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Synthesis of sulfonamides and sulfonic esters via reaction of amines and phenols with thiols using H_2O_2–$POCl_3$ system

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ABSTRACT

Phosphorus oxychloride efficiently promoted the synthesis of sulfonamides and sulfonic esters from thiols with hydrogen peroxide in the presence of Amberlite IRA-400 (OH^-). This method has been applied to a variety of substrates including nucleophilic and sterically hindered amines, and also phenols with excellent yields of sulfonamides and sulfonic esters. In most cases these reactions are highly selective, simple, and clean, affording products in excellent yields and high purity.

1. Introduction

The development of simple, efficient, and economically viable chemical processes or methodologies for widely used organic compounds is in great demand. Sulfonamides are extremely useful pharmaceutical compounds because they exhibit a wide range of biological activities such as anticancer, anti-inflammatory, and antiviral functions.[1] For example the sulfonamide E7070[1f] is used as an anticancer agent and the HIV protease inhibitor amprenavir[1g] is used for the treatment of AIDS and HIV infections (Fig. 1). Furthermore, sulfonamides have been used as protecting groups for OH or NH functionalities with easy removal under mild conditions.[2] Even though many synthetic methods have been reported,[3] the sulfonylation of amines with sulfonyl chlorides in the presence of a base is the most typical method for preparing of preparation sulfonamides.[4]

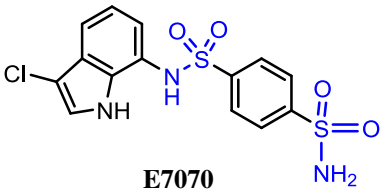
Although this method is efficient, it is limited by the formation of undesired disulfonamides with primary amines, and by the need for harsh reaction conditions for less nucleophilic amines such as anilines.[5] It also requires the availability of sulfonyl chlorides, some of which are difficult to store or handle.

In view of the above limitations and due to the versatile biological activity of sulfonamides, their synthesis under mild reaction conditions is a field of growing research interest.

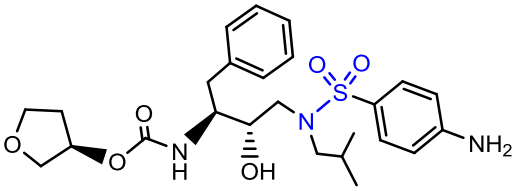
Ion-exchange resins are used in a variety of specialized applications such as chemical processing, pharmaceuticals, mining, food and beverage processing.[6] Organic reactions in the presence of ion-exchange resins is a growing field of research as the demand for clean and eco-friendly chemical processes is increasing. Their applicability as catalyst has been recognized in numerous publications.[6b,c,7–13]

Ion-exchange resins have certain inherent advantages over conventional acid and base catalysts. Their insolubility renders them environmentally compatible since the cycle of loading/regeneration/reloading allows them to be used for many years. At the end of the reaction, the resin can be quantitatively separated by filtration and recycled.

Phosphorus oxychloride ($POCl_3$) is a reactive chemical reagent, which plays very important roles in organic syntheses,[14] but it has



E7070



Amprenavir

Fig. 1. Structures of sulfonamides used as drug candidates.

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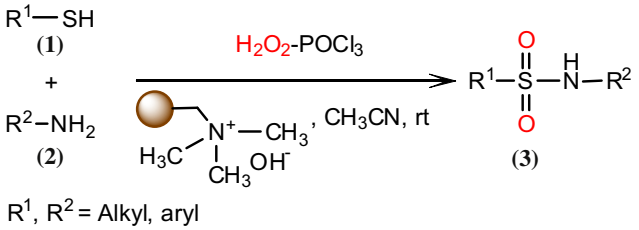
not been studied as promoter in the conversion of thiols to sulfonamides until now.

