A Knoevenagel-Type Synthesis of Styrene-ω-sulfonanilides*

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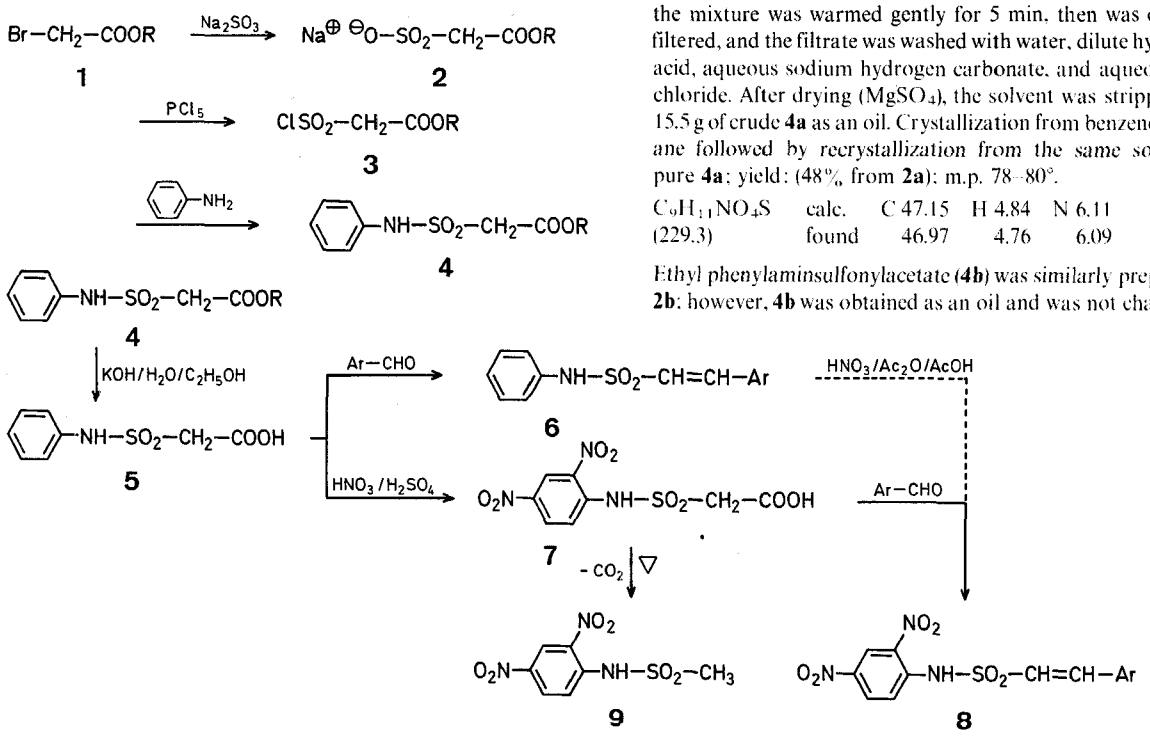
Because of the chemosterilant activity of a number of *N*-(2,4-dinitrophenyl)-benzenesulfonamides and *N*-(2,4-dinitro-1-naphthyl)-benzenesulfonamides against the house fly, *Musca domestica* L.[1], we became interested in examining a few *N*-(2,4-dinitrophenyl)-styrene-ω-sulfonamides. Styrene-ω-sulfonanilide (**6a**) was prepared by reacting styrylsulfonyl chloride with aniline[2], but because of various difficulties in obtaining certain other styrylsulfonyl chlorides, we sought a more general method of synthesizing styrene-ω-sulfonanilides. The Knoevenagel condensation has been an important means of preparing cinnamic acid derivatives[3] and has been used to synthesize unsaturated sulfones[3,4,5], but does not seem to have been applied to sulfonamides. We found that phenylaminosulfonylacetic acid (**5**; prepared from methyl or ethyl bromacetate as shown in the Scheme) condensed smoothly with several aromatic aldehydes in refluxing toluene containing ammonium acetate and pyridine to provide the styrene-ω-sulfonanilides **6a–e** in good yields.

Nitration of **6a–e** under various conditions proved to be unexpectedly difficult. Although **6a** and **6b** were converted to **8a** and **8b** in ~30% yields with fuming nitric acid in acetic acid/acetic anhydride, these and other conditions were less satisfactory for the nitration of other sulfonanilides. We therefore investigated condensations of 2,4-dinitrophenylaminosulfonylacetic acid (**7**). Nitration of **5** with a 2:1 mixture of concentrated nitric and sulfuric acids provided **7** almost quantitatively. Under the conditions employed for the condensations of **5**, compound **7** was largely decarboxylated to **9**. However, under milder conditions (piperidinium acetate in refluxing benzene) the nitrated styrene-ω-sulfonanilides **8a–g** were obtained in moderate yields. The decarboxylation product **9** was present in most or all of the crude reaction mixtures, but could be removed by recrystallization.



