Alkylation of α-Isocyanoacetamides; Synthesis of 1,4,4-Trisubstituted 5-Oxo-4,5-dihydroimidazoles[1]

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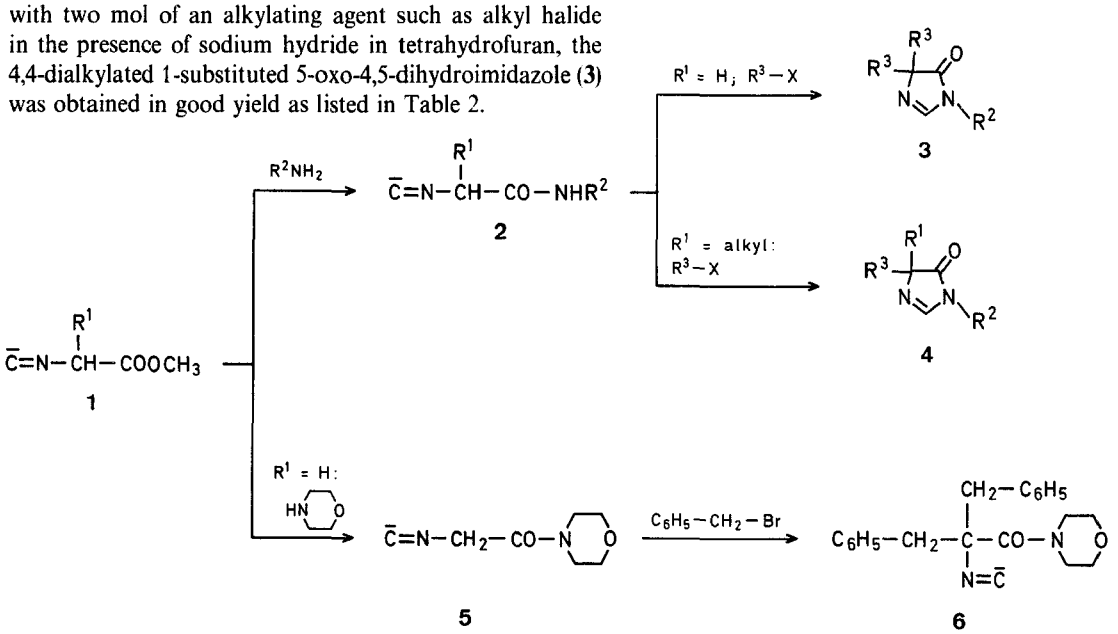
In the course of our studies on the syntheses of amino acids and related compounds, we have reported the reaction of α-isocyanoacetates with alkylating agents to produce α-alkylated amino acids[2]. In this study, the alkylation was extended to α-isocyanoacetamides to synthesize the 5-oxo-4,5-dihydroimidazole ring system which is not only a pharmaceutically interesting class of heterocyclic compounds, but also a useful intermediate for α-amino acids[3].

Namely, when *N*-monosubstituted α-isocyanoacetamide (**2**, $R^1 = H$), which is easily prepared by the amidation of methyl α-isocyanoacetate (**1**) (see Table 1), was allowed to react with two mol of an alkylating agent such as alkyl halide in the presence of sodium hydride in tetrahydrofuran, the 4,4-dialkylated 1-substituted 5-oxo-4,5-dihydroimidazole (**3**) was obtained in good yield as listed in Table 2.



Similarly, the reaction using α-alkyl-α-isocyanoacetamides (**2**, $R^1 = CH_3$, *i*-C_3H_7) was also carried out, the corresponding 4,5-dihydroimidazole derivatives (**4**) being formed.

The structures of the products (**3** and **4**) were confirmed by spectral and analytical data as summarized in Table 2. The formation of **3** or **4** would proceed as follows: the alkylating reagent should react with the α-carbon atom of the amide compound **2**, subsequently the cyclization probably occurred by an insertion of the isocyano group into the NH group of the amide moiety. Moreover, the alkylation of the tertiary amide compound, e.g. morpholinoisocyanoacetamide (**5**) with benzyl bromide, was also carried out and consequently α-isocyano-α-benzylphenylpropanoic acid morpholine amide (**6**), which is also converted into an amino acid by hydrolysis, was formed in 36% yield.

Preparation of α-Isocyanoacetamides (2); General Procedures:
A mixture of methyl α-isocyanoacetate (**1**, 0.03 mol), amine (0.07 mol) and methanol (20 ml) was stirred for 2–48 h at room temperature, then the reaction mixture was concentrated under reduced pressure, and the resultant residue extracted with ethyl acetate. The extract was washed with water, dried with sodium sulfate, and evaporated in vacuo. The residual crystals were washed with ether and then collected by filtration or chromatographed on silica gel (70 g, Kieselgel 60, 0.063–0.200 mm, Merck) with chloroform/ethyl acetate (10:1) as eluent to give the amide **2**. The results are summarized in Table 1.

