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Communications to the Editor

A Novel Conjugate Hydrocyanation with TiCl$_4$–*tert*-Butyl Isocyanide

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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$_2$CO$_3$ 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

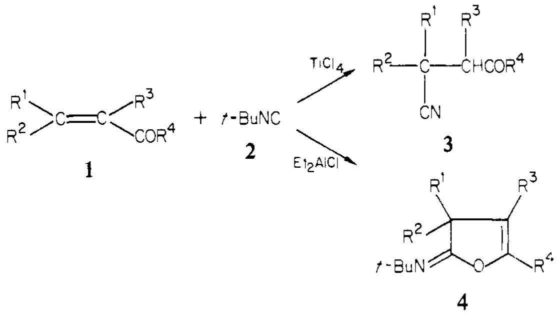
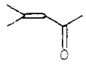
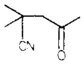
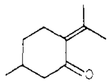
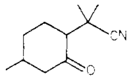
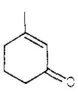
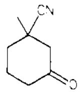
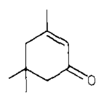
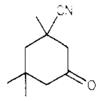
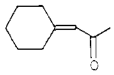
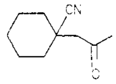
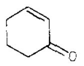
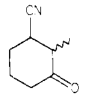
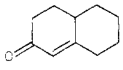
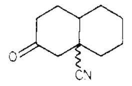
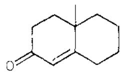
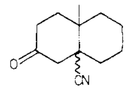


Table I. Conjugate Hydrocyanation with TiCl$_4$-*tert*-Butyl Isocyanide[a]

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]

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(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.

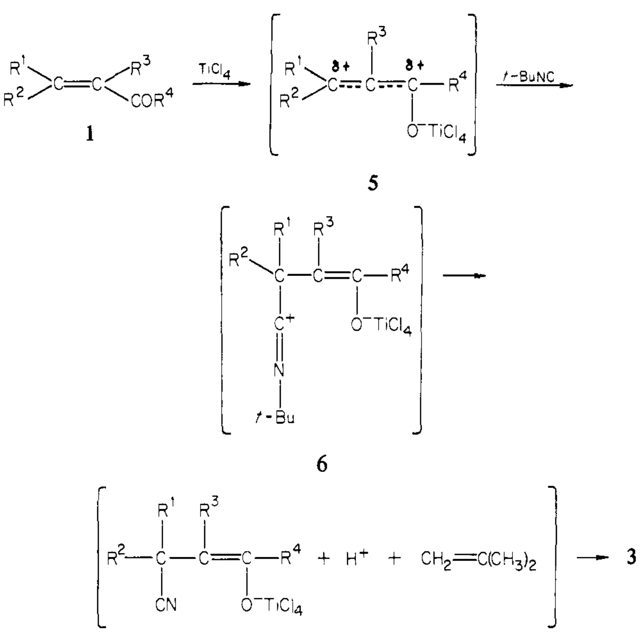
(4) Nagata, W.; Yoshioka, M.; Terasawa, T. *J. Am. Chem. Soc.* **1972**, *94*, 4672.

(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.

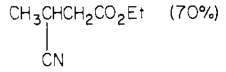
0002-7863/82/1504-6449$01.25/0

Scheme II



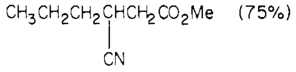
The successful hydrocyanation with *tert*-butyl isocyanide may lend support to the proposal that the corresponding metal isocyanide in equilibrium with metal cyanide might be the true cyanating agent for the hydrocyanation with organoaluminum cyanide[1,7] and cyanotrimethylsilane.[2,8]

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.



$CH_3CH(CN)CH_2CO_2Et$ (70%)

8

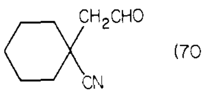


$CH_3CH_2CH_2CH(CN)CH_2CO_2Me$ (75%)

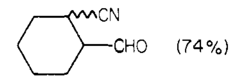
9

$NCCH_2CH_2CO_2Me$ (56%)

10

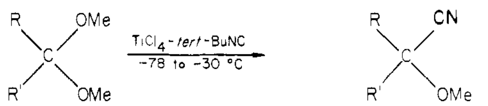


11



12

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 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.



(1)

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

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.

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(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).

$[Fe_3O(OCOR)_6L_3]^+$-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

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[†] 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.

(6) (a) Pokrovskii, V. A. *Usp. Khim.* **1956**, *25*, 1446. (b) Twigg, *G. H. Proc. R. Soc. London* **1946**, *92*, 105; (c) *Trans. Faraday Soc.* **1946**, *42*, 284, 657.

(7) Winkler, M. E.; Lerch, K.; Solomon, E. I. *J. Am. Chem. Soc.* **1981**, *103*, 7001.

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