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The Chemistry of Acylals. 3. Cyanohydrin Esters from Acylals with Cyanide Reagents

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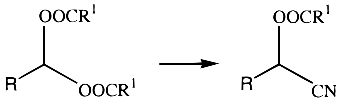
ABSTRACT



When treated with KCN in DMSO at room temperature, acylals from aliphatic aldehydes gave the corresponding cyanohydrin esters in good to excellent yields. Acylals from aromatic aldehydes were less reactive and gave several byproducts in addition to fair yields of cyanohydrin under the same conditions. Trimethylsilyl cyanide mixed with titanium(IV) chloride afforded cyanohydrin esters in good to excellent yields from both aliphatic and aromatic aldehydes.

Although acylals, or *gem*-bis(acyloxy)alkanes, are easily accessible by several methods[1] in large quantities, their chemical properties have not been extensively investigated.[2] Most studies have focused on acylal stability under basic and acidic conditions;[2] otherwise, only a few reactions, mainly involving nitrogen,[3] oxygen[4] and carbon[2,5] nucleophiles, have been reported. In general, useful products were obtained only when acylals from aldehydes were treated with various organometallic reagents containing carbanions; with such reagents one of the acyloxy groups is substituted by the carbanion, giving esters of secondary alcohols in moderate to good yields.[2,5] On the basis of these results and the fact that cyanide is a very reactive carbon nucleophile, we anticipated that treatment of acylals with cyanide under the right conditions would give cyanohydrin esters, which are useful intermediates in organic synthesis and compounds of potential commercial interest in their own right.[6] Such a

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(1) Selected references: (a) Knoevenagel, E. *J. Liebigs Ann. Chem.* **1914**, *402*, 111−125. (b) Hurd, C. D.; Cantor, S. M. *J. Am. Chem. Soc.* **1938**, *60*, 2677−2687. (c) Man, E. H.; Sanderson, J. J.; Hauser, C. H. *J. Am. Chem. Soc.* **1950**, *72*, 847−848. (d) Hopff, H.; Hegar, G. *Helv. Chim. Acta* **1961**, *44*, 2016−2021. (e) Scheeren, J. W.; Tax, W. J. M.; Schijf, R. *Synthesis* **1973**, 151−153. (f) Shaw, J. E.; Kunerth, D. C. *J. Org. Chem.* **1974**, *39*, 1968−1970. (g) Marshall, J. A.; Wuts, P. G. M. *J. Org. Chem.* **1977**, *42*, 1794−1798.

(2) For an overview, see Sydnes, L. K.; Sandberg, M. *Tetrahedron* **1997**, *53*, 12679−12690 (Part 1).

(3) (a) Michael, A.; Weiner, N. *J. Am. Chem. Soc.* **1936**, *58*, 680−684. (b) Hurd, C. D.; Green, F. O. *J. Am. Chem. Soc.* **1941**, *63*, 2201−2204. (c) Narayana, C.; Padmanabhan, S.; Kabalka, G. W. *Tetrahedron Lett.* **1990**, *31*, 6977−6978. (d) Sandberg, M.; Sydnes, L. K. *Tetrahedron Lett.* **1998**, *39*, 6361−6364 (Part 2).

(4) (a) Gallucci, R. R.; Going, R. C. *J. Org. Chem.* **1982**, *47*, 3517−3521. (b) Kochhar, K. S.; Bal, B. S.; Deshpande, R. P.; Rajadhyaksha, S. N.; Pinnick, H. W. *J. Org. Chem.* **1983**, *48*, 1765−1767. (c) Ku, Y.-Y.; Patel, R.; Sawick, D. *Tetrahedron Lett.* **1993**, *34*, 8037−8040.

