Asian Journal of Chemistry; Vol. 27, No. 1 (2015), 189-191

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2015.16853

A Convenient and Benign Synthesis of Sulphonamides in PEG-400

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Received: 11 December 2013; *Accepted*: 17 April 2014; *Published online*: 26 December 2014; AJC-16535

A simple and convenient method is reported for the synthesis of a series of sulphonamides in PEG-400 using potassium carbonate as the base. The reaction is carried out in a heterogeneous medium and consequently product recovery is simple. The desired products with a variety of aromatic amines could be synthesized in a short reaction time in good yield. The PEG could be recovered for reuse.

Keywords: Sulphonamide, Aromatic amines, Heterogeneous catalysis.

INTRODUCTION

Utilizing green solvents in synthesis is very important for sustainable development. Several reports on the use of PEG-400 as an alternative to the volatile organic carbons are available. The low cost, reduced inflammability, reduced toxicity, reduced environmental risks coupled with good solvating characteristics of PEG-400 and its high molecular weight variants offers enormous possibilities. Its use as a versatile green solvent is spurred by the appearance of several reports in literature notable among them are catalytic hydrogenation with PtO_2[1], Suzuki Miyaura cross coupling using $Pd(OAc)_2$ /TBAB/PEG-400[2], conversion of alkyl halides to nitroalkanes[3], reduction of alkynes to *cis* olefins[4], synthesis of 4-hydroxy chalcones[5], Michael addition reaction of αβ-unsaturated carbonyl compounds[6], synthesis of 2-amino-4*H*-chromenes[7], metal free synthesis of amides by direct oxidative amidation of aldehydes with amines[8], synthesis of 1,4 dihydropyridine[9] besides others.

Herein, we reported, a simple synthesis of sulphonamides in PEG-400 using K_2CO_3 in a heterogeneous reaction. Sulphonamides are compounds with important medicinal properties. They exhibit a broad spectrum of bacteriostatic activity, affecting Gram-positive, Gram-negative and many protozoan organisms and are commonly used for the treatment of infections of the central nervous system, respiratory tract, gastrointestinal tract and the urinary tract. A variety of sulphonamide derivatives have also been synthesized which are potent diuretics and hypoglycemics[10-13]. The use of sulphonamides as veterinary medicine is widespread particularly as mass medicant for control of diseases in food producing species. They are also reported to be potent and selective Adenosine A2B receptor antagonists[14].

EXPERIMENTAL

All aromatic amines, *p*-toluenesulphonyl chloride and benzenesulphonyl chloride were purchased from Spectrochem (India). The amines were purified by standard methods[24], the sulphonylchlorides and the liquid amines were used as received. Melting points were recorded in open capilliaries and are not corrected, IR spectra were recorded in Perkin Elmer FT-IR 1600, ^{1}H NMR spectra recorded in Bruker 300 MHz FT-NMR using TMS as the internal standard. The suphonamides were identified by comparing the m.p., IR, ^{1}H NMR, ^{13}C NMR and the values are in agreement with those reported in literature.

General procedure sulphonylation of amines in PEG-400: A mixture of appropriate sulphonylchloride (0.01 mol) and K_2CO_3 (0.01 M) is taken in 15 mL of PEG- 400 and stirred for 0.5 h thereafter the temperature increased to 60 °C and stirred for additional 2 h. To this mixture was added 0.01 mol of the aromatic amine and the temperature slowly increased to 120 °C and stirring continued. The progress of the reaction was monitored by TLC in prepared silica gel plates using pet ether (60-80) and 5 % EtOAc as the eluent. After completion of the reaction as indicated by the disappearance of the amine, the mixture was extracted with ether (50 mL × 3). The combined ether extract was successively washed with dil HCl to remove unreacted aniline and with water to remove unreacted sulphonylchloride, dried over anhydrous Na_2SO_4 and the solvent evaporated to obtain the desired products which were recrystalized from ethanol (95 % v/v). For the investigation of the probable effect of K_2CO_3 on the yield of the product, various weight of the base starting from 0.0005 to 0.002 mol was screened. Maximum yield was obtained with 1:1 equivalent

of the substrates and the base. Decrease in the quantity of the base gave low yield and increase in the amount of the base above 1 equivalent had no effect on the yield. All the known compounds were characterized by comparing their melting points with those reported in literature and by recording their IR, ^{1}H NMR and ^{13}C NMR spectra.

