Scandium Triflate Catalyzed One-Pot Synthesis of Diaryl Sulfoxides

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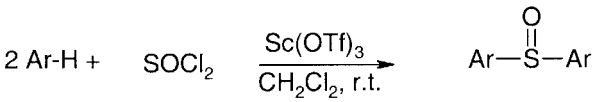
Abstract: Arenes react smoothly with thionyl chloride in the presence of a catalytic amount of scandium triflate at ambient temperature to afford the corresponding symmetrical diaryl sulfoxides in excellent yields with high regioselectivity.

Key words: scandium reagents, sulfinylation, arenes, aryl sulfoxides

Sulfoxides and sulfones are interesting functional groups possessing manifold reactivity for conversion of a variety of organic sulfur compounds in the field of drugs and pharmaceuticals.[1] Especially, sulfoxides deserved much attention as important chiral auxiliary in asymmetric synthesis,[2] and particularly in carbon-carbon bond forming processes.[3] In addition, aryl sulfonium salts have also been used extensively as photoactive cationic initiators[4] and for the photogeneration of protonic acid in the lithographic resist field.[5] In view of the importance of sulfoxides as chiral synthons in organic synthesis, a simple and high yielding one-pot approach for their synthesis is highly desirable. Sufoxides are usually prepared by indirect methods, which involve the oxidation of sulfides, the reduction of sulfones and the reaction of organometallic reagents with sulfinic acid esters, mixed anhydrides or sulfines.[6] The direct methods for the preparation of diaryl sulfoxides involve the Friedel–Crafts sulfinylation of arenes using Lewis acids[7] as well as Brønsted acids.[8] Other methods including the addition of aryl Grignard reagents to thionyl chloride[6] and the reaction of SO_2 with arenes in the presence of Magic acid[9] also produce aryl sulfoxides. However, many of these methods have limited synthetic scope due to the use of corrosive, hazardous, oxidizing and difficult to handle reagents, lack of selectivity, and the formation of a mixture of products containing sulfonium salts and chlorinated byproducts along with desired sulfoxides. Thus there is a need to develop a simple, convenient and high yielding method for the preparation of sulfoxides under mild reaction conditions. Metal triflates are unique Lewis acids that are currently of great research interest.[10] In particular, scandium salts are attractive because they are quite stable to water and reusable and in addition, they are highly effective for the activation of arenes in electrophilic substitution reactions. Therefore, scandium reagents are efficient catalysts compared to traditional Lewis acids in several carbon-carbon bond-forming reactions and have found wide applications in organic synthesis.[11]

In this report we wish to highlight our results on the electrophilic sulfinylation of arenes with thionyl chloride using a catalytic amount of scandium triflate. Thus treatment of anisole with thionyl chloride in the presence of 5% $Sc(OTf)_3$ at ambient temperature afforded dianisyl sulfoxide in 90% yield (Scheme).



Scheme

In a similar fashion, several arenes reacted smoothly with thionyl chloride to give the corresponding diaryl sulfoxides in high yields. In all cases, the reactions proceeded efficiently at ambient temperature with high regioselectivity. The extent of electron density and the nature of the substituent on the aromatic ring show some effect on this conversion. The activated arenes gave the products in excellent yields in a short reaction time (Table). However, unactivated arenes such as benzene, biphenyl, fluorobenzene, xylene and naphthalene also reacted well with thionyl chloride in the presence of 5% $Sc(OTf)_3$ to afford the corresponding aryl sulfoxides in high yields. In contrast, metal halides such as $InCl_3$, $ZrCl_4$, $BiCl_3$, $YbCl_3$ and $CeCl_3$ gave the products in moderate yields. The best results were obtained when metal triflates were used as catalysts. Similar yields and selectivity were also obtained with 5% $In(OTf)_3$ under the present reaction conditions. However, in the absence of catalyst, the reaction did not yield any product even at reflux temperature. The lowering of the reaction temperature was detrimental to the efficiency of this procedure. The scope of scandium triflate catalyzed sulfinylation of arenes was investigated with respect to the activated and unactivated aromatics and the results are presented in the Table. This method is simple, convenient and highly regioselective, affording high yields of products in a short reaction time. In addition, this method does not require any promoters or anhydrous conditions and no precautions need to be taken to exclude moisture from the reaction media. Scandium triflate was found to be the best catalyst for the synthesis of aryl sulfoxides from activated arenes, and surprisingly, the only catalyst effective for the sulfinylation of unactivated aromatics, albeit requiring longer reaction time (3–5 h). There are many advantages in the use of $Sc(OTf)_3$ for this

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transformation which include high yields of products, cleaner reaction profiles, mild reaction conditions, greater selectivity, short reaction times and operational simplicity. Finally, scandium triflate was recovered from aqueous layer during the work-up and reused in subsequent reactions with gradual decrease in activity; for example, anisole and thionyl chloride gave 90%, 85% and 81% yields over three cycles.

