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PEG-600: A facile, eco-friendly, reaction medium for synthesis of 1-(arylsulfonyl) aryl/heterylmethanes

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ABSTRACT

*Reaction of arylmethyl/heteryl methyl chloride **1** with aryl sulphinate sodium salt **2** yields the corresponding sulphone derivative promoted by polyethylene glycol-600 at room temperature.*

Keywords: Arylmethyl/heteryl methyl chloride, aryl sulphinate sodium salt, PEG-600.

INTRODUCTION

The aryl sulfones are common structures in valuable molecules in fields such as pharmaceuticals, agrochemicals and polymer sciences [1]. In particular, their immense utilities in medicinal chemistry and their unique bioactivities have attracted considerable attention on their synthesis. For example, diaryl sulfones have been reported to inhibit HIV-1 [2] reverse transcriptase and diphenyl sulfone [3] is used as an intermediate for the synthesis of 4,4'-diamino-diphenyl sulfone (DAPSONE), which is effective for leprosy treatment [4]. The aryl sulfones can be prepared from the transition metal-catalyzed reactions using sulfonic acids or sulfonyl chloride [5] but the pre-functionalizing such as metallisation or halogenations of arenas are required. A well-known process involving the formation of new C-S bond from aromatic C-H bonds is the Friedel-Crafts (FC) sulfonylation of various arenes, especially electron-rich arenas[6,7]. Sulfonchlorides or sulfoanhydrides are general substrates employed in the FC sulfonylation.

Polyethylene glycol (PEG-600) promoted reactions [8-11] have attracted attention of chemists due to their ease of workup, the ability to act as phase transfer catalysts and their inexpensive and ecofriendly nature. In continuation of our earlier work [12-15] on synthesis of new heteryl derivatives with potential biological activity, we explored the possibilities of exploiting the versatile features of this (PEG-600) green solvent. In this connection, we are reporting a synthesis of 1-(arylsulfonyl) aryl/heteryl methanes in the presence of PEG-600 as a facile and versatile reaction medium at room temperature without additional usage of any solvent and PTC's.

MATERIALS AND METHODS

Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC was performed on silica gel-G and spotting was done using iodine or UV-light. IR spectra were recorded with Perkin-Elmer 1000 instrument in KBr phase. ^{1}H NMR was recorded on VARIAN 400MHz instrument and Mass spectra were recorded on Agilent-LC-MS instrument. The following experimental procedures are representive of the general procedures used to synthesize all compounds.

General procedure for preparation of 3a-j

A mixture of **1** (10 mmol), **2** (10.1 mmol) and polyethylene glycol-600 were stirred at RT till the reaction was complete, as shown by TLC. After carrying out the reaction, the mixture was diluted with ice-cold water, then solid got separated which was filtered washed with water and dried. The physical and spectral data of the compounds **3a-i** are as follows.

2-(Toluene-4-sulfonylmethyl)-1H-benzimidazole (3a): M.P. (^oC): 201 [Lit: 202][16]; IR (KBr) cm^{-1}: 3000 (N**H**), 1302 (**SO**$_2$); ^{1}H-NMR (DMSO-d$_6$): δ 2.4 (s, 3H, -C**H**$_3$), 4.95 (s, 2H, -C**H**$_2$), 7.2-7.7 (m, 8H, **Ar-H**), 12.6 (bs, 1H, -N**H**, D$_2$O exchangeable); M $^{\cdot+}$+1: 287; Anal. Calcd. for ($C_{15}H_{14}N_2O_2S$) requires: C, 62.92; H, 4.93; N, 9.78%; Found: C, 62.86; H, 4.87; N, 9.74%.

