

## Direct Transformation of Primary Nitro Compounds into Nitriles. New Syntheses of $\alpha,\beta$ -Unsaturated Nitriles and Cyanohydrin Acetates

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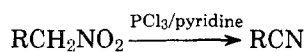
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Treatment of primary nitro compounds with phosphorus trichloride in pyridine yields nitriles in one step. In this fashion alkyl and aryl nitromethanes are converted to alkyl and aryl nitriles. Allylic nitromethanes lead to  $\alpha,\beta$ -unsaturated nitriles and  $\beta$ -acetoxy nitromethanes are converted directly into the corresponding aldehyde or ketone cyanohydrin acetates.

The transformation of a nitromethyl group into a nitrile classically involves a Nef reaction leading to the corresponding aldehyde, oxime formation with hydroxylamine, followed by dehydration.<sup>1</sup> This sequence is involved and often incompatible with other functional groups present in the starting molecule. Alternatively, direct conversions of primary nitro compounds into nitriles have been achieved by the reaction of alkali salts of nitromethyl compounds with diethylphosphorochloridite<sup>2</sup> or by subjecting primary nitro compounds to Vilsmeier-Haack formylation conditions at temperatures above 100 °C.<sup>3</sup>

This report describes novel and general reaction conditions for the direct conversion of a variety of primary nitro compounds into the corresponding nitriles. Thus, treatment of nitromethyl compounds in pyridine with phosphorus trichloride yields nitriles.



In contrast to the above-mentioned methods, this reaction proceeds in the presence of a number of other functional groups and does not require formation of alkali salts of nitroparaffins nor high temperatures. Thus, substituted aryl and alkyl nitriles, a functionalized  $\alpha,\beta$ -unsaturated nitrile, and a number of substituted cyanohydrin acetates have been prepared in an extremely facile manner (see Table I).

**(a) Aryl and Alkyl Nitriles.** Aryl nitriles are readily obtained from phenyl nitromethanes by treatment with phosphorus trichloride in pyridine solution at 60 °C. Primary nitroparaffins, substituted or unsubstituted, require substrate-dependant reaction conditions. It is noteworthy, however, that the reaction can proceed under very mild conditions, e.g. room temperature. These circumstances allowed the isolation of the sensitive  $\beta$ -chloropropionitrile and methyl

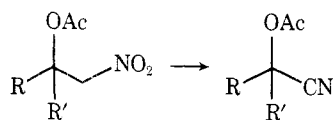
$\beta$ -cyanopropionate, two compounds which might be expected to eliminate under the reaction conditions.

**(b)  $\alpha,\beta$ -Unsaturated Nitriles.** These compounds are obtained by treatment of primary allylic nitro compounds with phosphorus trichloride in pyridine at room temperature. The yields are modest, but the procedure allows the preparation of a relatively unstable  $\gamma$ -functionalized  $\alpha,\beta$ -unsaturated nitrile.

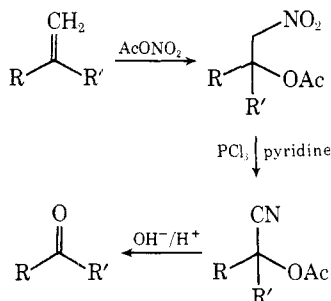
**(c) Cyanohydrin Acetates.** Treatment of  $\beta$ -acetoxy nitro compounds in pyridine solution with phosphorus trichloride furnishes cyanohydrin acetates (Scheme I). This process is particularly useful if the starting  $\beta$ -acetoxy nitro compound is obtained via nitroacetoxylation of a terminal double bond and, of course less so, if it is prepared from an aldehyde by nitromethane addition followed by *O*-acetylation. Illustrative examples include the conversions styrene  $\rightarrow$  benzaldehyde cyanohydrin acetate and isoprene  $\rightarrow$  methyl vinyl ketone cyanohydrin acetate. The reaction sequence (Scheme II) may also find application in chemical degradation work where an isopropylidene group is to be converted into a methyl ketone ( $\text{R}' = \text{CH}_3$ ). Thus, this overall conversion offers an alternative to the well-known ozonolysis reaction. If the starting terminal olefin is monosubstituted ( $\text{R}' = \text{H}$ ) the methodology of nitroacetoxylation followed by  $\text{PCl}_3$ /pyridine treatment furnishes aldehyde cyanohydrin acetates. Suitably protected anions of cyanohydrins have been utilized in alkylation<sup>4</sup> and Michael addition reactions.<sup>5</sup>

