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Mild and Efficient Synthesis of Aromatic Sulfonamides by in situ Preparation of the Corresponding Sulfonyl Isocyanates

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A new reaction between chlorosulfonyl isocyanate (**1**) and trialkylstannyl-stubstituted arenes **2a–k**, **7**, **9** is described. It provides the aromatic sulfonyl isocyanates **3** or their derivatives, the sulfonamides **4a–j**, the sulfonylcarbamates **5a–b**, or sulfonylureas **6**, respectively. The trialkylstannyl group as an efficient leaving group allows mild reaction conditions to be applied and unusual substitution patterns to be obtained, normally not accessible by electrophilic aromatic substitutions. Thus, sulfonamidation can be achieved in *meta* position to a trifluoromethyl group.

Trialkylarylstannanes have proved to be powerful and versatile building units in organic chemistry. This is impressively shown by the tin-mediated Vilsmeier formylations, Friedel-Crafts acylations etc. giving the corresponding aromatic or heteraromatic *ipso*-substitution products in excellent yields under very mild conditions[1,2]. Moreover, the electrophilic aromatic substitution patterns caused by directing substituents such as the methyl or methoxy group are overcompensated by the outstanding quality of the trialkylstannyl group as leaving group[1–3]. Thus, the *ipso*-substitution products are obtained with high or even exclusive isomer purity.

Recently, we have reported on the *ipso*-selective preparation of unusually substituted aromatic *N*-phenylamides by the reaction of triyalkylarylstannanes with aryl isocyanates and $AlCl_3$ as catalyst[1b]. The regiospecificity and high variability of this reaction in combination with the ready access of the stannanes[1a] has stimulated us to investigate the application of other isocyanates.

Chlorosulfonyl isocyanate (CSI) (**1**) has found a wide synthetic application[4], especially in heterocyclic chemistry[5]. Its chemical behavior is determined by the highly activated isocyanato group, and, in a few cases, by the sulfur–chlorine bond[4a]. Besides its reactivity towards compounds containing active hydrogen or in cycloaddition reactions[4a,4c] the use of CSI as electrophile, leading to carboxamides, has been reported[6]. Yet, the variability of this reaction is limited by the need for $AlCl_3$ as a catalyst or for highly activated aromatic substrates. Thus, in the benzene system two methoxy groups are necessary to ensure sufficient reactivity[6a].

Aromatic sulfonyl isocyanates are used as highly reactive intermediates, e.g. for the synthesis of a variety of sulfonylcarbamoyl derivatives, for sulfonylureas as hypoglycemic agents or for the preparation of a number of fungicides and herbicides[7]. The common synthetic access to these sulfonyl isocyanates usually needs drastic conditions, such as high temperatures and phosgene[8]. In this paper we present the reaction of **1** with trialkylarylstannanes **2** which leads, via the corresponding sulfonyl isocyanates **3**, to sulfonyl isocyanate derivatives, such as sulfonamides **4**, phenylsulfonylcarbamates **5** and ureas **6**. This procedure offers an interesting alternative since there is no need for isolating and purifying the isocyanates **3**. It avoids the use of any catalyst, allows very mild conditions, and causes complete *ipso* substitution also for positions which have not been accessible to electrophilic substitution so far.

Results and Discussion

CSI **1** reacts with trialkylarylstannanes **2** even at room temperature without a catalyst to give the sulfonamides **4** after in situ hydrolysis. The *ipso* isomers are obtained exclusively, eq. (1). The yields of isolated pure products range for the 10-mmol scale from 54 to 98%. By-products could not be detected.

This is a remarkable result as the electrophilic aromatic substitutions with **1** investigated so far usually lead after hydrolysis not to **4** but to the carboxamides. In our case attack to the aromatic ring does not take place with the activated isocyanato group but with the chlorine–sulfur bond. **1** behaves here, surprisingly, like an acyl halide.

The intermediate sulfonyl isocyanates **3** can be trapped with an alcohol or amine by formation of the corresponding arylsulfonylcarbamate **5** or the arylsulfonylurea **6**. Compounds **5** and **6** can be of interest for additional synthetic purposes, since the use of **5b** as an antidote for herbicides has been reported[7e].

