried under vacuum at 35-40 ^{o}C for 2 h.

Synthesis of 1H-indazoles (3a,3b,3e,3f)

The mixture of salicylaldehyde (1 mmol), hydrazine hydrate (1.5 mmol) and silica supported polyphosphoric acid (20 mole %) in a solvent (5 mL) was stirred for different time intervals at different temperatures (Table 1). The progress of the reaction was monitored by TLC using n-hexane:ethyl acetate (8:2) solvent. After completion of the reaction, the reaction mixture was cooled to room temperature and the catalyst was filtered off. The catalyst was washed with the solvent (2x2 mL) and reused for other reactions. The collected filtrate was poured onto crushed ice to obtain crude product. The product is filtered and purified by recrystallization using methanol.

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Synthesis of 1-phenyl-1H-indazole (3c,3d,3g,3h)

A mixture of 2-hydroxyacetophenone (1 mmol), phenylhydrazine/2,4-dinitrophenylhydrazine (1 mmol) and PPA-SiO_2 (20 mol %) in a solvent (5 mL) was heated to 75 to 95 ^oC. The progress of the reaction was monitored by TLC using n-hexane:ethyl acetate (8:2) solvent. After the completion of the reaction, the reaction mixture was cooled to room temperature and the catalyst was filtered off and washed with the solvent (2x2 mL) and to use in other reaction. The filtrate was collected and poured into crushed ice (20 g), the crude product was filtered and recrystallized using methanol as solvent.

Characterization and spectral data for selected products

The physical parameters of compound **3a-3h** are determined and reported in table no. 1and 2. The final products were characterized by ^1H NMR and ^{13}C NMR.

1H-Indazole (3a)

^1H NMR ($CDCl_3$): δ 7.10 (1H, d, Ar-H) 7.31 (1H, d, Ar-H) 7.53 (1H, dd, Ar-H) 7.55 (1H, dd, Ar-H) 8.25 (1H, s) 13.05 (1H, s, NH, D_2O, exchangeable). ^{13}CNMR ($CDCl_3$): δ 139.7, 133.2, 122.70, 120.0, 109.9, 78.8, 39.7.

3-Methyl-1H-indazole (3b)

^1H NMR ($CDCl_3$): δ 13.25 (1H, s, NH, D_2O, exchangeable), 6.91 (1H, d, Ar-H), 7.02 (1H, dd, Ar-H), 7.25 (1H, dd, Ar-H), 7.37 (1H, d, Ar-H), 2.57 (3H. s). ^{13}CNMR ($CDCl_3$): δ δ 168.1, 160.6, 132.9, 128.9, 119.0, 117.9, 77.3, 14.8.

1-(2,4-Dinitro-phenyl)-1H-indazole (3c)

^1H NMR ($CDCl_3$): δ 9.26 (1H, s, Ar-H), 8.67 (1H, d, Ar-H), 7.80 (1H, d, Ar-H), 8.40 (1H, s, Ar-H), 7.84 (1H, d, Ar-H), 7.37 (1H, dd, Ar-H), 7.34 (1H, dd, Ar-H), 7.12 (1H, d, Ar-H). ^{13}CNMR ($CDCl_3$): δ 119.8, 139.6, 148.8, 135.4, 153.5, 148.9, 134.8, 142.7, 128.4, 114.2, 121.1, 126.5.

1-(2,4-Dinitro-phenyl)-3-methyl-1H-indazole (3d)

^1H NMR ($CDCl_3$): δ 8.98 (1H, s, Ar-H), 8.38 (1H, d, Ar-H), 8.1 (1H, d, Ar-H), 7.89 (1H, d, Ar-H), 7.24 (1H, dd, Ar-H), 7.56 (1H, dd, Ar-H), 7.60 (1H, d, Ar-H), 2.92 (3H, s). ^{13}CNMR ($CDCl_3$): δ 24.1, 114.8, 1462, 134.3, 143.6, 161.0, 141.9, 117.3, 150.1, 135.4, 126.4, 120.2, 117.0, 108.4.

6-Nitro-1H-indazole (3e)

^1H NMR ($CDCl_3$): δ 8.41 (1H, s, Ar-H) 8.31 (1H, d, Ar-H) 7.82 (1H, d, Ar-H) 8.51 (1H, d, Ar-H), 12.08 (1H, s, NH, D_2O, exchangeable). ^{13}CNMR ($CDCl_3$): δ 128.4, 132.7, 149.4, 102.5, 165.4, 118.2, 114.2.

5-Nitro-1H-indazole (3f)

^1H NMR ($CDCl_3$): δ 8.21 (1H, s, Ar-H) 8.84 (1H, d, Ar-H) 7.94 (1H, d, Ar-H) 8.86 (1H, d, Ar-H), 13.18 (1H, s, NH, D_2O, exchangeable). ^{13}CNMR ($CDCl_3$): δ 117.5, 104.0, 144.3, 128.4, 112.0, 148.0, 146.8.