In recent work, we have shown H_2O_2 in combination with $SOCl_2$[15] and $ZrCl_4$[16] as efficient systems for the conversion of thiols into sulfonamides. As an extension to this work and also in continuation of our program directed to the development of efficient reagents for use under mild conditions[16,17] herein, we report a mild and efficient synthesis of such compounds via the reaction of amines and thiols with H_2O_2–$POCl_3$ system in acetonitrile at room temperature. To the best of our knowledge such a reagent system for the preparation of sulfonamides has not been described in the literature. The route for the synthesis of sulfonamides is shown in Scheme 1.

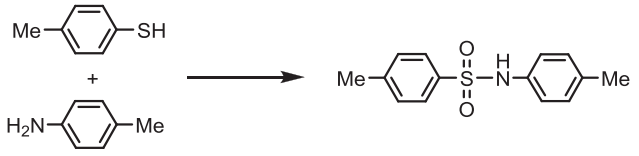


Scheme 1. Synthesis of sulfonamides from thiols.

2. Results and discussion

In order to find optimized conditions for the reaction, 4-methylthiophenol and 4-methylaniline were used as model substrates. After many optimization experiments with respect to the molar ratio of the reactants, reaction time, and possible solvents, the best result (95% yield) was achieved by using a 3:1:1:1 mole ratio of H_2O_2, $POCl_3$, 4-methylthiophenol, and 4-methylaniline in the presence of Amberlite IRA-400 (OH^-) (0.1 g, containing 0.1 mmol of OH^-) as a solid heterogeneous catalyst at 25 °C for 3 min in acetonitrile as solvent (Table 1). The reaction remains incomplete with lower amounts of H_2O_2 and $POCl_3$, for example, 2:1:1:1 and 3:0.7:1:1.

Table 1
Effect of increasing the amount of H_2O_2 and $POCl_3$ on preparation of 4-methyl-*N*-*p*-tolylbenzenesulfonamide[a]



Entry	$POCl_3$	30% H_2O_2	Yield%[b]
1	0.25	4	30
2	0.5	4	40
3	0.75	4	77
4	1	2	80
5	1	3	95, 95, 93, 94
6	1	4	96

[a] Reaction conditions: The reactions were performed with 4-methylthiophenol (1 mmol) and 4-methylaniline (1 mmol) in the presence of Amberlite IRA-400 (OH^-) (0.1 mmol) for 3 min in acetonitrile at 25 °C.
[b] Isolated yields.

In a typical reaction, upon completion of the reaction, the catalyst was filtered from the reaction mixture and reused. The reaction proceeded smoothly, and the desired product was obtained in 95, 95, 93, and 94% yields after runs 1–4, respectively (Table 1, entry 5). On the other hand, in a blank experiment in the absence of Amberlite IRA-400 (OH^-), only a low yield of product (37%) was obtained under similar reaction conditions after 4 h.

To find the best solvent, the reaction of thiophenol with 4-methylaniline was carried out under similar reaction conditions using various organic solvents. Among the various solvents such as chloroform, dichloromethane, toluene, acetonitrile, and ethanol used for this transformation, acetonitrile was the solvent of choice.

To extend the scope of the reaction and to generalize the procedure, we investigated the reaction of several amines with a variety of commercially available thiol derivatives. These substrates selectively reacted to produce the corresponding sulfonamides in excellent yields with high purity as suggested by NMR spectroscopic analyses of the products. As can be seen from the results in Table 2, aryl thiols containing electron-donating and electron-withdrawing groups were converted to the corresponding sulfonamides in excellent yields irrespective of electronic effects. The protocol worked efficiently in the conversion of benzyl thiol to the corresponding sulfonamide (Table 2, entry 10). The most notable feature is that we have been able to apply this procedure successfully in the conversion of dithiol to the disulfonamide, for example, 1,3-propanedithiol with cyclohexylamine formed the corresponding sulfonamide in excellent yield (Table 2, entry 8).