2-Benzenesulfonylmethyl-1H-benzimidazole (3b): M.P. (^oC): 199-201 [Lit: 198-200] [16]; IR (KBr) cm^{-1}: 3426 (N**H**), 1324 (**SO**$_2$); ^{1}H-NMR (DMSO-d$_6$): δ 4.85 (s, 2H, -C**H**$_2$), 7.15-7.80 (m, 9H, **Ar-H**), 12.65 (bs, 1H, -N**H**, D$_2$O exchange- able); M $^{\cdot+}$+1: 273; Anal. Calcd. for ($C_{14}H_{12}N_2O_2S$) requires: C, 61.75; H, 4.44; N, 10.29%; Found: C, 61.70; H, 4.40; N, 10.26%.

2-[1-(Toluene-4-sulfonyl)-ethyl]-1H-benzimidazole (3c): M.P. (^oC): 155 [Lit: 154-56][16]; IR (KBr) cm^{-1}: 3388 (**NH**), 1308 (**SO**$_2$); ^{1}H-NMR (DMSO-d$_6$): δ 1.84 (d, *J*=7.16 Hz, 3H, -CH-C**H**$_3$), 2.36 (s, 3H, -C$_6$H$_4$-C**H**$_3$-(*p*)), 4.68 (q, *J*=7.14 Hz, 1H, -C**H**-CH$_3$), 7.2-7.7 (m, 8H, **Ar-H**), 10.3 (bs, 1H, -N**H**-, D$_2$O exchangeable); M $^{\cdot+}$+1: 301; Anal. Calcd. for ($C_{16}H_{16}N_2O_2S$) requires: C, 63.98; H, 5.37; N, 9.33%; Found: C, 63.94; H, 5.35; N, 9.30%.

2-(1-Benzenesulfonyl-ethyl)-1H-benzimdazole (3d): M.P. (^oC): 181 [Lit: 180][16]; IR (KBr) cm^{-1}: 3000, 1308 (**SO**$_2$); ^{1}H-NMR (DMSO-d$_6$): δ 1.9 (d, *J*=7.16 Hz, 3H, -CH-C**H**$_3$), 4.7 (q, *J*=7.12Hz, 1H, -C**H**-CH$_3$), 7.2-7.7 (m, 9H, **Ar-H**), 10.3 (bs, 1H, -N**H**, D$_2$O exchangeable); M $^{\cdot+}$+1: 287; Anal. Calcd. for ($C_{15}H_{14}N_2O_2S$) requires: C, 62.92; H, 4.93; N, 9.78%; Found: C, 62.86; H, 4.91; N, 9.74%.

1-Methyl-2-(toluene-4-sulfonylmethyl)-1H-benzimidazole (3e): M.P. (^oC): 206; IR(KBr) cm^{-1}: 1300 (**SO**$_2$); ^{1}H NMR (CDCl$_3$): δ 2.45 (s, 3H, -C**H**$_3$), 3.95 (s, 3H, -NC**H**$_3$), 4.75 (s, 2H, -C**H**$_2$), 7.2-7.7 (m, 8H, **Ar-H**); **M $^{\cdot+}$+1:** 301; Anal. Calcd. for ($C_{16}H_{16}N_2O_2S$) requires: C, 63.98; H, 5.37; N, 9.33%; Found: C, 63.94; H, 5.32; N, 9.28%.

2-Benzenesulfonylmethyl-1-methyl-1H-benzimidazole (3g): M.P. (^oC): 172; IR(KBr) cm^{-1}: 1336 (**SO**$_2$); ^{1}H NMR (CDCl$_3$): δ 1.85 (d, *J*=7.18Hz, 3H, -CH$_2$-C**H**$_3$), 2.40 (s, 3H, - C$_6$H$_4$-C**H**$_3$-(*p*)), 3.95 (s, 3H, -NC**H**$_3$), 4.70 (q, *J*=7.0 Hz, 1H, -C**H**-CH$_3$), 7.2-7.7 (m, 8H, **Ar-H**); **M $^{\cdot+}$+1:** 315; Anal. Calcd. for ($C_{17}H_{18}N_2O_2S$) requires: C, 64.94; H, 5.77; N, 8.91%; Found: C, 64.90; H, 5.75; N, 8.86%.