This procedure may be understood as an extension of common sulfonyl isocyanate chemistry. The by-product Bu_3SnCl does not influence most of the following derivati-

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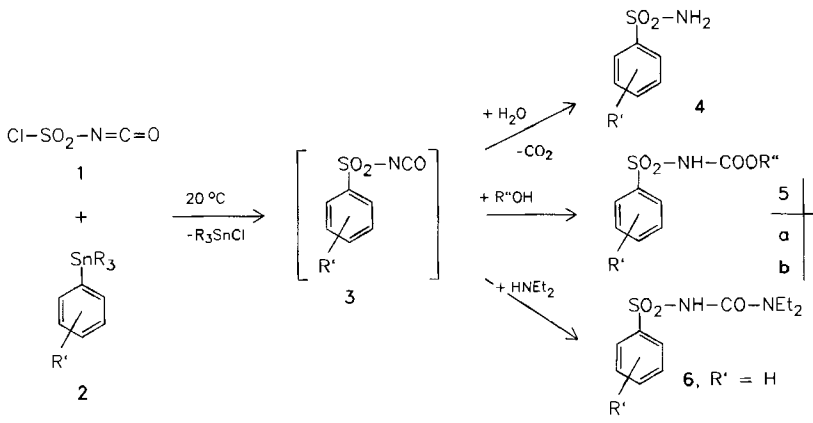


5

	R'	R"
a	H	Me
b	H	Et

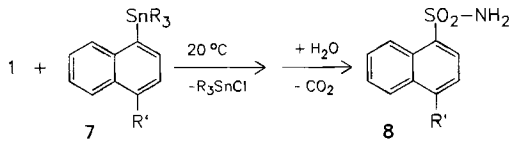
(1)

	a	b	c	d	e	f	g	h	i	j	k
2, R =	Me	Bu	Me	Bu	Bu	Me	Me	Bu	Me	Bu	Me
2, 4, R' =	H	H	2-Me	2-Et	3-Me	4-Me	2-Cl	3-Cl	4-Cl	4-Br	4-MeO

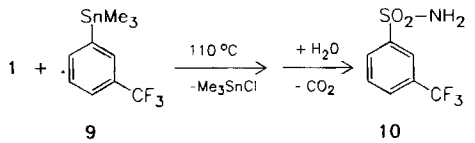
zation reactions and can easily be removed after completion of the reaction[1a].

Directing effects of 2-Me, 2-Et, 2-Cl, 3-Me or 3-Cl substituents are easily overcome by the outstanding quality of the tributylstannyl group as leaving group [see eq. (1)]. The reason for *ipso* substitution is presumably a pre-complexation of the π-system of **1** at the tin site by extension of the tetracoordination of Sn. For a detailed discussion of this phenomenon see ref.[1b].

This method can be extended to polycyclic ring systems such as naphthalene derivatives [eq. (2)].



(2)



(3)

	a	b
7, R =	Bu	Me
7, 8, R' =	H	Me

Under these conditions the nonstannylated arenes do not give rise to any substitution products, they can even be used as solvents for reactions with **1**[4a].

The drastic increase of reactivity by introducing the trialkylstannyl group into the aromatic ring is underlined by the fact that even with the deactivating halo substituents good yields are obtained [see eq. (1)]. Even the strongly deactivating effect of the trifluoromethyl group in *meta* position is overcompensated [**9**, see eq. (3)] and only the cyano and the *ortho*-trifluoromethyl group do not allow a substitution reaction to proceed.

Because of the versatility, efficiency and regiospecificity of the reactions described, further work will be performed to extend this method to other aromatic or heteroaromatic stannanes and different isocyanates.

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Experimental

Melting points: Büchi SMP 20. – IR (always in KBr): Shimadzu 3289. – NMR: Varian EM 360 (60 MHz, ^{1}H, always in [D_6]acetone) and Bruker AM 300 (300 MHz, ^{1}H: 75.47 MHz, ^{13}C, in [D_6]acetone, unless stated otherwise). – MS: Finnigan MAT 8230, 70 eV. – The arylstannanes have been prepared following ref.[1a].

Sulfonamides **4a–k**; **8a,b.** – *General Procedure:* To a solultion of chlorosulfonyl isocyanate (**1**) (15 mmol) in 20 ml of anhydrous dichloromethane the stannane (10 mmol) is added through a dropping funnel under argon. The mixture is stirred at 20°C for 15 h and then poured on 20 g of ice. After stirring for 30 min the precipitate is filtered off and recrystallized from the appropriate solvent.

