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A General and Efficient Synthesis of Sulfonylbenzotriazoles from *N*-Chlorobenzotriazole and Sulfinic Acid Salts

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One-pot reactions of sulfinic acid salts (produced from organometallic reagents with SO_2) with *N*-chlorobenzotriazole gave the corresponding *N*-alkane-, *N*-arene-, and *N*-heteroenesulfonylbenzotriazoles **3a**−**j** in 41−93% yields. Reagents **3a**−**j** are efficient sulfonylating agents, reacting at 20−80 °C with various primary and secondary aliphatic amines to yield the corresponding sulfonamides in 64−100% yields.

Introduction

Compounds containing sulfonyl groups have long been a research focus as a result of their biological importance and chemical applications. Sulfonamides occupy a unique position in the drug industry with their antibacterial and antimicrobial properties.[1] Sulfonamides are also diuretics and hypoglycemic agents as well as protease inhibitors.[2] Arylsulfonyl substituents have been used as protecting groups for oxygen and nitrogen functionalities.[3] Sulfonamide derivatives of azo dyes achieve improved light stability, water solubility, and fixation to fiber.[1]

Reactions of ammonia, or primary or secondary amines, with sulfonyl halides in the presence of a base are the usual routes for the formation of sulfonamides.[4] This approach requires the availability of the sulfonyl halide, some of which can be hard to prepare and difficult to store or handle. Also, side reactions are possible due to the presence of the base or the liberated chloride nucleophile, particularly under harsh conditions with relatively non-nucleophilic substrates. Moreover, the corresponding disulfonimide is stated[4] to be a byproduct in reactions of sulfonyl halides with primary amines or ammonia.

These issues have led to the development of several alternative protocols for sulfonamide synthesis (Scheme 1). Thus, sulfonamides are formed (i) by reaction of sulfinic acid salts with hydroxylamine-*O*-sulfonic acid,[5] (ii) by reduction of arylsulfonyl azides,[6] (iii) from aromatic and aliphatic sulfinic acid salts using bis(2,2,2-trichloroethyl)azodicarboxylate as an electrophilic nitrogen source,[7] (iv) from alkyl or aryl halides by means of sodium 3-methoxy-3-oxopropane-1-sulfinate as a sulfinate transfer reagent,[8] (v) by the radical addition of organo halides to pentafluorophenyl vinylsulfonate[9] followed by substitution of the pentafluorophenyl moiety by amines, and (vi) by the sulfamoylation of aromatics using sulfamoyl chloride.[10] Alkyl/arylsulfonylimidazoles, prepared from sulfonyl halides and 1*H*-imidazole or 1-trimethylsilylimidazole, have also been used as sulfonyl transfer reagents in the preparation of sulfonamides (vii in Scheme 1).[11] However, the imidazole ring requires activation as its 3-methylimidazolium triflate to act as a leaving group in its reactions with *N*- and *O*-nucleophiles.

Although these additional synthetic technologies have proven to be of great utility for specific substrate classes, there remains a need for straightforward and general methods toward accessing sulfonamides. It would be highly desirable to have a sulfonating reagent that would react under mild conditions in the absence of a strong base or competing nucleophile.

We have reported earlier the synthesis and utility of 1-phenylsulfonylbenzotriazole **3**,[12] which was shown to react with primary and secondary amines and with alcohols to give the corresponding sulfonamides and sulfonates, respectively[12] (Scheme 2), in good yields and under mild conditions (stirring in THF at rt). Thus, the sulfonylbenzotriazolyl motif is a practical replacement for the highly reactive, frequently labile, and often difficult to access sulfonyl halide unit. Other than its use as a benzenesulfonating agent, **3** and its analogues have also been widely used in the preparation of (i) *N*-acylbenzotriazoles (well-known synthetic equivalents to acyl halides;[13]) and (ii) *N*-imidoylbenzotriazoles[14] and (iii) for the benzotriazolylalkylation of aromatic compounds.[15]

