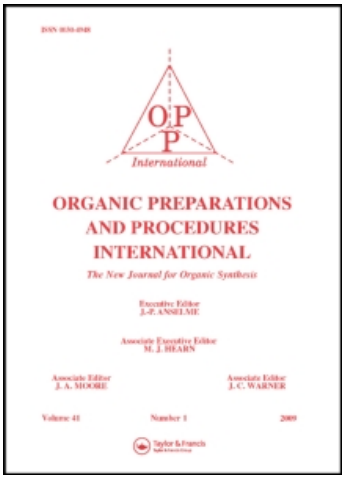

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A SIMPLE PREPARATION OF N,N-DIMETHYL-N'-ALKYL (ARYL) SULFONYLFORMAMIDINES

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REFERENCES

1. (a) M. G. Saulnier and G. W. Gribble, *Tetrahedron Lett.*, **24**, 5435 (1983). (b) G. W. Gribble, M. G. Saulnier, M. P. Sibi and J. A. Obaza-Nutaitis, *J. Org. Chem.*, **49**, 4518 (1984). (c) G. W. Gribble and M. G. Saulnier, *J. Chem. Soc., Chem. Commun.*, 168 (1984). (d) D. A. Davis and G. W. Gribble, *Tetrahedron Lett.*, **31**, 1081 (1990). (e) G. W. Gribble, D. J. Keavy, D. A. Davis, M. G. Saulnier, B. Pelcman, T. C. Barden, M. P. Sibi, E. R. Olson and J. J. BelBruno, *J. Org. Chem.*, **57**, 5878 (1992). (f) G. W. Gribble, R. A. Silva and M. G. Saulnier, *Synth. Commun.*, **29**, 729 (1999).

2. For other syntheses and/or uses of this ring system, see (a) T. Kuroda, M. Takahashi, T. Ogiku, H. Ohmizu, K. Kondo and T. Iwasaki, *Chem. Commun.*, 1635 (1991). (b) Y. Miki and H. Hachiken, *Synlett*, 333 (1993). (c) J.-S. Shiue and J.-M. Fang, *J. Chem. Soc., Chem. Commun.*, 1277 (1993). (d) J. Nagel, W. Friedrichsen and T. Debaerdamaeker, *Z. Naturforsch*, **48b**, 213 (1993). (e) T. Kuroda, M. Takahashi, T. Ogiku, H. Ohmizu, T. Nishitani, K. Kondo and T. Iwasaki, *J. Org. Chem.*, **59**, 7353 (1994). (f) C. O. Kappe and A. Padwa, *J. Org. Chem.*, **61**, 6166 (1996). (g) S.-C. Lin, F.-D. Yang, J.-S. Shiue, S.-M. Yang and J.-M. Fang, *J. Org. Chem.*, **63**, 2909 (1998). (h) M. T. Díaz, A. Cobas, E. Guitián and L. Castedo, *Synlett*, 157 (1998).

3. For an improved synthesis of C-3 substituted 4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indoles and the parent compound itself, see G. W. Gribble, J. Jiang and Y. Liu, *J. Org. Chem.*, **67**, 1001 (2002).

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A SIMPLE PREPARATION OF N,N-DIMETHYL-N'-ALKYL (ARYL) SULFONYLFORMAMIDINES

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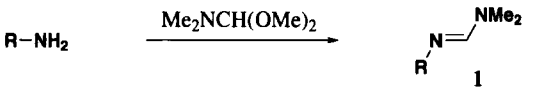
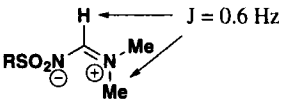
The reaction of primary amines with N,N-dimethylformamide dimethyl acetal (DMF dimethyl acetal) to give trisubstituted amidines **1** is a well known transformation.[1] However, the analogous reaction with unsubstituted sulfonamides to afford N,N-dimethyl-N'-alkyl(aryl)sulfonylformamidines **1** (R= alkyl or arylsulfonyl) has been reported only for analytical purposes,[2] not as a

preparative method.[3] We now report an experimental procedure to prepare these compounds in quantitative yields and under very mild conditions. This is important since methods of preparation of **1** usually involve high temperatures and corrosive or specially designed reagents.[4]

