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ORIGINAL PAPER

Sulfonylation of aromatic compounds with methyl *p*-toluenesulfonate as a sulfonylating precursor

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Abstract We have developed Friedel–Crafts (FC) sulfonylation of aromatic compounds with methyl *p*-toluenesulfonate as a sulfonylating precursor. In this procedure, methyl *p*-toluenesulfonate was treated and activated with pyridine to produce *N*-methylpyridinium *p*-toluenesulfonate as a sulfonylation reagent. Reactivity of this salt for the sulfonylation of mesitylene was investigated in the presence of three different promoters, such as triflic anhydride, dimethylsulfide ditriflate, and triphenylphosphine ditriflate (TPPD). All of the promoters show chemoselectivity and among them, TPPD presents a chemoselectivity in FC sulfonylation.

Keywords Sulfonylation · Arenes · Methyl *p*-toluenesulfonate · Triphenylphosphine ditriflate · Sulfones

Introduction

Friedel–Crafts (FC) sulfonylation reactions are one of the most important groups of aromatic electrophilic substitutions [1, 2]. These reactions provide fundamental and useful methods for the synthesis of aryl sulfones which are important compounds in industry and organic synthesis [3]. Diaryl sulfones are especially important intermediates for synthesizing pharmaceutical compounds [4] and are potent anti-HIV-1 agents [5, 6]. In addition, they are active against malaria, leishmaniasis, and infections in patients with discoid lupus erythematosus [7–9]. Typically, FC-sulfonylations are performed using sulfonyl chloride in the presence of a little more than 1 equivalent of Lewis acids, such as anhydrous $AlCl_3$, $TiCl_4$, and $FeCl_3$ [10–12]. Also, it has been reported that sulfonic anhydrides can be used for FC-sulfonylation [13, 14].

Over the last decade, FC-sulfonylation of aromatic compounds with sulfonic acids has been developed in the presence of various catalysts, such as Nafion-H [15], Montmorillonite clay [16] and P_2O_5/SiO_2 [17]. This reaction with sulfonic acid under microwave irradiation has been also reported [18]. Although these methods utilize sulfonic acids as the cheapest and the most available of all sulfonylating reagents, but most of these methods suffer from disadvantages, such as using reflux condition, long reaction times, and especially large amount of aromatic compound as both solvent and substrate. Very recently, Yao et al. [19] have reported the sulfonylation of aromatic compounds using sulfonamide as the new and unusual sulfonylating reagent in the presence of triflic anhydride (Tf_2O) at high temperature (120 °C) in long reaction times. Therefore, there is still a considerable interest in the developing of FC-sulfonylation of aromatic compounds using other sulfonylating reagents such as esters.

In contrast to FC-acylation with carboxylic ester [20–24], FC-sulfonylation using sulfonic ester, which is more stable and easier to handle than typical sulfonylating reagents, such as sulfonic acid, sulfonic anhydride, and sulfonyl chloride, was not developed. Thus, we herein report our results describing the first method for the FC-sulfonylation of aromatic compounds using methyl *p*-toluenesulfonate as a sulfonylating precursor.

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Experimental

Chemical and apparatus

All the chemicals were obtained from Merck Company and used as received. All products are known and characterized by a comparison of their melting points and spectral (^{1}H NMR, ^{13}C NMR) data with those reported in the literatures. All yields refer to isolated products. NMR spectra were recorded on Brucker Avance spectrophotometer (200 MHz) in $CDCl_3$ using TMS as an internal standard. Melting points were achieved on Barnstead electrothermal melting point (apparatus) instrument.

p-Toluenesulfonic anhydride (Scheme 1, a): white solid, mp 122–123 °C (lit [25] 129.5–131.5 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 2.47$ (s, 3H), 7.36 (d, $J = 8.2$ Hz, 2H), 7.85 (d, $J = 8.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 21.4$, 128.3, 129.5, 132.8, 146.2.