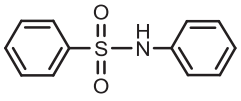
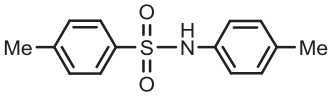
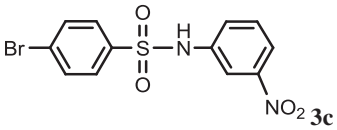
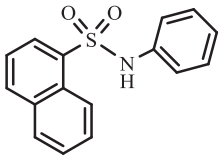
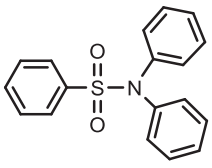
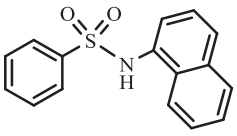
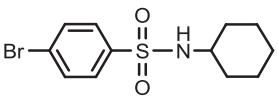
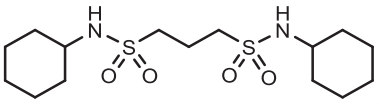
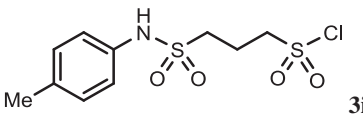
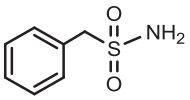
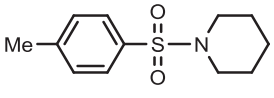
The preparation of 3-(*N*-*p*-tolylsulfamoyl)propane-1-sulfonyl chloride from 1,3-propanedithiol and dithiols more generally, has been of great interest, because the remaining sulfonyl group can be converted to other functional groups. Therefore, the reactions of 1,3-propanedithiol with 4-methylthiophenol were also investigated. The reaction of 1,3-propanedithiol under the optimized conditions led exclusively to mono-sulfonamidazole in excellent yield (Table 2, entry 9). The mechanism for the reaction was studied by NMR spectroscopy and sulfonyl chloride was confirmed as the reaction intermediate. When the reaction of 1,3-propanedithiol was carried out with 1:6:2 mole ratios of dithiol, H_2O_2, and $POCl_3$ in the absence of amine the desired disulfonyl chloride was produced as only product (a white solid, mp 46–47 °C).[18] The ^1H and ^{13}C NMR spectra of propane-1,3-disulfonyl dichloride are available as Supplementary data.

Arylamines carrying either electron-donating or -withdrawing substituents afforded excellent yields of products in high purity. Also, aryl amines appeared to be insensitive to substitution. Ammonia and primary and secondary amines undergo this reaction with equal efficiency. For example, 4-methylbenzenesulfonamide is produced in 94% yield (Table 2, entry 12), *N*-phenylbenzenesulfonamide in 95% yield (Table 2, entry 1), and *N*,*N*-diphenylbenzenesulfonamide in 94% yield (Table 2, entry 5). As shown in Table 2, this method proved to be very useful even for sterically hindered amines such as diphenylamine and piperidine, the corresponding sulfonamides were obtained in 94% and 95% yields, respectively (Table 2, entries 5 and 11). Moreover, this procedure worked efficiently in the sulfonylation of phenylhydrazine to afford an excellent yield of the product without the formation of any side products (Table 2, entry 13).

Sulfonic esters are a class of sulfonic acid derivatives that have drawn much attention because they are valuable intermediates in organic synthesis and are suitable precursors for sulfonamides.[19] In addition, various sulfonic esters inhibit interesting biological and pharmacological properties.[20] Therefore, it is not surprising that the synthesis of sulfonic esters has always been of great interest to organic chemists.

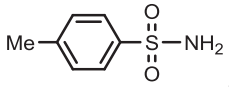
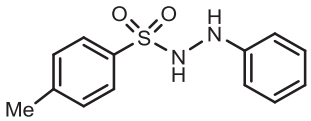
The most typical method for the preparation of sulfonic esters is the reaction of sulfonyl chlorides with alcohols or phenols in the presence of a base.[21,22] However, the preparation of sulfonic esters from phenols has been much less investigated as compared to the preparation of sulfonic esters from alcohols.

