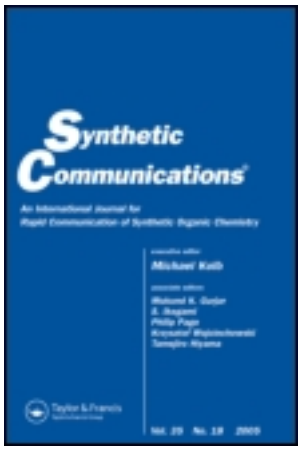

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One Pot Synthesis of Methyl Aminoacetylcyanoacetates

Stylianos Hamilakis [a] & Assistant Professor Athanase Tsolomitis [a]

[a] The Laboratory of Organic Chemistry, The School of Chemical Engineering, The National Technical University of Athens, Athens, Greece

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One Pot Synthesis of Methyl Aminoacetylcyanoacetates

Stylianos Hamilakis and Athanase Tsolomitis*

The Laboratory of Organic Chemistry, The School of Chemical Engineering, The National Technical University of Athens, Athens, Greece

ABSTRACT

The *C*-acylation reactions of the methyl cyanoacetate with N-protected glycines by simultaneous activation of the amino acid carbonyl group and the methyl cyanoacetate methylene group using carbonyl diimidazole (CDI) have been here performed. The corresponding aminoacetylcyanoacetates were isolated (devoided of any impurities) as enols **4** in high yields, with a simple experimental, one pot, procedure.

Key Words: Aminoacetylcyanoacetates; Imidazolides; CDI; Enol-imidazolinium salt; *C*-Aminoacetylation.

*Correspondence: Athanase Tsolomitis, Assistant Professor, The Laboratory of Organic Chemistry, The School of Chemical Engineering, The National Technical University of Athens, 9, Heroon Polytechniou Str., Zografou Campus, Athens 15780, Greece; E-mail: tsolom@chemeng.ntua.gr.

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Aminoacetyl derivatives of active methylene compounds (such as cyanoacetates) have been used as useful intermediates in synthesis of tetramic acids[1–3] and statines.[4,5] Therefore these compounds must be considered to be of interest as potential prodrugs.

The *C*-acylaion of methyl cyanoacetate with N-protected α-amino acids has been reported using hippuric acid chlorides,[6] hippuric acid esters,[7–9] mixed anhydrides[10] of hippuric acid or the hippuric acid azlactone, (2-phenyl-5(4*H*)-oxazolone), and salts of methyl cyanoacetate.

In that process, the N-protected amino acids were activated with a separate reaction and with a second reaction, followed the cyanoacetate anion formation by bases such as *t*-BuOK, NaH, or non nucleophilic bases e.g., triethylamine and 4-*N*,*N*-dimethylaminopyridine.

In a previous communication[11] we have reported the *C*-acylation of Meldrum's acid with N-protected glycines (via their imidazolides), using 1,1′-carbonyl diimidazole (CDI). We now report an investigation into the *C*-acylation reactions of methyl cyanoacetate, also using N-protected glycines as the acylating reagents and describe the procedure of formation of the intermediates imidazolides **2** and of the imidazolinium enol salts **3** we observed (see Sch. 1 and Table 1). In this process obviously the CDI is the amino acid activation reagent. Simultaneously the presence of imidazole (ImH), which is liberated during the formation of the amino acid imidazolide, is sufficient to create the basic medium required for the cyanoacetate anion formation. Actually, ^{1}H NMR spectroscopy revealed that amino acid **1** is rapidly and quantitatively converted to its imidazolide **2** and that addition of methyl cyanoacetate in the imidazolide solution results in a rather fast but remarkably clean reaction, to the imidazolinium enol salt **3**. The ^{1}H NMR of a sample of the reaction mixture withdrawn after 60 min at room temperature disclosed the disappearance of amino acid and the exclusive formation of the corresponding imidazolide **2**. After 24 h the transformation of imidazolide **2** to imidazolium salt **3** through a smooth and clean reaction was revealed with the same procedure. It is reasonable to assume that the upfield shift of signals for compounds **3** (relatively to the corresponding of compounds **4**) were assigned to the enol anion formed.

The samples (usually 1 mL) were withdrawn from the reaction flask mixture and concentrated in vacuo (at room temperature). Their solids or retinous mass residues showed clean ^{1}H NMR spectra (see Table 1) which were only indicative, without correspondence to the precise chemical shifts, because the samples contained some impurities (e.g., imidazole in the aromatic region). Attempts for purification (e.g., by recrystallization) of these intermediates were ineffective probably because of their thermal instability in the solvent.