Table $Sc(Otf)_3$-Catalyzed Synthesis of Diaryl Sulphoxides

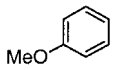
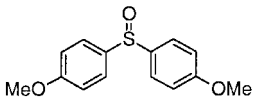
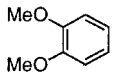
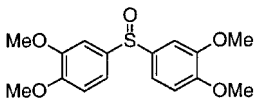
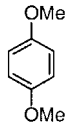
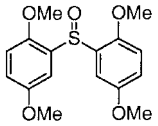
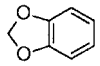
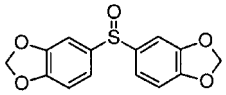
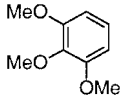
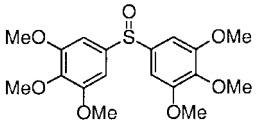
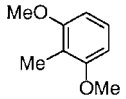
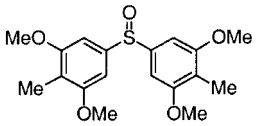
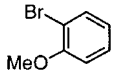
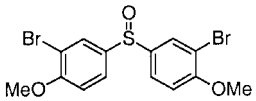
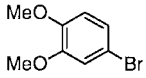
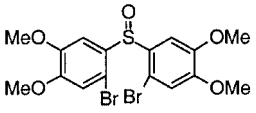
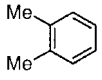
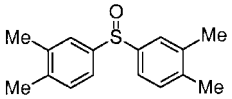
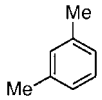
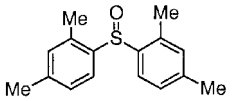
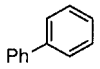
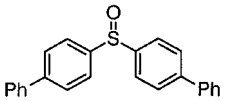
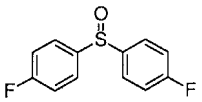
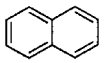
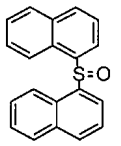
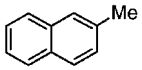
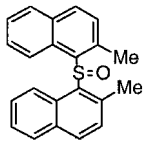
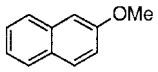
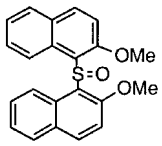
Entry	Arene **1**	Product[a] **2**	Time (h)	Yield (%)[b]
a			1.5	90
b			1.0	92
c			1.5	95
d			1.0	90
e			1.5	93
f			1.5	89
g			2.0	87
h			2.0	85
i			2.5	80
j			3.0	82
k			4.0	75

Table $Sc(Otf)_3$-Catalyzed Synthesis of Diaryl Sulphoxides (continued)

Entry	Arene **1**	Product[a] **2**	Time (h)	Yield (%)[b]
l			3.5	70
m			3.5	78
n			3.0	82
o			2.5	90

[a] All products were characterized by ^1H NMR, IR and Mass spectroscopy.[12,]
[b] Isolated and unoptimized yields.

In summary, scandium triflate is a novel and highly efficient Lewis acid for the synthesis of diaryl sulfoxides from arenes and thionyl chloride under mild reaction conditions. In addition to its efficiency and simplicity, this method provides excellent yields of products with high regioselectivity.

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(12) *Experimental procedure*: A mixture of arene (10 mmol), thionyl chloride (6 mmol) and $Sc(OTf)_3$ (5 mol%) in dichloromethane (15 mL) was stirred at ambient temperature under N_2 atmosphere for an appropriate time (Table). After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (10 mL), neutralized with sat. sodium bicabonate and extracted with dichloromethane (2×15 mL). The combined organic layers were dried over anhyd Na_2SO_4, concentrated in vacuo and the resulting product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 2:8) to afford pure diaryl sulfoxides. Spectral data for products:
Di-(3,4-dimethoxyphenyl) Sulfoxide (2b): ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.98 (s, 12 H), 6.97 (d, 2 H, *J* = 8.0 Hz), 7.40 (d, 2 H, *J* = 2.3 Hz), 7.65 (dd, 2 H, *J* = 2.3, 8.0 Hz). EIMS: *m/z*: 336 (M^+), 321, 293, 155, 69, 57. IR (KBr): 2925, 2855, 1585, 1474, 1359, 1254, 1208, 1033, 840, 778 cm^{-1}.
Di-(3,4-dimethylphenyl) Sulfoxide (2i): ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.40 (s, 12 H), 7.25 (d, 2 H, *J* = 1.2 Hz), 7.30 (d, 2 H, *J* = 8.0 Hz), 7.78 (dd, 2 H, *J* = 1.2 and 8.0 Hz). EIMS: *m/z*: 258 (M^+), 240, 226, 169, 141, 105, 77, 43. IR (KBr): 2924, 2853, 1585, 1450, 1325, 1124, 772, 601 cm^{-1}.
Di-(2-methoxy-1-naphthyl) Sulfoxide (2o): ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.0 (s, 6 H), 7.23 (d, 2 H, *J* = 8.0 Hz), 7.38 (t, 2 H, *J* = 7.8 Hz), 7.57 (t, 2 H, *J* = 7.8 Hz), 7.70 (d, 2 H, *J* = 8.0 Hz), 7.78 (d, 2 H, *J* = 8.0 Hz), 8.20 (d, 2 H, *J* = 8.0 Hz). FAB Mass: 362 (M^+), 346, 192, 177, 149, 126, 114, 63. IR (KBr): 2923, 2845, 1585, 1495, 1430,1355, 1320, 1255, 1210, 1178, 1024, 840 cm^{-1}.