Table 2
Formation of sulfonamide compounds[a]

Entry	Sulfonamide	Yield [%][b]/time (min)	Mp [°C]/(lit. mp)	Reference
1	 **3a**	95 (4)	110 (107–109)	25a
2	 **3b**	95 (3)	113–115 (114–115)	25a
3	 **3c**	92 (4)	118–120 (118–120)	15
4	 **3d**	92 (2)	158 (156–157)	25b
5	 **3e**	94 (3)	122–123 (124)	25c
6	 **3f**	94 (3)	166–168 (165–167)	25d
7	 **3g**	92 (3)	100 (100)	16
8	 **3h**	92 (3)	Oil	—
9	 **3i**	90 (5)	Oil	—
10	 **3j**	94 (2)	97 (98.5–100)	25e
11	 **3k**	95 (2)	92–93 (93)	25f

(*continued on next page*)

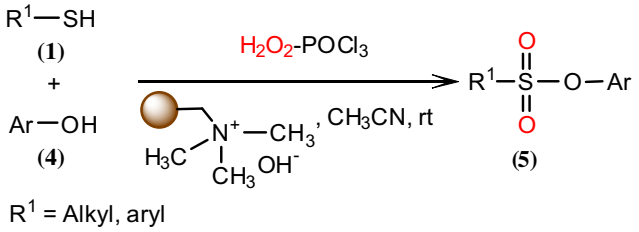
Table 2 (*continued*)

Entry	Sulfonamide	Yield [%][b]/time (min)	Mp [°C]/(lit. mp)	Reference
12	 **3l**	94 (2)	137 (136–138)	25g
13	 **3m**	93 (4)	154–156 (155)	25h

[a] The purified products were characterized by mp, ^{1}H and ^{13}C NMR spectroscopy.
[b] Yields refer to pure isolated products.

However, in spite of their potential utility, many of these methods involve various drawbacks such as the use of expensive or less easily available reagents, vigorous reaction conditions, long reaction time, tedious manipulations in the isolation of the pure products, and side reactions. In addition, these methods require the availability of sulfonyl chlorides. Often, sulfonic esters are prepared from the corresponding sulfonic acids by reaction with diazoalkanes,[23,24] which are toxic, explosive, and unavailable.

In order to demonstrate the efficiency and applicability of the H_2O_2–$POCl_3$ system further, the chemoselective conversion of phenols to sulfonic esters was also investigated (Scheme 2). The same reaction conditions were applied for the preparation of sulfonic esters via the reaction of thiol (1 mmol), phenol (1 mmol), H_2O_2 (3 mmol), and $POCl_3$ (1 mmol) in the presence of Amberlite IRA-400 (OH^-) (0.1 mmol).



Scheme 2. Synthesis of sulfonic esters from thiols.

To explore the scope of this transformation, we investigated sulfonylation of several additional examples. The results are presented in Table 3. Using optimized reaction conditions, the reactions of structurally and electronically diverse thiols and phenols were investigated. As shown, all the reactions proceeded efficiently and the desired sulfonic esters were obtained in excellent yields with high purity (as determined by NMR spectroscopy). The reactions were remarkably clean, and no chromatographic separation was necessary to get the spectroscopic-pure compounds. Aromatic thiols carrying either electron-donating or electron-withdrawing substituents all reacted very well to give the corresponding sulfonic esters with equal efficiency. The phenol starting material appeared to be more sensitive to substitution. Phenol itself and phenols with an electron-donating group (Table 3, entry 2) gave the corresponding sulfonic esters in excellent yields in short reaction times, while phenols with an electron-withdrawing group such as a nitro group required longer reaction times and produced product in good yield (Table 3, entry 4). Interestingly, 1- and 2-naphthol worked well and the desired sulfonic esters were obtained in excellent yields without the formation of any side products (Table 3, entries 8 and 9). Moreover, this procedure converted successfully dithiol to the disulfonic ester in excellent yield and short reaction times (Table 3, entry 12). More significantly, in a competitive sulfonylation reaction with an equimolar mixture of aniline and phenol by this procedure, the phenol is sulfonated selectively leaving the amine unaffected. Thus, sulfonylation of 4-aminophenol produced the corresponding sulfonic ester; the amine moiety remained untouched under the optimized reaction conditions (Table 3, entry 11). This is a noteworthy feature of the above protocol and represents a useful practical achievement in such sulfonylation reactions.