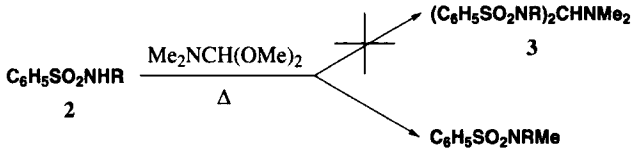


a) R = CH_3SO_2 b) R = $C_6H_5SO_2$ c) R = *p*-$MeC_6H_4SO_2$ d) *p*-$NH_2C_6H_4SO_2$

The method is very simple and consists in the addition of two equivalents of neat DMF dimethyl acetal to a suspension of the sulfonamide in dry CH_2Cl_2. The reaction is instantaneous and is virtually complete by the end of the addition (TLC). Nevertheless, the reaction mixture was refluxed gently for 30 min before work-up. It is worth noting that in compound **1d** the reaction proceeded chemoselectively at the sulfonamide nitrogen, due to the higher acidity of the SO_2NH_2 group which is easily deprotonated in the basic reaction medium. Yields of analytically pure, crystalline compounds **1a-1d** were quantitative, but partial water solubility of **1a** required its isolation under non-aqueous conditions (see Experimental Section). If an aqueous workup is used, **1a** is obtained in only 80% yield. Compounds **1a-1d** prepared herein are known and were characterized by conventional spectroscopy (see Table). Interestingly, their 300 MHz ^1H NMR spectra showed a small coupling (J= 0.6 Hz) between the CH and the *anti* high field N-CH_3 group in the canonical structure.[5]



Since in principle a N-monosubstituted sulfonamide **2** could afford **3** with DMF dimethyl acetal, our reaction conditions were also tested using **2a** as substrate, but it was unchanged even after a long period of reflux (24 h). However, in toluene at 95° (30 h) or preferably in refluxing neat DMF dimethyl acetal, N-methylation was observed to give reference to **4a**.[6] The methylating properties of DMF dimethyl acetal have been reported previously.[7] An alternative reaction mechanism involving a Me_2N group exchange was disproved since under the same reaction conditions **2b** gave the known[8] **4b** in 95% yield.



a) R = Me b) R = Et

EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra (KBr or film) were carried out on a FT-Nicolet SX apparatus. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian VXR 300 spectrometer with TMS as internal standard. $CDCl_3$ was used as solvent for **1a**, **1b**, and **1c** and $CDCl_3$-DMSO-d_6 for **1d**.

General Procedure.- The sulfonamide (1.5-2.5 mmol) suspended in 5 mL of dry CH_2Cl_2 was treated dropwise with two equivalents of DMF dimethyl acetal (Aldrich) under stirring. The solid dissolved rapidly and the solution was refluxed gently for 30 min with a moisture protecting tube. Two methods were followed for the work-up.

Aqueous work-up: After cooling, ice-water was added (5 mL), the organic phase separated, washed with water (5 mL), dried over anhydrous Na_2SO_4 and evaporated to give essentially pure crystalline residues.

Non aqueous work-up: The CH_2Cl_2 was removed in a rotary evaporator and the resulting wet solid dried under high vacuum (0.05-0.1 Torr) to afford quantitative yields of white crystalline products.

1a; mp 80-81°, *lit.*[4a] mp 80-81°. **1b**; mp 129-130°, *lit.*[4a] mp 128-130°. **1c**; mp 136-137°, *lit.*[4c] mp 133-134°. **1d**; mp 175-176°, *lit.*[3] mp 168.5-170°.

N,N-Dimethyl Benzenesulfonamide (4a).- N-Methylbenzenesulfonamide **2a** (0.51 g, 2.97 mmol) in 1.7 mL of DMF dimethyl acetal were heated at 90° for 10 h in an oil bath. The volatiles were removed under high vacuum (0.05-0.1 Torr) at 60° to afford 0.54 g (98%) of a very pale yellow oil which solidified in the refrigerator and was identified as **4a**, mp. 45°, *lit.*[6] 47° by comparison with an authentic sample prepared from benzenesulfonyl chloride and aqueous dimethylamine.

Under the conditions of the general procedure, no reaction was detected even after 24 h at reflux. In toluene containing 10 equivalents of DMF dimethyl acetal, compound **4a** was also formed but some starting material still remained after heating at 95° for 30 h.

