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ONE-POT SYNTHESIS OF α-CHLORONITRILES FROM ARYLCARBONYL COMPOUNDS

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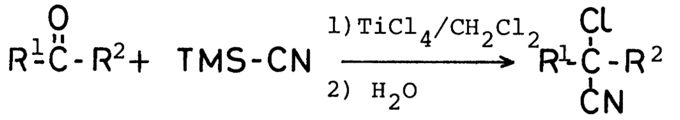
α-Chloronitriles are prepared by the reaction of arylcarbonyl compounds and trimethylsilyl cyanide with a stoichiometric amount of titanium tetrachloride in good yields.

Trimethylsilyl cyanide (TMS-CN) has been used to yield the corresponding cyanohydrin trimethylsilyl ether of carbonyl compound in the presence of a catalytic amount of Lewis acid, such as $AlCl_3$ and ZnI_2.[1)] Titanium tetrachloride ($TiCl_4$) is known to be a useful reagent for nucleophilic attack of silane derivatives on carbonyl groups.[2)] In the presence of a stoichiometric amount of $TiCl_4$, the reaction of titanium homoenolate from 1-ethoxy-1-trimethylsiloxycyclopropane with benzaldehyde was reported to give ethyl 4,4-chlorophenylbutyrate.[3)] The result suggests that the intermediate from homoenolate and aldehyde can be attacked by chloride. Then, the reaction of TMS-CN with aldehydes and ketones was attempted in the presence of a stoichiometric amount of $TiCl_4$ to carbonyl compound.

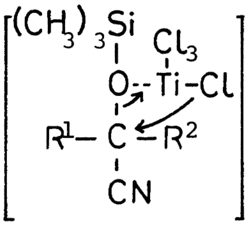
The reaction with alkylcarbonyl compounds gave only cyanohydrins. In the case of arylcarbonyl compounds, this reaction is available for the synthesis of α-chloronitriles, as shown in Table 1 (Eq. 1). The electron-releasing groups (p-OH and p-OMe) prevent the addition of TMS-CN under the standard conditions, described below (entries 4 and 11; 6 and 12). The electron-attracting groups (p-NO_2 Ph and CF_3) attached to carbonyl function reduce the attack of chloride and then give mainly the corresponding cyanohydrins.



$$R^1\overset{O}{\overset{\|}{C}}\text{-}R^2 + \text{TMS-CN} \xrightarrow[2)\ H_2O]{1)\ TiCl_4/CH_2Cl_2} R^1\text{-}\overset{Cl}{\underset{CN}{C}}\text{-}R^2 \qquad (1)$$

The reaction is considered to proceed through the following reaction pathway. A carbonyl compound activated with $TiCl_4$ reacts with TMS-CN to give the intermediate (1) or (2) which is converted to α-chloronitrile by fission of the C-O bond in the intermediate which has some carbocationic character.

1



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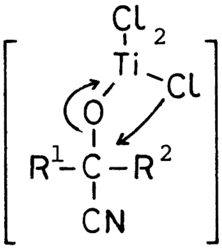

Table 1. Reactions of carbonyl compounds with TMS-CN in the presence of TiCl$_4$[4]

Entry	Carbonyl compds		Molar ratio[a] of TiCl$_4$	Conditions[b]	Isolated yield/% α-chloronitrile
	R^1	R^2			
1	Ph	H	1.2	24 h	85
2	p-Cl-Ph	H	1.2	24 h	90
3	p-Me-Ph	H	1.2	24 h	86
4	p-HO-Ph	H	1.2	24 h	no reaction
5	p-NO$_2$-Ph	H	1.2	24 h	78 (13)[c]
6	p-MeO-Ph	H	1.2	24 h	no reaction
7	p-MeO-Ph	H	1.2(TMS-CN 2.0)	5 h (reflux)	77
8	Ph	CH$_3$	1.2	24 h	34 (23)[c]
9	Ph	CH$_3$	1.2	8 h (reflux)	51 (14)[c]
10	Ph	CH$_3$	3.0	24 h	65
11	p-HO-Ph	CH$_3$	1.2	24 h	no reaction
12	p-MeO-Ph	CH$_3$	1.2	24 h	no reaction
13	p-MeO-Ph	CH$_3$	1.2	4 d	65
14	p-MeO-Ph	CH$_3$	1.2(TMS-CN 2.0)	5 h (reflux)	65
15	p-NO$_2$-Ph	CH$_3$	1.2	24 h	(45)[c]
16	p-Cl-Ph	CH$_3$	1.2	24 h	46 (32)[c]
17	p-Me-Ph	CH$_3$	1.2	24 h	48
18	Ph	CF$_3$	1.2	24 h	(78)[c]
19	P-MeO-Ph	CF$_3$	1.2	24 h	75
20	p-MeO-Ph	CF$_3$	catalytic amount	24 h	(26)[c]
21	Ph	Ph	1.2	24 h	61

a) Molar ratio to carbonyl compound (TMS-CN 1.0). b) Reaction was carried out at room temperature under nitrogen atmosphere. c) Yield of cyanohydrin.

A typical experimental procedure is as follows: titanium tetrachloride (0.24 mL, 2.38 mmol) was added dropwise to benzaldehyde (0.20 g, 1.98 mmol) in 5 mL of dry dichloromethane at 0 °C under nitrogen atmosphere. After 30 min, trimethylsilyl cyanide (0.30 mL, 1.98 mmol) was added at 0 °C and then the mixture was stirred for 24 h at room temperature. The reaction mixture was quenched with water and the organic layer was extracted with ether. The ether layer was washed with aq. NaHCO$_3$ solution and dried over MgSO$_4$. After evaporation of the solvent, the crude product was purified by silica-gel column chromatography to give pure α-chloronitrile.

References

1) D.A. Evans, J.M. Hoffman, and L.K. Truesdale, J. Am. Chem. Soc., 95, 5822 (1973); W. Lidy and W. Sundermeyer, Chem. Ber., 106, 587 (1973); P.G. Gassman and J.J. Talley, J. Am. Chem. Soc., 102, 4138 (1980); W.J. Greenlee and D.G. Hangauer, Tetrahedron Lett., 1983, 4559.
2) T. Mukaiyama, Angew. Chem., Int. Ed. Engl., 16, 817 (1977).
3) E. Nakamura and I. Kuwajima, J. Am. Chem. Soc., 105, 651 (1983).
4) All new compounds gave satisfactory ^{1}H-NMR, IR, and combution analyses.

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