Benzenesulfonamide (**4a**): (i) From 2.41 g (10 mmol) of **2a** or (ii) 3.67 g (10 mmol) of **2b** and 2.12 g (15 mmol) of **1**, (i) 1.44 g (92%) (ii) 1.53 g (98%) of **4a** is obtained, m.p. 151°C from ethanol (ref.[9] 152°C). – IR: $\tilde{\nu}$ = 1403, 1448, 1560, 1579, 3260, 3355 cm^{-1}. – ^{1}H NMR: δ = 4.50 (s, 2H, NH_2), 6.87–7.67 (m, 5H, aromatic H). – MS: *m/z* (%) = 157 (36), 141 (26), 93 (45), 77 (100).

2-Methylbenzenesulfonamide (**4c**): From 2.55 g (10 mmol) of **2c** and 2.12 g (15 mmol) of **1**, 1.39 g (82%) of **4b** is obtained, m.p. 151°C from ethanol (ref.[10] 153°C). – IR: $\tilde{\nu}$ = 1152, 1316, 1458, 1473, 1561, 3100, 3265, 3385 cm^{-1}. – ^{1}H NMR: δ = 2.30 (s, 3H, CH_3), 5.73 (s, 2H, NH_2), 6.80–7.73 (m, 4H, aromatic H). – MS: *m/z* (%) = 171 (48), 154 (12), 106 (85), 90 (100), 64 (52).

2-Ethylbenzenesulfonamide (**4d**): From 3.95 g (10 mmol) of **2d** and 2.12 g (15 mmol) of **1**, 1.26 g (69%) of **4d** is obtained, m.p. 118°C from ethanol (ref.[11] 126°C). – ^{1}H NMR: δ = 1.42 (t, *J* = 7.5 Hz, 3H, CH_3), 3.24 (q, *J* = 7.5 Hz, 2H, CH_2), 6.75 (s, 2H, NH_2),

7.43–8.14 (m, 4H, aromatic H). – MS: *m/z* (%) = 185 (23), 120 (35), 106 (51), 104 (100), 78 (42), 77 (45), 105 (30), 103 (41).

3-Methylbenzenesulfonamide (**4e**): From 3.81 g (10 mmol) of **2e** and 2.12 g (15 mmol) of **1**, 1.22 g (72%) of **4e** is obtained, m.p. 108°C from ethanol (ref.[12] 108°C). – IR: $\tilde{\nu}$ = 1482, 1561, 1578, 1603, 2965, 3105, 3240, 3330 cm^{-1}. – ^1H NMR: δ = 1.87 (s, 3H, CH_3), 5.17 (s, 2H, NH_2), 6.83–7.33 (m, 4H, aromatic H). – MS: *m/z* (%) = 171 (63), 155 (23), 107 (64), 91 (100), 64 (56).

4-Methylbenzenesulfonamide (**4f**): From 2.55 (10 mmol) of **2f** and 2.12 g (15 mmol) of **1**, 1.26 g (74%) of **4f** is obtained, m.p. 138°C from ethanol (ref.[13] 136°C). – ^1H NMR: δ = 2.31 (s, 3H, CH_3), 6.30 (s, 2H, NH_2), 7.10–7.82 (m, 4H, aromatic H). – MS: *m/z* (%) = 171 (43), 155 (34), 91 (100).

2-Chlorobenzenesulfonamide (**4 g**): From 2.76 g (10 mmol) of **2 g** and 2.12 g (15 mmol) of **1**, 1.36 g (72%) of **4 g** is obtained, m.p. 187°C from ethanol (ref.[14] 188°C). – ^1H NMR: δ = 3.15 (s, 2H, NH_2), 6.77–7.75 (m, 4H, aromatic H). – MS: *m/z* (%) = 191 (54), 175 (24), 128 (49), 111 (100).

3-Chlorobenzenesulfonamide (**4h**): From 4.01 g (10 mmol) of **2h** and 2.12 g (15 mmol) of **1**, 1.23 g (66%) of **4h** is obtained, m.p. 146°C from ethanol (ref.[15] 147°C). – ^1H NMR: δ = 6.13 (s, 2H, NH_2), 7.07–7.60 (m, 4H, aromatic H). – ^{13}C NMR: δ = 124.31, 125.78, 130.60, 131.73 (CH), 134.02, 145.56 (Cq). – MS: *m/z* (%) = 191 (78), 175 (20), 127 (69), 111 (100).