Spectral data of selected sulphonamides

N-Phenyl-*p*-toluenesulphonamide (entry 1): m.p. 100 °C, Yield 74 %, IR in (KBr, ν_{max}, cm^{-1}): 3248 (N-H), 1334 and 1153 (sulphonamides), 914 (C-N); δ_H (300 MHz, $CDCl_3$) 7.05-7.13 (5H$_{arom}$, m, C_6H_5-), 7.21-7.23 (2H$_{arom}$, m, CH_3-C_6H_4-), 64-7.67 (2H$_{arom}$, m, CH_3-C_6H_4), 6.83 (1H, NH), 2.18-2.47 (3H, s, -CH_3), δ_C (75 MHz) 21.56, 121.33, 125.14, 127.3, 129.29, 129.69, 135.9, 136.65, 143.91.

N-(4-Methylphenyl)-*p*-toluenesulphonamide (entry 2): m.p. 116-118 °C, yield 80 %, IR in (KBr, ν_{max}, cm^{-1}): 3278 (N-H), 1319 and 1157 (sulphonamides), 914 (C-N); δ_H (300 MHz, $CDCl_3$) 7.63-7.61 (4H$_{arom}$, d,), 7.02-7.23 (2H$_{arom}$, d,), 6.93-6.95 (2H$_{arom}$, d), 6.55 (s,N-H), 2.38 (s, 3H, -CH_3), 2.17 (s, 3H, -CH_3), δ_C (75 MHz) 20.93, 21.63, 122.49, 127.35, 129.66, 129.93, 133.75, 135.55, 136.18, 143.8.

N-(3-Bromophenyl)-*p*-toluenesulphonamide (entry 3): m.p.119-21 °C, yield 72 %, IR in (KBr, ν_{max}, cm^{-1}): 3244 (N-H), 1338 and 1153 (sulphonamides), 916 (C-N), 667 (C-Br); δ_H (300 MHz, $CDCl_3$) 2.40 (3H, s, CH_3), 6.59 (1H, s, N-H), 7.03-7.13 (4H$_{arom}$, m,), 7.24 (2H$_{arom}$, s) 7.68 (2H$_{arom}$, d) δ_C (75 MHz) 21.54, 119.32, 122.75, 123.71, 127.21, 128.07, 129.81, 130.55, 135.6, 137.93, 144.28.

N-(4-Methylphenyl)-*p*-toluenesulphonamide (entry 5): m.p. 106 °C. Yield 84 %. IR (KBr, ν_{max}, cm^{-1}): 3275 (N-H), 1330 and 1157 (sulphonamide), 902 (C-N), δ_H (300 MHz, $CDCl_3$) 1.96-2.03 (3H, d, -CH_3), 2.39-2.43 (3H, d, -CH_3), 6.35 (1H, s, N-H), 7.59-7.62 (2H$_{arom}$, d,), 7.30-7.33 (2H$_{arom}$, d), 7.17-7.23 (1H$_{arom}$, m), 7.14-7.15 (1H$_{arom}$, d), 7.14-7.11 (1H, d) 7.07-7.08 (1H$_{arom}$, d), δ_C (75 MHz) 17.52, 21.41, 124.31, 126.01, 126.66, 126.98, 129.46, 130.64, 131.57, 134.37, 136.53, 143.62.

N-(2-Chlorophenyl)-*p*-toluenesulphonamide (entry 6): m.p. 104 °C. Yield 85 % IR in (KBr, ν_{max}, cm^{-1}): 3259 (N-H), 2357 (Aromatic C-H), 1392 and 1161 (sulphonamide), 898 (C-N), 817 (C-Cl), δ_H (300 MHz, $CDCl_3$) 6.99 (N-H), 2.37-2.47 (3H, d, -CH_3), 7.0-7.06 (2H$_{arom}$, m,) 7.2-7.26 (4H$_{arom}$, m.) 7.63-7.67 (2H$_{arom}$, m) δ_C (75 MHz) 21.49, 122.3, 125.01, 125, 79, 127.15, 127.77, 129.28, 129.58, 133.33, 135.7, 144.15.

N-(4-Methoxyphenyl)-*p*-toluenesulphonamide (entry 7): m.p. 112 °C, Yield 80 % IR in (KBr, ν_{max}, cm^{-1}): 3267 (N-H), 1249 and 1026 (Ar-OCH_3), 1396 and 1157 (sulphonamide), 906 (C-N) δ_H (300 MHz, $CDCl_3$) 2.36 (3H,s, -CH_3), 3.73 (3H, s, -OCH_3), 6.97 (1H, s, N-H), 6.72-6.75 (2H$_{arom}$, m) 6.98-7.01 (2H$_{arom}$, m), 7.18-7.21 (2H$_{arom}$, m), 7.59-7.62 (2H$_{arom}$, m) δ_C (75 MHz) 21.48 (CH_3), 55.33 (OCH_3), 114.29, 125.17, 127.25, 128.91, 129.49, 135.78, 143.61, 157.71.