Dimesitylmethane (Scheme 1, b): white solid, mp 132–133 °C (lit [26] 134.4–135.4 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 2.14$ (s, 12H), 2.25 (s, 6H), 4.0 (s, 2H), 6.84 (s, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 20.3$, 20.4, 128.9, 134.4, 134.5, 136.3.

Preparation of *N*-methylpyridinium *p*-toluenesulfonate

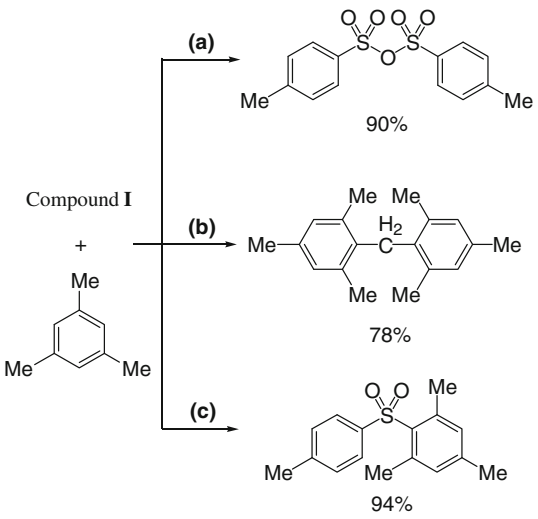
N-methylpyridinium *p*-toluenesulfonate (**I**) was obtained from the reaction of methyl *p*-toluenesulfonate (1 mmol) and pyridine (1 mmol) at room temperature under neat conditions. Melting point for this salt is 133–134 °C and its NMR spectroscopic data are [^{1}H NMR (200 MHz, DMSO-*d6*): $\delta = 2.26$, 4.33, 7.09 (d, $J = 7.8$ Hz, 2H), 7.46 (d, $J = 8.0$ Hz, 2H), 8.09 (t, 2H), 8.54 (t, 1H), 8.96 (d, $J = 5.4$ Hz, 2H). ^{13}C NMR (50 MHz, DMSO-*d6*): $\delta = 20.8$, 47.9, 125.5, 127.7, 128.1, 137.7, 145.0, 145.6, 145.8]. These data easily confirmed the formation of *N*-methylpyridinium *p*-toluenesulfonate.

General procedure

To a solution of Ph_3PO (0.278 g, 1 mmol) in CH_2Cl_2 (1 mL), Tf_2O (0.16 mL, 1 mmol) was added at 0 °C and the solution allowed to stir for 10 min at room temperature. *N*-methylpyridinium *p*-toluenesulfonate (0.266 g, 1 mmol) was added to the reaction mixture and the mixture allowed stirring for 30 min. Then, arene (1 mmol) was added to the mixture and the solution was stirred again for appropriate time (Table 1). Upon completion of the reaction, the organic solvent was evaporated and the crude product was purified by a column chromatography using ethyl acetate/*n*-hexane (2:8) to afford an aromatic sulfone. The products are all known compounds.

(2,4,6-Trimethyphenyl) *p*-tolyl sulfone (Table 1, entry 1): white solid, mp 115–116 °C (lit [27] 117 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 2.28$ (s, 3H), 2.38 (s, 3H), 2.59 (s, 6H), 6.92 (s, 2H), 7.24 (d, $J = 8.2$ Hz, 2H), 7.67 (d, $J = 8.2$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 20.6$, 21.1, 22.4, 125.9, 129.0, 131.7, 139.5, 140.2, 142.8, 143.0.

(2,5-Dimethylphenyl) *p*-tolyl sulfone (Table 1, entry 4): white solid, mp 104–105 °C (lit [28] 108–110 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 2.37$ (s, 3H), 2.40 (s, 6H), 7.08 (d, $J = 7.7$ Hz, ^{1}H), 7.27 (d, $J = 7.5$ Hz, 2H), 7.69 (m, 3H), 8.02 (s, 1H).



