A Comparative Investigation of the Reactions of α-Metallomethyl Isocyanides with α,β-Unsaturated Ketones

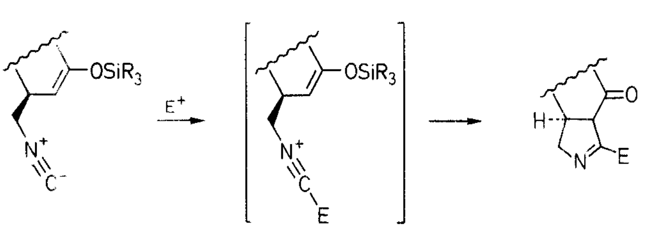
Mark Westling, Tom Livinghouse*

Department of Chemistry, University of Minnesota, Minneapolis, MN 55455, U.S.A.

The nucleophilic addition of lithiomethyl isocyanide to representative α,β-unsaturated ketones has been examined. The ratio of 1,2- to 1,4-addition is dependent upon the inclusion of ligating cosolvents. In addition, the reactions of alternative α-metallomethyl isocyanides with α,β-unsaturated ketones have been studied.

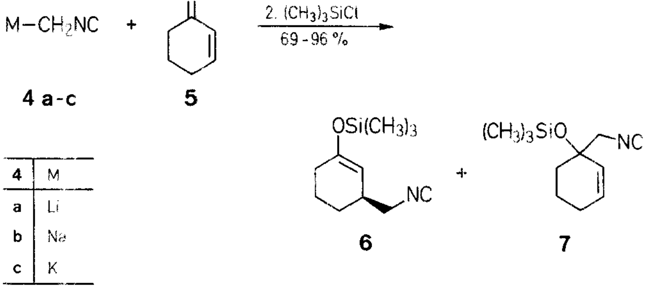
Subsequent to the discovery that alkyl isocyanides could be lithiated, numerous accounts concerned with the behavior of these species towards carbon electrophiles have appeared.[1] The vast majority of these investigations have focused on the reactions of lithiated isocyanides with substrates (e.g., simple carbonyl compounds, imines, and halides) for which the regiochemistry of addition is not a factor.[2] In this communication we wish to describe the first study of the 1,4- and 1,2-addition reactions between a variety of α-metallomethyl isocyanides and α,β-unsaturated ketones.[3]

Our interest in this transformation was stimulated by the possibility that the silylated 1,4-adducts (e.g., **1**) could be cyclized to highly functionalized Δ′-pyrrolines (e.g., **3**) upon treatment with suitable electrophiles.



1 **3**

The reaction of lithiomethyl isocyanide (**4a**) with a typical α,β-unsaturated ketone was initially examined as described below. Lithiation of methyl isocyanide (with *n*-butyllithium in tetrahydrofuran furnished a suspension of lithiomethyl isocyanide (**4a**). Sequential treatment of this mixture with 2-cyclohexen-1-one (**5**) followed by chlorotrimethylsilane afforded a 47:53[4] mixture of the isocyanides, **6** and **7**, in 96% yield.[5] Analogous treatment of lithiomethyl isocyanide (**4a**) with **5** at −40 °C, followed by silylation was found to provide the isocyanides **6** and **7**, in a 39:61 ratio.



4a-c **5** **6** **7**

4	M
a	Li
b	Na
c	K

The effects of additives and cosolvents on the course of the nucleophilic addition of **4a** to **5** at −78 °C was then examined. In general, the introduction of ligating additives was found to moderately increase the relative proportion of **6** arising from 1,4-addition of **4a** to the enone. A compilation of these data is presented in Table 1.

Table 1. Effect of Additives on the Formation of Products **6** and **7**

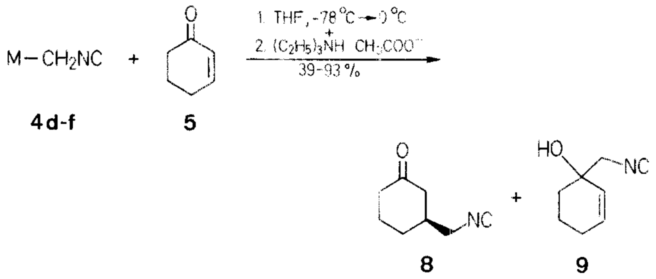
Additive[a]	Ratio of Additive/**4a**	Percentage Ratio of **6**:**7**
TMEDA	3.0	59 : 41
HMPA	3.0	71 : 29
12-Crown-4	1.5	58 : 42

[a] All reactions were conducted at −78 °C for 2 h using 1 equivalent of **4a** to 0.66 equivalent of **5**.

