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CONJUGATE ADDITION OF COPPER(I) ALDIMINES TO α,β-UNSATURATED CARBONYL COMPOUNDS —— SYNTHESIS OF 1,4-DIKETONES

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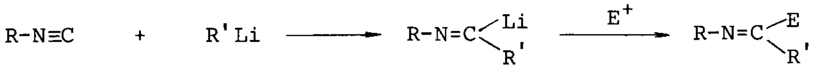
Abstract: This paper describes the finding that BF_3 etherate effectuates the conjugate additions of copper(I) aldimines, generated in situ from lithium aldimines and Cu(I) halide, to α,β-unsaturated carbonyl compounds to produce 4-(N-alkylimino)-ketones, which give on acid hydrolysis 1,4-diketone derivatives.

Acylmetal complexes are important intermediates in metal catalyzed carbonylation reactions. In the carbonylation of organocopper compounds such as lithium dialkylcuprate leading to ketone synthesis[1)], acylcopper(I) intermediate has also been assumed. However, acylcopper itself has not yet been utilized probably due to its instability, although organocopper compound has widely been exploited in organic syntheses.

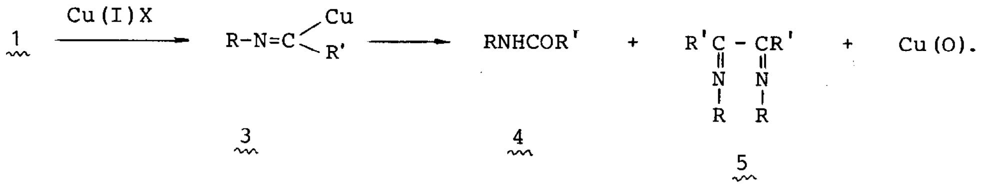
Herein, we wish to report a BF_3 induced conjugate addition of copper(I) aldimine, which is structurely equivalent to acylcopper(I), to α,β-unsaturated carbonyl compounds. The α-addition of organolithium and Grignard reagents to *tert*-alkyl isocyanide has extensively been studied by Walborsky[2)]. The resulting metallo N-*tert*-alkyl aldimines, which may be taken as a masked acyl carbanion, were shown to react with a wide range of electrophiles including alkyl halides, carbon dioxide, ethyl chloroformate and benzaldehyde.[2)]



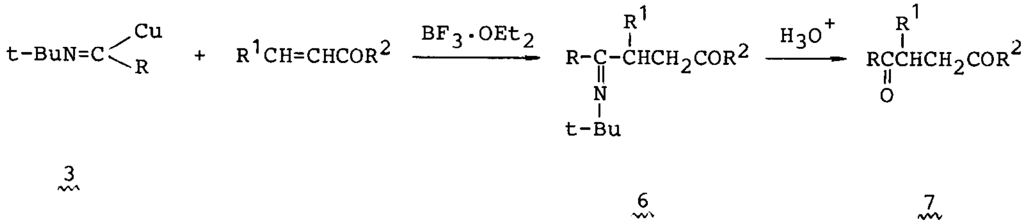
$$R\text{-}N{\equiv}C \quad + \quad R'Li \longrightarrow R\text{-}N{=}C\begin{smallmatrix}Li\\R'\end{smallmatrix} \xrightarrow{E^+} R\text{-}N{=}C\begin{smallmatrix}E\\R'\end{smallmatrix}$$

1 **2**

Copper(I) N-*tert*-butylvaleraldimine (**3a**), which is generated in situ from lithium N-*tert*-butylvaleraldimine (**1a**) and copper(I) halide[3)], is not stable at room temperature and decomposed to give, after aqueous workup, N-*tert*-butylvaleramide (**4a**) and α-di-(N-*tert*-butyl)imine **5a**[4)] with metallic copper.

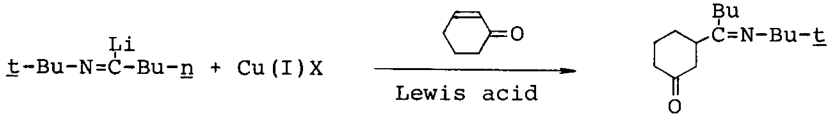


Indeed, a reaction of copper(I) N-*tert*-butylvaleraldimine (3a) with α,β-unsaturated carbonyl compound at -78°C to room temperature did not afford the desired conjugate adduct 6 but N-*tert*-butylvaleramide as the major product. However, it was found that some Lewis acids effectuated the conjugate addition of 3 to α,β-unsaturated carbonyl compounds.



