

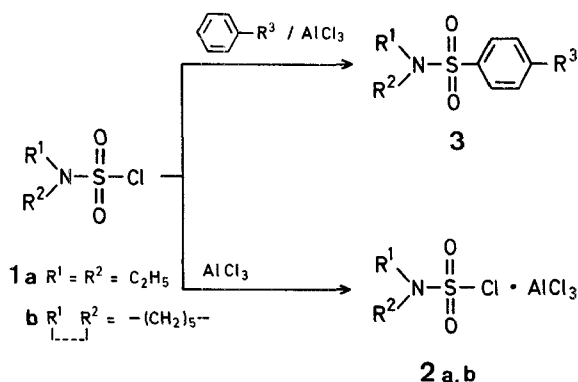
New Reactions and Reagents; VI.¹ A Simple Synthesis of *N,N*-Dialkylsulfonamides via the Reaction of Dialkylsulfamyl Chlorides with Aromatic Hydrocarbons

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We wish to report a new synthesis of *N,N*-dialkylsulfonamides (**3**) via the reaction of dialkylsulfamyl chlorides (**1**) with aromatic hydrocarbons in the presence of aluminum chloride. Alternatively, the preparation of **3** may be carried out by reacting novel dialkylsulfamyl chloride-aluminum chloride complexes (**2**) with aromatic hydrocarbons (Scheme **A**).

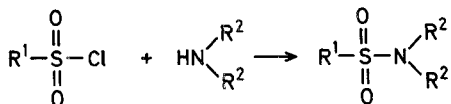
The reaction of **1** and **2** with aromatic compounds containing an *o,p*-directing substituent proceeded to place the entering dialkylsulfamyl group almost exclusively at the position *para* to that substituent to give **3**².



3	R^1	R^2	R^3
a	C_2H_5	C_2H_5	H
b	C_2H_5	C_2H_5	CH_3
c	C_2H_5	C_2H_5	Cl
d	$-(CH_2)_5-$		H
e	$-(CH_2)_5-$		CH_3
f	$-(CH_2)_5-$		Cl

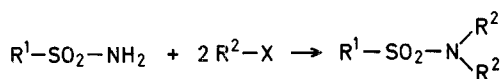
Scheme A

N,N-Disubstituted sulfonamides have traditionally been obtained by the reaction of a sulfonyl halide with an amine³.

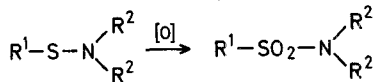


Other less frequently utilized procedures include:

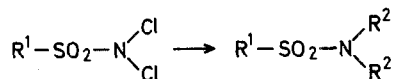
(a) the alkylation of a sulfonamide with an alkyl halide⁴,



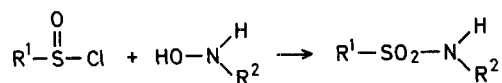
(b) the oxidation of a sulfenamide derivative⁵,



(c) the substitution of an *N,N*-dichlorosulfonamide⁶,

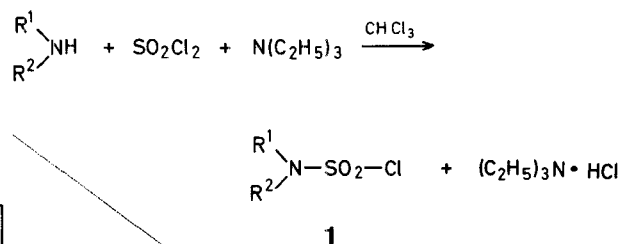


(d) and the reaction of a sulfinyl halide with a hydroxylamine derivative⁷.



The present reaction, therefore, provides a simple alternative for the synthesis of *N,N*-dialkylsulfonamides via direct introduction of a dialkylsulfamyl moiety into an aromatic nucleus.

Dialkylsulfamyl chlorides (**1**) were obtained from the corresponding secondary amines⁸.



The addition compounds **2** were prepared by stirring an equimolar quantity of **1** and aluminum chloride in a non-reacting hydrocarbon or chlorinated hydrocarbon medium for about 5 min. The reaction of **2** with aromatic hydrocarbons was carried out by stirring the reactants together at 60–80° for 1–4 h (Method A). In order to facilitate the mixing of the reactants, chlorinated hydrocarbons (dichloroethane, tetrachloromethane, trichloromethane) may be used as solvents in these reactions.

The alternate procedure for the amidosulfonation of aromatic compounds using dialkylsulfamyl chlorides **1** required the presence of a Lewis acid catalyst (Methods B and C). Aluminum chloride was found to be the catalyst of choice. Other catalysts, such as zinc(II) chloride and boron trifluoride etherate, were found to be less effective.

The results on the preparation of *N,N*-dialkylsulfonamides **3** by above procedures are summarized in the Table.