Table. IR, ^1H NMR, and ^{13}C NMR Data for Compounds **1**

Compd	IR (cm^{-1})	^1H NMR (δ)	^{13}C NMR (δ)
1a	3011, 2934, 1638, 1430, 1348, 1276, 1117, 973, 903, 852, 768, 570, 549, 522	8.07 (q, 1H, J = 0.6 Hz), 3.15 (s, 3H), 3.05 (s, 3H), 2.96 (d, 3H, J = 0.6 Hz)	159.1, 41.9, 41.3, 35.3
1b	2930, 1621, 1449, 1429, 1341, 1284, 1152, 1089, 908, 848, 753, 724, 687, 606, 578, 559	8.16 (q, 1H, J = 0.6 Hz), 7.87-7.92 (m, 2H), 7.43-7.55 (m, 3H), 3.13 (s, 3H), 3.02 (d, 3H, J = 0.6 Hz)	159.2, 142.4, 131.8, 128.7, 126.4, 41.5, 35.5
1c	2931, 1626, 1430, 1345, 1283, 1141, 1084, 906, 852, 809, 673, 590, 549	8.13 (q, 1H, J = 0.6 Hz), 7.77 (d, 2H, J = 8.4 Hz), 7.26 (d, 2H, J = 8.4 Hz), 3.12 (s, 3H), 3.01 (d, 3H, J = 0.6 Hz), 2.40 (s, 3H)	159.1, 142.4, 139.5, 129.3, 126.4, 41.4, 35.5, 21.4
1d	3452, 3352, 3245, 2955, 2926, 1628, 1595, 1502, 1431, 1345, 1327, 1276, 1136, 1087, 907, 845, 689, 595, 573, 541	8.07 (q, 1H, J = 0.6 Hz), 7.61 (d, 2H, J = 9 Hz), 6.66 (d, 2 H, J = 9 Hz), 3.40-3.90 (broad, NH_2), 3.10 (s, 3H), 2.99 (d, 3H, J = 0.6 Hz)	158.5, 150.0, 130.3, 128.1, 113.6, 41.1, 35.1

N-Ethyl-N-Methyl Benzenesulfonamide (4b).- N-Ethylbenzenesulfonamide **2b** (0.51 g, 2.81 mmol) in 1.5 mL of DMF dimethyl acetal were heated at 90° for 15 h in an oil bath. After removal of the volatiles under high vacuum (0.05-0.1 Torr), it was obtained 0.70 g of the crude product contaminated with DMF as a yellow oil, which was purified by flash chromatography (hexanes-AcOEt, 4:1) to give 0.52 g of **4b** and 0.028 g of recovered **2b**. IR (film): 3065, 2978, 2936, 2878, 2816, 1448, 1338, 1162, 1090, 996, 912, 761, 736, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.77-7.82 (2H), 7.48-7.63 (3H), 3.11 (q, J = 7.2 Hz, 2H), 2.74 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 137.7, 132.4, 128.9, 127.2, 44.8, 33.9, 12.9.

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REFERENCES

1. G. V. Boyd, "*Recent Advances in the Synthesis of Amidines*" in S. Patai and Z. Rapoport, "*The Chemistry of Amidines and Imidates*", Vol. 2, pp. 339-366, Wiley Interscience, John Wiley & Sons, Chichester, 1991.

2. W. J. A. Vandenheuvel and V. F. Gruber, *J. Chromatogr.*, **112**, 513 (1975).

3. I. A. Ivanova, B. P. Fedorov and F. M. Stoyanovich, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 2179 (**1965**) [*Chem. Abstr.*, **64**, 12538h (1965)]. These authors reported, as an isolated case, the preparation of **1d** in 30% yield by heating at 110° sulfanilamide and DMF dimethyl acetal.

