Communications to the Editor

A Novel Conjugate Hydrocyanation with $TiCl_4$–*tert*-Butyl Isocyanide

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Received May 24, 1982

Conjugate hydrocyanation of α,β-unsaturated carbonyl compounds is one of the fundamental and traditional methodologies for carbon–carbon bond formation, which has been extensively studied and utilized.[1] The discovery by Nagata and co-workers[1] of the organoaluminum-promoted hydrocyanation has made the methodology more useful and applicable in modern organic synthesis. A new development of conjugate hydrocyanation with cyanotrimethylsilane has been also reported recently.[2]

In a preceding paper,[3] we described an organoaluminum-promoted cycloaddition of isocyanide to α,β-unsaturated carbonyl compounds to produce unsaturated N-substituted iminolactones (**4**, Scheme I), which could be stereoselectively converted to γ-butyrolactones. It was now found that use of $TiCl_4$ in place of diethylaluminum chloride caused a dramatic change in the reaction of α,β-unsaturated ketones with *tert*-butyl isocyanide, resulting in the formation of the conjugate hydrocyanation product **3**.

The novel reaction is illustrated by the preparation of 10-cyanooctalin-3-one (**3g**). To a stirred solution of 1.05 g (5.5 mmol) of $TiCl_4$ in 10 mL of methylene chloride were added at once at 0 °C 0.75 g (5.0 mmol) of $\Delta^{4,10}$-octalin-3-one (**1g**) and then a solution of 0.46 g (5.5 mmol) of *tert*-butyl isocyanide in 10 mL of methylene chloride. After stirring at 0 °C overnight, the reaction mixture was poured into aqueous Na_2CO_3 and extracted with ether. The ether extract was subjected to distillation to give a 9:1 mixture of *trans*- and *cis*-10-cyano-octalin-3-one (**3g**), which were identified by comparison of IR and NMR spectra and gas chromatography retention times with those of authentic samples.[4] The ratio of *trans*- to *cis*-10-cyano-octalin-3-one (**3g**), which is comparable to that of the hydrocyanation of **1g** with $HCN–AlEt_3$,[4] was not altered by prolonging reaction times. Moreover, each stereoisomer of **3g** isolated was not isomerized under the reaction conditions (0 °C to room temperature, 40 h).

Some conjugate hydrocyanations of α,β-unsaturated ketones with the $TiCl_4$–*tert*-butyl isocyanide system are summarized in Table I. The hydrocyanation with $TiCl_4$–*tert*-butyl isocyanide was most successfully performed in methylene chloride at 0 °C and was sometimes accompanied by side reactions at temperatures higher than room temperature. For instance, treatment of pulegone (**1b**), which has *s*-cis configuration, with $TiCl_4$ and *tert*-butyl isocyanide in refluxing methylene chloride produced the desired **3b** (60%) together with the cycloadduct (15%) corresponding to **4**.[3]

The present conjugate hydrocyanation, which is kinetically controlled, may be explained in terms of nucleophilic β addition of *tert*-butyl isocyanide onto the activated enone **5** (Scheme II), which is formed by coordination of $TiCl_4$ to the α,β-unsaturated ketone **1**. The resultant *N*-*tert*-butylimidoyl cation intermediate **6** may rapidly undergo β elimination to give β-cyano enolate **7** and *tert*-butyl cation, which then gives proton with isobutene. The β-cyano enolate **7** thus generated is irreversibly transformed by protolysis to afford β-cyano ketone **3**.

In this hydrocyanation, *tert*-butyl isocyanide may be regarded to function as a masked hydrogen cyanide. It has been known that *tert*-butyl isocyanide, which is most conveniently available by dehydration of *N*-*tert*-butylformamide,[5] can be also prepared from isobutene and hydrogen cyanide.[6]

