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A FACIAL SYNTHESIS OF SUBSTITUTED PHENYL SULFONAMIDE DERIVATIVES

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Abstract:
*At present work we synthesized substituted furan sulfonamides compounds. We have developed reaction conditions for series of 5-(substituted phenyl)-N-(2-oxo-2-substituted-phenylethyl)-N-methylfuran-2-sulfonamide derivatives **(4a-4e)**. We have optimized methodology for targets from milligram scale to multi gram scale. The structure of synthesized compounds were elucidated and confirmed by ^{1}H NMR, ^{13}C NMR, LCMS and purity was checked by HPLC.*

Keyword: *Furan; Suzuki; sulfonamide derivatives.*

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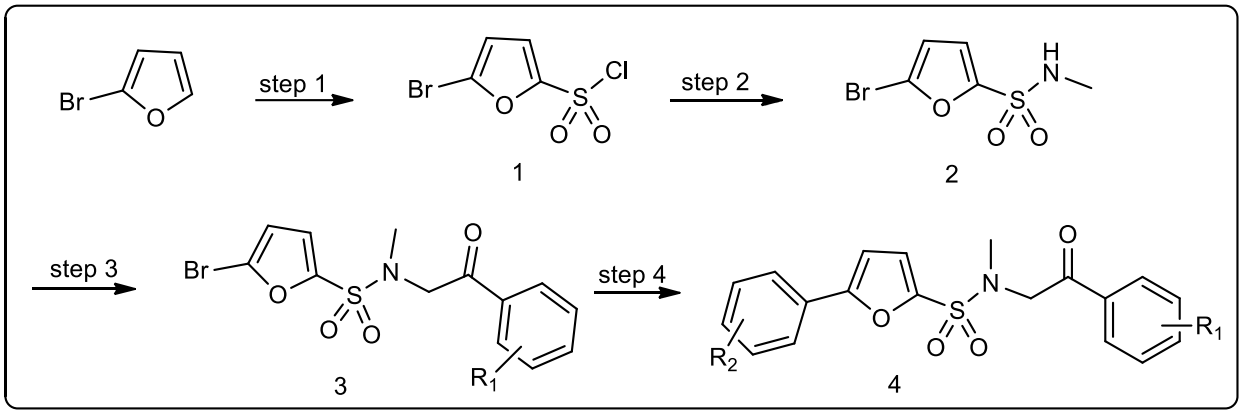
1. INTRODUCTION:

The development of novel antimicrobial drugs with different mechanisms of action to the currently available antimicrobial drugs is still demands [1-2]. Furan derivatives are an important class of heterocycles that is used in various types of biological activities. Furan coupled with different groups showed varied biological activities such as antioxidant [3], antimicrobial [4], anti-inflammatory [5], antitumor and antiviral [6]. Furan coupled with benzothiazepine acts as H^+/K^+ ATPase inhibitors [7]. Furan derivatives are used in variety of biological activities [8].

By considering the biological importance of furan and research of our group for the development of antimicrobial agent [9], we have developed new entities having furan coupled with phencyl bromide (Scheme 1). In the present communication we have synthesize targets which are novel, we have used series of reaction on 2-bromofuran to synthesize 5-(substituted phenyl)-N-(2-hydroxy-2-phenylethyl)-N-methylfuran-2-sulfonamide derivatives.

2. EXPERIMENTAL:

In table 1 here we have optimized the condition for aromatic chlorosulfonation of 2-bromofuran. The reactivity changes according to the equivalence of chlorosulfonic acid used. 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 time 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 varied results are shown in table 1.



	R_1	R_2
4a	H	2-Methyl
4b	H	3-Methyl
4c	H	4-Methyl
4d	H	H
4e	2-Methyl	H

Scheme 1 Synthesis 5-(substituted phenyl)-N-(2-oxo-2-substituted-phenylethyl)-N-methylfuran-2-sulfonamide derivatives **(4a-4e): Step 1-** Chlorosulfonic acid, DCM rt 1h **, Step 2-** $MeNH_2$, TEA, DCM rt 3h,**Step 3-** Phencyl bromide, K_2CO_3, Acetone, rt 2h **,Step 4-** Substituted boranic acid, $Pd(dppf)Cl_2$, Na_2CO_3,X-phos, Dioxane-H_2O

