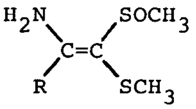
Tetrahedron Letters No. 27, pp 2525 - 2528.
©Pergamon Press Ltd. 1979. Printed in Great Britain.
0040-4039/79/0701-2525$02.00/0

CARBON-CARBON BOND FORMATION FROM ETHYL CYANOFORMATE AND ACTIVE METHYLENE COMPOUNDS

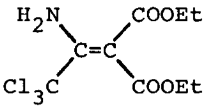
Takamasa Iimori, Yasushi Nii, Toshio Izawa, Susumu Kobayashi, and Masaji Ohno*
Faculty of Pharmaceutical Sciences, University of Tokyo,
Bunkyo-ku, Tokyo 113, Japan

A new methodology which leads to α,β-unsaturated α-amino acids has been developed through a carbon-carbon forming reaction using ethyl cyanoformate and active methylene compounds in the presence of zinc chloride and triethyl amine.

In the foregoing papers[1,2] we described efficient routes to a variety of N-substituted amidinoformic acids and regioselective synthesis of virazole, using benzyl cyanoformate as a synthon. This note is primarily concerned with a new carbon-carbon bond forming reaction using ethyl cyanoformate and active methylene compounds. The reaction of nitriles and active methylene compounds has been investigated to some extent[3], but no direct preparation of unsaturated α-amino acids is reported. For instance, Tsuchihashi and his co-workers investigated a reaction of nitriles and methyl methylthiomethyl sulfoxide and developed a methodology to synthesize α-amino acids[4], α-keto acids, α-keto thioesters, and α-keto amides by modification of enaminosulfoxide moiety[5] (**1**). However, such a C-C bond forming reaction is limited to the usual nitriles such as acetonitrile or benzonitrile. Trichloroacetonitrile reacts easily with common nucleophiles including amines[6], alcohols[7], and malonic acid ester[7]. However, trichloromethyl group of **2** resists base-catalyzed hydrolysis affording decomposed products[8]. Therefore, the electron-withdrawing group cannot be used as a carboxylic acid equivalent. Dornow and Grabhöfer found that ethyl cyanoformate reacts with malononitrile in the presence of triethylamine to afford ethyl 1,1-dicyanoacetate (**3**) by nucleophilic substitution at the carbon of the ester[9].



1

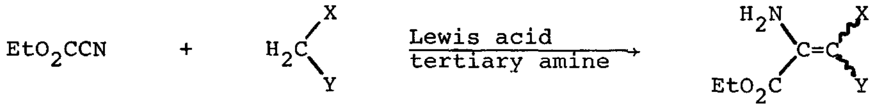


2

$EtO_2C\text{-}CH(CN)_2$

3

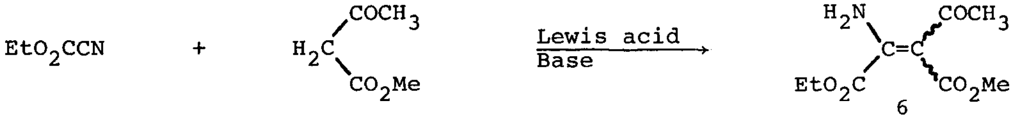
We now report that regiospecific C-C bond formation between the cyano group of ethyl cyanoformate and active methylene compounds has successfully been effected by using a combination of Lewis acid and tertiary amine as the nucleophilic addition reagent.



