Tetrahedron Letters,Vol.26,No.47,pp 5781-5784,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

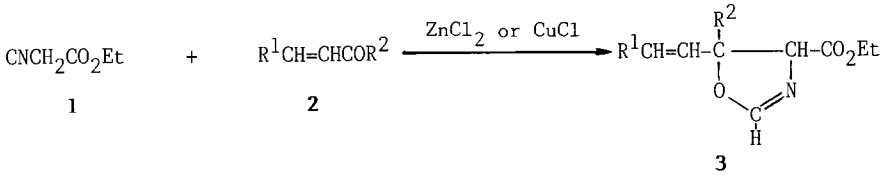
$ZnCl_2$ AND CuCl PROMOTED ALDOL REACTIONS OF ISOCYANOACETATE WITH α,β-UNSATURATED CARBONYL COMPOUNDS

Yoshihiko Ito*, Takaharu Matsuura and Takeo Saegusa
Department of Synthetic Chemistry, Kyoto University, Kyoto 606, Japan

Abstract: Reaction of ethyl isocyanoacetate with α,β-unsaturated carbonyl compounds was promoted by a stoichiometric amount of $ZnCl_2$ or a catalytic amount of $CuCl/Et_3N$ (1:1) to give 5-alkenyl-4-carboethoxyoxazolines (**3**) in moderate yields. The oxazolines (**3**) were converted by palladium catalyst to 2-formamino-2,4-alkadienoic acid ethyl esters (**5**).

Synthetic utility of isocyanides has been widely developed, since α-metalation of isocyanides was accomplished by schöllkopf.[1] Carbon-carbon bond formation with the α-metalated isocyanide provides a convenient method for α-aminoalkylation, because the resultant isocyanide is readily hydrolyzed to the corresponding primary amine. α-Isocyanoacetate, which has more acidic α-hydrogen, was easily deprotonated even with mild bases such as triethylamine and potassium carbonate and reacted with acetaldehyde to afford β-hydroxy-α-isocyanobutyrate, of which acid hydrolysis provided threonine.[2]

Herein, we wish to describe that $ZnCl_2$ and CuCl promoted reactions of ethyl α-isocyanoacetate (**1**) with α,β-unsaturated aldehydes and ketones (**2**) to give 5-alkenyl-4-carboethoxy oxazolines (**3**) in moderate to good yields. Use of triethylamine instead of $ZnCl_2$ and CuCl in the reaction gave rise to a complex mixture of products including low yield of **3**.



A stoichiometric amount of $ZnCl_2$ promoted the reaction of isocyanoacetate with α,β-unsaturated aldehydes and ketones in THF at room temperature, although the reaction proceeded slowly over 20-30 hr. The progress of the reaction was monitored by IR absorption band at 2150 cm^{-1}, which is ascribed to $\nu_{N\equiv C}$ of the isocyanide. However, a rise in the reaction temperature resulted in lower yields of **3**.

A sample procedure for the $ZnCl_2$ promoted reaction of α-isocyanoacetate with α,β-unsaturated carbonyl compounds is as follows. A mixture of (E)-crotonaldehyde (2.4 mmol), ethyl isocyanoacetate (2.0 mmol) and anhydrous $ZnCl_2$ (2.0 mmol) in THF (1.5 mL) was stirred at room

temperature for 25 hr. The reaction mixture was poured into aqueous $NaHCO_3$ and extracted with methylene chloride. The methylene chloride extract was dried on anhydrous Na_2CO_3 and distilled to give a 5 : 2 mixture of trans and cis-5-((E)-1- propenyl)-4-carboethoxyoxazoline (**3a**) [bp 98-100°C (1 mmHg)].[3] Some $ZnCl_2$ promoted syntheses of oxazoline derivatives **3** are summarized in Table 1.

Table 1.

RCOR'	R(R')C—CHCO$_2$C$_2$H$_5$ (O, N, C=H)	Yield (%) (trans:cis)	
		$ZnCl_2$	CuCl/NEt_3
(E)-CH_3CH=CHCHO (**1a**)	**3a**	95(5:2)	60(4:1)
(E)-$CH_3CH_2CH_2CH$=CHCHO (**1b**)	**3b**	72(3:1)	
(E)-$(CH_3)_2C$=$CHCH_2CH_2C(CH_3)$=CHCHO (**1c**)	**3c**	59(2:1)	
(E)-PhCH=CHCHO (**1d**)	**3d**	66(5:2)	75(-)
(E)-CH_3CH=$C(CH_3)$CHO (**1e**)	**3e**	67(5:3)	
CH_2=CHCHO (**1f**)	**3f**	55(2:1)	
2-Cyclohexenone (**1g**)	**3g**	29(1:1)	
CH_3CH=CHCOCH$_3$ (**1h**)	**3h**	59(5:3)	
PhCHO (**1i**)	**3i**	64(7:1)	
2-Furaldehyde (**1j**)	3j	87(5:1)	
CH_3CHO (**1k**)	**3k**	13(-)	∿100(2:1)
$(C_2H_5)_2CHCHO$ (**1l**)	**3l**	7(-)	75[1]