Scheme 1 **a** Tf_2O (1 mmol), mesitylene (1 mmol) in CH_2Cl_2 (1 mL), rt. **b** 1: DMSD (1 mmol), CH_2Cl_2 (1 mL), time = 10 min. 2: Mesitylene (1 mmol), rt, time = 24 h. **c** 1: TPPD (1 mmol), CH_2Cl_2 (1 mL). 2: Mesitylene (1 mmol), rt, time = 30 min

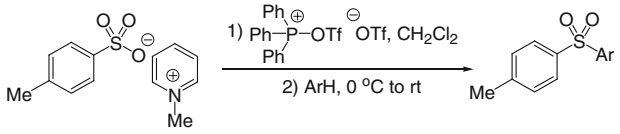
Results and discussion

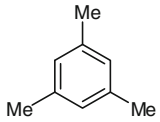
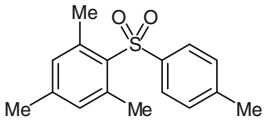
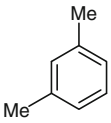
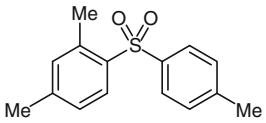
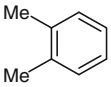
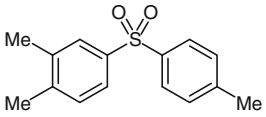
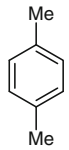
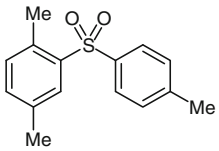
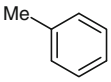
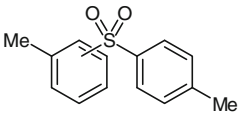
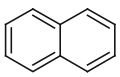
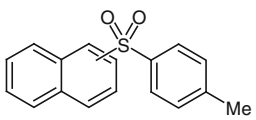
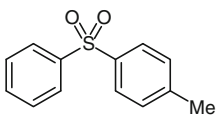
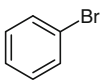
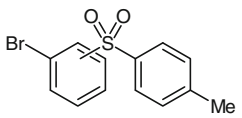
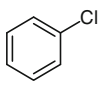
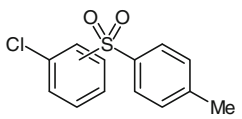
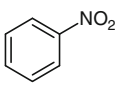
In our studies on FC-reactions [29–37], we have demonstrated that a methyl-donor compound such as dimethyl sulfate can be easily activated with pyridine and Tf_2O for preparation of symmetrical diaryl sulfones [36]. Encouraged by this success; we decided to use methyl *p*-toluenesulfonate to react with pyridine for production of *N*-methylpyridinium *p*-toluenesulfonate (**I**) as a new sulfonylating reagent (Scheme 2).

Reactivity of this salt was examined for the sulfonylation of mesitylene in the presence of three different promoters in CH_2Cl_2 as the solvent, and the results are shown in Scheme 1. It is noticeable that we utilized CH_2Cl_2 as a non-nucleophilic solvent to create the homogeneous reaction conditions, and also non-nucleophilic feature of this solvent does not allow CH_2Cl_2 to react with the promoters.

At first as shown in Scheme 1 (path a), when 1 equivalent of Tf_2O was applied to promote **I** for the sulfonylation of mesitylene, no sulfone product was observed, but

Table 1 Friedel-Crafts sulfonylation of aromatic compounds with *N*-mthylpyridinium *p*-methytoluenesulfonate in the presence of TPPD