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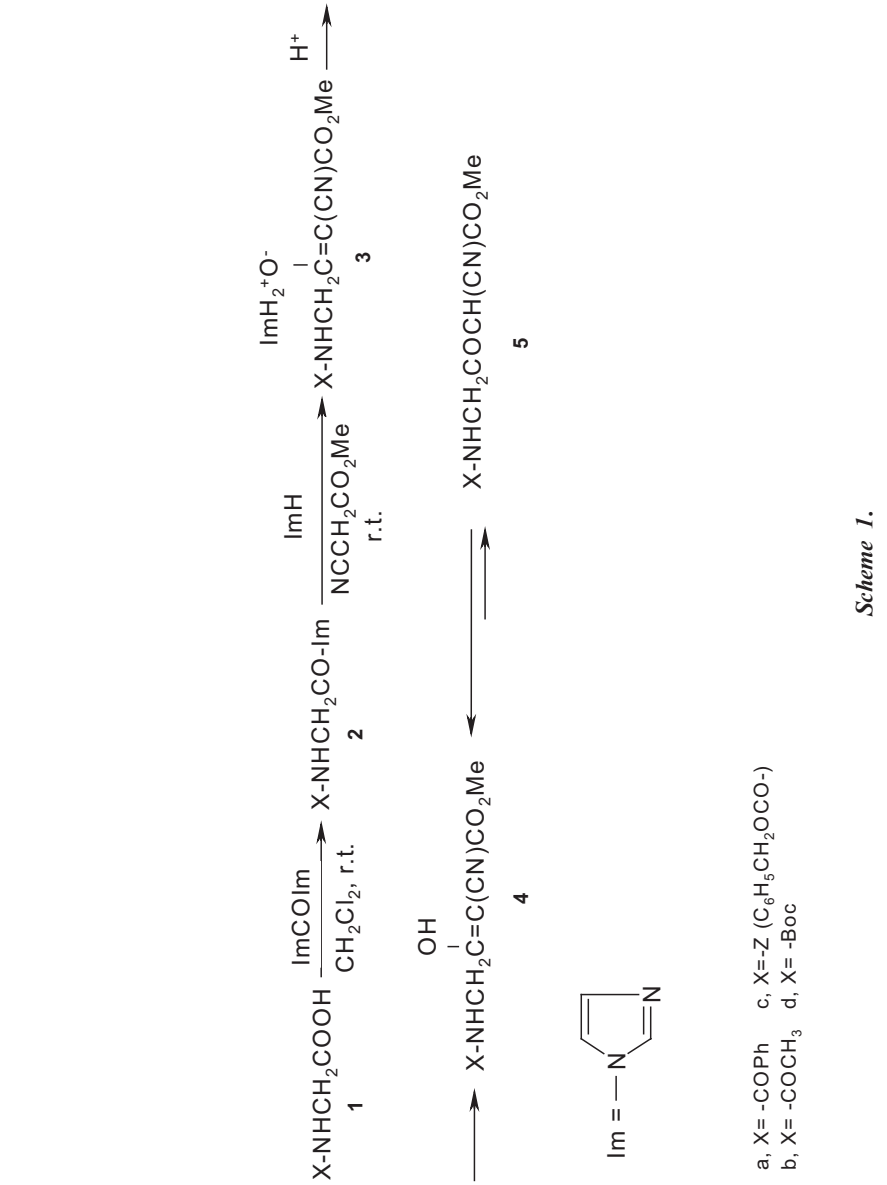

Scheme 1.

Table 1.

	X-NHCH$_2$CO$_2$H		*X*-NHCH$_2$COIm		*X*-NHCH$_2$C(OImH$_2^+$)=C(CN)CO$_2$Me			*X*-NHCH$_2$C(OH)=C(CN)CO$_2$Me		
		1		**2**		**3**			**4**	
Compound	*X*	NCH$_2$CO	*X*	NCH$_2$CO	*X*	NCH$_2$CO	CO$_2$Me	*X*	NCH$_2$CO	CO$_2$Me
a, *X*= -COPh		4.13, d *J*=4.5 Hz		4.78, d *J*=5 Hz		4.42, br s[a]	3.58, s[a]		4.56, d *J*=6 Hz	3.88, s
b, *X*= -COMe	2.02, s	3.93, d *J*=4.5 Hz	2.12, s	4.62, d *J*=6 Hz	1.88, s[a]	4.15, br s[a]	3.51, s[a]	2.05, s	4.28, d *J*=6 Hz	3.89, s
c, *X*= -*Z*	5.06, s CH$_2$	3.87, d *J*=4.5 Hz	5.13, s CH$_2$	4.52, br s	5.05, s CH$_2$	4.46, br s	3.62, s	5.12, s CH$_2$	4.27, d *J*=6 Hz	3.88, s
d, *X*= -Boc	1.45, s	3.85, d *J*=4.5 Hz	1.49, s	4.51, br s	1.46, s	4.45, br s	3.65, s	1.46, s	4.23, d *J*=6 Hz	3.90, s

[1]H NMR spectra were registered in $CDCl_3$ or in $CDCl_3$/DMSO-d_6[a], the phenyl aromatic protons, which superimposed with imidazole aromatics are not characteristic and not referred.