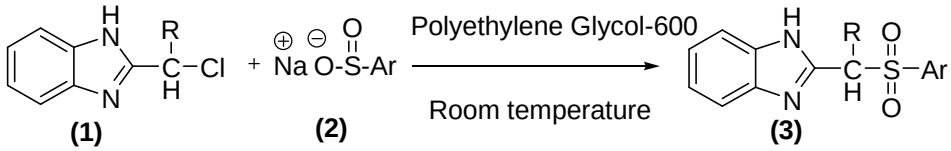
1-Methyl-2-[1-toluene-4-sulfonyl)-ethyl]-1H-benzimidazole (3h): M.P. (^oC): 182; IR(KBr): ^{1}H NMR (CDCl$_3$): δ 1.70 (d, *J*=7.18 Hz, 3H, -CH-C**H**$_3$), 3.85 (s, 3H, -NC**H**$_3$), 5.10 (q, *J*=7.0 Hz, 1H, -C**H**-CH$_3$), 7.2-7.87 (m, 9H, **Ar-H**); **M $^{\cdot+}$+1:** 301; Anal. Calcd. for ($C_{16}H_{16}N_2O_2S$) requires: C, 63.98; H, 5.37; N, 9.33%; Found: C, 63.95; H, 5.33; N, 9.29%.

1-Methyl-4-phenylmethanesulfonyl-benzene (3i): M.P. (^oC): 190- 201; IR (KBr) cm^{-1}: 1312 (**SO**$_2$); ^{1}H NMR (CDCl$_3$): δ 2.38 (s, 3H, -C**H**$_3$), 4.61 (s, 2H, -C**H**$_2$), 7.11-7.57 (m, 9H, **aromatic protons**); **M $^{\cdot+}$+1:** 247.

RESULTS AND DISCUSSION

In our initial attempts, PEG-600 was used in the place of triethyl benzylammonium chloride (TEBAC) [21], which acts as phase transfer catalyst (PTC), in acetonitrile as solvent, used for the synthesis of 1*H*-2-(*p*-tolylsulfonyl methyl)benzimidazole. To verify the existence of such an auxiliary effect, we have investigated the use of PEG-600 as reaction medium which itself gives relief from using phase transfer catalyst as well as from using additional solvent (table 1). It was found that the condensation of 2-(α-Chloromethyl) benzimidazole **1a** (i.e. **1**, R=H) with *p*-tolylsulphinate sodium salt **2a** (i.e. **2**, Ar =C$_6$H$_4$-CH$_3$(*p*)) in PEG-600 at room temperature yielded a neat product on simple aqueous workup. The product has been characterized as 1*H*-2-(*p*-tolylsulfonyl methyl)benzimidazole **3a** (i.e. **3**, R=H, Ar= C$_6$H$_4$-CH$_3$ (*p*)), based on spectral and analytical data and also it was found to be identical with the product reported under phase transfer catalytic conditions [16].

Scheme 1



The plausible mechanism: (for formation of 3)