4 5 6

A systematic survey and experimental variation of tertiary amines and Lewis acids for the nucleophilic addition was carried out as shown in Table I in case of methyl acetoacetate and ethyl cyanoformate. The use of such combination for this critical step is based on the idea of activating the cyano group selectively with a Lewis acid through chelation and generating carbanion with a tertiary

Table I. Nucleophilic Addition of Methyl Acetoacetate to Ethyl Cyanoformate[a]

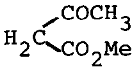
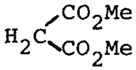
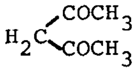
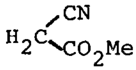
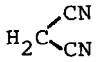


6

Lewis Acid[b]	Base	Solvent	Conditions	6 Yield[c] (%)
$ZnCl_2$	Et_3N	CH_2Cl_2	refl. 3 h	92
$ZnCl_2$	Et_3N	CH_2Cl_2	0°, 1 h ⟶ r. t., 6 h	85
$ZnCl_2$	Et_3N	THF	0°, 25 h ⟶ r. t., 5 h	57
$ZnCl_2$	Pyridine	CH_2Cl_2	r. t., 6 h	20
$ZnCl_2$	d	CH_2Cl_2	r. t., 6 h	40
$ZnCl_2$	DBU	CH_2Cl_2	r. t., 6 h	40
$ZnCl_2$	NaH	THF	0°, 1 h ⟶ r. t., 24 h	50
$ZnCl_2$	NaH	CH_2Cl_2	0°, 30 min ⟶ r. t., 12 h	65
$ZnCl_2$	n-BuLi	THF	0°, 30 min ⟶ r. t., 24 h	42
$BF_3\cdot OEt_2$	Et_3N	CH_2Cl_2	0°, 1 h ⟶ r. t., 48 h	0
$BF_3\cdot OEt_2$	NaH	THF	0°, 2 h ⟶ r. t., 24 h	0
$SnCl_4$	Et_3N	CH_2Cl_2	0°, 10 min ⟶ r. t., 6 h	14
$FeCl_3$	Et_3N	CH_2Cl_2	0°, 10 min ⟶ r. t., 6 h	10
$TiCl_4$	Et_3N	CH_2Cl_2	0°, 10 min ⟶ r. t., 6 h	12
$AlCl_3$	Et_3N	CH_2Cl_2	0°, 10 min ⟶ r. t., 6 h	0
CuI	NaH	THF	0°, 3 h	0[e]

(a) Preparation of the adduct 6 was all performed on 1.0-2.0 mmol scales. (b) Lewis acids and bases were used in a little excess, 1.2 and 1.0-1.1 equiv, respectively. (c) Isolated yields after preparative TLC. Product 6 showed mp 81-82° after recrystallization from diethylether-hexane and exhibited the expected pmr, ir, and analytical data. (d) N-Methylmorpholine. (e) Only 2-methoxycarbonyl-3-oxobutanoic acid ethyl ester was obtained in poor yield.

Table II. Carbon-Carbon Bond Formation between Ethyl Cyanoformate and Active Methylene Compounds Using $ZnCl_2$-Et_3N in CH_2Cl_2[a]

5	Conditions	Yield[b] **6** (%), mp
 $H_2C(COCH_3)CO_2Me$	refl. 3 h	92 , 81-82
	0°, 1 h, then r. t., 6 h	85
 $H_2C(CO_2Me)CO_2Me$	refl. 3 h	93 , 72.5-73
	r. t., overnight	82
 $H_2C(COCH_3)COCH_3$	refl. 5 h	42 , 75-76
	r. t., 24 h	49
 $H_2C(CN)CO_2Me$	refl. 3 h	63 , 114-115
	r. t., 8 h	63
 $H_2C(CN)CN$	r. t., overnight	26[c], 144-146
CH_3NO_2	10°C overnight	18[d], 93-94

(a) The reactions were all performed on 1.0-2.0 mmol scales. (b) Isolated yields after preparative TLC. All products exhibited the expected pmr, ir, and analytical data. (c) Tetrahydrofuran was used as solvent. (d) The product was confirmed to be one component probably stabler isomer by chelation based on ir and nmr data.