The aryl regions in the N.M.R. spectra of most of the styrene-ω-sulfonanilides were rather complex: however, the spectra of **6a** and **8a** were simple enough that the signals of the vinyl hydrogens could be assigned. In each case, a pair of doublets, $J = 16$ Hz, confirmed a *trans* configuration. From these examples, and from the general rule of *trans*-cinnamic acids resulting from the condensation of malonic acid with aldehydes[6], we assume that the other entries in the Table have the *trans* configuration also.

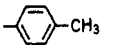
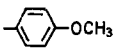
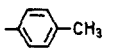
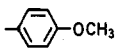
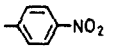
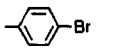
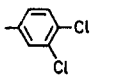
Sodium Ethyl and Methyl Sulfoacetates (2a and 2b):
A solution of sodium sulfite (1 mol) in water (400 ml) was cooled and stirred while a solution of ethyl (or methyl) bromoacetate (1 mol) in ethanol (200 ml) was added dropwise. After the addition was complete the mixture was heated briefly to 50°, then concentrated to dryness (two portions of ethanol/benzene were added and stripped to aid in the removal of water). The solid residue was extracted with boiling 2:1 acetic acid/ethyl acetate (total ~900 ml) and the hot solution was filtered through Celite and chilled overnight. The sodium sulfonates **2a** and **2b** separated as white solids and were collected by filtration. Subsequent crops could often be obtained by diluting the mother liquors with additional ethyl acetate. The yields were 70–80%. Sodium ethyl sulfoacetate (**2b**) did not have a well defined m.p., but usually began to decompose at ~158°. Sodium methyl sulfoacetate (**2a**) had m.p. 191–193°. We did not obtain satisfactory elemental analyses for either **2a** or **2b**, probably because of solvents of crystallization.

Methyl Phenylaminosulfonylacetate (4a):
The sodium salt **2a** (17.6 g, 0.1 mol) and phosphorus(V) chloride (23 g, 0.11 mol) were separately pulverized then combined in a flask equipped with a condenser and drying tube. After swirling a few minutes, a reaction occurred; after the exothermic reaction subsided the flask was warmed on a steam bath 45 min, then the phosphoryl chloride was stripped in vacuo. A portion of benzene was added and the resulting solution was filtered through Celite and evaporated leaving 14.7 g (85%) of **3a** as a clear oil. Benzene (65 ml) was again added, and the solution was stirred and cooled, then was treated dropwise with a solution of aniline (8.3 ml) and triethylamine (15 ml) in benzene (50 ml). After addition was complete, the mixture was warmed gently for 5 min, then was cooled and filtered, and the filtrate was washed with water, dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and aqueous sodium chloride. After drying ($MgSO_4$), the solvent was stripped to give 15.5 g of crude **4a** as an oil. Crystallization from benzene/cyclohexane followed by recrystallization from the same solvent gave pure **4a**; yield: (48% from **2a**); m.p. 78–80°.

$C_9H_{11}NO_4S$	calc.	C 47.15	H 4.84	N 6.11
(229.3)	found	46.97	4.76	6.09

Ethyl phenylaminsulfonylacetate (**4b**) was similarly prepared from **2b**: however, **4b** was obtained as an oil and was not characterized.

Table. Styrene-ω-sulfonanilides **6** and **8** prepared

	Ar	Yield (%)	m.p.		Elemental Analyses			
6a		67	113°	$C_{14}H_{13}NO_2S$ (259.3)	Ref. 2			
6b		83	122–124°	$C_{15}H_{15}NO_2S$ (273.3)	calc.	C 65.90	H 5.53	N 5.13
					found	65.95	5.55	5.10
6c		83	115°	$C_{15}H_{15}NO_3S$ (289.3)	calc.	C 62.26	H 5.23	N 4.84
					found	62.41	5.23	4.91
6d		63	149.5–151°	$C_{18}H_{15}NO_2S$ (309.4)	calc.	C 69.88	H 4.89	N 4.53
					found	69.72	4.94	4.42
6e		68	97–98°	$C_{12}H_{12}NO_2S_2$ (266.4)	calc.	C 54.31	H 4.18	N 5.28
					found	54.53	3.99	5.46
8a		51	156–158°	$C_{14}H_{11}N_3O_6S$ (349.3)	calc.	C 48.13	H 3.17	N 12.03
					found	47.96	3.11	11.76
8b		41	177–179°	$C_{15}H_{13}N_3O_6S$ (363.3)	calc.	C 49.58	H 3.61	N 11.57
					found	49.40	3.60	11.76
8c		33	181.5–183.5°	$C_{15}H_{13}N_3O_7S$ (379.3)	calc.	C 47.49	H 3.45	N 11.08
					found	47.67	3.46	10.96
8d		28	190–191°	$C_{18}H_{13}N_3O_6S$ (399.4)	calc.	C 54.13	H 3.28	N 10.52
					found	54.22	3.12	10.54
8e		48	248–250°	$C_{14}H_{10}N_4O_8S$ (394.3)	calc.	C 42.64	H 2.56	N 14.21
					found	42.70	2.57	14.13
8f		58	170–170.5°	$C_{14}H_{10}BrN_3O_6S$ (428.2)	calc.	C 39.26	H 2.35	N 9.81
					found	39.43	2.26	9.75
8g		36	174.5–176.5°	$C_{14}H_8Cl_2N_3O_6S$ (418.2)	calc.	C 40.20	H 2.17	N 10.05
					found	40.30	2.08	10.13

