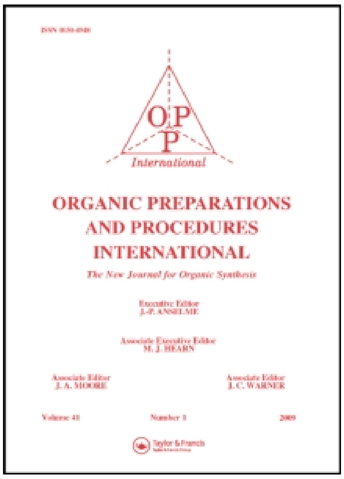

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A SIMPLE PROCEDURE FOR THE PREPARATION OF (METHYL- AND PHENYLTHIO)ARYLOXYACETONITRILES

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A SIMPLE PROCEDURE FOR THE PREPARATION OF (METHYL- AND PHENYLTHIO)ARYLOXYACETONITRILES

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Monothioacetals of unstable formyl cyanide[1] are useful substrates, they serve as acyl anion equivalents,[2] synthons for esters[3,4] or carbonyl 1,1-zwitterion synthons for macrolide syntheses.[4] Phenylthio(methoxy)acetonitrile has been synthesized by the electrolytic methoxylation of phenylthioacetonitrile[3] and by substitution of chloro(phenylthio)acetonitrile by methoxide ion.[4] The former method has also been applied to obtain alkylthio(methoxy)acetonitriles[3] while methyl~hio(phenoxy) analogue was prepared by methylthiolation of phenoxyacetonitrile with dimethyl disulfide in the presence of a base.[2] We now report that the latter approach is a simple and fairly a general method for the preparation of (methylthio- or phenylthio)aryloxyacetonitriles (**2**) starting from the easily available aryloxyacetonitriles **1**.

$$\underset{\mathbf{1}}{\mathrm{ArOCH_2CN}} \xrightarrow{\mathrm{NaH,\ DMF,\ RSSR}} \underset{\mathbf{2}}{\mathrm{ArOCH(SR)CN}}$$

a) Ar = C_6H_5, R = Me b) Ar = p-MeC_6H_4, R = Me c) Ar = o-ClC_6H_4, R = Me d) Ar = p-BrC_6H_4, R = Me e) Ar = p-MeOC_6H_4, R = Me f) Ar = R = Ph g) Ar = p-MeC_6H_4, R = Ph h) Ar = o-ClC_6H_4, R = Ph i) Ar = p-BrC_6H_4, R = Ph j) Ar = 2-$C_{10}H_7$, R = Ph

The reaction is conveniently carried out in the sodium hydride/DMF base-solvent system at a temperature of -18° to -15° (Table 1).

It was found that the temperature conditions mentioned above are important since at ≤ -35°, the reactions proceeded rather slowly while at 35° only slight amounts of the products 2 were formed. In the majority of cases, the products were isolated by simple vacuum distillation or crystallization and identified by the presence of signals of methine proton in their ^{1}H NMR spectra (Table 2).

The yields of crystalline phenylthiolated products **2** are usually better than that of the corresponding methylthio derivatives, a testimony to the higher activity of diphenyl disulfide toward carbanions of **1** compared to dimethyl disulfide. The noticeably low yield of **2e** is due to its cleavage (or of **1e**) under the reaction conditions, indeed p-hydroxyanisole was detected in the crude products mixture. In the case of **2g**, a large amount of **1g** and diphenyl disulfide remained unchanged. The presence of two acidic hydrogen atoms did not result in bisalkylthiolation possibly because of the use of excess base.

TABLE 1. Yields, Physical Constants and Elemental Analyses of Nitriles **2**

Compd	Yield (%)	bp(°C/torr)	mp (°C)[a]	Elemental Analyses (Found)			
				C	H	N	S
2a	65 (68)[b]	100-102/1 (88-90/0.3)[b]	--	–	–	–	–
2b	62	112-115/0.3	--	62.1.7 (61.88)	5.69 (5.48)	7.25 (7.21)	16.58 (16.11)
2c	69	108-110/0.4	--	50.58 (50.73)	3.74 (3.76)	6.55 (6.52)	14.98 (15.27)
2d	51	132-135/0.1	--	41.86 (42.16)	3.10 (3.20)	5.42 (5.30)	12.40 (12.79)
2e	22	126-128/0.4	--	57.41 (57.47)	5.26 (5.26)	6.69 (6.37)	15.31 (15.01)
2f	80	--	90-92	69.68 (69.60)	4.59 (4.62)	5.80 (5.73)	13.29 (13.22)
2g	32	--	67-69	70.58 (70.60)	5.09 (5.23)	5.49 (5.32)	12.54 (12.66)
2h	71	156-158/0.2	39-41[c]	60.98 (60.92)	3.62 (3.82)	5.08 (5.01)	11.61 (11.74)
2i	85	145-148/0.1	89-90	52.50 (52.59)	3.12 (3.34)	4.37 (4.46)	10.00 (10.33)
2j	72	--	66-68	74.22 (74.04)	4.46 (4.38)	4.81 (4.40)	10.99 (11.03)

a) Unless otherwise stated, the solid products were crystallized from methanol. b)Yield and bp. from ref. 2. c)From aq. methanol.

