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Cyano Group Transfer of Acetone Cyanohydrin to Aldehyde Mediated by Titanium Alkoxide and Aluminum Alkyls

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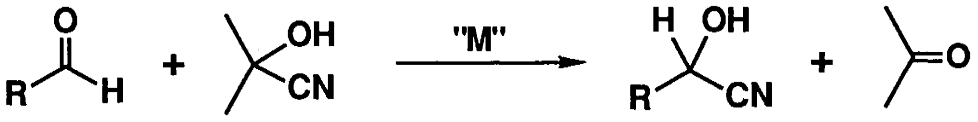
Cyano group transfer reaction of acetone cyanohydrin to various aldehydes in the presence of titanium alkoxide and aluminum alkyls to give the corresponding aldehyde cyanohydrins in high yield is described.

Synthesis of cyanohydrin by the reaction of hydrogen cyanide with carbonyl compound has been recognized important in organic synthesis since the reaction forms carbon-carbon bond and the resulting cyanohydrin can be transformed to various organic compounds.[1] On the other hand, acetone cyanohydrin which is known to act as a cyanating agent by transhydrocyanation in the presence of bases such as tertiary amines[2] and potassium carbonate[3] has also been widely employed as an alternative of hazardous and volatile hydrogen cyanide. Herein, cyano group transfer of acetone cyanohydrin to aldehydes mediated by titanium alkoxide and aluminum alkyls as novel reagents is described.

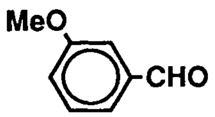
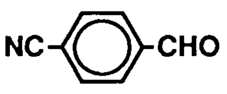
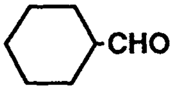


$$\text{"M"} = R_3Al \text{ or } Ti(OPr^i)_4$$

Results of the cyano group transfer of acetone cyanohydrin to aldehydes are summarized in Table 1. The reaction of acetone cyanohydrin with aldehyde was examined by various readily available metal alkoxides among which titanium (IV) isopropoxide was found to be effective to give the corresponding cyanohydrin along with the formation of acetone.[4] For example, the reaction of *m*-methoxybenzaldehyde in the presence of an equimolar amount of titanium (IV) isopropoxide with 3.0 equiv. of acetone cyanohydrin in methylene chloride afforded the corresponding cyanohydrin in 99% yield after stirring at room temperature for 19 h. The transfer was also feasible by using organoaluminum reagents such as trimethylaluminum and diisobutylaluminum hydride. The reaction of an aldehyde with the mixture of acetone cyanohydrin and organoaluminum compound at 0 °C similarly gave the aldehyde cyanohydrin in high yield. Neither alkylation nor reduction of aldehydes by aluminum reagents was observed as side reactions. It is remarkable that organoaluminum reagents were more reactive than titanium (IV) isopropoxide. Thus, the organoaluminum mediated transfer reactions were carried out at 0 °C (at room temperature for titanium reagent). Particularly, the reaction by diisobutylaluminum hydride was very fast, and even a catalytic amount (10 mol%) of the reagent induced the successful transfer. The transhydrocyanation by titanium alkoxide and aluminum alkyls are considered to proceed *via* the metal alkoxides of acetone cyanohydrin with which aldehyde constitutes a six-membered cyclic transition state to induce the cyano group transfer. The reactions to several aldehydes were examined in similar manners, and the corresponding cyanohydrins were obtained in excellent yield.

Cyano group transfer mediated by organometallic reagents is expected to be a powerful method for cyanohydrin synthesis with possibility of synthetic design toward various reactivities and selectivities. Further studies are in progress.

Table 1. Cyano Group Transfer Reactions of Acetone Cyanohydrin to Aldehydes in the Presence of Titanium Alkoxide and Aluminum Alkyls

Aldehyde	Reagent[a]		Temp/°C	Time/h	Yield/%[b]
	$Ti(OPr^i)_4$	(1.0)	rt	19	99
	Me_3Al	(1.5)	0	29	93
	Bu^i_2AlH	(1.5)	0	4	94
	Bu^i_2AlH	(0.1)	0	24	75
	$Ti(OPr^i)_4$	(1.0)	rt	52	77
	Bu^i_2AlH	(1.5)	0	4	97
$CH_3(CH_2)_9CHO$	$Ti(OPr^i)_4$	(1.0)	rt	21	>99
	Me_3Al	(1.5)	0	24	>99
	$Ti(OPr^i)_4$	(1.0)	rt	44	>99
	Bu^i_2AlH	(1.5)	0	4	>99

a) In parenthesis, amount of reagent based on aldehyde. For titanium (IV) isopropoxide, the reactions were carried out by using 3.0 equiv. of acetone cyanohydrin; for aluminum reagents, by using 1.5 equiv. of acetone cyanohydrin. b) Based on ^1H NMR analyses.

References

1) A. Mori, Y. Ikeda, K. Kinoshita, and S. Inoue, *Chem. Lett.*, **1989**, 2119; K. Tanaka, A. Mori, and S. Inoue, *J. Org. Chem.*, **55**, 181 (1990) and references cited therein.
2) Y. Kobayashi, H. Hayashi, K. Miyaji, and S. Inoue, *Chem. Lett.*, **1986**, 931.
3) I. N. Nazarov, A. A. Akhrem, and A. V. Kamernitskii, *Zh. Obshch. Khim.*, **25**, 1345 (1955).
4) $B(OPr^i)_3$ and $Al(OPr^i)_3$ were less effective.

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