Scheme I

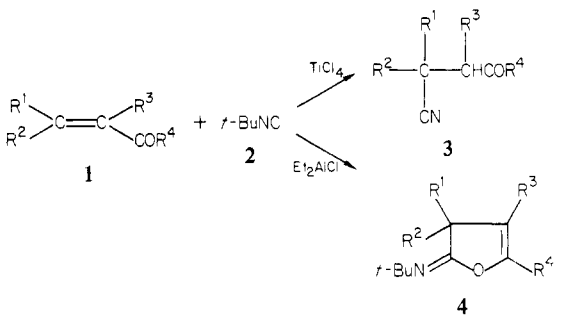
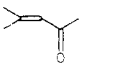
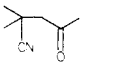
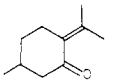
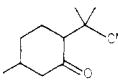
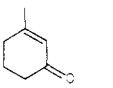
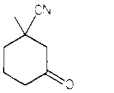
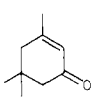
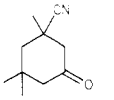
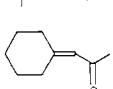
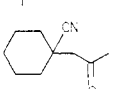
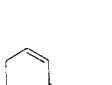
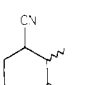
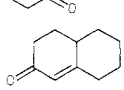
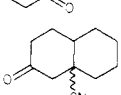
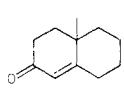
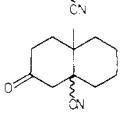


Table I. Conjugate Hydrocyanation with $TiCl_4$–*tert*-Butyl Isocyanide[a]

α,β-unsaturated ketones		hydrocyanation products (%)[b,c]	
	1a		3a (80)
	1b		3b (87)
	1c		3c (84)
	1d		3d (63)
	1e		3e (85)
	1f		3f (84)[d]
	1g		3g (85)[e]
	1h		3h (82)[f]

[a] The conjugate hydrocyanation was carried out at 0 °C in methylene chloride. [b] Isolated yields. [c] Identities of the hydrocyanation products were established by comparison of IR and NMR spectra with those of authentic samples prepared by the reported procedures.[1] [d] A 6:4 mixture of stereoisomers. [e] A 9:1 mixture of trans and cis isomers.[4] [f] A 7:3 mixture of trans and cis isomers.[4]

(1) Nagata, W.; Yoshioka, M. "Organic Reactions"; Wiley: 1979; Vol. 25, pp 256–476.
(2) Utimoto, K.; Obayashi, M.; Shishiyama, Y.; Inoue, M.; Nozaki, H., *Tetrahedron Lett.* **1978**, 3389.
(3) Ito, Y.; Kato, H.; Saegusa, T. *J. Org. Chem.* **1982**, *47*, 741.
(4) Nagata, W.; Yoshioka, M.; Terasawa, T. *J. Am. Chem. Soc.* **1972**, *94*, 4672.
(5) Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. "Newer Methods of Preparative Organic Chemistry"; Verlag Chemie: 1966; Vol. IV, pp 37–63.
(6) Otsuka, S.; Mori, K.; Yamagami, K. *J. Org. Chem.* **1966**, *31*, 4170.

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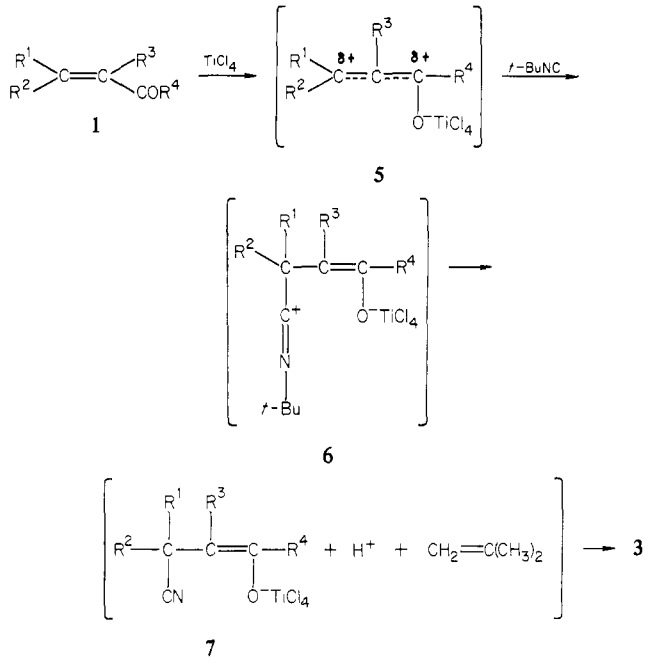
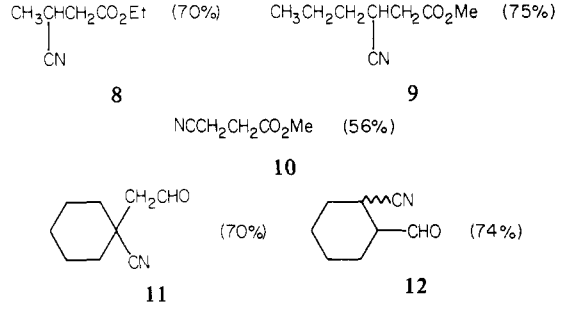
Scheme II



