CHEMISTRY LETTERS, pp. 937 - 940, 1984.

CYANATION OF ACETALS WITH t-BUTYL ISOCYANIDE—$TiCl_4$ SYSTEM

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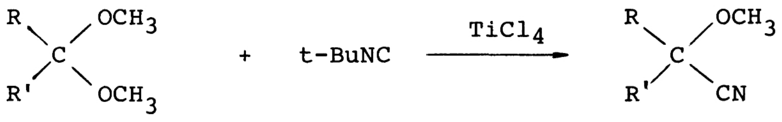
Cyanation of acetals was achieved by t-butyl isocyanide in the presence of $TiCl_4$, producing cyanohydrin ethers in good yields. β-(Trimethylsilyl)ethyl isocyanide in the combination with $TiCl_4$ effected the cyanation as well.

Cyantion is an important synthetic reaction which introduces one carbon unit into the substrate. Methods utilizing metal cyanides such as diethylaluminum cyanide[1)] and trimethylsilyl cyanide[2)] have been developed for cyanation reactions. Recently, we reported a novel conjugate hydrocyanation of α,β-unsaturated ketones with t-butyl isocyanide in combination with $TiCl_4$.[3)] The equivalency of t-butyl isocyanide to HCN in the cyanation reaction is not only mechanistically interesting but also practically useful.

Now we wish to describe here a new cyanation of acetals with the t-butyl isocyanide—$TiCl_4$ system.

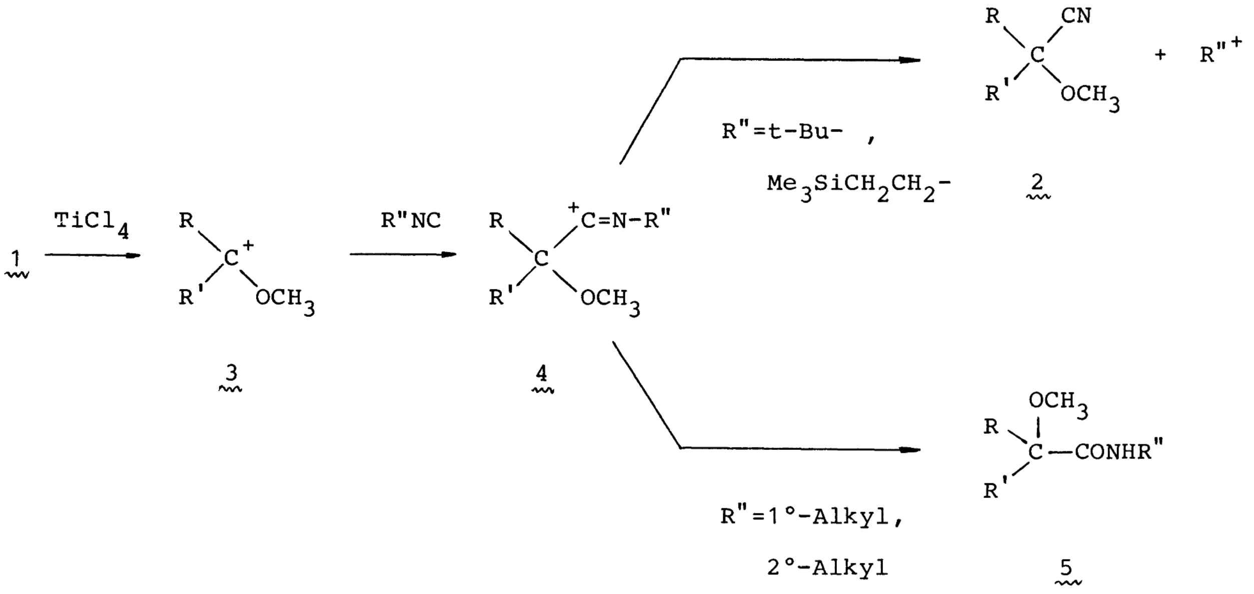


1 2

The procedure of cyanation with t-butyl isocyanide—$TiCl_4$ system is quite simple, which is carried out as follows. To a stirred solution of 288 mg (2 mmol) of cyclohexanone dimethyl acetal and 0.22 mL (2 mmol) of $TiCl_4$ in 6 mL of methylene chloride, 166 mg (2 mmol) of t-butyl isocyanide was dropwise added at -70 °C, and then allowed to warm up to 20 °C over 2-3 h, and finally quenched with aqueous

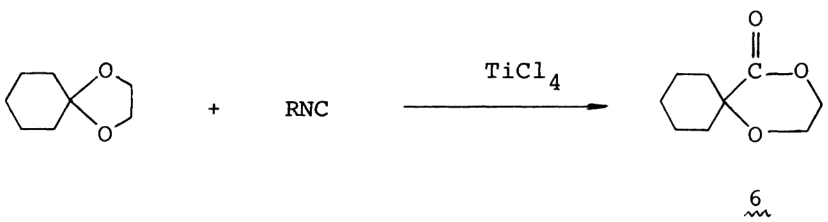
$NaHCO_3$. Extractive workup with methylene chloride followed by Kugel Rohr distillation afforded cyclohexanone cyanohydrin methyl ether (92% yield). Some results of cyanation of acetals are summarized in Table 1.