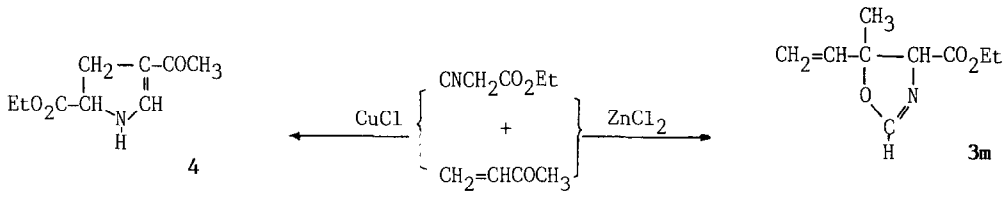
1) Trans isomer was exclusively produced.

Noteworthy is that acrolein (**1f**), which is readily polymerized by not only base, but also CuCl catalyst, gave the desired 5-vinyl-4-carboethoxyoxazoline (**3f**) in moderate yield. $ZnCl_2$ was also effective for the reaction with aromatic aldehydes. However, $ZnCl_2$ gave poor results with aliphatic aldehydes, being interestingly compared with CuCl catalyst, which is described below.

Unlike with $ZnCl_2$, a catalytic amount of CuCl was enough to induce the reaction of isocyanoacetate with α,β-unsaturated aldehydes. The CuCl catalyzed reaction was much slower in THF at room temperature, taking no less than 2 days. However, it is noted that an addition of one or two equivalent of amine[4] to the CuCl catalyst caused a remarkable acceleration of the reaction rate. The reaction of crotonaldehyde with ethyl isocyanoacetate in the presence of 5 mol % of CuCl and 5 mol% of triethylamine in THF was almost complete in ca. 10 hr at room temperature. The CuCl/amine (1:1) catalyst was also an excellent catalyst for the reaction with aliphatic aldehydes as shown in the Table 1.

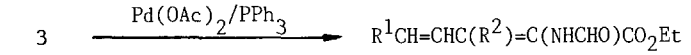
The marked difference of the $ZnCl_2$ and CuCl catalysts in the present reaction is further demonstrated in a following reaction, which led to different products depending on the use of $ZnCl_2$ and CuCl. Reaction of methyl vinyl ketone with ethyl isocyanoacetate was carried out in

the presence of $ZnCl_2$ and $CuCl/Et_3N$ catalyst to afford the expected oxazoline (**3m**) (47% yield) and pyrroline derivative (**4**) (44% yield)[5], respectively.[6]



The present synthesis of 5-(1-alkenyl)-4-carboalkoxyoxazolines (**3**) provides a convenient access to α-amino acid derivatives from glycine, because the oxazoline structure is easily hydrolyzed to the corresponding amino alcohol. Finally, we describe a palladium catalyzed conversion of **3** so far prepared to α-amino acid derivatives. For instance, 5-vinyl-4-carboethoxyoxazoline (**3f**) was converted to 2-formamino-2,4-pentadienoic acid ethyl ester (**5a**) on treatment with 2.5 mol% $Pd(OAc)_2$ and 5 mol% PPh_3 in THF at room temperature. Some preparations of 2-formamino-2,4-alkadienoic acid esters (**5**)[7] are summarized in Table 2.

Table 2.



5

R^1	R^2	Conditions	(Yield %)
H	H	r.t., 1 hr	89 (**5a**)
CH_3	H	r.t., 1 hr	100 (**5b**)
CH_3	CH_3	r.t., 2 days	97 (**5c**)
$-(CH_2)_3-$		r.t., 2 days	99 (**5d**)

The palladium catalyzed reaction is reasonably explained by a catalytic cycle involving a formation of π-allylpalladium intermediate via oxidative addition of the allylic carbon-oxygen bond of **3** on Pd(0) species generated in situ and the subsequent β-elimination of Pd-H. This mechanism is consistent with a finding that 5-methyl-4-carboethoxy oxazoline (**3k**) was completely inert at the reaction conditions.

References and Notes

1) a) U. Schöllkopf, Angew. Chem. Int. Ed. Engl., 16, 339 (1977). b) D. Hoppe, Angew. Chem. Int. Ed. Engl., 13, 789 (1974).

2) a) K. Matsumoto, M. Suzuki, M. Miyoshi and K. Okumura, Synthesis, 1974, 500. b) K. Matsumoto, M. Suzuki and M. Miyoshi, J. Org. Chem., 38, 2094 (1973).