3. Conclusion

In conclusion, this letter describes a method in which H_2O_2/$POCl_3$ is a highly efficient reagent system for the synthesis of sulfonamides and sulfonic esters by using various substrates as amines and phenols from thiols in the presence of Amberlite IRA-400 (OH^-). The advantages include low cost, excellent yields, short reaction times, ease of reagent system handling, mild reaction conditions, and reactions carried out at room temperature. The remarkable selectivity under mild conditions of this commercially available inexpensive catalyst is an attractive feature of this method. The method is quite general for a wide range of substrates including less nucleophilic and sterically hindered anilines. This methodology also overcomes the formation of unwanted byproducts; thus, we believe that the present methodology opens up new possibilities for medicinal chemistry and materials science and could be an important addition to the existing methodologies.

4. Experimental

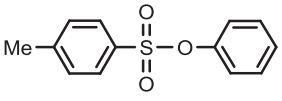
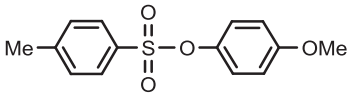
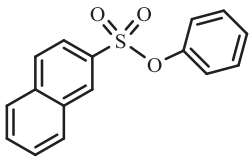
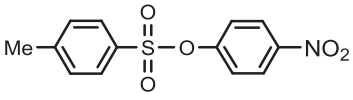
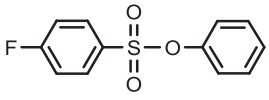
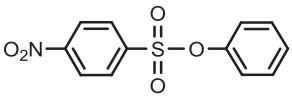
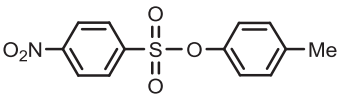
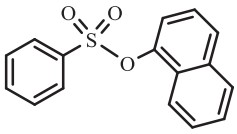
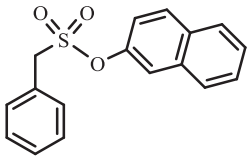
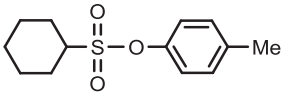
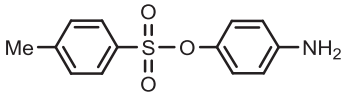
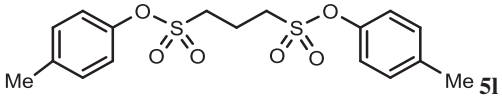
4.1. General remark

Amberlite IRA-400 (OH^-) as well as phosphoryl chloride, hydrogen peroxide, thiols, amines, and phenol derivatives are commercial products (Merck chemical company) and were used without further purification. Melting points were determined in a capillary tube and are not corrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker-200 NMR spectrometer using TMS as internal standard. IR spectra in the 4000–400 cm^{-1} range were measured with a WQF-510 FT-IR spectrometer using KBr discs.

4.2. General procedure for the synthesis of sulfonamides

A mixture of thiol (1 mmol), H_2O_2 (30%, 3 mmol, 0.3 mL), and $POCl_3$ (1 mmol, 0.153 g) was stirred in CH_3CN (5 mL) at 25 °C for the appropriate period of time. After consumption of the thiol as indicated by TLC, a solution of amine (1 mmol) and Amberlite IRA-400 (OH^-) (0.1 g, containing 0.1 mmol of OH^-) in CH_3CN (2 mL) was added. The resulting mixture was stirred at room temperature until TLC showed complete disappearance of substrates. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3×10 mL). The combined ethyl acetate

Table 3
Formation of sulfonic ester compound[a]