TABLE 2. ^{2}H NMR of Nitriles 2

Compd	^{1}H NMR (CDCl$_3$, δ)
2a[a]	2.39 (s, 3H, CH$_3$S), 5.77 (s, 1H, CH), 6.81-7.52 (m, ArH)
2b	2.34 (s, 3H, CH$_3$), 2.41 (s, 3H, CH$_3$), 5.77 (s, 1H, CH), 6.92-7.14 (m, 4H, ArH)
2c	2.46 (s, 3H, CH$_3$), 5.84 (s, 1H, CH), 6.94-7.51 (m, 4H, ArH)
2d	2.39 (s, 3H, CH$_3$), 5.78 (s, 1H, CH), 6.85-7.55 (m, 4H, ArH)
2e	2.37 (s, 3H, CH$_3$S), 3.75 (s, 3H, CH$_3$O), 5.68 (s, 1H, CH), 6.71-7.08 (m, 4H, ArH)
2f	5.95 (s, 1H, CH), 6.90-7.80 (m, 10H, ArH)
2g	2.13 (s, 3H, CH$_3$), 5.90 (s, 1H, CH), 6.80-7.75 (m, 9H, ArH)
2h	5.95 (s, 1H, CH), 6.94-7.80 (m, 9H, ArH)
2i	5.92 (s, 1H, CH), 6.76-7.72 (m, 9H, ArH)
2j	6.10 (s, 1H, CH), 7.15-7.94 (m, 12H, ArH)

a) From ref 2.

The present method using inexpensive and easily available materials, is simpler and more general than known methods.[3,4] The present results constitute a useful extension of the alkyl- and arylthiolation of different C-H acids *via* their carbanions.[5]

EXPERIMENTAL SECTION

All boiling points and melting points are uncorrected. ^1H NMR spectra were recorded on a Bruker WP-100 spectrometer at 100 MHz, using $CDCl_3$ as solvent. Chemical shifts are reported in ppm downfield from TMS ($\delta = 0.00$ ppm). The gas chromatography (GC) analyses were carried out on a GCHF 18.3 chromatograph, OV-17 (5%) on Chromosorb W-HP (80-100 mesh) column. DMF was dried as reported.[6] The oil from 50% dispersion of NaH (Koch-Light Laboratories Ltd.) was washed out with benzene. Column chromatography (CC) was performed on Merck silica gel 60 (230-240 mesh), hexane-ethyl acetate (gradient) as eluent. All reactions were carried out under nitrogen.

The nitriles **1** were prepared as previously described: **1a**, bp. 116°/12 torr, lit.[7] bp. 120-123°/12 torr, **1b**, mp. 37-39°, lit.[7] mp. 35-36°; **1c**, bp. 137-139°/14 torr, lit.[8] bp. 109°/1 torr; **1d**, mp. 54-56°, lit.[9] mp. 54°, **1e**, bp.118-120°/0.4 torr, mp. 24-26° (from MeOH), lit.[10] bp. 167-169°/18 torr; **1j**, mp. 75-77° CCl_4), lit.[11] mp. 76°.

Methylthio(aryloxy)acetonitriles (2a-e). General Procedure.- To a suspension of 50% NaH in oil (2.12 g, 0.044 mol), previously washed with benzene, in DMF (20 mL), a mixture of nitrile **1** (0.020 mol) and dimethyl disulfide (2.26 g, 0.024 mol) (in the case of the solid **1**, a minimum amount of DMF was used to dissolve **1**) was added at -18° to -15° for 10 min., with stirring. After the addition of ca 20% of this mixture, 1-2 drops of methanol were added which helped to start the reaction. Stirring was continued at this temperature for 50 min., the mixture was poured into water with ice (ca 100 mL), and extracted with dichloromethane (3 x 20 mL). The organic extracts were washed with water, dried ($MgSO_4$), the solvent was evaporated and the products were isolated by vacuum distillation (Table 1).

The crude mixture after the reaction of **1e** with dimethyl disulfide was distilled, and the fraction of bp. 125-130°/0.4 torr was collected; its GC analysis revealed the presence of *p*-hydroxyanisole and of **2e**. This fraction was dissolved in benzene, washed with aq. NaOH (ca 20%), dried ($MgSO_4$) and distilled (Table 1).

Phenylthio(aryloxy)acetonitriles (2f-j). General Procedure.- To a suspension of 50% NaH in oil (2.12 g, 0.044 mol), previously washed with benzene in DMF (20 mL), a solution of nitrile **1** (0.021 mol) and diphenyl disulfide (4.36 g, 0.020 mol) in DMF (ca 7 mL) was added dropwise at -18° to -15° for 10 min. with stirring. The reaction was worked up as described above. The products were isolated by crystallization (**2f,g**), distillation and crystallization (**2h,i**) or by column chromatography and crystallization (**2j**).

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A CONVENIENT METHOD FOR THE SYNTHESIS OF FLAVANONES by the SELECTIVE OXIDATION OF FLAVAN-4-OLS with HYPERVALENT IODINE

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The oxidation of flavan-4-ols with dimethyl sulfoxide[1] and sodium dichromate[2] has been reported to produce flavanones whereas with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) flavones are formed along with flavanones as minor products.[3] Phenyliodo *bis*(trifluoroacetate) (PIFA) is a powerful dehydrogenating agent[4] and most reactions proceed under mild conditions. These observations, coupled with our continued interest in flavonoids[5] and hypervalent iodine chemistry,[6] prompted the use of PIFA for the oxidation of flavan-4-ols (**1a-g**).