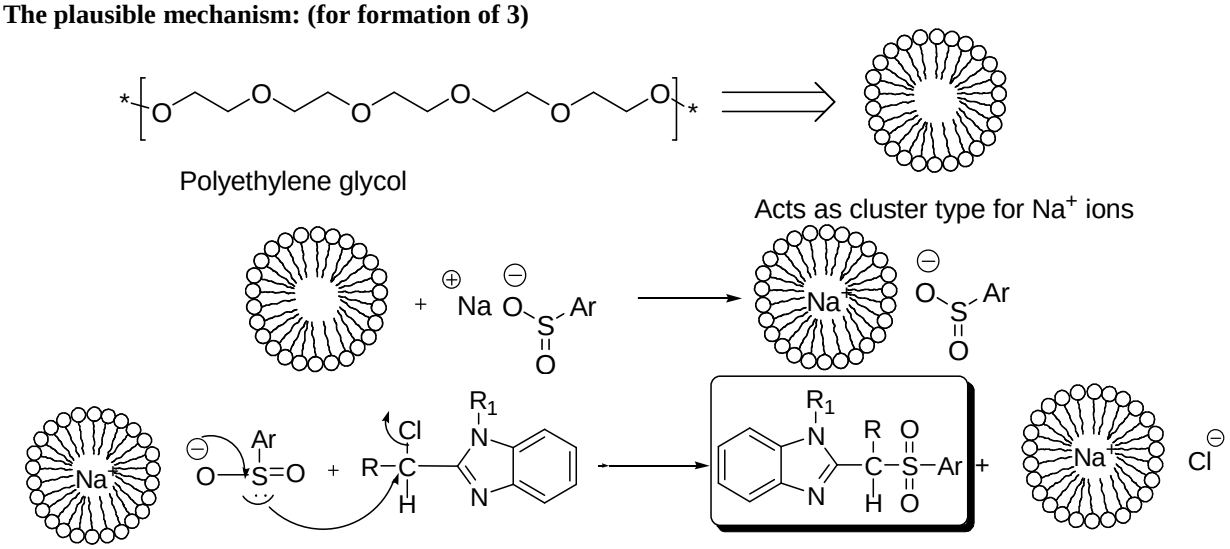
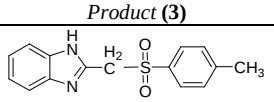
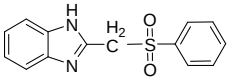
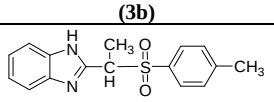
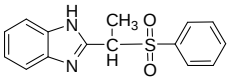
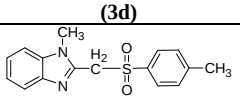
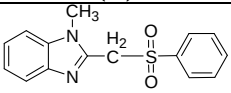


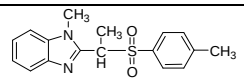
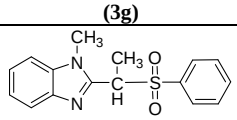
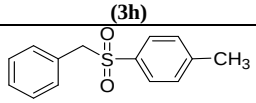
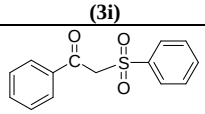
Table 1: (In general)

Entry	Solvent	Catalyst	Reaction time (hr)	Yield (%)
1	CH_3CN	TEBAC	3 -4	70-85
2	CH_3CN	PEG-600	3-3.5	75-85
3	PEG-600	-	1.5-2.0	80-89

The above reaction has been found to be a general one and has been extended to other **1a** & **2a** i.e. with various halo compounds and sulfinate derivatives, which resulted in the formation of different sulphones (Table 2).

Table-2: PEG-600: A facile and eco-friendly reaction medium for phase transfer catalyst – free synthesis of 1-(arylsulfonyl) aryl/heteryl methanes

Entry	*Reagent*	*Product* **(3)**	*Time (h)*	*Yield (%)*
1a	**2a**	 **(3a)**	2.0	85
1a	**2b**	 **(3b)**	1.5	85
1b	**2a**	 **(3c)**	1.5	88
1b	**2b**	 **(3d)**	1.5	80
1c	**2a**	 **(3e)**	1.5	80
1c	**2b**	 **(3f)**	2.0	85

1d	**2a**	 **(3g)**	2.5	78
1d	**2b**	 **(3h)**	2.0	89
1e	**2a**	 **(3i)**	2.0	88
1f	**2b**	 **(3j)**	2.0	85

In order to examine the scope of this method in preparing different sulphone derivatives, we have examined the reactions of benzyl chlorides and phenacyl bromides with sodium benzene sulfinates under the above mentioned conditions. As shown in table, moderate to good yields of the title compounds were obtained.

CONCLUSION

We have presented herein an efficient method for the synthesis of title compounds using PEG-600 as the eco-friendly solvent in good to excellent yields. Moreover, this method is advantageous than the previously reported method by us by using simple water workup.

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