3) NMR spectra of oxazolines **3** exhibited two sets of signals corresponding to their trans and cis isomers. Doublet signal (J=ca. 2 Hz) at around δ 7 ppm, which is assigned to -OCH=N-,

appeared at higher magnetic field for the trans isomer. Spectra data are presented for some selected products. **3a** : IR (neat) 1740, 1630 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 1.32 and 1.26 (two t, 3H), 1.77 and 1.73 (two d, 3H, J=6.5 Hz), 4.26 (q, 2H), 4.38 and 4.79 (two dd, 1H, J=7.50 and 2.00 Hz for trans-oxazoline, J=10.50 and 2.00 Hz for cis-oxazoline), 5.07 (dd, 1H, J=7.50 and 7.50 Hz), 5.51 and 5.43 (two dd, 1H, J=15.0 and 7.50 Hz), 5.89 (qd, 1H, J=6.50 and 15.0 Hz), 6.94 and 7.03 (two d, 1H, J=2.00 Hz). **3b** [bp 100-102°C (1.0 mmHg)]: NMR ($CDCl_3$) δ 0.95 (t, 3H), 1.35 and 1.30 (two t, 3H), 1.85-2.30 (m, 4H), 4.25 and 4.20 (q, 2H), 4.50-6.80 (m, 4H), 7.00 and 7.08 (two d, 1H, J=1.80 Hz). **3f** [bp 95-98° (1.0 mmHg)]: IR (neat) 1740, 1625 cm^{-1}; NMR ($CDCl_3$) δ 1.33 and 1.28 (two t, 3H), 4.32 and 4.25 (two q, 2H), 4.75-6.35 (m, 5H), 7.05 and 7.16 (two d, 1H, J=1.80 Hz). **3g** [bp 81-83° (0.1 mmHg]: IR (neat) 1740, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.25 and 1.30 (t, 3H), 1.55-2.40 (m, 6H), 4.20 and 4.25 (q, 2H), 4.40 and 4.48 (two d, 1H, J=1.50 Hz), 5.40-6.25 (m, 2H), 6.98 and 7.02 (two d, 1H, J=1.50 Hz). **3i** [bp 118-121°C (1.0 mmHg)]: IR (neat) 1735, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.30 and 0.80 (two t, 3H), 4.30 (q, 2H), 4.60 and 5.03 (two dd, 1H, J=7.80 and 1.95 Hz for trans-oxazoline, J=11.25 and 1.95 Hz for cis-oxazoline), 5.70 (d, 1H, J=7.80 Hz), 7.10 and 7.25 (two d, 1H, J=1.95 Hz), 7.25-7.50 (broad s, 5H).

4) Use of (1R, 2S)-(-)-ephedrine as a chiral amine additive in the reaction of crotonaldehyde with ethyl isocyanoacetate caused some asymmetric induction, which is now intensively being studied.

5) T. Saegusa, Y. Ito , H. Kinoshita and S. Tomita, J. Org. Chem., 36, 3316 (1971).

6) **3m** is a 5:3 mixture of the trans and cis isomers. **3m** [bp 72-78°C (0.8 mmHg)]: IR (neat) 1750, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.30 and 1.25 (two t, 3H), 1.40 and 1.60 (two s, 3H), 4.25 and 4.15 (two q, 2H), 4.53 and 4.42 (two d, 1H, J=1.95 Hz), 5.05-5.50 (m, 2H), 5.85 and 6.15 (two t, 1H, J=10.8 Hz), 7.00 and 7.05 (two d, 1H, J=1.95 Hz). **4**: IR (neat) 1735, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, 3H), 2.13 (s, 3H), 3.04 (d, 2H, J=9.00 Hz), 4.18 (q, 2H), 4.45 (m, 1H), 5.15-5.50 (broad 1H), 7.30 (broad 1H).

7) Compound **5** was an inseparable trans and cis mixture. **5a**: IR (neat) 3400-3050, 2970, 1700, 1500 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (t, 3H), 4.30 (q, 2H), 5.40-5.95, 6.20-6.90, 7.65-8.10 (m, 5H), 8.20-8.50 (broad 1H). **5b**: IR (neat) 3350-3150, 3150-2850, 1700, 1500 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (t, 3H), 1.99 (d, 3H), 4.30 (q, 2H), 6.00-6.50, 7.00-8.00 (m, 4H), 8.15-8.50 (broad 1H). **5d**: IR (KBr disk) 3250, 2990-2920, 1710, 1660, 1510 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, 3H), 1.55-3.10 (m, 6H), 4.22 (q, 2H), 5.65-6.47 (broad 2H), 7.05-7.57 (broad 1H), 7.81-8.20 (broad 1H).

(Received in Japan 21 September 1985)