N-(4-Carboxyphenyl)-*p*-toluenesulphonamide (entry 9), m.p. 231 °C, Yield 80 % IR in (KBr, ν_{max}, cm^{-1}): δ_H (300 MHz, $CDCl_3$) 2.48 (3H, s, -CH_3), 7.14-7.17 (2H$_{arom}$, d), 7.32-7.35 (2H d), 7.66-7.69 (2H$_{arom}$, d,), 7.75-7.77 (2H, d, merged N-H) 10.8 1H, s, -COOH) δ_C (75 MHz) 21.14, 118.16, 125.62, 126.93, 130.05, 130.93, 136.45, 142.21, 143.93, 166.97

N-Benzyl-*p*-toluenesulphonamide (entry 11): m.p. 110 °C, Yield 88 % IR in (KBr, ν_{max}, cm^{-1}): 3267 (N-H), 2333 (C-H) , 1323 and 1157 (sulphonamide), 875 (C-N) δ_H (300 MHz, $CDCl_3$) 2.43 (3H, s, -CH_3), 4.09-4.1 (2H, d, -CH_2-), 7.18-7.23 (6H$_{arom}$, m, N-H merged), 7.74-7.76 (2H$_{arom}$ d), δ_C (75 MHz) 21.5, 47.16, 127.11, 127.81, 128.6, m 129.69, 136.21, 136.68, 143.47.

N-Phenylbenzenesulphonamide (entry 14): m.p. 100-102 °C, Yield 78 %, IR in (KBr, ν_{max}, cm^{-1}): 3214 (N-H), 2333 (C-H), 1330 and 1157 (sulphonamide), 910 (C-N) δ_H (300 MHz, $CDCl_3$) 6.82 (1H, NH), 7.06-7.8 (10H, m,) δ_C (75 MHz) 121.53, 125.31, 127.19, 129, 129.26, 132.99, 136.38, 138.85.

N-(4-Methoxyphenyl)benzenesulphonamide (entry 15): m.p. 88-90 °C. Yield 88 % IR in (KBr, ν_{max}, cm^{-1}): 3256 (N-H), 2333 (C-H), 1334 and 1157 (sulphonamide), 924 (C-N) δ_H (300 MHz, $CDCl_3$) 3.75 (3H, s) 6.77 (1H, s, NH), 7.26-7.72 (9H, m,) δ_C (75 MHz) 55.28, 114.3, 125.17, 127.18, 128.82, 132, 75, 138.72, 157.75.

N-(4-Nitrophenyl)benzenesulphonamide (entry 18): m.p. 128-130 °C. Yield 82 % IR in (KBr, ν_{max}, cm^{-1}): 3329 (N-H)., 1342 and 1157 (sulphonamide), 1519 and 1342 (-NO_2) δ_H (300 MHz, $CDCl_3$) 7.25-7.29 (2H$_{arom}$, d), 7.53-7.62 (2H$_{arom}$, q), 7.84-7.86 (2H$_{arom}$, d), 8.07-8.1 (2H$_{arom}$, d) δ_C (75 MHz) 118.3, 125.62, 127.04, 129.9, 133.94, 139.08, 142.9, 144.34.

RESULTS AND DISCUSSION

In view of their diverse applications, the synthesis of sulphonamides have assumed importance. There are a variety of methods available for the synthesis notable among them are conversion of alcohols to tosylamides[15], use of MnO_2 under solvent free condition[16], Pd-catalyzed cross-coupling of methanesulfonamide with aryl bromides[17]. The arylation of NH and OH containing compounds at room temperature with phenylboronic acids[18]. Selective conversion of benzylic hydrocarbons to sulfonamides by $Cu(CH_3CN)_4]PF_6$ catalyzed reaction with anhydrous $TolSO_2NNaCl$[19] and A Zn/CuI-mediated coupling of alkyl halides with vinylsulfones[20], Horner reaction of aldehydes and diphenylphosphorylmethane-sulfonamide[21] and N-heterocyclization reactions of primary amines[22].