(5) (a) Kryshtal, G. V.; Bogdanov, V. S.; Yanovskaya, L. A.; Volkov, Y. P.; Trusova, E. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1981**, 2820−2823. (b) Kryshtal, G. V.; Bogdanov, V. S.; Yanovskaya, L. A.; Volkov, Y. P.; Trusova, E. I. *Tetrahedron Lett.* **1982**, *23*, 3607−3610. (c) Trost, B. M.; Vercauteren, J. *Tetrahedron Lett.* **1985**, *26*, 131−134. (d) Ghribi, A.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 3079−3082.

(6) (a) Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1555. (b) Elliot, M. In *The Future for Insecticides; Needs and Prospects*; Metcalf, M. L., McKelvey, J. J., Eds.; Wiley and Sons: New York, 1976; Vol. 6, pp 163−190.

(7) (a) Torii, S.; Inokuchi, T.; Kobayashi, T. *Chem. Lett.* **1984**, 897−898. (b) Soga, T.; Takenoshita, H.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3122−3131. (c) Ito, Y.; Imai, H.; Segoe, K.; Saegusa, T. *Chem. Lett.* **1984**, 937−940.

(8) The acylals were obtained in the following yields: **2a**, 78%; **2b**, 83%; **2c**, 90%; **2d**, 79%; **2e**, 70%; **2f**, 65%; **2g**, 80%; **2h**, 51%; **2i**, 82%; **2j**, 60%; **2k**, 88%; **2l**, 75%; **2m**, 75%; **2n**, 84%; **2o**, 75%.

(9) All compounds were characterized by their IR, ^{1}H NMR, and ^{13}C NMR spectra, and most new compounds also by HRMS.

(10) **Reactions of acylals with potassium cyanide in DMSO.** In a typical experiment a dry, nitrogen-filled, 50 mL, round-bottomed flask was charged with an aliphatic acylal (4.94 mmol), and a mixture of KCN (0.33 g, 5.04 mmol, 1.2 equiv) and dry DMSO (10 mL) was added. The reaction was completed by stirring overnight, at room temperature to 80 °C for the aromatic acylals and at room temperature for the aliphatic acylals. Workup was carried out by addition of H_2O (50 mL) and extraction with Et_2O (3 × 30 mL). The combined ethereal extracts were washed with H_2O (5 × 50 mL). Drying ($MgSO_4$), filteration, and concentration under vacuum afforded spectroscopically pure products as pale yellow liquids.

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transformation would be analogous to the conversion of acetals to the corresponding cyanohydrin ethers, which has been achieved by using several reagents.[7]

The acylals (**2**), obtained by reacting the corresponding aldehydes (**1**) with carboxylic anhydrides under boron trifluoride catalysis (Scheme 1),[1c,2] were obtained in good to excellent yields[8,9] and were reacted with cyanide under a variety of reaction conditions. Exploratory experiments, carried out with selected acylals, showed that the cleanest product mixtures[9] and the best results were obtained with potassium cyanide in dimethyl sulfoxide (KCN/DMSO) and trimethylsilyl cyanide in the presence of a Lewi acid catalyst (titanium(IV) chloride) (TMSCN/$TiCl_4$). Thus, reactions with these reagents were thoroughly investigated.

Scheme 1

$$(RCO)_2O \quad + \quad \underset{\mathbf{1}}{R^1CHO} \quad \xrightarrow{BF_3} \quad \underset{\mathbf{2}}{R^1CH(OOCR)_2}$$

2a: R = Me, R^1 = Ph
2b: R = Me, R^1 = 4-MeC_6H_4
2c: R = Me, R^1 = 4-$MeOC_6H_4$
2d: R = Me, R^1 = 4-ClC_6H_4
2e: R = Me, R^1 = 4-$NO_2C_6H_4$
2f: R = Me, R^1 = Me
2g: R = Et, R^1 = Me
2h: R = Me, R^1 = *n*-Pentyl
2i: R = Me, R^1 = $CH_3CH{=}CH$
2j: R = Me, R^1 = Cyclohexyl
2k: R = $CH_3CH{=}CH$, R^1 = *n*-Propyl
2l: R = *n*-Pentyl, R^1 = *n*-Pentyl
2m: R = Me, R^1 = *n*-Undecyl
2n: R = $CH_3CH{=}CH$, R^1 = Ph
2o: R = *n*-Pentyl, R^1 = Ph