Entry	$ClSO_3H$	Solvent	Time (h)	Yield[a] (%)
1	(3 eq)	Neat	1	35
2	(2 eq)	Neat	1	40
3	(3 eq)	DCM	1	50
4	(2 eq)	DCM	1	60
5	(1.1 eq)	DCM	1	80
6	(Excess)	DCM	1	30
7	(Excess)	Neat	1	20

[a] Isolated yield, sulfonyl chloride (2 eq)

The entries (1, 2, 3 and 4) shows there is formation product along with side products, the yields are 35% to 60%. When we consider (entries 5) the yield is 80% when we used equivalent amount of chlorosulfonic acid (1.1 eq.) and DCM as solvent. Mainly there is formation of product and less side products in entries 3 and 4. But in entries 1 and 2 there is formation of multiple spots on TLC. The yields are isolated yields after series of reactions optimization and the condition of (entry 5) works well for 2-bromofuran. 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 three is formation of polar junk material, which required purification by column chromatography so the yields are less, but in latter case purification not required pure compound obtained by washing with cold pentane and cold diethyl ether to obtain compound 1.

In step 2 we have done N-methylation by using 2 molar solution of methyl amine in THF. We have dome reaction using compound 2 and 3 eq. of methyl amine in acetonitrile from 0°C to room temperature for 4 h there is no any formation of desired product. Then we have used 3 eq. of methyl amine in DCM along with 3 eq. of triethyl amine as base there is formation of 35% of product after 4h after isolation by column chromatography. Then we have used 3 eq. of methyl amine in THF at 0 °C to room temperature for 6 h there is 90% formation of compound 2. The reaction profile is very clean on TLC. We have modified the work up by not evaporating the reaction mixture we have diluted it to 10 times by water and extracted it twice with ethyl acetate to obtain the desired compound 3. The obtained solid compound washed with 10 ml of 20% Ethyl acetate: n-hexane and 10 ml of cold pentane and 10 ml cold diethyl ether to obtained compound 2 as white solid with purity more than 90%.

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

For step 3 we have treated compound 2 (1 eq.) with phenacyl bromide (1 eq.) by using inorganic base like potassium carbonate and cesium carbonate in acetone and tetra-hydro furan respectively. The base used is 2 eq. in both the cases and reaction stirred for 2 h at room temperature. The first reaction with potassium carbonate (2 eq.) with phenacyl bromide (1 eq.) in acetone at room temperature gives 85% of product formation by LCMS and TLC so no need for further optimization and compound isolated by simple work up procedure evaporating acetone under reduced pressure and obtained gummy material added water to it and stirred reaction mass for 1 h. Solid precipitates out filter it and wash it with excess of water and dry it properly to obtain compound 3 as white solid which is used further for Suzuki reaction.

Experimental Procedure for compound of Synthesis of 5-bromofuran-2-sulfonyl chloride (1).

To a stirred solution of 2-bromofuran (10g, 68.03 mmol) in DCM (100 ml). Cooled reaction mass to 0 °C, and then added chlorosulfonic acid (5.41 ml, 81.63 mmol) drop wise. Allowed reaction mass to come to room temperature and stirred for 1h. Progress of reaction monitored by TLC . Evaporate reaction mixture under reduced pressure and obtained gummy material which is washed with cold hexane (100 ml) and it is crystalized

Table 2: Screening of catalyst, bases and solvent of compound (4a-4e)

Entry	Catalyst 10 mol%	Legand 20 mol%	Base 2 eq	solvent	Time (h)	Temp °C	Yield %
1	$Pd(PPh_3)_4$	-	Na_2CO_3	Dioxane:H_2O	6	100	75
2	$Pd(PPh_3)_4$	-	CS_2CO_3	Dioxane:H_2O	6	100	65
3	$Pd(PPh_3)_4$	-	K_3PO_4	Dioxane:H_2O	6	100	60
4	$Pd(PPh_3)_4$	X-PhOS	K_3PO_4	DMF:H_2O	6	100	80
5	$Pd(OAc)_2$	X-PhOS	K_3PO_4	DMF:H_2O	6	100	70
6	$Pd(OAc)_2$	-	K_3PO_4	DMF:H_2O	6	100	50
7	$Pd(dppf)Cl_2$	-	Na_2CO_3	Dioxane:H_2O	6	100	55
8	$Pd(dppf)Cl_2$	-	CS_2CO_3	Dioxane:H_2O	6	100	60
9	$Pd(dppf)Cl_2$	X-PhOS	Na_2CO_3	**Dioxane:H_2O**	**6**	**100**	**90**

from 10% ethyl acetate: hexane (50 ml) mixture to obtain 5-bromofuran-2-sulfonyl chloride as white solid. Yield- 14 g (83.8%).