A plausible reaction mechanism (Scheme III) for the direct nitromethyl  $\rightarrow$  nitrile conversion involves oxidation of trivalent phosphorus to the pentavalent state. Attack of  $\text{P}^{\text{III}}$  at the oxygen of the nitro group can lead to a cyclic intermediate<sup>6</sup> in which the nitrogen has formally been reduced to the nitroso oxidation level. Abstraction of an  $\alpha$  hydrogen gives an oxime phosphate ester which, in pyridine, eliminates readily to yield a nitrile. However, since attempts at intercepting the reaction at the oxime level proved fruitless, this mechanistic proposal has to be regarded as a working hypothesis.

Scheme I



Scheme II



Scheme III

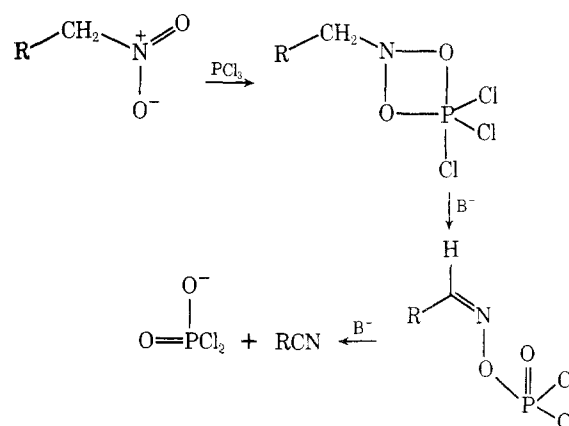


Table I<sup>a</sup>

Substrate	Registry no.	Product	Registry no.	Isolated yield, %	Reaction conditions
Aryl and Alkyl Nitriles					
Phenylnitromethane	622-42-4	Benzonitrile <sup>b</sup>	100-47-0	62	10 min, 60 °C
( <i>p</i> -Methoxyphenyl)nitromethane	29559-26-0	<i>p</i> -Methoxybenzonitrile <sup>c</sup>	874-90-8	77	1 h, 60 °C
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub> CH <sub>2</sub> NO <sub>2</sub>	16891-99-9	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub> CN <sup>d</sup>	2437-25-4	74	95 °C overnight
ClCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> NO <sub>2</sub>	16694-52-3	ClCH <sub>2</sub> CH <sub>2</sub> CN <sup>e</sup>	542-76-7	42	1 day room temp
O <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> COOCH <sub>3</sub>	13013-02-0	CNCH <sub>2</sub> CH <sub>2</sub> COOCH <sub>3</sub> <sup>f</sup>	4107-62-4	43	5 h, 50 °C
α,β-Unsaturated Nitriles					
	61447-06-1		24928-96-9	31	1 h, 25 °C
	5330-61-0		27456-25-3	43	1 day, 25 °C
	63731-02-2		63765-55-9	54 <sup>t</sup>	18 h, 25 °C
	63731-03-3		63731-04-4	48	18 h, 25 °C
	18942-90-0		5762-35-6	74	18 h, 25 °C
	3164-74-7		32379-37-6	52	6 h, 60 °C
	61447-07-2		24928-95-8	32	18 h, 25 °C