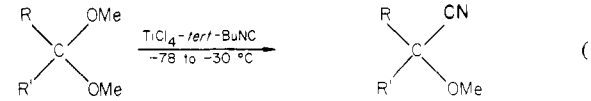
The successful hydrocyanation with *tert*-butyl isocyanide may lend support to the proposal that the corresponding metal isocyanide in equilibrium with metal cyanide might be the true cyanating agent for the hydrocyanation with organoaluminum cyanide[1,7] and cyanotrimethylsilane.[2,8]

Conjugate hydrocyanations of α,β-unsaturated aldehydes and esters, which were not satisfactory by means of the $TiCl_4$–*tert*-butyl isocyanide, were achieved[9] in moderate yields by the ethylaluminum dichloride–*tert*-butyl isocyanide system and by the aluminum trichloride–*tert*-butyl isocyanide system, respectively, as shown, e.g., by **8–12**. However, the conjugate hydrocyanations



of α,β-unsaturated aldehydes such as crotonaldehyde and 2-hexenal were accompanied by product mixtures, which may be due to the competing 1,2-addition of *tert*-butyl isocyanide to the aldehyde carbonyl.

In conjunction with the 1,2-addition of *tert*-butyl isocyanide to the carbonyl group, we recently found that the $TiCl_4$–*tert*-butyl isocyanide system is able to serve as a mild cyanation agent of ketal and acetal (see eq 1). The conjugate hydrocyanation of



(1)

R = R′ = $-(CH_2)_5-$ (~100%)
R = Ph; R′ = H (~100%)

α,β-unsaturated ketones in this study is very unique and useful because of the high yield and the mild conditions in addition to not needing dangerous cyanide sources.

Registry No. 1a, 141-79-7; **1b**, 15932-80-6; **1c**, 1193-18-6; **1d**, 78-59-1; **1e**, 874-68-0; **1f**, 930-68-7; **1g**, 1196-55-0; **1h**, 4087-39-2; **2**, 7188-38-7; **3a**, 33235-13-1; **3b**, 83268-53-5; **3c**, 33235-14-2; **3d**, 7027-11-4; **3e**, 83268-54-6; *cis*-**3f**, 83268-55-7; *trans*-**3f**, 83268-56-8; *cis*-**3g**, 200-83-1; *trans*-**3g**, 3954-08-3; *cis*-**3h**, 880-38-6; *trans*-**3h**, 943-95-3; **8**, 22584-00-5; **9**, 83268-58-0; **10**, 4107-62-4; **11**, 29940-82-7; **12**, 83268-59-1; $TiCl_4$, 7550-45-0; 1,1-dimethoxycyclohexane, 933-40-4; benzaldehyde dimethyl acetal, 1125-88-8; 1-methoxy-1-cyclohexanecarbonitrile, 83268-57-9; α-methoxybenzeneacetonitrile, 13031-13-5; ethyl crotonate, 2396-77-2; methyl acrylate, 96-33-3; cyclohexylideneacetaldehyde, 1713-63-9; 1-cyclohexene-1-carboxaldehyde, 1192-88-7; aluminum trichloride, 7446-70-0; ethylaluminum dichloride, 563-43-9.

