

THE OXIDATIVE DECYANATION OF ARYLACETONITRILES

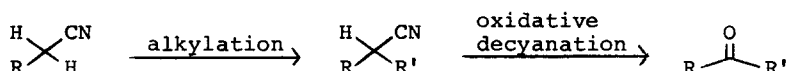
via α -THIOPHENOXY ARYLACETONITRILES

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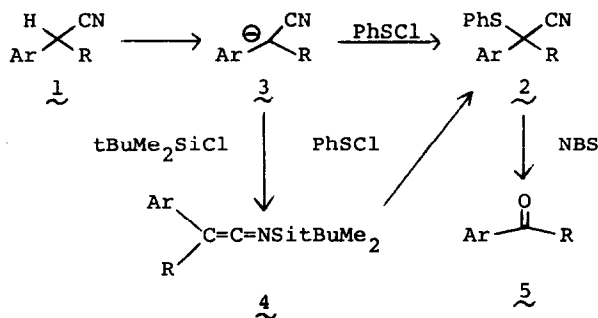
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To demonstrate the utility of nitriles as acyl carbanion equivalents required methods for effecting the monoalkylation of primary nitriles¹ and the oxidative decyanation of secondary nitriles.²



No systematic study of the latter transformation has been reported. We now wish to report a convenient procedure for effecting the oxidative decyanation of substituted arylacetoneitriles 1 via the intermediate α -thiophenoxy nitriles 2.

We have utilized two sequences for the preparation of α -thiophenoxy nitriles 2: the reaction of nitrile anions 3 or silylketenimines³ 4 with phenylsulfenyl chloride. The direct sulfenylation of anions 3 derived from nitriles 1 using lithium dialkylamides⁴ or n-butyl lithium⁵ (Method A) provided 2 in good yield. The preparation of α -thiophenoxy nitriles 2 from silylketenimines³ 4 (Method B) required an additional synthetic operation but offered the advantages of generality⁶ and excellent yields.



The sequential treatment of α -thiophenoxy nitriles 2 with N-bromosuccinimide and sodium hydroxide in aqueous acetonitrile provided ketones 5 in good yield (Table 1). Bromine, N-bromoacetamide and N-chlorosuccinimide proved less effective than N-bromosuccinimide.⁷ Deletion of the sodium hydroxide step led to the isolation of the corresponding cyanohydrins. Concomitant electrophilic aromatic substitution was problematical only in the case of 2-(4-biphenyl)propionitrile which afforded a 75% yield of 4-acetyl-4'-bromobiphenyl.⁸


Unfortunately, this methodology is limited to the preparation of alkylaryl or diarylketones 5. The formation of a cyanohydrin from 2 presumably involved the development of some carbonium ion character which the aryl group served to stabilize. In the absence of such stabilization, cyanohydrin formation was blocked.⁹

The following is a typical experimental procedure. To 636 mg (4.0 mmol) of 1 (Ar=Ph, R=iPr) in 6.4 ml of anhydrous THF at -78° under a nitrogen atmosphere was added 1.76 ml of 2.29 M (4.0 mmol) n-butyl lithium in hexane followed by 0.54 ml (4.6 mmol) of PhSCl. The solution was stirred for 30 min at -78° and 30 min at 25° . Following an aqueous acidic workup, the product was chromatographed on Merck silica gel F254 preparative layer plates in 1:9 ether:hexane to provide 1086 mg (85%) of 2 (R_f .43) (Ar=Ph, R=iPr).