1-Phenyl-1H-indazole (3g)

^1H NMR($CDCl_3$): δ 8.13 (d, 1H, Ar-H), 7.75 (dd, 1H, Ar-H), 7.69-7.77 (m, 2H, Ar-H), 7.57-7.65 (m, 3H, Ar-H), 7.46 (m, 1H, Ar-H), 7.29-7.35 (m, 1H, Ar-H), 7.19 (m, 1H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 140.1, 138.6, 135.3, 129.3, 127.0, 126.5, 125.2, 122.6, 121.4, 121.2, 110.3.

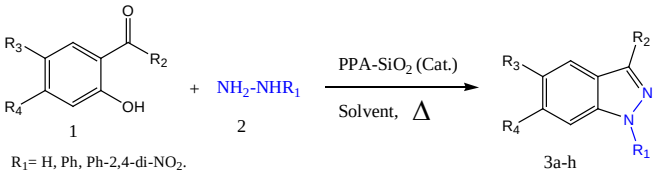
3-Methyl-1-phenyl-1H-indazole (3h)

^1H NMR ($CDCl_3$): δ 7.94 (1H, d, Ar-H), 7.20 (1H, dd, Ar), 7.25 (1H, dd, Ar), 7.37 (1H, d, Ar), 3.09 (3H. s), 7.8-8.5 (5H, m, Ar-H). ^{13}CNMR ($CDCl_3$): δ 18.2, 122.0, 117.2, 128.0, 135.1, 104.0, 124.1, 123.1, 114.2, 129.8, 152.8.

Result and Discussion

The condensation reaction of substituted salicylaldehyde and hydrazine hydrate using silica supported polyphosphoric acid catalyst could successfully perform according to Scheme 1. Similar type synthetic protocols were also studied using various acid catalysts such as PTSA, Montmorillonite KSF, Amberlite-15, Zeolite-HY and Montmorillonite K-10, the desired indazoles were obtained in 17, 64, 38, 57 and 85 % yields respectively.[15-23] The above-mentioned acid-catalyzed reactions were carried at reflux temperature for 3 h using 20 % weight of catalyst concerning the weight of all the reactant was used. Thus, silica supported polyphosphoric acid was found to be a moderate heterogeneous acid catalyst as compared with the above acid catalyst used for the synthesis of indazole derivatives.

The synthesis of indazole derivatives has been reported in two different solvents such as ethanol and DMSO. We found that the reaction in the presence of DMSO solvent at 90 to 95 ^oC affords good yields as compared to reflux in ethanol using the catalytic amount of silica supported polyphosphoric acid.



R_1= H, Ph, Ph-2,4-di-NO_2.
R_2= H, Me.
R_3= H, NO_2.
R_4= H, NO_2.

Scheme 1. Synthesis of substituted indazoles **3a-3h**

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Table 1. Physical parameters of the substituted indazoles at reflux in ethanol solvents.

Entry	R_1	R_2	R_3	R_4	Time, h	M.p. ºC	Yield, %
3a	H	H	H	H	5	147[6]	48
3b	H	Me	H	H	5	113-115[6]	45
3c	Ph-2,4-di-NO_2	H	H	H	8	237	31
3d	Ph-2,4-di-NO_2	Me	H	H	8	194-196	38
3e	H	H	H	NO_2	4	180[6]	40
3f	H	H	NO_2	H	5	208[6]	35
3g	Ph	H	H	H	8	77-79[7]	32
3h	Ph	Me	H	H	8	85-87[7]	37

m. p. : melting point.

Table 2. Physical parameters of the substituted indazoles at 90-95 °C in DMSO solvents.

Entry	R_1	R_2	R_3	R_4	Time, h	M.p. ºC	Yield, %
3a	H	H	H	H	3	147[6]	82
3b	H	Me	H	H	3	113-115[6]	85
3c	Ph-2,4-di-NO_2	H	H	H	4	237	72
3d	Ph-2,4-di-NO_2	Me	H	H	4	194-196	81
3e	H	H	H	NO_2	4	180[6]	80
3f	H	H	NO_2	H	4	208[6]	68
3g	Ph	H	H	H	4	77-79[7]	87
3h	Ph	Me	H	H	4	85-87[7]	86

m. p. : melting point.

Conclusion

In summary, the efficient methodology is developed for the synthesis of indazole and its derivatives by condensation of hydrazine and an o-hydroxy aromatic carbonyl compound in the presence of a catalytic quantity of PPA-SiO_2 is reported. Reusability of the catalyst, moderated yields and simple technique used for product isolation is the crucial importance of this methodology.

The reusability of the silica supported polyphosphoric acid catalyst is an essential factor for the environmental and economic point of view. The catalyst exists in solid state and can be easily separated from the reaction mass by simple filtration. The catalyst is reusable several times with the small loss of efficacy. Hence it is cost effective and more convenient catalyst for the synthesis of indazoles. The reaction does not need hazard organic solvent since this methodology is green and eco-friendly.

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Compliance with ethical standards

The authors declare that there are no conflicts of interest in this work.

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