amine[8,9]. The use of either component did not give any expected product. As shown in Table II, methyl acetoacetate (**5**, X=$COCH_3$, Y=COOMe) and methyl malonate (**5**, X=Y=CO_2Me) afforded the corresponding adducts **6** in excellent yields by use of $ZnCl_2$-Et_3N. Acetylacetone (**5**, X=Y=$COCH_3$), methyl cyanoacetate (**5**, X=CN, Y=CO_2Me), and malononitrile (**5**, X=Y=CN) afforded the corresponding adducts **6** in fair to good yields. Nitromethane (**5**, X=H, Y=NO_2) gave adduct **6** in poor yield. No adduct was obtained from methyl methylthiomethyl sulfoxide (**5**, X=$SOCH_3$, Y=SCH_3). In case of methyl acetoacetate and ethyl cyanoacetate, the adduct **6** was found to be a mixture of geometrical isomers based on the ^{13}C-NMR[10], but it was difficult to separate by TLC. Since cyanoformates are now easily available[1], the methodology developed here provides polyfunctional unsaturated amino acids and may be useful for introduction of a variety of other amino acids and heterocyclic compounds.

Reaction of ethyl cyanoformate with methyl malonate: To a suspension of $ZnCl_2$ (3.271 g, 24 mmol) in 5 ml of CH_2Cl_2 were added ethyl cyanoformate **4** (2.378 g, 24 mmol) in 5 ml of CH_2Cl_2, methyl malonate **4** (2.642 g, 20 mmol) in 5 ml of CH_2Cl_2, and Et_3N (2.226 g, 22 mmol) in CH_2Cl_2 in order, under cooling with ice. The solution was brought to room temperature and allowed to stand overnight with stirring. The reaction mixture was washed with 20 ml of 2N-HCl and then with saturated NaCl solution, and the organic layer was passed through a SiO_2 column. Removal of the solvent under a reduced pressure afforded an oily substance which solidified upon standing. It was recrystallized from ether-hexane, affording

3.424 g of 6, mp 72-73°, (X=Y=COOMe) in 74% yield. The mother liquor was concentrated and the concentrate was developed with preparative TLC (SiO_2) using CH_2Cl_2 as an eluent, affording additional 6 (0.379 g, 8%).

Acknowledgement: The work was financially supported by Grants-in-aid for General Scientific Research (No. 347115) from the Ministry of Education, Science and Culture of Japan.

References and Notes

1. Y. Nii, K. Okano, S. Kobayashi, and M. Ohno, *Tetrahedron Lett.*, preceding paper.
2. Y. Ito, Y. Nii, S. Kobayashi, and M. Ohno, *Tetrahedron Lett.*, preceding paper.
3. F. C. Schaffer in "The Chemistry of the Cyano Group" Z. Rappoport, ed., Interscience Publishers, London, 1970, pp. 239~305.
4. K. Ogura and G. Tsuchihashi, *J. Am. Chem. Soc.*, **96**, 1960 (1974).
5. K. Ogura, N. Katoh, I. Yoshimura, and G. Tsuchihashi, *Tetrahedron Lett.*, 375 (1978).
6. J. C. Grivas and A. Taurins, *Can. J. Chem.*, **36**, 771 (1958).
7. F. Cramer, K. Pawelzik, and H. J. Baldauf, *Chem. Ber.*, **91**, 1049 (1958).
8. Unpublished result from our laboratories.
9. A. Dornow and H. Grabhöfer, *Chem. Ber.*, **91**, 1824 (1958).
10. For condensation of aldehydes and active methylene compounds in Knoevenagel reaction, $TiCl_4$-pyridine reagent was used. W. Lehnert, *Tetrahedron*, **29**, 635 (1973) and references cited therein.
11. Dibenzylammonium trifluoroacetate was used for position-specific aldol condensation as an outstanding selective agent. E. J. Corey, R. L. Danheiser, S. Chandrasekaran, P. Siret, G. E. Keck, J-L Gras, *J. Amer. Chem. Soc.*, **100**, 8031 (1978).
12. The ^{13}C-NMR showed that one of the geometrical isomers is predominating in a ratio of 5:1.

(Received in Japan 5 March 1979)