Phenylaminosulfonylacetic Acid (5):
Ester **4a** or **4b** (0.5 mol) was refluxed 2.5 h in a solution of potassium hydroxide (70 g) in water (500 ml) and ethanol (200 ml). Charcoal was added, the solution was heated to boiling for 5 min, filtered through Celite, washed with ether, acidified with hydrochloric acid, and extracted with ether. The ether extract was washed with water, dried, and evaporated leaving 67.7 g (63%) of crude **5** that was crystallized from benzene; yield: 36 g (33%); m.p. 109–110°.

$C_8H_9NO_4S$	calc.	C 44.64	H 4.21	N 6.51
(215.2)	found	44.77	4.10	6.43

***N*-(2,4-Dinitrophenyl)-aminosulfonylacetic Acid (7):**
A mixture of conc. nitric acid (66 ml) and sulfuric acid (33 ml) was stirred and maintained at 20–25° while compound **5** (13.25 g) was added in portions over ~20 min. A clear solution resulted that deposited a mass of a yellow solid within 30 min. Ice was added and the pasty solid was collected and directly recrystallized from methanol/water to give pure **7**; yield: 14.14 g (84%); m.p. 170°.

$C_8H_7N_3O_8S$	calc.	C 31.48	H 2.31	N 13.77
(305.2)	found	31.43	2.23	13.96

Styrene-ω-sulfonanilides (6a–e); Typical Procedure:
Preparation of **6b**. 4-Methylbenzaldehyde (5.5 ml), pyridine (4 ml), ammonium acetate (1 g), and **5** (8.60 g) were refluxed 22 h[7] in toluene with azeotropic removal of water. The solution was cooled, washed with water, dilute hydrochloric acid, and aqueous sodium hydrogen carbonate, then was extracted with 10% potassium hydroxide (the potassium salt of **6b** separated as an oil with the aqueous phase). The two-phase aqueous extract was washed with ether, then was acidified with hydrochloric acid, and extracted with ether to give **6b**; yield: 9.04 g (83%); m.p. 108–112°. Recrystallization from cyclohexane/benzene and then from methanol gave an analytical sample, m.p. 120°.

Nitration of the Styrene-ω-sulfonanilides 6a and 6b:
A cautiously prepared mixture of fuming nitric acid (0.7 g), acetic anhydride (1 ml), and acetic acid (1 ml) was added dropwise to a cold slurry of **6b** (1.37 g) in acetic anhydride (5 ml). The solution was then heated at 60–65° for 15 min (exothermic reaction at ~60°), then was cooled and poured into water. The water was decanted, the gummy precipitate was taken up in chloroform, and the chloroform solution was washed with water, dried, and evaporated. The residual oil (1.91 g) crystallized upon trituration with hot ethanol, m.p. 150–174° (0.72 g). Recrystallization from acetonitrile gave pure **8b**; yield: 0.58 g (32%); m.p. 177–179°. The same procedure was applied to **6a** except that the crude **8a** was chromatographed on silica gel (eluted with benzene) then recrystallized twice from ethanol to pure **8a**; yield: 27%.

2',4'-Dinitrostyrene-ω-sulfonanilides (8a–g); Typical Procedure:
Preparation of **8a**. A mixture of **7** (2.73 g, 0.01 mol) and benzaldehyde (1.3 ml) in benzene (40 ml) containing 0.001 mol of piperidinium acetate was refluxed 3.5 h, then the solvent was stripped. The N.M.R. spectrum of the remaining yellow solid indicated the presence of *N*-(2,4-dinitro)-methanesulfonanilide (**9**), but recrystallization from wet acetic acid gave essentially pure **8a**; yield: 1.77 g (51%); m.p. 147.5–149°.

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[a] Mention of a proprietary product or company does not imply endorsement by the U.S. Department of Agriculture.
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[6] Ref. 3, p. 200.

[7] Subsequent work has indicated that considerably shorter reaction times probably would have been adequate.