Use of primary and secondary alkyl isocyanides instead of t-butyl isocyanide in the present reaction did not afford cyanohydrin ether 2, but it gave N-alkyl α-alkoxycarboxamide 5 as already reported by Mukaiyama.4) However, β-(trimethylsilyl)ethyl isocyanide5) in combination with $TiCl_4$ effectuated the cyanation of acetal as well. These findings are consistent with the following mechanism involving N-substituted imidoyl cation intermediate 4, followed by β-elimination.



It is conceivable that the so-called β-effect of silicon6) facilitates the elimination of β-(trimethylsilyl)ethyl carbonium ion from intermediate 4.

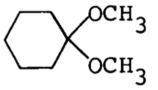
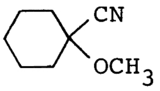
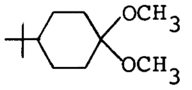
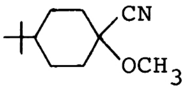
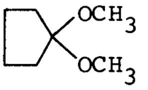
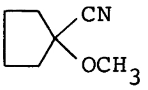
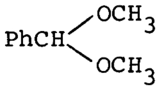
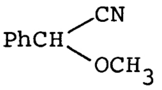
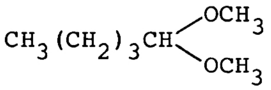
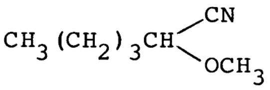
The reaction of ethylene acetals with t-butyl isocyanide or β-(trimethylsilyl) ethyl isocyanide in the presence of $TiCl_4$ gave spiro-lactones7,8) in high yields, after aqueous workup.



R = t-Bu 82%

R = $Me_3SiCH_2CH_2$ 75%

Table 1. A Cyanation of Acetals with Isonitrile-$TiCl_4$ System

Acetal	Isonitrile	Cyanohydrin ether	(Yield/%)
	t-BuNC		(92)
	$Me_3SiCH_2CH_2NC$[a]		(88)
	t-BuNC		(95)[b]
	$Me_3SiCH_2CH_2NC$[a]		(90)[c]
	t-BuNC		(86)
 $PhCH(OCH_3)_2$	t-BuNC	 $PhCH(CN)OCH_3$	(96)
 $CH_3(CH_2)_3CH(OCH_3)_2$	t-BuNC	 $CH_3(CH_2)_3CH(CN)OCH_3$	(81)
	$Me_3SiCH_2CH_2NC$[a]		(82)

a) Cyanation with $Me_3SiCH_2CH_2NC$ was performed by stirring the reaction mixture at -78 °C to room temperature over 6 h.

b) Axial cyanide : Equatorial cyanide = 73 : 27[2c] c) Axial cyanide : Equtorial cyanide = 69 : 31[2c]

This work was supported by the Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture.

References

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2) a) D. A. Evans, L. K. Truesdale, and G. L. Carroll, J. Chem. Soc., Chem. Commun., 1973, 55.

b) K. Utimoto, M. Obayashi, Y. Shishiyama, M. Inoue, and H. Nozaki, Tetrahedron Lett., 1978, 3389.

c) R. Noyori, S. Murata, and M. Suzuki, Tetrahedron, 37, 3899 (1981).

3) Y. Ito, H. Kato, H. Imai, and T. Saegusa, J. Am. Chem. Soc., 104, 6449 (1982).

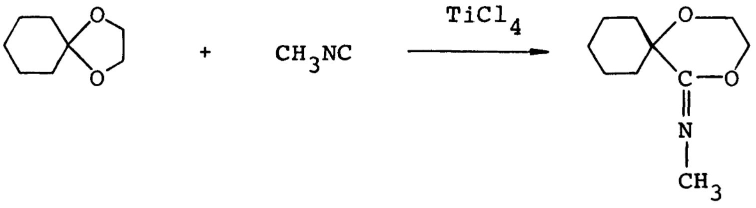
4) T. Mukaiyama, K. Watanabe, and M. Shiono, Chem. Lett., 1974, 1457.

5) β-(Trimethylsilyl)ethyl isocyanide was prepared by a reaction of α-lithiomethyl isocyanide with trimethylsilylmethyl chloride. [IR(neat) 2150, 1250, 840 cm^{-1}; NMR ($CDCl_3$) δ 0.07 (s, 9H), 1.02 (tt, 2H), 3.39 (tt, 2H)]

6) E. W. Colvin, "Silicon in Organic Synthesis," Butterworths (1981), pp. 15 - 20.

7) **6** : IR (neat) 1735, 1105 cm^{-1}; NMR ($CKCl_3$) δ 0.8 - 2.2 (m, 10H), 3.44 (t, 2H), 4.11 (t, 2H)

8) Reaction of cyclohexanone ethylene acetal with methyl isocyanide—$TiCl_4$ system afforded spiro-N-methyliminolactone (**7**). **7** : IR (neat) 1680, 1105 cm^{-1}; NMR ($CDCl_3$) δ 1.0 - 2.0 (m, 10H), 2.75 (s, 3H), 3.6 - 4.2 (A_2B_2 m, 4H).



7 45%

(Received March 30, 1984)