However, to prepare aryl/alkylsulfonylbenzotriazoles[12] from the corresponding sulfonyl halides by reactions with

(1) Hansch, C.; Sammes, P. G.; Taylor, J. B. *Comprehensive Medicinal Chemistry*; Pergamon Press: Oxford, 1990; Vol. 2, Chapter 7.1.
(2) Roush, W. R.; Gwaltney, S. L., II; Cheng, J.; Scheidt, K. A.; McKerrow, J. H.; Hansell, E. *J. Am. Chem. Soc.* **1998**, *120*, 10994.
(3) O'Connel, J. F.; Rapoport, H. *J. Org. Chem.* **1992**, *57*, 4775.
(4) Andersen, K. K. In *Comprehensive Organic Chemistry*; Jones, D. N., Ed.; Pergamon Press: Oxford, 1979; Vol. 3.
(5) Graham, S. L.; Scholz, T. H. *Synthesis* **1986**, 1031.
(6) (a) Boruah, A.; Baruah, M.; Prajapati, D.; Sandhu, J. S. *Synlett* **1997**, 1253; (b) Iyer, S.; Sattar, A. K. *Synth. Commun.* **1998**, *28*, 1721.
(7) Chan, W. Y.; Berthelette, C. *Tetrahedron Lett.* **2002**, *43*, 4537.
(8) Baskin, J. M.; Wang, Z. *Tetrahedron Lett.* **2002**, *43*, 8479.
(9) Caddick, S.; Wilden, J. D.; Bush, H. D.; Wadman, S. N.; Judd, D. B. *Org. Lett.* **2002**, *4*, 2549.
(10) Frost, C. G.; Hartely, J. P.; Griffin, D. *Synlett* **2002**, 1928.
(11) O'Connell, J. F.; Rapoport, H. *J. Org. Chem.* **1992**, *57*, 4775.
(12) Katritzky, A. R.; Zhang, G.; Wu, J. *Synth. Commun.* **1994**, *24*, 205.

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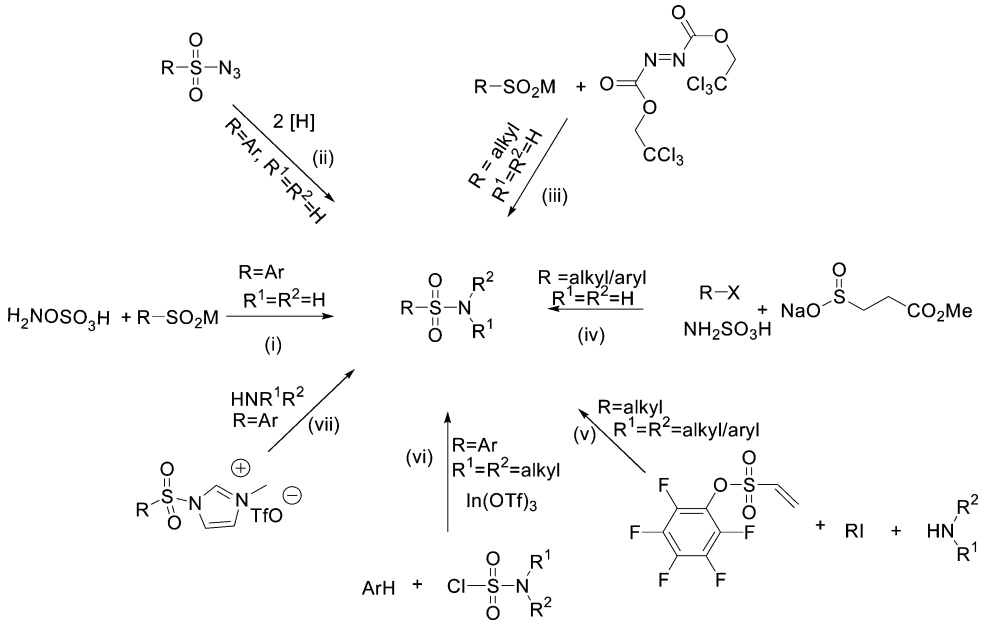
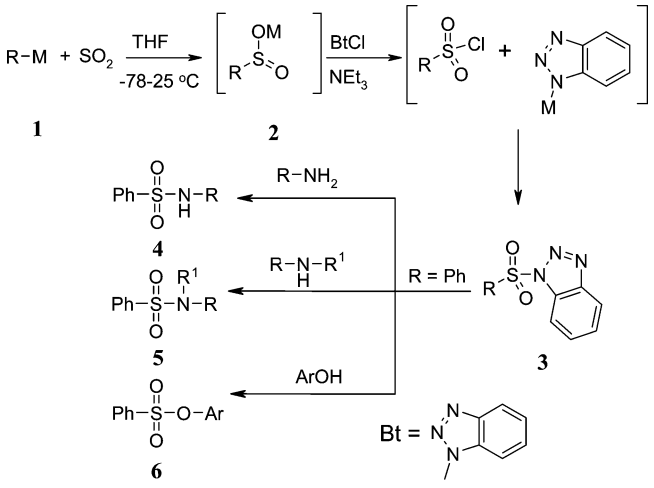
SCHEME 1