The possibility that the lithiated adducts resulting from competing 1,2- and 1,4-addition of **4a** to **5** were interconvertable was eliminated by the following study. Protonation of the reaction mixture formed by treatment of **4a** with **5** (triethylammonium acetate, tetrahydrofuran, −35 °C) provided a mixture of the adducts **8** and **9** (91% combined yield). Exposure of the purified alcohol to either *n*-butyllithium of lithium diisopropylamide under a variety of experimental conditions and subsequent silylation afforded the adduct **7**, as the exclusive product (95%–100% yield). Similarly, treatment of the ketone **8**, with lithium diisopropylamide (−78 °C) followed by silylation furnished a mixture of the two possible silyl enol ethers and no detectable quantity of **7**.

In light of the cosolvent effects mentioned previously, an effort was made to determine the influence of the electropositive counterions, Na^+ and K^+, on the mode selectivity of addition. Unfortunately, attempts to generate the α-metallomethyl isocyanides, **4b** and **4c**, by the deprotonation of methyl isocyanide using the sodium attempts potassium derivatives of either hexamethyldisilazane or triphenylmethane were unsuccessful.[6] Surprisingly, the use of potassium diisopropylamide-lithium *t*-butoxide (KDA)[7] for the deprotonation of methyl isocyanide (tetrahydrofuran, −78 °C) generated an α-metalloisocyanide (e.g., **4c** or an alkoxide ligated **4a**) which afforded **7** as the predominant product upon reaction with **5** and subsequent silylation (**6**/**7** = 16:84, 69% yield).

The propensity of organolithium reagents to form a variety of mixed "metallate" complexes has been widely recognized. It was anticipated that the modification of lithiomethyl isocyanide (**4a**) in this manner would alter its reaction profile with 2-cyclohexenone (**5**). Accordingly, treatment of lithiomethyl isocyanide (**4a**) with titanium isopropoxide (1 equiv) in tetrahydrofuran and subsequent exposure of the resultant organometallic **4d** to **5** (1 equiv,, −78 °C → 0 °C) followed by protonation (triethylammonium acetate)[8] afforded the adducts **8** and **9** in a 55:45 ratio. In contrast to this observation, treatment of **5** with the aluminum "ate" complex, **4e**, furnished the alcohol, **9**, as the exclusive product (39% yield) while analogous exposure of **5** to the cuprate, **4f** (−78 °C → 0 °C) produced neither of the anticipated products.



4d-f **5** **8** **9**

A clearer indication of the regioselectivity associated with the addition of lithiomethyl isocyanide (**4a**) to representative α,β-unsaturated ketones was provided by the following experiments.

Downloaded by: University of Illinois at Chicago. Copyrighted material.

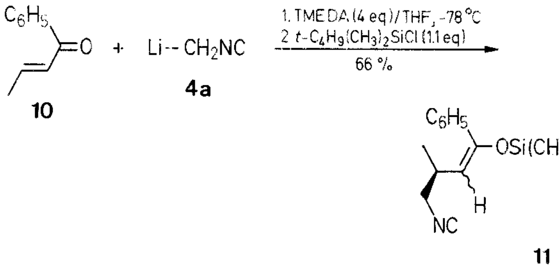
Table 2. Effect of Organometallics on the Formation of Products **8** and **9**

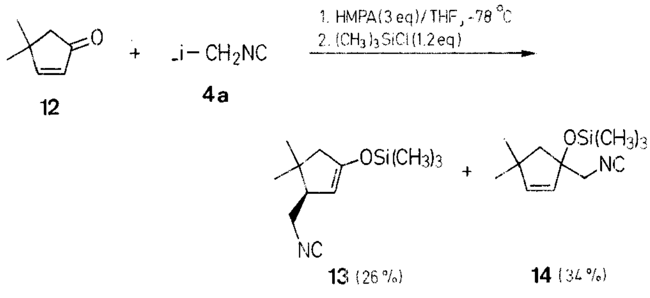
Organo-metallic Additive	M	Ratio of **4**/**5**	Percentage Ratio of **8**:**9**	Yield (%)
4d	$Ti(OC_3H_7\text{-}i)^-$	1.0	55 : 45	93
4e	$Al(CH_3)_3^-$	1.0	0 : 100	39[a]
4f	$CuSC_6H_5^-$	1.0	–	0[b]

[a] In addition, 61% of the starting enone was recovered.