<sup>a</sup> Starting materials, when commercially available, were used without purification. Satisfactory physical data were obtained for all products and, when available, were compared with those from authentic samples or from published data. None of the yields have been optimized. <sup>b</sup> The Aldrich Library of Infrared Spectra, 1970, p. 825F. <sup>c</sup> Mp 57.5–59 °C; P. Oxley, M. W. Partridge, T. D. Robson, and W. F. Short, *J. Chem. Soc.*, 763 (1946). <sup>d</sup> The Aldrich Library of NMR Spectra, Vol. III, 1974, p. 155C. <sup>e</sup> *Ibid.*, Vol. III, 1974, p. 162D. <sup>f</sup> P. Kurtz, *Justus Liebigs Ann. Chem.*, 572, 23 (1951). <sup>g</sup> P. A. Wehrli and B. Schaer, *J. Org. Chem.*, in press. <sup>h</sup> V. Kabaivanov, M. Michailov, and N. Gursov, *God. Khim.-Tekhnol. Inst.*, 2, 201 (1956); *Chem. Abstr.*, 52 13620h (1958). <sup>i</sup> H. B. Fraser and G. A. R. Kon, *J. Chem. Soc.*, 604 (1934). <sup>j</sup> L. Ruzicka and W. Brugger, *Helv. Chim. Acta*, 9, 399 (1926). <sup>k</sup> Prepared via mononitroacetylation of 1,5-hexadiene analogous to literature cited under footnote o. MS *m/e* M<sup>+</sup> not observed, 81 (21% M<sup>+</sup> – AcOH-NO<sub>2</sub>), 43 (100%); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.7–2.2 (m, 4 H), 2.07 (s, 3 H, OAc), 4.53 (d, *J* = 6 Hz, 2 H), 5.0–6.0 (m, 4 H, vinyl and HCO). <sup>l</sup> Raman 2280 s, 1775 w, 1660 s cm<sup>-1</sup>; MS *m/e* M<sup>+</sup> not observed, 110 (3%, M<sup>+</sup> – Ac), 93 (12%, M<sup>+</sup> – AcOH), 66 (40%, M<sup>+</sup> – AcOH-HCN), 43 (100%); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.9–2.4 (m, 4 H), 2.14 (s, 3 H, OAc), 5.0–6.0 (m, 4 H vinyl and HC-O). <sup>m</sup> C. A. Grob and H. Von Sprecher, *Helv. Chim. Acta*, 35, 885 (1952). <sup>n</sup> Raman 2270 s, 1750 m cm<sup>-1</sup> (split signals at 1745 and 1755 cm<sup>-1</sup>); MS *m/e* M<sup>+</sup> not observed, 182 (2% M<sup>+</sup> – OCH<sub>3</sub>), 170 (5%, M<sup>+</sup> – Ac), 138 (13%, 170 – CH<sub>3</sub>OH), 43 (100%); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.5–2.55 (m, 8 H), 2.14 (s, 3 H), 3.65 (s, 3 H), 5.26 (t, *J* = 5 Hz, 1 H). <sup>o</sup> F. Bordwell and E. Garbisch Jr., *J. Org. Chem.*, 27, 2322 (1962). <sup>p</sup> A. Albert, *Chem. Ber.*, 49, 1382 (1916). <sup>q</sup> Z. Eckstein, T. Urbanski, and H. Wojnowska, *Rocz. Chem.*, 31, 1177–87 (1951); *Chem. Abstr.*, 52, 9971 (1958). <sup>r</sup> R. Burns, D. T. Jones, and P. D. Ritchie, *J. Chem. Soc.*, 400 (1935). <sup>s</sup> M. Tanaka and N. Murata, *Kogyo Kagaku Zasshi*, 60, 433, 435 (1957); *Chem. Abstr.*, 53, 9043f,h (1959). <sup>t</sup> This is an estimated yield, based on crude nitro acetate (see footnote k).

### Experimental Section

**General Reaction Conditions.** To a 10% solution of the starting nitro compound in pyridine was added 1 mol equiv (in some cases a 2–3 M excess) of phosphorus trichloride with stirring and temperature control. The reaction proceeds under the conditions given in the table. Workup involved quenching with cold dilute HCl and extraction with ether.<sup>7</sup> The crude products were typically purified via silica gel chromatography and/or Kugelrohr distillation. None of the conditions have been optimized. A specific example is described below.

**Conversion of 1-Nitrododecane into Laurylnitrile.** To a solution of 2.013 g (9.35 mmol) of 1-nitrododecane in 20 mL of pyridine was added, via a pipet, 0.87 mL (10 mmol) of phosphorus trichloride. The reaction was stirred and heated at 95 °C overnight. Workup involved quenching in ice and 6 N HCl 1:1, extracting three times with

100 mL of ether, washing with 50 mL of 6 N HCl followed by 50 mL of saturated NaCl solution, drying over sodium sulfate, and evaporation of the solvent in vacuo. There was obtained 1.472 g of crude product which was distilled in a Kugelrohr apparatus (oven temperature 140 °C (1 mm)) to give 1.245 g (74%) of distilled, colorless laurylnitrile.

