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Synthesis of α -Arylated Phenylsulfonylacetonitriles. A Useful Precursor for
Substituted α -Arylalkanoic Acid and Their Derivatives

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Copper(I) iodide-catalyzed reaction of aryl iodides with anion derived from phenylsulfonylacetonitrile in hot hexamethylphosphoric triamide affords α -arylated nitriles in good to moderate yields. Further alkylation of these nitriles followed by reductive removal of sulfonyl group provides a simple route to α -arylalkanenitriles.

Reaction of aryl halides with carbon nucleophiles are known to be catalyzed by various transition metal compounds, among which copper and palladium compounds appear to be most general and versatile.¹⁾ As previously reported,²⁾ non-activated aryl iodides react smoothly with anions derived from some active methylene compounds in the presence of copper(I) iodide in hot hexamethylphosphoric triamide (HMPA) to give the corresponding arylation products in good to moderate yields. We have now extended this methodology to a novel synthesis of α -arylated phenylsulfonylacetonitriles (**3**), which are attractive starting materials for a variety of α -arylalkanoic acids and their derivatives of pharmaceutical interest.³⁾

Phenylsulfonylacetonitrile, readily accessible from the reaction of chloro-

acetonitrile with anhydrous sodium benzenesulfinate,⁴⁾ was dissolved in HMPA and treated with an equivalent amount of sodium hydride to generate anion (2).⁵⁾ To the resulting mixture was added copper(I) iodide and aryl iodide (1), and the system was gradually heated to 140–150 °C with stirring under nitrogen. The reaction was clean and no polymeric substances were formed. After appropriate duration of time the reaction was quenched by the addition of water and the mixture was worked up as usual to give the corresponding arylation product (3) in 45–88% isolated yields. Neither desulfonylation nor decyanation occurred during the arylation. Although the present procedure can be successfully applicable to various nonactivated aryl iodides, it is subject to a considerable steric effect. Thus the arylation with 2,3,5,6-tetramethyliodobenzene afforded 3f only in 13% yield. Aryl bromides are less effective as arylating agent and aryl chlorides fail to react.

α -Arylated nitriles 3 were easily alkylated by successive treatment with sodium hydride and alkyl halide to afford the corresponding α -alkyl- α -phenylsulfonalkanenitriles (4) in good yields. Alkylation with tertiary alkyl halides failed. The latter nitriles 4 underwent reductive desulfonylation with Raney nickel alloy,⁶⁾ giving α -arylalkanenitriles (5). Thus, by choosing an appropriate combination of aryl iodide and alkyl halide, a wide variety of α -alkylated alkanenitriles are easily accessible. Based on the sequence described above, 2-(isobutylphenyl)-propanoic acid (6), a nonsteroidal anti-inflammatory drug Ibuprofen, was prepared from 4-isobutyliodobenzene in ca. 40% overall yield.

To our knowledge, only one paper deals with the preparation of α -arylphenylsulfonacetonitriles, in which aromatic aldehydes are reacted with phenylsulfonyl chloride in the presence of sodium cyanide and subsequently treated with thiourea.⁷⁾

Some attempts were made to extend the present procedure to the arylation of anion derived from phenylselenoacetonitrile (7). Rather disappointingly, nitrile 7 underwent facile decomposition to give diphenyl diselenide 9 as the sole product. When the reaction was carried out in THF using copper powder as catalyst, the main product was bis(phenylseleno)acetonitrile (8), which decomposed to 9 on prolonged reaction. No α -arylated product could be obtained.⁸⁾

Table 1. Cu(I)-Promoted arylation of phenylsulfonylacetonitrile anion with aryl iodides

	Aryl iodide <u>1</u>					Reaction time/h	Temperature /°C	Arylated nitrile <u>3</u> ^{a)}	
	R ¹	R ²	R ³	R ⁴	R ⁵			Mp/°C	Yield/%
a	H	H	CH ₃	H	H	4	150	115-116	75
b	H	H	(CH ₃) ₂ CHCH ₂	H	H	5	150	90-91	84
c	H	H	CH ₃ O	H	H	5	140	115-116	45
d	H	CH ₃ O	CH ₃ O	H	H	4	150	---	78
e	H	-O-CH ₂ -O-		H	H	6	140	134-135	88
f	CH ₃	CH ₃	H	CH ₃	CH ₃	10	150	211-212	13
g	H	H	C ₆ H ₅	H	H	5	150	208-209	48
h	H	H	Cl	H	H	5	150	128-129	52
i	H	H	NO ₂	H	H	5	150	177-178	48
j	H	H	CO ₂ C ₂ H ₅	H	H	5	150	115-116	52

a) Structures of the products were assigned on the basis of IR, ¹H NMR, and MS spectra as well as elemental analyses. Yields refer to the isolated ones and are not optimized.