4-Chlorobenzenesulfonamide (**4i**): From 2.76 g (10 mmol) of **2i** and 2.12 g (15 mmol) of **1**, 1.30 g (68%) of **4i** is obtained, m.p. 142°C from ethanol (ref.[16] 143°C). – ^1H NMR: δ = 6.01 (2H, NH_2), 7.02–7.67 (m, 4H, aromatic H). – ^{13}C NMR: δ = 127.90, 129.01 (CH), 137.52, 142.80 (Cq). – MS: *m/z* (%) = 191 (44), 175 (41), 127 (20), 111 (100).

4-Bromobenzenesulfonamide (**4j**): From 4.46 g (10 mmol) of **2j** and 2.12 g (15 mmol) of **1**, 1.88 g (82%) of **4j** is obtained, m.p. 162°C from ethanol (ref.[17] 161°C). – ^1H NMR: δ = 7.10–7.42 (m). – MS: *m/z* (%) = 235 (78), 219 (47), 155 (100), 76 (78), 75 (86).

4-Methoxybenzenesulfonamide (**4k**): 2.71 g (10 mmol) of **2k** in 5 ml of dichloromethane is added with stirring to 1.55 g (11 mmol) of **1** in 10 ml of dichloromethane within 15 min. After additional stirring for 15 min the mixture is poured on 20 g of ice. The aqueous layer is extracted with two 20-ml portions of dichloromethane. The solvent is evaporated at 20°C/15 Torr from the combined organic layers. The residue is crystalllized by addition of heptane and recrystallized from ethanol. The yield is 1.80 g (96%) of **4k**, m.p. 109°C from ethanol/water (ref.[18] 110°C). – ^1H NMR: δ = 3.42 (s, 3H, OCH_3), 5.92 (s, 2H, NH_2), 6.38–7.52 (m, 4H, aromatic H). – MS: *m/z* (%) = 187 (100), 171 (98), 123 (31), 107 (60), 92 (41), 77 (70).

Methyl Phenylsufonylcarbamate (**5a**): 7.34 g (20 mmol) of **2b** and 2.83 g (20 mmol) of **1** in 20 ml anhydrous dichloromethane are stirred for 17 h at 20°C. Then 20 ml of dry methanol is added. After stirring for 1 h the solvent is distilled off, the residue crystallized after addition of pentane and recrystallized from methanol/water; 2.70 g (64%) of **5a** is obtained, m.p. 129°C from methanol/water (ref.[19a] 131°C). – IR: $\tilde{\nu}$ = 1419, 1454, 1684, 1761, 2920, 2970, 3020, 3090, 3245 cm^{-1}. – ^1H NMR: δ = 3.01 (s, 3H, CH_3), 6.87–7.67 (m, 5H, aromatic H), 9.80 (s, 1H, NH). – ^{13}C NMR: δ = 52.84 (CH_3), 128.10, 129.19, 133.84 (CH), 139.74 (Cq), 151.56 (CO). – MS: *m/z* (%) = 184 (9), 183 (11), 151 (66), 141 (52), 119 (10), 94 (85), 77 (100).

Ethyl Phenylsulfonylcarbamate (**5b**): According to the procedure described for **5a** from 3.67 g (10 mmol) of **2b**, 1.41 g (10 mmol) of **1**, and 10 ml of anhydrous ethanol, 1.95 g (85%) of **5b** is obtained, m.p. 105°C from ethanol (ref.[19b] 109°C). – ^1H NMR: δ = 0.70 (t, *J* = 7.0 Hz, 3H, CH_3), 3.62 (q, *J* = 7.0 Hz, 2H, CH_2), 7.00–7.77 (m, 5H, aromatic H), 9.80 (s, 1H, NH). – ^{13}C NMR: δ = 13.86 (CH_3), 62.55 (CH_2), 128.25, 129.30, 133.92 (CH), 140.04 (Cq), 151.17 (CO). – IR: $\tilde{\nu}$ = 1450, 1460, 1485, 1715, 1730, 2925, 2960, 3210 cm^{-1}.