SCHEME 2



either 1*H*-benzotriazole or 1-trimethylsilylbenzotriazoles limits their application to the synthesis of sulfonamides. Therefore, a general method to prepare sulfonylbenzotriazoles starting from easily available materials would be useful. We herein report such an approach starting from aryl/alkyllithiums or Grignard reagents by reacting successively with SO_2 and *N*-chlorobenzotriazole.

Results and Discussion

Preparation of benzotriazole Reagents 3. Conversion of organometallic reagents to sulfinic acid salts by reaction with sulfur dioxide has been discussed by Pinnic and co-workers.[16] Furukawa[17] was the first to report the reaction of sulfinic acids and chloramines to produce a ca. 50:50 mixture of sulfonamide and sulfonyl chloride. We now show that addition of *N*-chlorobenzotriazole to an intermediate sulfinic acid salt gives the corresponding sulfonylbenzotriazole. For example, the reaction of *p*-tolylmagnesium bromide and sulfur dioxide[21] followed by treating the intermediate sulfinic acid salt with chlorobenzotriazole proceeded smoothly at 20 °C, giving the *p*-tolylsulfonylbenzotriazole in 68% yield (Scheme 2) along with traces of *p*-toluenesulfonyl chloride. Use of 1 equiv of triethylamine with the *N*-chlorobenzotriazole made a significant improvement: *p*-tolylsulfonylbenzotriazole was isolated in 93% yield under this modified condition. The mechanism may involve nucleophilic counterattack of the benzotriazolyl anion on an intermediate sulfonyl chloride (Scheme 2). The effect of triethylamine may be to coordinate with the magnesium cation. Other organomagnesium reagents also afforded the corresponding sulfonylbenzotriazoles in good to excellent yields, as shown in Table 1.

Arylorganolithiums can also be used in the preparation of arylsulfonylbenzotriazoles. Thus, thiophene was lithi-

TABLE 1. Alkyl/arylsulfonylbenzotriazoles 3

3	R	M	yield (%)	mp (°C)
a	*n*-butyl	Li	65	oil
b	cyclohexyl	MgCl	71	117−119
c	isobutyl	MgBr	75	oil
d	*p*-$CH_3C_6H_5$	MgBr	93	133−134[a]
e	2-pyridyl	Li	71	132−135
f	3-pyridyl	Li	41	128−129
g	2-furyl	Li	83	107−109
h	2-thienyl	Li	82	143−144
i	1-methyl-2-indolyl	Li	20	131−132
j	1-methylimidazolyl	Li	80	147−150

[a] Reference 20 gives mp 134−135; all other compounds are novel.