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**Registry No.**—PCl<sub>3</sub>, 7719-12-2.

### References and Notes

- (1) G. P. Ellis and I. L. Thomas, *Prog. Med. Chem.*, 10, 245 (1974).

- (2) T. Mukaiyama and H. Nambu, *J. Org. Chem.*, **27**, 2201, (1962).  
 (3) J. Skramstad, *Acta Chem. Scand.*, **24**, 3424 (1970).  
 (4) G. Stork, J. C. Depezay, and J. Dangelo, *Tetrahedron Lett.*, 389 (1975).  
 (5) G. Stork and L. Maldonado, *J. Am. Chem. Soc.*, **96**, 5272 (1974).  
 (6) A nitrogen containing phosphorane as an intermediate in deoxygenation reactions of aromatic nitro compounds has been postulated. J. I. G. Cadogan,

- D. S. B. Brace, P. K. K. Lim, and B. S. Tait, *J. Chem. Soc., Perkin Trans. 1*, 2376 (1975).  
 (7) Cyanohydrin acetates were worked up in the same manner, except that the acid quench was rapidly extracted with ether in the presence of ice and immediately thereafter washed with a saturated sodium bicarbonate solution.

## Notes

### Conformational Changes Induced by Europium Shift Reagent in Medium-Ring 3-Methoxycycloalkanones

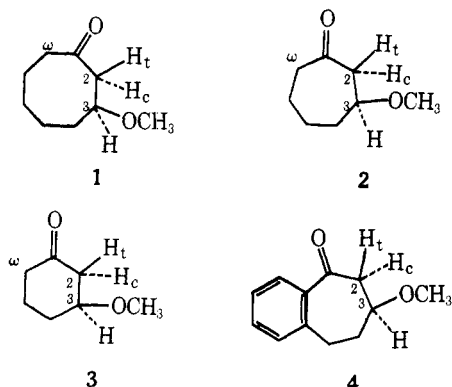
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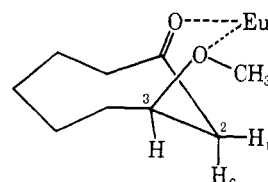
In connection with stereochemical studies on the photochemical<sup>1</sup> and base-catalyzed<sup>2</sup> addition of methanol to 2-cycloalkanones we investigated the LIS<sup>3</sup> spectra of the resulting 3-methoxycycloalkanones with Eu(fod)<sub>3</sub>.<sup>3,4</sup> We observed a dramatic conformational change between the free and europium-coordinated forms of these compounds when the rings were sufficiently large so that the substrate could act as a bidentate ligand toward the europium.<sup>5</sup>

The four compounds whose spectra were studied in detail are 1-4. Their complete spectra are described in the Experi-



mental Section. Table I presents the data which supply conformational information, Figure 1 shows the most distinctive regions of the free and Eu-shifted spectra of 1, and Figure 2 shows a plot of chemical shifts of selected protons in 1 as a function of added shift reagent.<sup>6</sup>

The H<sub>2</sub>-H<sub>3</sub> coupling constants, which are approximately equal for the trans and cis protons in free 1 (7 Hz), change dramatically (to 8 and 3 Hz, respectively) when shift reagent is added. This difference can be attributed to changes in the dihedral angles as a consequence of bidentate coordination with the shift reagent.<sup>7</sup> The methoxyl group in coordinated 1 is pseudoaxial as shown,<sup>8</sup> whereas in free 1 the methoxyl is probably pseudoequatorial. This model for complexed 1 gives dihedral angles for H<sub>3</sub>-H<sub>2t</sub> and H<sub>3</sub>-H<sub>2c</sub> of 30 and 115°, respectively, consistent with the observed large and small coupling constants.<sup>9</sup> Eu-complexed 1 has a sufficiently rigid structure that the geminal coupling between the H<sub>2</sub> protons (12 Hz) was readily observed. Other data which support this structure are the appreciable difference between Δ's for H<sub>2t</sub> and H<sub>2c</sub> with Δ(H<sub>2t</sub> > H<sub>2c</sub>) as expected from the model, and the approximately equal Δ's for the methoxyl and ω protons.