$[Fe_3O(OCOR)_6L_3]^+$-Catalyzed Epoxidation of Olefinic Alcohol Acetates by Molecular Oxygen†

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Selective monooxygenation of complicated olefins by molecular oxygen to yield epoxides is one of the crucial problems in connection with studies on both biological processes[1] and organic synthesis. Many kinds of transition metals are well-known to catalyze the epoxidation of olefins with hydroperoxides.[2] Little is known, however, about efficient catalytic epoxidation by molecular oxygen except for that of simple olefins such as ethylene.[3]

A plausible mechanism for the silver-catalyzed epoxidation of ethylene includes the participation of at least two metal atoms in the activation of an oxygen molecule.[6] In addition, the oxygenase tyrosinase has recently been found to possess a binuclear metal-active site.[7] These facts suggested to us the use of polynuclear transition-metal complexes as catalysts for the epoxidation of olefins by molecular oxygen.

To attain this purpose, we selected (μ_3-oxo)triiron cluster complexes as catalysts, since a ruthenium analogue, $[Ru_3O(OAc)_6(H_2O)_3]^+$, is capable of reversibly binding the central triply bridging oxygen atom.[8] The characteristic features of the epoxidation of olefins by molecular oxygen with the (μ_3-oxo)triiron

(7) Nagata, W. *Proc. R. A. Welch Foundation on Chem. Res., XVII*, **1973**, 185.

(8) (a) Evans, D. A.; Hoffmann, J. M.; Truesdale, L. K. *J. Am. Chem. Soc.* **1973**, *95*, 5822. (b) Utimoto, K.; Horiie, T. *Tetrahedron Lett.* **1982**, 237.

(9) Conjugate hydrocyanations of α,β-unsaturated aldehyde and ester were carried out by slowly adding a solution of *tert*-butyl isocyanide (2 mmol) in methylene chloride (6 mL) to a solution of aldehyde (1 mmol)–$EtAlCl_2$ (1 mmol) or ester (1 mmol)–$AlCl_3$ (1 mmol) in methylene chloride (3 mL) at room temperature over 7 h. **9**: IR (neat) 2242, 1738 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 0.92 (t, 3 H), 1.25–1.67 (m, 4 H), 2.38–2.59 (m, 2 H), 2.62–3.03 (m, 1 H), 3.56 (s, 3 H). **11** (bp 72 °C (0.5 mmHg)): IR (neat) 2226, 1728 cm^{-1}; NMR ($CDCl_3$) δ 0.75–2.38 (m, 10 H), 2.50 (d, 2 H, J = 2.6 Hz), 9.78 (t, 1 H, J = 2.6 Hz). **12** (bp 64 °C (0.5 mmHg)): IR (neat) 2244, 1728 cm^{-1}; NMR ($CDCl_3$) δ 0.75–3.28 (m, 10 H), 9.57 and 9.58 (two s, 1 H).

† Dedicated to Emeritus Professor Takeo Sakan on the occasion of his 70th birthday.

(1) For a review, see: Hamberg, M.; Samuelsson, B.; Björkhem, I.; Danielsson, H. In "Molecular Mechanisms of Oxygen Activation"; Hayaishi, O., Ed.; Academic Press: New York, 1974; Chapter 2.

(2) For reviews, see: (a) Hiatt, R. In "Oxidation"; Augustine, R. L., Trecker, D. J., Eds.; Marcel Dekker: New York, 1971; Vol. 2, Chapter 3. (b) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.

(3) For a review, see: Mayo, F. R. *Acc. Chem. Res.* **1968**, *1*, 193. Metal-catalyzed epoxidation of cyclohexene[4] and styrene[5] by molecular oxygen have been reported, but the efficiency of the catalyst and selectivity of the reaction are low.

(4) (a) Lyons, J. E. *Tetrahedron Lett.* **1974**, 2737. (b) Tabushi, I.; Yazaki, A. *J. Am. Chem. Soc.* **1981**, *103*, 7371.

(5) (a) Takao, K.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1153. (b) Collman, J. P.; Kubota, M.; Hosking, J. W. *J. Am. Chem. Soc.* **1967**, *89*, 4809.

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