(13) (a) Katritzky, A. R.; He, H.-Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210; (b) Katritzky, A. R.; Shobana, N.; Pernak, J.; Afridi, A. S.; Fan, W.-Q. *Tetrahedron* **1992**, *48*, 7817.

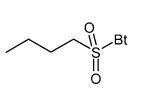
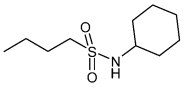
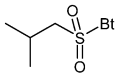
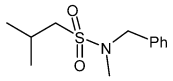
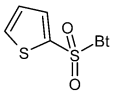
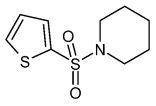
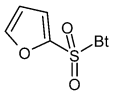
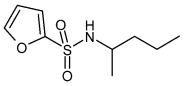
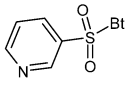
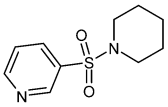
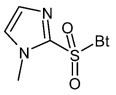
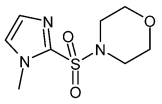
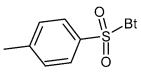
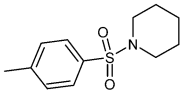
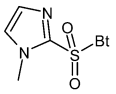
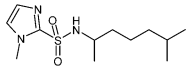
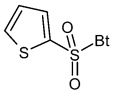
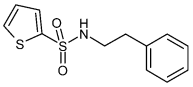
(14) Katritzky, A. R.; Monteux, D. A.; Tymoshenko, D. O. *Org. Lett.* **1999**, *1*, 577.

(15) Katritzky, A. R.; Gupta, V.; Garot, C.; Stevens, C. V.; Gordeev, M. F. *Heterocycles* **1994**, *38*, 345.

(16) Pinnick, H. W.; Reynold, M. A. *J. Org. Chem.* **1979**, *44*, 160.

(17) Nishikawa, M.; Inaba, Y.; Furukawa, M. *Chem. Pharm. Bull.* **1983**, *31*, 1374.

TABLE 2. Sulfonamides 7 Prepared Using Reagents 3

Reagent 3	Amine	Condition	Sulfonamide	Yield (%)
	Cyclohexylamine	THF/rt/ 18 h	 **7**	89
	*N*-Methylbenzyl-amine	THF/rt/ 15 h	 **8**	72
	Piperidine	THF/rt/ 42 h	 **9**	85
	2-Aminopentane	DMF/80 °C /24 h	 **10**	100
	Piperidine	DMF/80 °C /48 h	 **11**	100
	Morpholine	DMF/80 °C /24 h	 **12**	91
	Piperidine	THF/rt/ 20 h	 **13**	100
	1, 5-Dimethyl-hexylamine	DMF/80 °C /24 h	 **14**	64
	Phenethylamine	DMF/80 °C /48 h	 **15**	80

ated at C2, and the lithium reagent was allowed to react with SO_2 and *N*-chlorobenzotriazole under the conditions described above. Thiophene-2-sulfonylbenzotriazole was isolated in 82% yield (Table 1, **3h**). We have used a variety of alkyl- and arylorganometallic reagents to check the general applicability and functional group tolerance of this method. The respective sulfonylbenzotriazoles were isolated in good yields (41−93%, Table 1). In the case of 1-methylindole, the expected 2-sulfonylated product was isolated in 20% yield along with 11% of 2-benzotriazolyl-1-methylindole, which might have formed by the addition of 2-lithio-1-methylindole to *N*-chlorobenzotriazole.

Attempts to react prop-2-enesulfinic acid salt, formed from the reaction of allylmagnesium bromide and SO_2, with *N*-chlorobenzotriazole to make allylsulfonylbenzotriazole gave only unidentifiable byproducts and benzotriazole. Prop-2-enesulfinic acids are known to be very unstable and to undergo acid-catalyzed decomposition to SO_2 and the olefin.[18] Similar unsatisfactory results were also obtained with acetylenic Grignard reagents.