N,N-Diethyl-N'-phenylsulfonylurea (**6**): 7.34 g (20 mmol) of **2b** and 2.83 g (20 mmol) of **1** are stirred for 20 h at 20°C in 20 ml of anhydrous dichloromethane. Then 1.46 g (20 mmol) of diethylamine is added through a dropping funnel. The mixture is stirred for 40 min, then the solvent is distilled off, and the residue crystallized by addition of pentane and recrystallized from $CHCl_3$; 3.84 g (75%) of **6** is obtained, m.p. 125°C from $CHCl_3$. – ^1H NMR: δ = 1.08 (t, *J* = 7.1 Hz, 6H, CH_3), 3.31 (q, *J* = 7.1 Hz, 4H, CH_2), 7.53–8.06 (m, 5H, aromatic H), 8.37 (s, 1H, NH). – ^{13}C NMR: δ = 13.81 (CH_3), 41.79 (CH_2), 128.72, 129.19, 133.41 (CH), 141.97 (Cq), 152.03 (CO). – IR: $\tilde{\nu}$ = 1448, 1460, 1479, 1656, 2990, 3065, 3165 cm^{-1}.

Naphthalene-1-sulfonamide (**8a**): According to the general procedure from 4.17 g (10 mmol) of **7a** and 2.12 g (15 mmol) of **1**, 1.50 g (74%) of **8a** is obtained, m.p. 155°C from ethanol (ref.[20] 150°C). – ^1H NMR: δ = 3.30 (s, 2H, NH_2), 6.73–8.33 (m, 7H, aromatic H). – MS: *m/z* (%) = 207 (77), 143 (63), 127 (100). – IR: $\tilde{\nu}$ = 1327, 1351, 1506, 1597, 3115, 3285, 3385 cm^{-1}.

4-Methylnaphthalene-1-sulfonamide (**8b**): According to the general procedure from 3.05 g (10 mmol) of **7b** and 2.12 g (15 mmol) of **1**, 1.88 g (86%) of **8b** is obtained, m.p. 177°C from ethanol (ref.[21] 177°C). – ^1H NMR: δ = 2.27 (s, 3H, CH_3), 3.78 (s, 2H, NH_2), 6.83–8.52 (m, 6H, aromatic H). – MS: *m/z* (%) = 221 (100), 157 (46), 141 (67), 115 (37).

3-(Trifluoromethyl)benzenesulfonamide (**10**): 6.20 g (20 mmol) of **9** and 3.25 g (23 mmol) of **1** in 10 ml dry chlorobenzene is refluxed for 8 h. After workup according to the general procedure, 1.40 g (32%) of **10** is obtained, m.p. 122°C from methanol/water (ref.[22] 121–122°C). – IR: $\tilde{\nu}$ = 1421, 1439, 1562, 1613, 3080, 3265, 3340 cm^{-1}. – ^1H NMR: δ = 6.07 (s, 2H, NH_2), 7.01–7.62 (m, 4H, aromatic H). – ^{13}C NMR (MeOH/[D_6]acetone): δ = 120.07 (CH), 120.96 [q, $^1J(^{13}C,^{19}F)$ = 272.12 Hz, CF_3], 125.75, 126.85, 127.38 (CH), 128.23 [d, $^2J(^{13}C,^{19}F)$ = 33.47 Hz, Cq], 142.46 (Cq). – MS: *m/z* (%) = 225 (56), 209 (33), 162 (33), 161 (46), 145 (100), 95 (30).

CAS Registry Numbers

1: 1189-71-5 / **2a**: 934-56-5 / **2b**: 960-16-7 / **2c**: 17113-82-5 / **2d**: 127686-16-2 / **2e**: 68971-88-0 / **2f**: 937-12-2 / **2g**: 17315-42-3 / **2h**: 24344-58-9 / **2i**: 14064-15-4 / **2j**: 17151-49-4 / **2k**: 940-00-1 / **4a**: 98-10-2 / **4c**: 88-9-7 / **4d**: 85-92-7 / **4e**: 1899-94-1 / **4f**: 70-55-3 / **4g**: 6961-82-6 / **4h**: 17260-71-8 / **4i**: 98-64-6 / **4j**: 701-34-8 / **4k**: 1129-26-6 / **5a**: 32324-23-5 / **5b**: 32111-09-4 / **6**: 50618-71-8 / **7a**: 972-09-8 / **7b**: 127686-17-3 / **8a**: 606-25-7 / **8b**: 10447-10-6 / **9**: 17113-81-4 / **10**: 672-58-2

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