Table 2. Alkylation of α-aryl-α-phenylsulfonylacetonitrile anion with alkyl halides

	Nitrile <u>3</u>					Alkyl halide		Reaction time/h	Alkylated nitrile <u>4</u> ^{a)}
	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	X		Mp/°C Yield/%
a	H		-O-CH ₂ -O-	H	H	CH ₃	I	5	138-139 92
b	H		-O-CH ₂ -O-	H	H	C ₂ H ₅	Br	6	139-140 96
c	H		-O-CH ₂ -O-	H	H	(CH ₃) ₂ CH	Br	11	147-148 58
d	H	H	(CH ₃) ₂ CHCH ₂	H	H	CH ₃	I	5	111-112 99
e	H	H	(CH ₃) ₂ CHCH ₂	H	H	C ₂ H ₅	Br	7	--- 70
f	H	H	(CH ₃) ₂ CHCH ₂	H	H	(CH ₃) ₂ CH	Br	10	97-98 57
g	H	H	C ₆ H ₅	H	H	CH ₃	I	6	171-172 98
h	H	H	C ₆ H ₅	H	H	(CH ₃) ₂ CH	Br	12	193-194 87

a) See footnotes in Table 1.

Typical procedures for arylation and subsequent alkylation are as follows:

A commercial 60% sodium hydride dispersion (0.80 g; 20 mmol) was placed in a 100 ml flask and paraffin was removed by washing with dry hexane (10ml x 3). The remaining solid was covered with HMPA (20 ml) and phenylsulfonylacetonitrile (3.62 g; 20 mmol) was added dropwise with stirring under nitrogen. The resulting mixture was gradually heated to 60 °C to obtain a yellow clear solution, to which copper(I) iodide (3.82 g; 20 mmol) followed by 4-isobutyl-iodobenzene (**1b**; 2.60 g; 10 mmol) was added and heated to 140-150 °C. The color turned from grey to almost black with the rise of temperature. After 5 h the mixture was cooled to room temperature, diluted by the addition of ether (40 ml) and made weakly acidic with dilute hydrochloric acid. Precipitated copper(I) salt was filtered off by suction. The organic phase was separated, washed with dilute hydrochloric acid to remove any trace of HMPA and dried with sodium sulfate. Evaporation of the solvent followed by recrystallization of the residue from ethanol gave (4-isobutylphenyl)-(phenylsulfonyl)acetonitrile (**3b**) as a crystalline solid, mp 90-91 °C. Yield, 2.63 g (8.4 mmol; 84%). ¹H NMR (CDCl₃): δ = 0.89(d, 6H, J=6 Hz), 1.55-1.88(m, 1H), 2.43(d, 2H, J=6 Hz), 4.91(s, 1H), and 7.15-7.72(m, 9H); IR(KBr): 2915, 2240, 1335, 1158, 1080, 860, and 680 cm⁻¹. Found: C, 68.72; H, 5.95; N, 4.52%. Calcd for C₁₈H₁₉NO₂S: C, 68.98; H, 6.11; N, 4.47%.

To a suspension of sodium hydride (0.15 g; 6.0 mmol) in HMPA (10 ml) was added with stirring arylsulfonylnitrile **3b** (1.88 g; 6.0 mmol) followed by methyl iodide (0.86 g; 6.0 mmol) at appropriate interval and the resulting yellow mixture was stirred at ambient temperatures. After 5 h the reaction was quenched by the addition of water and worked up as usual to give 2-(4-isobutylphenyl)-2-(phenylsulfonyl)propanenitrile (**4b**), mp 111-112 °C. Yield, 1.96 g (5.99 mmol, 99%).

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