Entry	Sulfonic Ester	Yield [%][b]/time (min)	Mp [°C]/(lit. mp)	Reference
1	 **5a**	94 (2)	92–95 (95)	26a
2	 **5b**	96 (3)	69–72 (69–71)	26a
3	 **5c**	94 (3)	91–92	—
4	 **5d**	80 (20)	95–96 (98)	22a
5	 **5e**	92 (3)	Oil (oil)	26b
6	 **5f**	92 (2)	108–111(92)	22a
7	 **5g**	95 (1)	104 (98)	22a
8	 **5h**	93 (2)	113–115 (116–117)	26c
9	 **5i**	94 (2)	73–75	—
10	 **5j**	95 (3)	Oil	—
11	 **5k**	94 (1)	149–150 (145)	26d
12	 **5l**	95 (2)	Oil	—

[a] The purified products were characterized by mp, ^{1}H and ^{13}C NMR spectroscopy.
[b] Yields refer to pure isolated products.

extracts were dried with $MgSO_4$ and concentrated under reduced pressure to give the corresponding sulfonamide product in excellent yield.

4.3. General procedure for the synthesis of sulfonic ester

A mixture of thiol (1 mmol), H_2O_2 (30%, 3 mmol, 0.3 mL), and $POCl_3$ (1 mmol, 0.153 g) was stirred in CH_3CN (5 mL) at 25 °C for the appropriate period of time. When TLC showed complete consumption of the thiol, a solution of phenol derivative (1 mmol) and Amberlite IRA-400 (OH^-) (0.1 g, containing 0.1 mmol of OH^-) in CH_3CN (2 mL) was added. The resulting mixture was stirred at room temperature until TLC showed the disappearance of all the starting material. The catalyst was filtered off and the filtrate was concentrated in vacuo. The reaction mixture was then diluted with water (10 mL) and extracted with EtOAc (3×10 mL). The combined ethyl acetate extracts were dried with $MgSO_4$ and concentrated under reduced pressure to give the corresponding sulfonic ester as only product. In all the cases, the product obtained after the usual work up gave satisfactory spectral data. Spectral and analytical data for new compounds follow.

*4.3.1. N^1,N^3-Dicyclohexylpropane-1,3-disulfonamide (**3h**).* Light beige oil. Found: C, 48.90; H, 8.21; N, 7.40 S, 17.48. $C_{15}H_{30}N_2S_2O_4$ requires C, 49.15; H, 8.25; N, 7.64 S, 17.50. R_f=0.78 (8:3 *n*-hexane/EtOAc); IR (liquid film, cm^{-1}) 3294, 2931, 2856, 1724, 1452, 1309, 1128; ^1H NMR (200 MHz, $CDCl_3$): δ_H=0.85–1.52 (12H, m, CH_2 cyclohexyl), 1.62–2.27 (8H, m, CH_2 of cyclohexyl), 2.31–2.51 (2H, m, $-CH_2-CH_2-SO_2-$), 2.81–2.93 (2H, m, CH cyclohexyl), 3.11–3.51 (4H, m, CH_2-SO_2-), 6.08 (2H, br, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C=24.3, 24.8, 25.1, 34.5, 51.8, 52.9.

*4.3.2. 3-(N-p-Tolylsulfamoyl)propane-1-sulfonyl chloride (**3i**).* Orange oil. Found: C, 38.35; H, 4.55; N, 4.28; S, 20.34. $C_{10}H_{14}NS_2O_4Cl$ requires C, 38.52; H, 4.53; N, 4.49; S, 20.57. R_f=0.73 (8:3 *n*-hexane/EtOAc); IR (liquid film, cm^{-1}) 3290, 2929, 2860, 1724, 1453, 1306, 1167, 1128; ^1H NMR (200 MHz, $CDCl_3$): δ_H=2.37 (3H, s, CH_3), 2.64–2.71 (2H, m, $CH_2-CH_2-CH_2$), 3.49 (2H, t, *J*=6.7 Hz, $-CH_2-SO_2-NH-$), 3.78 (2H, t, *J*=6.7 Hz, $-CH_2-SO_2Cl$), 4.27 (1H, br, NH), 7.17–7.19 (4H, m, Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C=21.0, 24.6, 36.4, 57.9, 121.2, 129.8, 133.4, 135.1.