Table. Preparation of *N,N*-Dialkylsulfonamides **3**

Compound	Method	Yield [%]	m.p.	Lit. m.p. (ref.)
3a	A	98	40°	42° (9)
3a	B	94	40°	
3b	B	90	58.5°	60° (10)
3c	B	60	37.5°	37° (11)
3d	A	100	89°	92° (12)
3d	B	100	89°	
3e	B	93	89°	98° (13)
3f	B	55	95°	109° (14)
3f	C	51	95°	

Preparation of Dialkylsulfamyl Chlorides (**1**); Typical Procedure:

The preparation of 1-chlorosulfonylpiperidine (**1b**) is illustrative of the general procedure. A mixture of piperidine (25.5 g, 300 mmol) and triethylamine (30.3 g, 300 mmol) was added to a solution of sulfonyl chloride (24 ml, 300 mmol) in trichloromethane (300 ml) at 0° to 5° in 1 h. After stirring for an additional hour, the reaction mixture was washed with water, 10% aqueous hydrochloric acid, and dried. The removal of the solvent gave an oil which soon crystallized partially. It was stirred with hexane (100 ml) and then filtered to remove a solid, presumably 1,1-dipiperidyl sulfone. Distillation of the filtrate gave the desired product; yield: 27.7 g (50%); b.p. 114°/5 torr; lit.⁸ b.p. 112°/5 torr.

Diethylsulfamyl chloride (**1a**) was similarly obtained in 42% yield; b.p. 75°/5 torr; lit.¹⁵ b.p. 69°/5 torr.

¹H-N.M.R. (CDCl₃)¹⁶: δ = 1.3 (t), 3.40 ppm (q).

¹³C-N.M.R. (CDCl₃)¹⁶: δ = 12.46, 44.91 ppm.

Preparation of Dialkylsulfamyl Chloride-Aluminum Chloride Addition Compounds **2**:

Diethylsulfamyl chloride (**1a**; 1.71 g, 10 mmol) was dissolved in hexane (10 ml) and anhydrous aluminum chloride (1.33 g, 10 mmol) was added to it. Following a mildly exothermic reaction (23° → 26°),

a liquid product separated out. After stirring for 5 min, the liquid (bottom layer) was removed by decantation and dried in a vacuum desiccator over phosphorus pentoxide (25°–28° for 2 h) to give **2a** ($R^1 = R^2 = C_2H_5$) as an oil; yield: 3.0 g (99%).



(305.0)

calc. C 15.75 H 3.30 Cl 46.49 N 4.59 S 10.49
found 16.20 3.40 45.89 4.52 10.67

¹H-N.M.R. (CDCl₃)¹⁶: δ = 1.41 (t), 3.6 ppm (q).

¹³C-N.M.R. (CDCl₃)¹⁶: δ = 12.11, 45.67 ppm.

1-Chlorosulfonylpiperidine-aluminum chloride addition compound (**2b**) was similarly prepared (oil) in 95% yield.

Preparation of N,N-Dialkylsulfonamides (3); General Procedures:
Method A: A mixture of **2a** (3.04 g, 10 mmol) and benzene (10 ml) was refluxed for 4 h. The resulting solution was cooled, then poured over 10% aqueous hydrochloric acid (200 ml) and extracted with benzene. After washing and drying, the solvent was removed to give 1-[benzenesulfonyl]diethylamine (see Table).

Method B: A mixture of 1-chlorosulfonylpiperidine (**1b**: 4.57 g, 25 mmol), toluene (25 ml), and anhydrous aluminum chloride (3.75 g, 28 mmol) was stirred at 65–70° for 4 h. The clear solution was poured over 10% aqueous hydrochloric acid (200 ml) and the mixture was extracted with toluene. The organic extract was washed, dried, and stripped to give an oil. Crystallization from hexane gave 1-[4-(methylphenyl)sulfonyl]piperidine; yield: 5.52 g (97%).

¹H-N.M.R. (DMSO-*d*₆, 60 MHz): δ = 1.50 (br m, 6H), 2.40 (s, 3H), 2.93 (br m, 4H), 7.40 ppm (q, 4H, *J* = 8.5 Hz).

Method B, Example II: A mixture of diethylsulfamyl chloride (**1a**: 3.43 g, 20 mmol), chlorobenzene (2.25 g, 20 mmol), and aluminum chloride (3.0 g, 22 mmol) was stirred at 100° for 4 h. After quenching with 10% aqueous hydrochloric acid, the product was extracted with chloroform. The organic extract was washed, dried and stripped to give 1-[4-(chlorophenyl)sulfonyl]diethylamine after recrystallization from hexane; yield: 3.0 g (60%).

¹H-N.M.R. (DMSO-*d*₆, 60 MHz): δ = 1.1 (t, 6H, *J* = 7 Hz), 3.18 (q, 4H, *J* = 7 Hz), 7.66 ppm (q, 4H, *J* = 8.5 Hz).

Method C: A mixture of 1-chlorosulfonylpiperidine (7.3 g, 40 mmol), chlorobenzene (9.0 g, 80 mmol), aluminum chloride (5.85 g, 44 mmol), and dichloroethane (75 ml) was refluxed for 4 h. The resulting solution was quenched into 10% aqueous hydrochloric acid (100 ml), the organic layer was separated, washed, and dried. After removal of the solvent, the residual oil was crystallized from hexane to give 1-[4-(chlorophenyl)sulfonyl]piperidine; yield: 5.3 g (51%).

¹H-N.M.R. (CDCl₃, 60 MHz): δ = 1.53 (br m, 6H), 2.96 (br m, 4H), 7.53 ppm (q, 4H, *J* = 8 Hz).

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² This was ascertained from the analysis of crude reaction mixtures by H.P.L.C. [Varian micropak-CH column, H₂O:-CH₃OH:HCOOH = 70:30:0.2 system, U.V. (254 nm) detection].

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