[b] Approximately 25% of 3-thiophenoxycyclohexanone was isolated.

Treatment of 1-phenylbut-2-en-1-one **(10)** with **4a** in the presence of 4 equivalents of tetramethylethylenediamine (tetrahydrofuran, –78 °C) followed by *t*-butyldimethylchlorosilane (1.1 equiv) afforded the isonitriles **11** as the exclusive adducts in 66 % yield. Exposure of 4,4-dimethylcyclopent-2-en-1-one **(12)** to 1.1 equivalents of **4a** (3 equiv hexamethylphosphoramide, tetrahydrofuran, – 78 °C) followed by silylation with chlorotrimethylsilane, (1.2 equiv) furnished the silylenol ether **13** and the corresponding 1,2-adduct **14** (**13**/**14** = 43 : 57) in 64 % yield. The relatively inefficient formation of the 1,4 adduct **13** in this instance can be attributed to the sterically congested β-carbon of the precursor enone **(12)**.





A detailed investigation of the electrophile initiated cyclization reactions of the isocyanosilyl enol ethers described above is currently underway. The synthesis of functionalized Δ'-pyrrolines *via* this expedient will be reported in due course.

1-(3-Trimethylsilyloxycyclohex-2-en-1-yl)methyl Isocyanide (6); Typical Procedure:

A 50 ml, three-necked flask equipped with a magnetic stirring bar, thermometer, low temperature addition funnel, and nitrogen inlet is charged with 2.8 molar *n*-butyllithium in hexane (3.36 ml, 9.4 mmol) and dry tetrahydrofuran (20 ml). The mixture is cooled to – 78 °C and a solution of methyl isocyanide (0.48 ml, 9 mmol) in dry tetrahydrofuran (10 ml) is added dropwise via the addition funnel so that the temperature does not exceed – 60 °C. After completion of the addition, the resultant white suspension is stirred for an additional 10 min at – 78 °C. A solution of hexamethylphosphoramide (4.83 g, 27 mmol) in tetrahydrofuran (5 ml) followed by a solution of cyclohex-2-en-1-one (0.58 ml, 6 mmol) in tetrahydrofuran (10 ml) are then added dropwise at – 78 °C. After stirring for an additional 2 h at – 78 °C, the mixture is treated with triethylamine (2.50 ml, 18 mmol) followed by chlorotrimethylsilane (2.28 ml, 18 mmol) at – 78 °C and then allowed to warm to room temperature. The mixture is concentrated under reduced pressure, diluted with ether/pentane (1 : 1, 20 ml) and filtered. The solvent is evaporated from the filtrate *in vacuo* and the residue is purified by bulb to bulb distillation to give the pure mixture of 1,2- and 1,4-adducts; yield: 1.15 g (92 %); oven temp. 60 °C/0.30 mbar. Chromatography on Florisil (50 % ethyl acetate hexane) furnished the silylenol ether **6** as a colorless liquid after a forerun; yield: 803 mg (64 %) containing 326 mg (26 %) of the 1,2-adduct **7**.

6:

$C_{11}H_{19}NOSi$	calc.	C 63.10	H 9.15
(209.2)	found	62.96	8.99

IR (Film): ν = 2950 (br), 2150, 1640 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 0.13 (s, 9 H); 1.31 (m, 1 H); 1.61 (m, 1 H); 1.78 (m, 2 H); 2.01 (m, 2 H); 2.53 (m, 1 H); 3.25 (dt, 2 H, *J* = 6.7, 1.6 Hz); 4.73 ppm (apparent t, 1 H, *J* = 1.4 Hz).