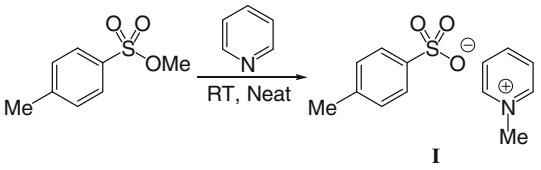


Entry	Aromatic	Time (h)	Product	Yield (%)[a]	Mp (°C, observed)	Mp (°C, observed)[ref]
1		0.5		94	115–116	117 [27]
2		1		85	51–52	52 [38]
3		1		74	113–114	117 [39]
4		1		68	104–105	108–110 [28]
5		2		80 *o:p* = 23:78[b]	147–148	155 [27]
6		2		85 $\alpha:\beta$ = 90:10	118–119	119 [27]
7		3		55	126–127	126–127 [40]
8		6		43 *o:p* = 7:93[b]	132–133	132–134 [40]
9		6		40 *o:p* = 10:90[b]	115–116	115–117 [40]
10		24	–	0	–	–

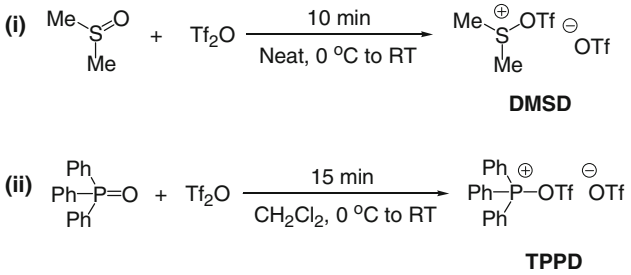
[a] Isolated yields

[b] The ratio of *ortho:para* was determined with ^{1}H NMR

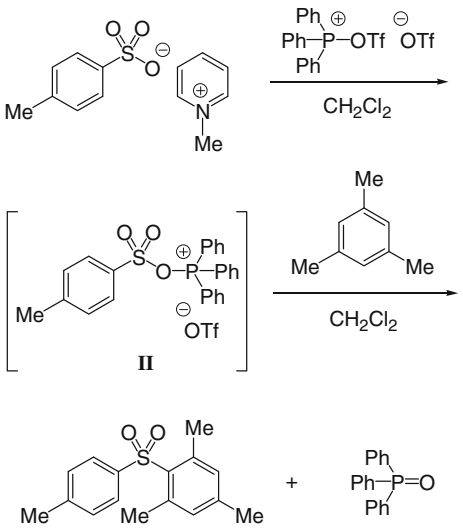
[c] The ratio of $\alpha:\beta$ was determined with ^{1}H NMR



Scheme 2



Scheme 3



Scheme 4

p-toluenesulfonic anhydride was achieved in 90% yield. The reason for this observation may have arisen from this fact that there is a hard–soft interaction between *p*-toluenesulfonate anion and *N*-methylpyridinium cation. This hard–soft interaction intensifies the nucleophilic ability of *p*-toluenesulfonate anion in comparison with mesitylene; so, *p*-toluenesulfonate anion reacts rapidly with itself and it does not allow mesitylene to react. Thus, in order to prepare the desired product (sulfones), we decided to apply other promoters with oxophile atoms such as sulfur and phosphorous.

Early studies by Hendrickson and Schwartzman [41] established that Tf_2O adds to dimethylsulfoxide to form the relatively unstable, air, oxygen, and water-sensitive dimethylsulfide ditriflate (DMSD). To produce 1 mmol of DMSD, one equivalent of Tf_2O was added dropwise to 1 mmol of Me_2SO at 0 °C and the mixture allowed to stir at room temperature. After 10 min, a white solid formed as DMSD (Scheme 3, (i)).

In the second attempt, 1 mmol of *N*-methylpyridinium *p*-toluenesulfonate was added to the solution of 1 mmol of DMSD as the promoter in 1 mL of CH_2Cl_2 at room temperature and the reaction mixture allowed stirring for 15 min. Finally, 1 mmol of mesitylene was added and after 24 h, dimesityl methane was obtained in 78% (Scheme 1, path b). In the absence of either *N*-methylpyridinium *p*-toluenesulfonate or DMSD, the reaction was not carried out which implies that the presence of these compounds is necessary to perform the reaction.