Synthesis of Sulfonamides Using Reagents 3. The benzotriazolylsulfonamides **3a**−**j** reacted as expected with diverse amines to generate novel sulfonamides. On the basis of our previous experience,[12] we tried the reaction in THF at rt in the absence of a base. Thus, when **3a** was treated with cyclohexylamine, the corresponding sulfonamide **7a** was obtained in 89% yield (Table 1). Sulfonylbenzotriazoles **3c** and **3h** also reacted under the same conditions with *N*-methylbenzylamine and piperidine, yielding the resultant sulfonamides in 72% and 85% yields, respectively. However, for reagents **3f**, **3g**, **3j**, and **3i** the smooth displacement of benzotriazole took place

(18) Masilamani, D.; Rogic, M. M. *J. Am. Chem. Soc.* **1978**, *100*, 4634.

(19) (a) Biellmann, J.-F.; Ducep, J.-B. *Organic Reactions*; John Wiley & Sons: New York, 1982; Vol. 27, Chapter 1. (b) Gschwend, H. W.; Rodriguez, H. R. *Organic Reactions*; John Wiley & Sons: New York, 1982; Vol. 26, Chapter 1.

(20) Katritzky, A. R.; Kurz, T.; Zhang, S.; Voronkov, M.; Steel, P. J. *Heterocycles* **2001**, *55*, 1703.

(21) Sulfur dioxide is a gas, which may cause eye, skin, and respiratory irritation. Handle with care.

with aliphatic amines (Table 2) in DMF at 80 °C but not in refluxing THF or acetonitrile.

In summary, *N*-chlorobenzotriazole is a useful reagent for converting sulfinate salts to sulfonylbenzotriazoles, which offer access to a wide variety of sulfonamides where the corresponding sulfonyl halide is not readily available. In addition, the approach obviates the formation of disulfonimides that can arise during the ammonolysis of sulfonyl halides.[4] The particular usefulness of the method lies in the ease with which the benzotriazole group can be replaced by *N*-nucleophiles. The easy accessibility of sulfinic acid salts from SO_2 and organometallics and the preparative ease of *N*-chlorobenzotriazole should give the approach substantial utility.

Experimental Section

1-(Butane-l-sulfonyl)-1*H*-1,2,3-benzotriazole (3a). 3a was purified by column chromatography with hexanes/EtOAc (4:1) as eluent and obtained as a brown oil (65%). ^{1}H NMR: δ 0.88 (t, J = 7.4 Hz, 3H), 1.35−1.48 (m, 2H), 1.69−1.79 (m, 2H), 3.62 (t, J = 8.0 Hz, 2H), 7.54 (t, J = 8.1 Hz, 1H), 7.68 (t, J = 7.2 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H). ^{13}C NMR: δ 13.1, 20.9, 24.6, 55.3, 111.8, 120.4, 125.8, 130.3, 132.1, 145.0. Anal. Calcd For $C_{10}H_{13}N_3O_2S$: C, 50.19; H, 5.48; N, 17.56. Found: C, 50.41; H, 5.39; N, 17.89.

***N*-Cyclohexyl-1-butanesulfonamide (7). 7** was purified by column chromatography with $CHCl_3$ as eluent and obtained as colorless prisms (89%), mp 64−65 °C. ^{1}H NMR: δ 0.95 (t, J = 7.2 Hz, 3H), 1.14−1.49 (m, 7H), 1.56−1.84 (m, 5H), 1.95−1.99 (m, 2H), 3.01 (t, J = 8.0 Hz, 2H), 3.20−3.33 (m, 1H), 4.31 (d, J = 6.6 Hz, 1H). ^{13}C NMR: δ 13.6, 21.5, 24.8, 25.1, 25.8, 34.7, 52.7, 53.9. Anal. Calcd For $C_{10}H_{21}NO_2S$: C, 54.76; H, 9.65; N, 6.39. Found: C, 54.77; H, 9.67; N, 6.34.

Supporting Information Available: Procedures, experimental details, and structural data for all new compounds not described in the text (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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