Also, the large difference in Δ's for the C-2 and ω protons would be inconsistent with having the europium coordinated symmetrically with the carbonyl oxygen.

As the ring size decreases (1 → 2 → 3) a series of changes in the spectral data occurs which indicates that bidentate coordination with the shift reagent decreases. The H<sub>3</sub>-H<sub>2</sub> coupling constant differences in free and complexed 2 are still evident, though somewhat smaller than in 1; in 3 (and in 4, which has a more rigid seven-membered ring than 2 because of the benzene ring) this difference has vanished. The difference in Δ's for H<sub>2t</sub> and H<sub>2c</sub> decreases with decreasing ring size, as does the Δ for H<sub>3</sub> and for the methoxyl protons. Finally, the Δ for the ω protons increases and becomes comparable to that of the H<sub>2</sub> protons, suggesting that coordination becomes more symmetric at the carbonyl oxygen. It seems likely from these data that some bidentate coordination is still important in 2, but that in 3 and 4 the shift reagent coordinates predominantly with the carbonyl oxygen.<sup>10</sup> All coordinated structures are fairly rigid, however, since in each case a large geminal coupling constant for the H<sub>2</sub> protons is readily observable in the europium-shifted spectra.

### Experimental Section

**Materials.** 3-Methoxycycloalkanones were obtained by known procedures<sup>1,11,12</sup> and were purified by GLC and/or column chromatography.

**NMR Measurements.** All NMR spectra were measured in CDCl<sub>3</sub> with Me<sub>4</sub>Si as an internal reference, using a Varian T60 or HA-100 spectrometer. LIS spectra were recorded by adding increasing weighed amounts of Eu(fod)<sub>3</sub> (Aldrich Chemical Co.) to a known weight of the substrate in CDCl<sub>3</sub>. The LIS chemical shifts were plotted against the weight of Eu(fod)<sub>3</sub>, and Δ (Table I) is the extrapolated value of the chemical shift difference in parts per million for a mole ratio of 1:1 of shift reagent/substrate. All coupling constants in the LIS shifted spectra were verified by appropriate decoupling experiments.

**NMR Data.** For 1 (unshifted spectrum): δ 1.05-2.10 (m, 8 H, C-4-C-7 methylenes), 2.25-2.45 (m, 2 H, C-8 methylene), 2.55-2.75 (m, 2 H, C-2 methylene), 3.30 (s, 3 H, methoxyl), 3.45 (m, 1 H, C-3 methine); irradiation at δ 1.85 (C-4 methylene) caused the multiplet at δ 3.45 to become a triplet, *J* = 7 Hz. For 1 (LIS shifted spectrum; mole ratio of Eu(fod)<sub>3</sub>/1 = 0.39): δ 2.50-5.70 (m, 10 H, C-4-C-8), 6.22 (s, 3 H, methoxyl), 8.20 (m, 1 H, C-3 methine), 7.20 (d × d, 1 H, *J* = 12, 3 Hz, H<sub>2c</sub>), 9.15 (d × d, 1 H, *J* = 12, 8 Hz, H<sub>2t</sub>).

For 2 (unshifted spectrum): δ 1.50-1.96 (m, 6 H, C-4-C-6 methylenes), 2.27-2.43 (m, 2 H, C-7 methylene), 2.63-2.73 (m, 2 H, C-2 methylene), 3.20 (s, 3 H, methoxyl), 3.45 (m, 1 H, C-3 methine); irradiation at δ 1.73 (C-4 methylene) converted the C-3 methine signal to a doublet of doublets, *J* = 6.5, 4 Hz. For 2 (LIS shifted spectrum; mole ratio of Eu(fod)<sub>3</sub>/2 = 0.53): δ 3.20-4.50 (m, 6 H, C-4-C-6 methylenes), 5.20 (s, 3 H, methoxyl), 6.90 (m, 1 H, C-3 methine), 7.90-8.30