4. From sulfonamides and a) Vilsmeier reagents: G. R. Pettit and R. E. Kadunce, *J. Org. Chem.*, **27**, 4566 (1962). See also: *Chem. Abstr.*, **53**, P9250g (1959), b) DMF mercaptals: F. M. Stoyanovich, B. P. Fedorov and G. M. Andrianova, *Dokl. Akad. Nauk. SSSR*, **145**, 584 (1962) [*Chem. Abstr.*, **58**, 4448c (1963)], c) Diethyl (or dimethyl) phosphonomethylene dimethylimmonium chloride: H. Gross and B. Costisella, *Justus Liebigs Ann. Chem.*, **750**, 44 (1971), d) Dichloromethyl dimethylamine: V. P. Kukhar and V. Ya. Semenii, *Zh. Org. Khim.*, **6**, 1885 (1970) [*Chem. Abstr.*, **73**, 130732h (1970)], and from sulfonamide derived reagents (RSO_2NZ_2, where Z is an "activating" group on the sulfonamide nitrogen): e) Z_2= C=O and DMF: W. Logemann and D. Artini, *Chem. Ber.*, **90**, 2527 (1957); C. King, *J. Org. Chem.*, **25**, 352 (1960); H. Klug, *Chem. Abstr.*, **99**, P122071p (1983), f) Z_2= S=O and DMF: R. Albrecht, G. Kresze and B. Mlakar, *Ber.*, **97**, 483 (1964), g) Z_2= Br_2 and DMF: S. Takemura, H. Niizato and Y. Ueno, *Chem. Pharm. Bull.*, **19**, 1606 (1971), h) Z_2= CCl_2 and DMF: V. N. Sevastyanov, E. A. Abrazhanova and V. I. Skripets, *Vopr. Khim. Khim. Teknol.*, **72**, 82 (1983) [*Chem. Abstr.*, **102**, 45566e (1985)], i) Z_2= $C(CF_3)_2$ and DMF: A. V. Fokin, N. D. Chkanikov, V. L. Vershinin and A. F. Kolomiets, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 949 (**1984**) [*Chem. Abstr.*, **101**, 90864r (1984)], j) Z_2= S(Cl)-N=C(Cl)NR_2 and DMF: L. N. Markovskii, Yu. G. Shermolovich, Yu. A. Nuzhdina and V. I. Shevchenko, *Zh. Org. Khim.*, **10**, 1000 (1974) [*Chem. Abstr.*, **81**, 49238v (1974)], k) Z_2= Cl_2 and dichloromethyl dimethylamine: V. P. Kukhar, A. M. Pinchuk and M. V. Shevchenko, *Zh. Org. Khim.*, **9**, 43 (1973) [*Chem. Abstr.*, **78**, 83996p (1973)], l) Z_2= $CHCCl_3$ and dimethylamine: V. L. Krasnov, G. I. Vasyanina and I. V. Bodrikov, *Zh. Org. Khim.*, **23**, 441 (1987) [*Chem. Abstr.*, **108**, 37314e (1988)]; A. N. Mirskova, G. G. Leskovskaya, A. A. Bryuzgin, T. I. Drozdova, I. D. Kalikhman

and M. G. Voronkov, *ibid.*, **26**, 140 (1990) [*Chem. Abstr.*, **113**, 5817h (1990)]; *Chem. Abstr.*, **113**, P5958e (1990).

5. R. L. Shriner, R. C. Fuson and D. Y. Curtin; *"The Systematic Identification of Organic Compounds"*, 4th Ed., p. 288, John Wiley & Sons, New York, NY, 1956.

6. U. Pindur; *"N,N-Dimethylformamide diethyl acetal"* in L. A. Paquette, *"Encyclopedia of Reagents for Organic Synthesis"*, Vol. 3, pp. 2075-2078, John Wiley & Sons, Chichester, 1995.

7. Studies on the NMR spectra of sulfonylformamidines have been reported previously: P. Jakobsen and S. Treppendahl, *Tetrahedron*, **33**, 3137 (1977); **37**, 829 (1981).

8. T. L. Cairns and J. C. Sauer, *J. Org. Chem.*, **20**, 627 (1955); A. R. Katritzky, G. Liso, E. Lunt, R. C. Patel, S. S. Thind and A. Zia, *J. Chem. Soc. Perkin I*, 849 (**1980**).

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A RAPID SYNTHESIS OF DIISOPROPYL 4-(CHLOROMETHYLBENZYL) AND 4-(BROMOMETHYLBENZYL) PHOSPHONATES

Submitted by (12/06/01)

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Our interest in the synthesis of 4-(chloromethylbenzyl) and 4-(bromomethylbenzyl) phosphonic acids esters **2** stems from their possible use for the preparation of mixed metal-phosphonate materials[1] which generally possess a layered structure.[2] The use of these esters in the synthesis of such materials could offer hybrid organic-inorganic materials possessing a halomethyl group in the interlayer space as found in Merrifield resins.[3] Such materials should have better thermal stability and larger porosity than the classical Merrifield resin. The diethyl ester of 4-(chloromethylbenzyl) phosphonic acid had been obtained by Bigge *et al.*[4] in poor yield (20-25%) by the Michaelis reaction of sodium diethyl phosphite with α,α'-dichloro-*p*-xylene. The dimethyl ester of 4-(bromomethylbenzyl) phosphonic acid was prepared by Baczco *et al.*[5] from *p*-methylbenzyl bromide as the substrate *via* an Arbuzov reaction, followed by radical bromination; although the overall yield is good (52%), the presence of polybromination side-products makes purification of the product difficult.