To 267 mg (1.0 mmol) of 2 in 5 ml of 25% aqueous acetonitrile was added 1780 mg (10 mmol) of recrystallized NBS. The reaction was stirred for 1.5 hr and quenched with saturated Na_2SO_3 solution and 2 M NaOH. Following an ether extraction, the product was chromatographed as described above to afford 139.1 mg (94%) of isobutyrophenone.¹⁰

We are continuing our search for a general oxidative decyanation procedure.¹¹

Table 1
The Oxidative Decyanation of
Substituted Arylacetonitriles ArCHRCN

Ar	R	Isolated Yield of α -Thiophenoxy-nitrile <u>2</u>		Isolated Yield of Ketone <u>5</u>
		Method A	Method B	
Ph	Me	91%	96%	82% ^a
Ph	Et	70%	93%	74% ^b
Ph	iPr	85%	96%	94% ^a
Ph		87%	96%	84% ^a
Ph	n-Oc	75%	88%	81% ^a
Ph	Ph	88%	100%	100% ^a
pFPh	Me	83%	97%	89% ^b
pClPh	Me	88%	82%	85% ^b
pMeOPh	Me	74%	87%	68% ^{b,c}
α -Np	Me	78%	99%	64% ^a

(a) isolated by thick layer chromatography on Merck silica gel F254,

(b) isolated using Girard T reagent according to O. H. Wheeler, Chem.

Rev., 62, 205 (1962), (c) used only 2.5 equivalents of NBS.

References

- (a) A. C. Cope, H. L. Holmes, H. O. House, Org. Reactions, 9, 107 (1957); (b) M. Makosza, Tetrahedron, 24, 175 (1968); (c) S. Miyano, N. Abe, J. Org. Chem., 36, 2948 (1971); (d) E. J. Corey, I. Kuwajima, Tetrahedron Lett., 487 (1972) and (e) D. S. Watt, Ibid., 707 (1974).
- (a) P. K. Freeman, D. M. Balls, Ibid., 437 (1967) and (b) J. Damiano, S. Geribaldi, G. Torri, M. Azzaro, Ibid., 2301 (1973).
- The silylation of 3 using tert-butyldimethylsilyl chloride afforded high yields of 4 but using trimethylsilyl chloride afforded predominantly the C-silylated product ArRC(SiMe₃)CN: (a) J. Llonch, E. Frainnet, C. R. Acad. Sci., Paris, Ser. C, 276, 1803 (1973) and (b) D. S. Watt, Synthetic Commun., 4, 127 (1974).
- In the case of non-aryl substituted acetonitriles, higher yields of sulfonylated products were obtained using lithium dialkylamides rather than n-butyl lithium. For example, the reaction of 2-methyloctanonitrile with lithium N,N-diisopropylamide (1.5 equiv) followed by PhSCl (3.0 equiv) in THF-hexane at -78° afforded 2-methyl-2-thiophenoxyoctanonitrile in 85% yield. The corresponding reaction using n-butyl lithium (1.0 equiv) and PhSCl (1.1 equiv) afforded the same α -thiophenoxy nitrile in only 21% yield.

5. In the case of arylacetonitriles 1, higher yields of 2 were isolated from reactions employing n-butyl lithium rather than lithium dialkylamides. For example, the reaction of 1 (Ar=Ph, R=Me) with lithium N-cyclohexyl-N-isopropylamide (1.0 equiv) in THF-hexane at -78° followed by PhSCl (2.0 equiv) afforded 2 (Ar=Ph, R=Me) in 53% yield. In contrast, the use of n-butyl lithium provided 2 (Ar=Ph, R=Me) in 91% yield (Table 1, Method A).
6. For example, Method A failed completely in the reaction of 3 (Ar=Ph, R=Me) with 2,4-dinitrophenylsulfenyl chloride because of the base-sensitive nitro groups but Method B provided 2-(2,4-dinitrothiophenoxy)-2-phenylpropionitrile in 81% yield.
7. For example, the reaction of 2 (Ar=Ph, R=Me) with NBS, NBA, NCS and Br₂ afforded acetophenone in 82, 73, 60 and 30% yield, respectively.
8. B. R. Carpenter, E. E. Turner, J. Chem. Soc., 869 (1934).
9. For example, application of the NBS-NaOH procedure to 2-methyl-2-thiophenoxyoctanonitrile afforded the corresponding sulfoxide. No 2-octanone was detected.
10. All compounds had infrared, nmr and mass spectral data in accord with assigned structures. New compounds gave satisfactory elemental analyses.
11. We would like to thank the University of Colorado and the Research Corporation for their generous support.