The effect of Lewis acids on the conjugate addition of copper(I) N-*tert*-butylvaleraldimine 3a to 2-cyclohexen-1-one is demonstrated in Table 1. As evident in Table 1, $BF_3 \cdot OEt_2$ is quite effective to promote the conjugate addition of copper(I) aldimine to α,β-unsaturated carbonyl compound. The effect of Lewis acids in the present reaction may be pertinent to the finding that the conjugate additions of alkylcopper and lithium dialkylcuprate are facilitated by Lewis acids such as $BF_3 \cdot OEt_2$ and $AlCl_3$[5])

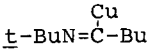
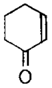
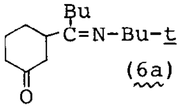
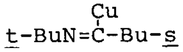
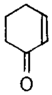
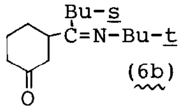
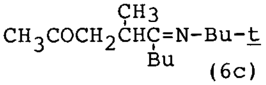
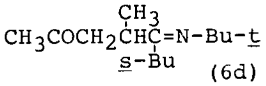
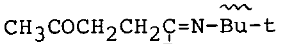
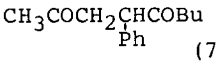
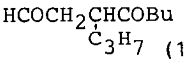
Table 1. Effect of Lewis Acid on Conjugate Addition of Copper(I) Aldimine



Cu(I)X	Lewis Acid	(%)
CuI	$BF_3 \cdot OEt_2$	71
	Et_2AlCl	10
	$EtAlCl_2$	10
	$AlCl_3$	5
	$TiCl_4$	10
$CuBr \cdot SMe_2$	$BF_3 \cdot OEt_2$	65
$CuI \cdot P(OMe)_3$	$BF_3 \cdot OEt_2$	77
	$EtAlCl_2$	28

The procedure of the conjugate addition of copper(I) aldimines 3 to α,β-unsaturated carbonyl compounds is illustrated as follows. Lithium N-tert-butylvaleraldimine (3a)[2], which was generated in situ at -10°C from 166 mg (2 mmol) of tert-butyl isocyanide and 2 mmol of butyllithium (1.6M Hexane solution) in ether (3 mL), was added to a suspension of 381 mg (2 mmol) of cuprous iodide in 4 mL of ether at -78°C. After 30 min, $BF_3 \cdot OEt_2$ (2 mmol), and then 84 mg (1 mmol) of 3-penten-2-one were added at -78°C to the mixture and allowed to warm up to 0°C. Work-up of the reaction mixture with aqueous Na_2CO_3 afforded 4-methyl-5-(N-tert-butylimino)-2-nonanone (6c) (95% yield), bp 76 - 77°C (5 mmHg). 6c: ^1H NMR($CDCl_3$ with TMS) δ 0.60 - 2.40 (m, 11H), 0.98 (d, 3H), 1.20 (s, 9H), 2.12 (s, 3H), 2.80 - 3.15 (m, 1H); IR(neat) 1718, 1660 cm^{-1}. 6c was readily hydrolyzed with aqueous oxalic acid to furnish 4-methylnonane-2,5-dione (7c), bp 70°C (5 mmHg). 7c: ^1H NMR($CDCl_3$ with TMS) δ 0.60 - 3.30 (m, 12H), 1.32 (d, 3H), 2.13 (s, 3H); IR(neat) 1708 cm^{-1}. Some conjugate additions of copper(I) N-tert-butyl aldimines 3 were summarized in Table 2.

Table 2. Conjugate Addition of Copper(I) Aldimine to α,β-Unsaturated Carbonyl Compound[a]