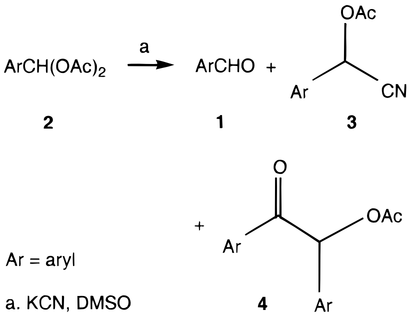
KCN/DMSO. When this reagent was used it appeared that *acylals derived from aliphatic aldehydes* were consumed much faster and gave less complex reaction mixtures than acylals from aromatic aldehydes. The former acylal group reacted smoothly at room temperature[10] and afforded the corresponding cyanohydrin esters **3** as the only product in good to excellent yields when reacted overnight (Table 1). At elevated temperatures (50−80 °C) the reaction was considerably faster, but the yields were in general slightly lower due to formation of the corresponding cyanohydrins. Cyanide displacement at room temperature is therefore preferred.

Table 1. Cyanohydrin Esters (**3**) from Reactions of Aliphatic Acylals with Potassium Cyanide in DMSO at Room Temperature

substrate	isolated yield of **3** (%)
2f	87
2g	82
2h	91
2i	80
2j	92
2k	43
2l	91
2m	97

Acylals from aromatic aldehydes, however, reacted differently and gave more complex reaction mixtures. The corresponding cyanohydrin esters **3** were still formed, but in fair yields at best (<45%). The low yields are obviously in part due to low acylal reactivity because significant amounts of unreacted starting material were present even after stirring for 10 h at ambient temperature. Furthermore, two other products were formed in most cases: the corresponding aldehyde **1**, obtained in minor amounts, and the ester of the symmetric benzoin adduct (**4**) from the same aldehyde (Scheme 2). Both products were obtained in variable yields. The situation did not improve when the reaction temperature was increased; although the relative amount of unreacted acylal decreased, a concomitant increase in the yields of the byproducts was observed as well.

Scheme 2



Ar = aryl

a. KCN, DMSO

Aldehyde formation in reactions with acylals from aromatic aldehydes might be anticipated since acylals give significant amounts of the corresponding aldehydes in reactions with Grignard reagents at room temperature.[2] Furthermore, when aldehydes are formed, subsequent formation of **4** is not unexpected under these conditions, because a benzoin-type condensation may conceivably occur. Such a reaction sequence is supported by the observation that the expected benzoin acetate was obtained when a mixture of benzaldehyde and the corresponding acylal **2f** was stirred at room temperature with potassium cyanide in DMSO.

TMSCN/$TiCl_4$. Trimethylsilyl cyanide combined with a Lewis acid has been used to convert acetals to the corresponding cyanohydrin ethers in good yields.[7,11] The successful Lewis acid originally used was titanium(IV) chloride,[12] which was therefore employed.

When **2** was reacted at room temperature with a mixture of TMSCN and $TiCl_4$,[13] both used in 10% molar excess, the

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(11) (a) Utimoto, K.; Wakabayashi, Y.; Shishiyama, Y.; Inoue, M.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4279−4282. (b) Utimoto, K.; Wakabayashi, Y.; Horrie, T.; Inoue, M.; Shishiyama, Y.; Obayashi, M.; Nozaki, H. *Tetrahedron* **1983**, *39*, 967−973. (c) Mukaiyama, T.; Soga, T.; Takenoshita, H. *Chem. Lett.* **1989**, 997−1000. (d) Mukaiyama, T.; Soga, T.; Takenoshita, H. *Chem. Lett.* **1989**, 1273−1276.

(12) Au, A. T. *Synth. Commun.* **1984**, *14*, 743−748.