Synthesis of 5- bromofuran -2-sulfonyl amide (2).
To a stirred solution of 5- bromofuran -2-sulfonyl chloride (10g, 40.73 mmol) in THF (100 ml). Cooled reaction mass to 0 ^{0}C, and then added methyl amine (61 ml, 122 mmol). Allowed reaction mass to come to room temperature and stirred for 6h. Progress of reaction monitored by TLC . Diluted reaction mass by water (100 ml) and extracted it twice with ethyl acetate (50 ml) to obtain white solid. Obtained solid compound washed with 20% EtOAc:Hexane (50 ml), cold pentane (50 ml) and cold diethyl ether (50 ml) to obtained compound 5-bromofuran-2-sulfonyl amide as white solid with purity more than 90%. Yield- 8g (81.86%).

Synthesis of 5- bromofuran -2-sulfonyl amide coupled compound (3a-3e).
To a stirred solution of 5-bromofuran-2-sulfonyl amide (1.0 mmol) in acetone (25 ml) and potassium carbonate (2 eq). Added Substituted phenacyl bromide (1 eq). Stirred reaction mass at room temperature for 2h . Progress of reaction monitored by TLC. Evaporated reaction mass under reduced pressure and obtained gummy material added cold water (100 ml) to it and stirred reaction mass for 1 h. Solid precipitates out filter it and wash it with excess of water and dry it properly to obtain compound **3a-3e** as white solid. Yield- 60% to 86.7%.

General step for the Suzuki reaction (4a-4m).
To a stirred solution of compounds **3a-3e** (1 eq.) in dioxane:water added substituted boranic acid (1.5 eq.) Added sodium carbonate (2 eq.) again added dikis(10 mol%) with x-phos (20 mol%) , degas reaction mass for 10 min. and heat reaction mixture to 100 ^{o}C for 6h. Progress of reaction was monitored by TLC. Filtered through a pad of celite and obtain filtrate which was evaporated under reduced pressure to obtain crude compound with reasonably pure up to 90% by HPLC for all the compounds **4a-e**.
Representative compound

N-(2-oxo-2-phenylethyl)-N-methyl-5-(o-tolyl)furan-2-sulfonamide (4a): White Solid, LC-MS m/z (%): 370 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 7.64 (d, *J* = 4 Hz, 1H), 7.43 (d, *J* = 7.2 Hz, 1H), 7.35-7.32 (m, 5H), 7.31-7.26 (m, 4H), 5.63 (d, *J* = 4.4 Hz, 1H, OH), 4.79-4.77 (m, 1H), 3.15 (m, 2H), 2.79 (s, 3H), 2.39 (s, 3H). HPLC-97.3% RT 8.23 min. ^{13}C NMR ($CDCl_3$,100 MHZ): 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, 71.58, 57.38, 36.35, 24.45.

RESULT AND DISCUSSIONS:

For step 4 we have screened different catalysts, ligands, base and solvents for doing all the step 4

derivatives for all the compound **4a-e**, all results tabulated in table 2. For the first 4 entries we have used tetrakis as constant catalysts and we have varied different bases and ligands entry 1 and entry 4 giving 80% yields in Dioxane:water and DMF: water. In entries 5 and 6 we have used palladium acetate along with X-phos as ligand with potassium phosphate as base in DMF:water solvent is giving 70% yield that compared with entry 6 without ligand giving 50% yield. For entries 7 to 9 the reaction in entry 9 is giving 90% yield as compared it with entry 7 and 8 where we have not used any ligands the yield decreases. In entry 10 we have used nickel chloride/N-methyl piperazine combination in potassium phosphate base in DME gives 70% yield. All tabulated in table 2. The entry 9 reaction having dikis compound with x-phos as ligands in Dioxane:Water combination and sodium carbonate base gives yield in the range of 85-95% for all the examples. For work up of that reaction mass filtered through a pad of celite and obtain filtrate, which was evaporated under reduced pressure to obtain crude compound with reasonable purities more than 90% by HPLC for all the compounds **4a-e.**

CONCLUSIONS:

In the present communication we have synthesized substituted Furan sulfonamides compounds having tert-nitrogen and methylene group. We have optimized methodology for synthesis of these types of targets from milligram scale to multi gram scale.

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