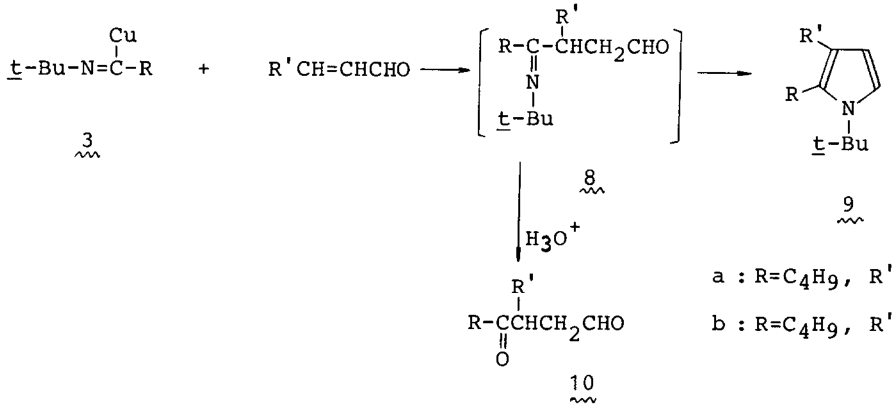
No.	Cu(I) Aldimine	α,β-Unsaturated Carbonyl Compd.	Conjugate Adduct (%)[b]
1	 $\underline{t}\text{-BuN}{=}\overset{\text{Cu}}{\text{C}}\text{-Bu}$ (3a)		 (71) (6a)
2	 $\underline{t}\text{-BuN}{=}\overset{\text{Cu}}{\text{C}}\text{-Bu-}\underline{s}$ (3b)		 (65) (6b)
3	3a	$CH_3COCH{=}CHCH_3$	 $\mathrm{CH_3COCH_2\overset{CH_3}{C}H\underset{Bu}{C}{=}N{-}Bu{-}\underline{t}}$ (95) (6c)
4	3b	$CH_3COCH{=}CHCH_3$	 $\mathrm{CH_3COCH_2\overset{CH_3}{C}H\underset{\underline{s}\text{-}Bu}{C}{=}N{-}Bu{-}\underline{t}}$ (87) (6d)
5	3a	$CH_3COCH{=}CH_2$	 $\mathrm{CH_3COCH_2CH_2\underset{Bu}{C}{=}N{-}Bu{-}t}$ (39) (6e)
6	3a	$CH_3COCH{=}CHPh$	 $\mathrm{CH_3COCH_2\underset{Ph}{C}HCOBu}$ (69)[c] (7f)
7	3a	$HCOCH{=}CHC_3H_7$	 $\mathrm{HCOCH_2\underset{C_3H_7}{C}HCOBu}$ (88)[c],[d] (10a)

a) CuI was employed as Cu(I)halide compound. b) Ref. 6

c) Reaction mixture was worked up with aqueous oxalic acid.

d) Ref. 7.

The conjugate additions of copper(I) aldimines 3 to α,β-unsaturated aldehydes according to the procedure described above did not afford the expected 4-(N-tert-butylimino)aldehydes 8, but it gave pyrrole derivatives 9 in high yields, which may be derived from the cyclization of 8 once formed. On the other hand, when the reaction mixture was treated with aqueous oxalic acid, 4-keto aldehyde (10) was obtained together with pyrrole derivative (9)[8]



a : $R=C_4H_9$, $R'=C_3H_7$ 90%

b : $R=C_4H_9$, $R'=$ Ph 93%

References and Notes

1) J. Schwartz, Tetrahedron Lett., 2803 (1972)

2) a) H. M. Walborsky and G. E. Niznik, J. Am. Chem. Soc., 91, 7778 (1969)
b) G. E. Niznik, W. H. Morrison, III, and H. M. Walborsky, J. Org. Chem., 39, 600 (1974)

3) M. P. Periasamy and H. M. Walborsky, J. Org. Chem., 39, 611 (1974)

4) 5a: NMR($CDCl_3$ with TMS) δ 1.23; IR(neat) 1640 cm^{-1}; Mass 280 (M^+)

5) Y. Yamamoto, S. Yamamoto, H. Yatagai, Y. Ishihara and K. Maruyama, J. Org. Chem., 47, 119 (1982)

6) 6a [bp 78-79°C (2 mmHg)]: NMR($CDCl_3$) δ 0.65-2.79 (m, 18H), 1.33 (s, 9H), IR(neat) 1712, 1663 cm^{-1}. 6d [bp 85-87°C (4 mmHg)]: NMR($CDCl_3$) δ 0.65-1.60 (m, 11H), 1.24 (s, 9H), 2.08 (s, 3H), 2.15-3.10 (m, 4H); IR(neat) 1718, 1653 cm^{-1}. 7f [bp 70-73°C (0.1 mmHg)]: NMR($CDCl_3$) δ 0.6-2.0 (m, 7H), 2.15 (s, 3H), 2.2-3.0 (m, 3H), 3.45 (dd, 1H, J=10.2 and 18.0 Hz), 4.20 (dd, 1H, J=4.5 and 10.2 Hz), 7.10-8.00 (m, 5H); IR(neat) 1720, 1710 cm^{-1}. 10a [bp 63-64°C (3 mmHg)]: NMR($CDCl_3$) δ 0.66-1.87 (m, 14H), 2.15-3.18 (m, 5H), 9.78 (s, 1H); IR(neat) 1720, 1708 cm^{-1}. 9a [bp 80-81°C (3 mmHg)]: NMR($CDCl_3$) δ 0.68-2.12 (m, 12H), 1.32 (s, 9H), 2.23-2.96 (m, 4H), 6.18 (d, 1H, J=3.3 Hz), 6.68 (d, 1H, J=3.3 Hz).

7) Reaction of 3a with 2-hexenal afforded only 10a by workup with aqueous oxalic acid.

8) Reaction of 3a with cinnamaldehyde gave 3-phenyl-4-oxo-octanal (50%) with pyrrole 9b (30%) after workup with aqueous oxalic acid.

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