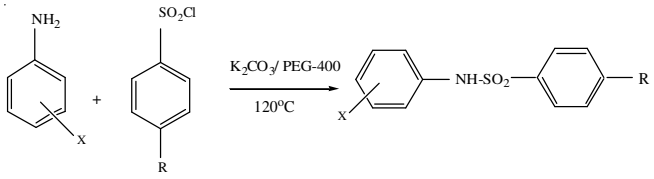
However, almost all the methods use costly reagents, organic solvents and some require heavy metals and complex salts as catalyst and are often not environment friendly. In search for effective green methodologies in organic synthesis, it is observed that sulphonamides can be synthesized by a reaction of an amine and suitable sulphonylchloride in a green solvent namely PEG-400 under heterogeneous condition using K_2CO_3 as the base. The procedure precludes the use of VOCs and being heterogeneous, products recovery is simple. The best operative experimental condition involves mixing *p*-toluenesulphonylchloride or benzenesulphonyl- chloride (0.02 mole) and 0.01 mol of K_2CO_3 in 15 mL of PEG-400. The mixture is preheated in an oil bath to 60 °C. To this mixture was added 0.01 mol of the aromatic amine and the temperature was slowly increased to 120 °C with stirring. After completion of the reaction, the mixture was extracted with diethyl ether. The ether layer was washed with dil. HCl to remove any trace of amine followed by washing with demineralized water to

TABLE-1
PHYSICAL CHARACTERISTICS OF SULPHONAMIDES OBTAINED FROM VARIOUS AMINES

Entry	Amine	Sulphonamide	m.p. (°C)	
			Observed	Literature[23]
1	Aniline	N-Phenyl-*p*-toluenesulphonamide	102	103
2	*p*-Toluidine	N-(4-Methylphenyl)-*p*-toluenesulphonamide	115-116	116-117
3	3-Bromoaniline	N-(3-Bromophenyl)-*p*-toluenesulphonamide	118-20	122-125
4	Anthranilic acid	N-(2-Carboxyphenyl)-*p*-toluenesulphonamide	225-228	227-29
5	*o*-Toluidine	N-(2-Methylphenyl)-*p*-toluenesulphonamide	106	109
6	2-Chloroaniline	N-(2-Chlorophenyl)-*p*-toluenesulphonamide	104	105
7	*p*-Anisidine	N-(4-Methoxyphenyl)-*p*-toluenesulphonamide	112	114
8	2-Aminonaphthalene	N-(2-Naphthyl)-*p*-toluenesulphonamide	132	133
9	4-Aminobenzoic acid	N-(4-Carboxyphenyl)-*p*-toluenesulphonamide	231-232	235
10	*o*-Phenylenediamine	1,2-*bis*-(*p*-Toluenesulphonamido)benzene	201	201
11	Benzylamine	N-Benzyl-*p*-toluenesulphonamide	108-10	116
12	Ethylenediamine	1,2-*bis*-(*p*-Toluenesulphonamido)ethylene	158	160
13	Benzidine	4.4-(*bis*-*p*-Toluenesulphonamido)benzidine	242	243
14	Aniline	N-Phenylbenzenesulphonamide	101	100-102
15	*p*-Anisidine	N-(4-Methoxyphenyl)benzenesulphonamide	86-89	88-89
16	2-Bromoaniline	N-(2-Bromophenyl)benzenesulphonamide	126-128	127
17	2-Chloroaniline	N-(2-Chlorophenyl)benzenesulphonamide	128-130	131
18	4-Nitroaniline	N-(4-Nitrophenyl)benzenesulphonamide	128-130	130

*p-Toluenesulphonylchloride used for entry 1-13 benzenesulphonylchloride used entry 14-18

remove unreacted sulphonylchloride. Ether layer was separated, dried with anhydrous Na_2SO_4, filtered and solvent evaporated to afford the sulphonamide which are recrystallized from ethanol. The reaction is also performed in a homogeneous medium using Et_3N as the base however product recovery is difficult as Et_3N is soluble in ether as well as water and consequently not amenable to complete removal. Further the yield of the product with Et_3N as the base, is observed to be low (40 %). Recovery of the sulphonamides also tried by diluting the reaction mixture with large excess of water and extracting the product in the comparatively benign solvent, ethylacetate, however, incomplete recovery resulted in low yields. The reaction sequence leading to the formation of sulphonamides is outlined in **Scheme-I** and the results are given in Table-1.



Scheme-I

Conclusion

In conclusion, a simple an efficient synthesis of several sulphonamides has been reported. The procedure is environmentally benign as the solvent, PEG-400 has all the characteristics of a green solvent. Further the reaction is catalyzed by a heterogeneous base which makes product recovery simple and easy.

ACKNOWLEDGEMENTS

One of the authors (Bhaskar Sarmah), is grateful to University Grants Commission, New Delhi, for financial assistance in the form of Research fellowship under Major Research project.

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