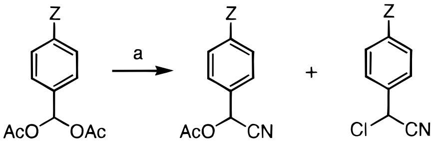
corresponding cyanohydrin esters **3** were obtained, usually in very good yield (Table 2). Under these conditions, acylals from aliphatic aldehydes (entries 6−13) exhibited reactivities similar to those of the aromatic analogues (entries 1−5, 14, and 15). However, two aromatic acylals show a somewhat deviating behavior: 4-methylbenzylidene diacetate (**2b**) and 4-chlorobenzylidene diacetate (**2d**) (entries 2 and 4, respectively), which gave a significant amount of the corresponding α-chloronitrile in addition to **3** (Scheme 3). The reason for this deviating behavior is not clear.

Table 2. Cyanohydrin Esters (**3**) from Reactions of Acylals with Trimethylsilyl Cyanide in the Presence of a Stoichiometric Amount of Titanium(IV) Chloride

entry	substrate	isolated yield of **3** (%)
1	**2a**	93
2	**2b**	75[a]
3	**2c**	87
4	**2d**	53[b]
5	**2e**	96
6	**2f**	82
7	**2g**	80
8	**2h**	74
9	**2i**	93
10	**2j**	94
11	**2k**	87
12	**2l**	89
13	**2m**	92
14	**2n**	96
15	**2o**	91

[a] In addition, the corresponding α-chloronitrile was obtained in 21% yield. [b] In addition, the corresponding α-chloronitrile was obtained in 42% yield.

Scheme 3



Z = Me (**2b**), Cl (**2d**). a.TMSCN, $TiCl_4$, CH_2Cl_2

Experiments were also performed to reduce the amount of $TiCl_4$ to a catalytic level without affecting the yield of **3**. The goal was reached with the acylals from the aromatic aldehydes; with these substrates the yield of the corresponding cyanohydrin esters did not drop significantly even when the amount of Lewis acid was reduced to 0.10 equiv. The consumption of the aliphatic acylals, on the other hand, dropped considerably when the amount of $TiCl_4$ was reduced below a 1:1 ratio.

Finally, it should be mentioned that treatment of acylals with KCN under phase-transfer conditions[14] also furnished cyanohydrin esters, but in most cases additional products were obtained. Acylals from aromatic aldehydes gave a 70−80% yield of the esters, sometimes with small amounts of the parent aldehyde being formed as well. Acylals derived from alkanals and alkenals generally afforded cyanohydrin esters in around 70% yield, but in these cases 10−20% of the corresponding cyanohydrins were also obtained. It is also noteworthy that both **2e** and **2n**, which afford the respective cyanohydrin esters (**3e** and **3n**) in 96% yield with TMSCN/$TiCl_4$ (Table 2, entries 5 and 14), are completely unreactive toward KCN under phase-transfer conditions.

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Supporting Information Available: Spectroscopic and spectrometric data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) **Treatment of 2 with trimethylsilyl cyanide in the presence of titanium(IV) chloride.** The acylals were reacted on a 3.5−5.0 mmol scale. In a typical experiment a 50 mL, nitrogen-filled round-bottom flask was charged with acylal in CH_2Cl_2 (5 mL) and trimethylsilyl cyanide (TMSCN) (1.10 equiv). The reaction mixture was cooled to −78 °C with a dry ice−acetone bath, and titanium(IV) chloride (1.10 equiv) was added with stirring. The mixture was allowed to reach room temperature and was stirred at this temperature for 2 h. H_2O (50 mL) was added, and the products were extracted with Et_2O (3 × 30 mL). The combined extracts were washed with H_2O (2 × 50 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. The crude products were subjected to further purification by flash chromatography if necessary.

(14) (a) Starks, C. M.; Liotta, C. *Phase Transfer Catalysis*; Academic Press: New York, 1978; Chapter 4.II, pp 94−112 (b) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*, 3rd ed.; VCH: Weinheim, Germany, 1993.