In continuation with more accurate search on reported literatures, we observed that triphenylphosphine oxide reacts exothermically with Tf_2O in CH_2Cl_2 to give white precipitates of the corresponding triphenylphosphine ditriflate (TPPD) and diphosphonium triflate salt [42–44]. These salts were shown to be a powerful dehydrating agent and also a promising reagent for the conversion of carboxylic acids to anhydrides [45] esters, amides [42, 45] and also the conversion of sulfonic acids to sulfonamides [46]. We decided to utilize TPPD as the promoter for FC-sulfonylation of mesitylene with *N*-methylpyridinium *p*-toluenesulfonate.

To prepare 1 mmol of TPPD, 1 mmol of Tf_2O was added dropwise to 1 mmol of Ph_3PO in 1 mL of CH_2Cl_2 at 0 °C and the solution allowed to stir at room temperature for 15 min (Scheme 3, (ii)). Then mesitylene (1 mmol) and *N*-methylpyridinium *p*-toluenesulfonate (1 mmol) were added to the reaction mixture. After 30 min, we observed quiet satisfactory results in FC-sulfonylation of mesitylene and (2,4,6-trimethylphenyl)phenyl sulfone was achieved in 94% yield (Scheme 1, path 3).

A possible reaction mechanism is presented in Scheme 4 in which *N*-methylpyridinium *p*-toluenesulfonate was initially reacted with TPPD to produce intermediate **II** having Ph_3PO as an inert and excellent leaving group. As a result **II** reacted with mesitylene and Ph_3PO was sent out and desirable sulfone was produced. It seems that TPPD acts as both a promoter and a scavenger for *N*-methylpyridinium *p*-toluenesulfonate.

It is noteworthy that when trifluoroacetic anhydride (TFAA) and Ph_3PO were used instead of Tf_2O and Ph_3PO in the reaction of mesitylene with *N*-methylpyridinium *p*-methyl toluenesulfonate, the reaction was not completed even after 3 h.

The activity of TPPD as a promoter for FC-sulfonylation of different aromatic compounds with *N*-methylpyridinium *p*-methyltoluenesulfonate was examined and the results are

summarized in Table 1. These results show that this novel method afforded diaryl sulfones in good to excellent yields. After the success of mesitylene in performing of the reaction and to show the generality of the method, different isomers of xylene were utilized under these reaction conditions; the best result was obtained for *meta* isomer and the corresponding sulfone was produced after 1 h in 85% yield (Table 1, entry 2), whereas in the case of *ortho* and *para* isomers, lower yields were obtained (Table 1, entries 3 and 4). This observation may have arisen from this fact that the reaction site in *m*-xylene is activated with two methyl groups. When toluene was reacted with *N*-methylpyridinium *p*-toluenesulfonate in the presence of TPPD, the corresponding sulfone was produced in 80% yield with an *ortho*:*para* ratio of 23:78.

Naphthalene was also sulfonylated under the above conditions and produced the corresponding product in 85% yield. In the case of benzene, (*p*-tolyl)phenyl sulfone was achieved after 3 h in 55% yield. Also, deactivated arenes such as chlorobenzene and bromobenzene were successfully sulfonylated and obtained results have shown high *p*-selectivity in these compounds (Table 1, entries 8 and 9). However, the reactions of nitrobenzene, benzaldehyde, and acetophenone were unsuccessful even after 24 h.

Triphenylphosphine ditriflate shows chemoselectivity in all of the FC-sulfonylation reactions.

Conclusions

In summary, we have developed FC-sulfonylation of aromatic compounds with methyl *p*-toluenesulfonate as a new sulfonylating precursor. Performing of the reaction under mild reaction conditions at room temperature and sulfonylation of deactivated benzene such as chlorobenzene are remarkable features of the present procedure. Triphenylphosphine ditriflate shows chemoselectivity in all of the FC-sulfonylation reactions.

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