*4.3.3. Phenyl naphthalene-2-sulfonate (**5c**).* Cream solid: mp= 91–92 °C. Found: C, 67.47; H, 4.15; S, 11.12. $C_{16}H_{12}SO_3$ requires C, 67.59; H, 4.25; S, 11.28. R_f=0.58 (8:3 *n*-hexane/EtOAc); IR (KBr, cm^{-1}) 3059, 2920, 1502, 1375, 1460, 1375, 1176, 1149; ^1H NMR (200 MHz, $CDCl_3$): δ_H=6.98–7.03 (2H, m, *o*-H of Ph), 7.23–7.28 (3H, m, Ph), 7.70–7.98 (6H, m, naphthyl), 8.38 (1H, s, α-H of naphthyl). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C=122.0 122.5, 126.8, 127.4, 127.8, 129.0 129.1, 129.2, 129.3, 130.0, 131.3, 131.3, 136.0, 149.6.

*4.3.4. Naphthalen-2-yl phenylmethanesulfonate (**5i**).* Light pink solid: mp=73–75 °C. Found: C, 68.21; H, 4.50; S, 10.65. $C_{17}H_{14}SO_3$ requires C, 68.44; H, 4.73; S, 10.75. R_f=0.55 (8:3 *n*-hexane/EtOAc); IR (KBr, cm^{-1}) 3055, 2995, 2949, 1463, 1360, 1213, 1173, 1146; ^1H NMR (200 MHz, $CDCl_3$): δ_H=4.61 (2H, s, $-CH_2-$Ph), 7.26–7.31 (1H, m, H-3 of naphthyl), 7.46–7.64 (8H, m, 5CH of Ph, 3CH of naphthyl), 7.81–7.90 (3H, m, 3H of naphthyl). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C=56.4, 119.0, 120.5, 126.1, 126.6, 126.8, 127.4, 127.5, 128.6, 128.9, 129.7, 130.5, 131.5, 133.1, 146.4.

*4.3.5. p-Tolyl cyclohexanesulfonate (**5j**).* Brown oil. Found: C, 61.15; H, 7.23; S, 12.43. $C_{13}H_{18}SO_3$ requires C, 61.39; H, 7.13; S, 12.61. R_f=0.64 (8:3 *n*-hexane/EtOAc); IR (Liquid film, cm^{-1}) 3062, 2941, 2862, 1616, 1514, 1464, 1354, 1194, 1144; ^1H NMR (200 MHz, $CDCl_3$): δ_H=1.26–1.37 (3H, m, CH_2 of cyclohexyl), 1.55–1.82 (3H, m, CH_2 of cyclohexyl), 1.91–1.96 (2H, m, CH_2 of cyclohexyl), 2.30–2.34 (2H, m, CH_2 of cyclohexyl), 2.35 (3H, s, CH_3), 3.11–3.23 (1H, m, CH of cyclohexyl), 7.10–7.21 (4H, m, Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C=20.4, 25.5, 24.6, 26.1, 59.5, 121.3, 129.9, 136.4, 146.4.

*4.3.6. Dip-tolyl propane-1,3-disulfonate (**5l**).* Yellow oil. Found: C, 53.18; H, 5.11; S, 16.34. $C_{17}H_{20}S_2O_6$ requires C, 53.11; H, 5.24; S, 16.68. R_f=0.37 (8:3 *n*-hexane/EtOAc); IR (liquid film, cm^{-1}) 3035, 2929, 1502, 1462, 1361, 1173, 1146; ^1H NMR (200 MHz, $CDCl_3$): δ_H=2.41 (6H, s, $2CH_3$), 2.62–2.69 (2H, m, $-CH_2-CH_2-CH_2-$), 3.53 (4H, t, *J*=7.2 Hz, $-SO_2-CH_2-$), 7.18–7.28 (8H, m, 2Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C=18.6, 20.9, 47.9, 121.7, 130.6, 137.5, 146.7.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.04.040.

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