Table 3. Addition of Lithiomethyl Isocyanide to α,β-Unsaturated Ketones

Product	Yield[a] (%)	b.p. °C/mbar	Molecular Formula[b]	IR (Film)[c] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$)[d] δ (ppm)
8	43	50/0.50	$C_8H_{11}NO$ (137.2)	2910 (br), 2150, 1715	1.63 (m, 2H); 2.29 (m, 7H); 3.37 (m, 2H)
9	48	50/0.50	$C_8H_{11}NO$ (137.2)	3585 (br), 2150, 2925 (br)	1.73 (m, 4H); 1.99 (s, 1H); 2.06 (m, 2H); 3.39 (d with fine structure, 1H, *J* = 14.6 Hz); 3.45 (d with fine structure, 1H, *J* = 14.6 Hz); 5.67 (d, 1H, *J* = 10.1 Hz); 6.00 (dt, 1H, *J* = 10.1, 4.3 Hz)
11	66	100/0.15	$C_{18}H_{27}NOSi$ (301.5)	2965 (br), 2150, 1645	–0.08 (s, 3H); –0.04 (s, 3H); 0.97 (s, 9H); 1.19 (d, 3H, *J* = 6.8 Hz); 3.06 (m, 1H); 3.31 (dd with fine structure, 1H, *J* = 14.4, 5.1 Hz); 3.43 (dd with fine structure, 1H, *J* = 14.4, 5.1 Hz); 4.88 (d, 1H, *J* = 9.1 Hz); 7.28 (m, 3H); 7.41 (m, 2H)
13	26	60/0.30	$C_{12}H_{21}NOSi$ (223.4)	2900 (br), 2150, 1645	0.16 (s, 9H); 1.04 (s, 3H); 1.16 (s, 3H); 2.06 (dt, 1H, *J* = 15.9, 1.5 Hz); 2.21 (dt, 1H, *J* = 15.9, 1.5 Hz); 2.47 (m, 1H); 3.22 (ddt, 1H, *J* = 14.5, 7.2, 1.8 Hz); 3.34 (ddt, 1H, *J* = 14.5, 7.2, 1.8 Hz); 4.55 (d, 1H, *J* = 1.8 Hz)
14	34	60/0.30	$C_{12}H_{21}NOSi$ (223.4)	2940 (br), 2150, 1650	0.13 (s, 9H); 1.07 (s, 3H); 1.16 (s, 3H); 1.85 (d, 1H, *J* = 14.2 Hz); 1.92 (d, 1H, *J* = 14.2 Hz); 3.35 (d with fine structure, 1H, *J* = 14.4 Hz); 3.45 (d with fine structure, 1H, *J* = 14.4 Hz); 5.61 (d, 1H, *J* = 5.5 Hz); 5.78 (d, 1H, *J* = 5.5 Hz)

[a] All yields correspond to isolated, analytically pure products.

[b] Satisfactory microanalyses were obtained; C ±0.15, H ±0.13.

[c] Recorded on a Beckman 4250 Infrared spectrophotometer.

[d] Obtained on a Nickolet NT-300 spectrometer.

Downloaded by: University of Illinois at Chicago. Copyrighted material.

7:

$C_{11}H_{19}NOSi$	calc.	C 63.10	H 9.15
(209.2)	found	63.21	9.06

IR (Film): $\nu = 2920$ (br), 2150, 1650 cm^{-1}.

^{1}H-NMR ($CDCl_3$): $\delta = 0.13$ (s, 9H); 1.70 (m, 4H); 2.02 (m, 2H); 3.35 (m, 2H); 5.67 (d, 1H, $J = 10.1$ Hz); 5.95 ppm (dt, 1H, $J = 10.1, 3.7$ Hz).

Support for this research by a grant from the National Institutes of Health is gratefully acknowledged.

This manuscript is dedicated to the memory of Professor Robert V. Stevens.

Received: 5 August 1985
(Revised form: 14 October 1986)

(1) Schöllkopf, U., Gerhart, F. *Angew. Chem.* **1968**, *80*, 842; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 805.

(2) Schöllkopf, U. *Angew. Chem.* **1977**, *89*, 351; *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 339.

(3) Schöllkopf, U., Hantke, K. *Justus Liebigs Ann. Chem.* **1973**, 1571. In this article, the addition reactions of *highly stabilized* α-metallo-isocyanides with α,β-unsaturated systems were investigated.

(4) The identity of all new compounds was established by chromatographic separation followed by characterization *via* 300 MHz ^{1}H-NMR and IR spectrometry. All new compounds gave satisfactory elemental (C,H) analyses.

(5) All yields refer to chromatographed and/or distilled products.

(6) The estimated pKa range for methyl isocyanide is 33–35; F. Bordwell, private communication.

(7) Raucher, S., Koolpe, G.A. *J. Org. Chem.* **1978**, *43*, 3794.

(8) Attempts to trap the enolates and/or alkoxides obtained from the reaction of either **4d** or **4e** with **5** by silylation were unsuccessful.

Downloaded by: University of Illinois at Chicago. Copyrighted material.