Table 1. Yields, Physical, and Analytical Data of α-Isocyanoacetamides (**2a–e** and **6**)

Compound	R^1	R^2	m.p.[a]	Yield [%]	I.R. (nujol) ν_{max} [cm^{-1}]	Molecular-formula[b]
2a	H	*n*-C_3H_7	40–41°	79	3320, 2150, 1680	C_6H_9NO (111.1)
2b	H	$-CH_2C_6H_5$	120–122°	82	3300, 2160, 1655	$C_{10}H_{10}N_2O$ (174.2)
2c	H	*cyclo*-C_6H_{11}	121–122°	72	3280, 2160, 1663	$C_9H_{14}N_2O$ (166.2)
2d	CH_3	$-CH_2C_6H_5$	68–70°	80	3300, 2150, 1660	$C_{11}H_{12}N_2O$ (188.2)
2e	*i*-C_3H_7	$-CH_2C_6H_5$	77–79°	56	3300, 2140, 1655	$C_{13}H_{16}N_2O$ (216.3)
6	—	—	63–65°	81	2160, 1665	$C_7H_{10}N_2O_2$ (154.2)

[a] Recrystallization from a mixture of benzene and *n*-hexane.
[b] All products gave satisfactory microanalyses (C ±0.29%, H ±0.19%, N ±0.40%).

Table 2. Yield, Physical, and Analytical Data of 1,4,4-Trisubstituted 5-Oxo-4,5-dihydroimidazoles (**3a–d** and **4a, b**).

Compound	R^1	R^2	R^3	m.p. (solvent)	Yield [%]	I.R. (nujol) ν_{max} [cm^{-1}]	Molecular formula[a]
3a	—	*i*-C_3H_7	$-CH_2C_6H_5$	99–100° (aq. ethanol)	69	1712, 1610	$C_{20}H_{22}N_2O$ (306.4)
3b	—	$-CH_2C_6H_5$	$-CH_2C_6H_5$	128–130° (ethanol)	76	1705, 1620	$C_{24}H_{22}N_2O$ (354.5)
3c	—	*cyclo*-C_6H_{11}	$-CH_2C_6H_5$	134–135° (aq. ethanol)	78	1710, 1615	$C_{23}H_{26}N_2O$ (346.5)
3d	—	$-CH_2C_6H_5$	CH_3	oil[b]	77	(1720, 1610)[c]	—
4a	CH_3	$-CH_2C_6H_5$	$-CH_2C_6H_5$	101–103° (benzene)	87	1710, 1615	$C_{18}H_{18}N_2O$ (278.4)
4b	*i*-C_3H_7	$-CH_2C_6H_5$	$-CH_2C_6H_5$	70–71° (*n*-hexane)	70	1708, 1610	$C_{20}H_{22}N_2O$ (306.4)

[a] All products gave satisfactory microanalyses (C ±0.31%, H ±0.07%, N ±0.08%).
[b] Purification by silica gel column chromatography (Kieselgel 60, 0.063–0.200 mm, Merck, chloroform eluent).
[c] Film.

Preparation of 1,4,4-Trisubstituted 5-Oxo-4,5-dihydroimidazoles (3 and 4); Typical Procedure:

A mixture of *N*-benzyl isocyanoacetamide (1.74 g, 0.01 mol), benzyl bromide (3.42 g, 0.02 mol) and tetrahydrofuran (20 ml) was added dropwise to a stirred suspension of sodium hydride (66%, 0.8 g, 0.022 mol) and tetrahydrofuran (30 ml) at 25°, during this time the internal temperature rose up to 40°. After stirring was continued for 1 h at room temperature, the mixture was neutralized with 10% acetic acid under cooling and then concentrated under reduced pressure. The resultant residue was extracted with ethyl acetate and the extract was washed with water, dried with sodium sulfate, and then evaporated in vacuo. The residual crystals were washed with ether and isolated by suction. Recrystallization from ethanol gave *1,4,4-tribenzyl-5-oxo-4,5-dihydroimidazole* (**3b**) as colorless needles: yield 2.70 g (76%).

^{1}H-N.M.R. ($CDCl_3$): δ = 7.00–7.30 (m, 14H, CH and 13H_{arom}), 6.20–6.50 (m, 2H_{arom}), 4.10 (s, 2H, NCH_2), 3.22 ppm (s, 4H, CH_2).

α-Isocyano-α-benzylphenylpropanoic Acid Morpholine Amide (6):

A mixture of morpholinoisocyanoacetamide (**5**, 1.0 g, 6.5 mmol), benzyl bromide (2.23 g, 0.013 mol) and tetrahydrofuran (15 ml) was added dropwise to a stirred suspension of sodium hydride (66%, 0.57 g, 0.016 mol) and tetrahydrofuran (15 ml) at 27–30°. After stirring was continued for 1.5 h at room temperature, the mixture was neutralized with 10% acetic acid under cooling and then concentrated under reduced pressure. The resultant residue was chromatographed on silica gel (50 g, Kieselgel 60, 0.063–0.200 mm, Merck) with chloroform/ethyl acetate (10 : 1) and recrystallization of the resultant product from n-hexane gave **6** as colorless prisms; yield 0.75 g (36%); m.p. 69–70°.

$C_{21}H_{22}N_2O_2$	calc.	C 75.42	H 6.63	N 8.38
(334.4)	found	75.14	6.79	8.26

I.R. (Nujol): ν_{max} = 2220, 1630 cm^{-1}

^{1}H-N.M.R. ($CDCl_3$): δ = 7.35 (s, 10H_{arom}), 2.90–3.80 ppm (m, 12H, CH_2 and morpholine H).

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