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The acylation compounds **4** were isolated, after acidification of the reaction mixture, in high yields, 85–87.5% after recrystallization. It must be pointed out that the crude compounds **4** showed clean ^{1}H NMR spectra, devoid of any impurities, such as the by-products which were observed when N-protected amino acids were acylated under different activation conditionst.[7,8,10]

The ^{1}H NMR spectra of compounds **4** (see Experimental) are consistent with the enolic (and not the keto tautomer **5**) structure of the acylated cyanoacetates, as shown by the presence of a broad singlet at low field, δ 11.30–13.30 ppm; this signal is assigned to the enol-OH proton which participates in an intramolecular hydrogen bond.[11] In agreement with their enolic structure, compounds **4a–d** give an intense orange color with an aqueous solution of ferric chloride.

In conclusion, the *C*-acylation of methyl cyanoacetate with N-protected glycines has been performed by a simple experimental procedure using the imidazolide activation method. The ^{1}H NMR spectra of aminoacetylcyanoacetates, are consistent with their enolic structure. The progress of formation and the purity of intermediates (imidazolides and enol-imidazolinium salts) has been examined. The application of the imidazolide activation to acylation reactions with chiral N-protected amino acids is currently being investigated.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. The ^{1}H NMR spectra were recorded on a Varian EM-360 60 MHz spectrometer, chemical shifts are given in ppm (δ) downfield from TMS (internal standard). The IR spectra were obtained with a Nicolet Magna 560 spectrometer; as nujol mulls and were calibrated against the polystyrene 1601 cm^{-1} band, and given in reciprocal centimetres.

General Procedure for the Aminoacetylation Reaction

To a solution or suspension of the acid **1** (10 mmol) in dichloromethane (40 mL), 1,1′-carbonyldiimidazole (10.1 mmol) was added. The reaction flask was protected with a calcium chloride drying tube and the mixture stirred for 60 min, until the gas (CO_2) evolution ceased and a solution was obtained. Methyl cyanoacetate (10 mmol) was then added and the solution was stirred at room temperature for an additional 20 h.

The solution (or suspension), was cooled with ice-water and 20 mL of 10% hydrochloric acid were added dropwise under vigorous stirring. If a suspension was formed additional dichloromethane was added until a solution was obtained. The organic phase was separated and the aqueous layer was extracted thrice with 10 mL of dichloromethane, the combined organic layers were dried (magnesium sulfate) and concentrated to a solid which proved to be almost pure (^{1}H NMR) compound **4**.

2-Hippuryl-2-cyano-methylacetate (4a). Yield, 86.5%, m.p. 145–146°C, Lit. m.p. 146–147°C.[7] IR (Nujol mull): 1530, 1640, 2222, 3270. ^{1}H NMR ($CDCl_3$): δ 3.88 (s, 3H, -CH_3,), 4.56 (d, $J = 6$ Hz, 2H, -CH_2-), 6.80 (br m, 1H, NH), 7.28–7.98 (m, 5H, Ph-), 11.80 (br s, 1H, enolic -OH).

Methyl 4-acetylamino-2-cyano-3-hydroxybut-2-enoate (4b). Yield, 85%, m.p. 149–151°C, Lit. m.p. 151–152°C.[8] IR (Nujol mull): 1550, 1665, 2221, 3290. ^{1}H NMR ($CDCl_3$): δ 2.05 (s, 3H, -COMe), 3.89 (s, 3H, OMe), 4.28 (d, $J = 6$ Hz, 2H, $-CH_2$-), 7.66 (br m, 1H, NH), 11.30 (br s, 1H, enolic -OH).

2-(*N*-*Z*-Glycyl)-2-cyano-methylacetate (4c). Yield, 86%, m.p. 101–102°C, Lit. m.p. 104–105°C.[9] IR (Nujol mull): 1535, 1660, 1694, 2225, 3320. ^{1}H NMR ($CDCl_3$): δ 3.88 (s, 3H, -CH_3), 4.27 (d, $J = 6$ Hz, 2H, -CH_2-), 5.12 (s, 2H, OCH_2Ph), 5.35 (br m, 1H, NH), 13.30 (br s, lH, enolic -OH).

2-(*N*-Boc-glycyl)-2-cyano-methylacetate (4d). Yield, 87.5%, m.p. 104–106°C, Lit. m.p. 105–107°C.[9] IR (Nujol mull): 1515, 1660, 1690, 2230, 3365. ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9H, CMe_3), 3.90 (s, 3H, OMe), 4.23 (d, $J = 6$ Hz, 2H, -CH_2-), 5.16 (br m, 1H, NH), 12.90 (br s, 1H, enolic -OH).

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