A Facile Synthesis of Methyl 1,5-Disubstituted Imidazole-4-carboxylates[1]

Kiwamu Hiramatsu, Ken-ichi Nunami,* Kimiaki Hayashi, Kazuo Matsumoto

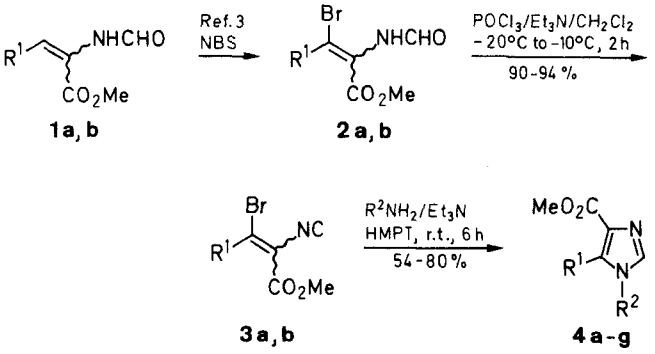
Research Laboratory of Applied Biochemistry. Tanabe Seiyaku Co., Ltd., 16–89 Kashima-3-chome, Yodogawa-ku, Osaka 532, Japan

Various methyl 1,5-disubstituted imidazole-4-carboxylates are synthesized by the reaction of methyl 3-bromo-2-isocyanoacrylates with a variety of primary amines in the presence of triethylamine.

In connection with the synthetic studies[2] on biologically interesting amino acids and heterocyclic compounds using isocyanoacetic acid analogs, we have recently focused our attention on the multifunctional 3-bromo-2-isocyanoacrylic acid derivatives. We previously reported the facile synthesis of β-substituted β-amino-α,β-didehydro-α-amino acid, α,β-didehydrocysteine, and α,β-didehydroserine derivatives utilizing these kind of reactive molecules.[3]

In this paper, we wish to report an extension of the reactivity of these molecules to the synthesis of methyl 1,5-disubstituted imidazole-4-carboxylates, useful intermediates in pharmaceutical and agricultural science, for which only one direct synthetic method has been reported[4] so far.

3-Substituted 2-formylaminoacrylates **1** were first converted to 3-substituted 3-bromo-2-isocyanoacrylates **3** via 3-substituted 3-bromo-2-formylaminoacrylates **2** by treatment with *N*-bromosuccinimide (NBS)[3] followed by dehydration of the formyl group with phosphoryl chloride and triethylamine.[5] Reaction of 3-bromo analogs **3** with two equimolar of primary amines in hexamethylphosphoric triamide (HMPT) at room temperature directly gave methyl 1,5-disubstituted imidazole-4-carboxylates **4** in good yield (Table). The formation of **4** was detected by Dragendorff reagent on TLC and the ^{1}H-NMR spectra showed imidazole N=CH–N signals at $\delta = 7.38 - 7.70$. This facile method can be applied not only for the regioselective synthesis of not easily attainable N^1-substituted imidazoles, but also for the preparation of 5-aryl- or 1,5-diarylimidazoles.



1–3	R^1	4	R^1	R^2
a	Ph	a	Ph	$PhCH_2$
b	Et_2CH	b	Et_2CH	$PhCH_2$
		c	Ph	$PhCH_2CH_2$
		d	Ph	3-Picolyl
		e	Ph	Me
		f	Et_2CH	4-MeOPh
		g	Ph	Ph

Table. Methyl 1,5-Disubstituted Imidazole-4-carboxylates **4a–g** Prepared

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula[a]	IR (Nujol) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)		
					OCH_3	$CH_{imidazole}$	others
4a	80	111–113 (EtOAc/*i*-Pr_2O)	$C_{18}H_{16}N_2O_2$ (292.3)	1700	3.76	7.56	4.96 (s, 2H, CH_2), 6.84–7.52 (m, 10H_{arom})
4b	61	80–81 (*i*-Pr_2O)	$C_{17}H_{22}N_2O_2$ (286.4)	3100, 1710	3.64	7.40	0.62 (t, 6H, J = 7.4, CH_2CH_3), 1.58–1.96 (m, 4H, CH_2CH_3), 2.71–3.34 (m, 1H, CH), 5.12 (s, 2H, CH_2Ph), 7.04–7.11 (m, 2H_{arom}), 7.24–7.34 (m, 3H_{arom})
4c	78	Syrup	$C_{19}H_{18}N_2O_2$ (306.4)	3200, 1720[b]	3.76	7.38	2.80 (t, 2H, J = 7.0, CH_2Ph), 4.03 (t, 2H, J = 7.0, CH_2N), 6.82–6.91 (m, 2H_{arom}), 7.19–7.21 (m, 5H_{arom}), 7.41–7.49 (m, 3H_{arom})
4d	71	115–116 (EtOAc/*i*-Pr_2O)	$C_{17}H_{15}N_3O_2$ (293.3)	3010, 1700	3.78	7.64	5.02 (s, 2H, CH_2), 7.20–7.28 (m, 4H_{arom}), 7.38–7.45 (m, 3H_{arom}), 8.20 (s, 1H_{arom}), 8.53 (t, J = 3.2, 1H_{arom})
4e	74	140–141 (EtOAc/*i*-Pr_2O)	$C_{12}H_{12}N_2O_2$ (216.2)	3100, 1690	3.74	7.50	3.48 (s, 3H, NCH_3), 7.24–7.59 (m, 5H_{arom})
4f	54	130–131 (EtOAc/*i*-Pr_2O)	$C_{17}H_{22}N_2O_3$ (302.4)	1700	3.85	7.40	0.71 (t, 6H, J = 7.4, CH_2CH_3), 1.49–1.94 (m, 4H, CH_2CH_3), 2.61–2.94 (m, 1H, CH), 3.88 (s, 3H, Ar–OCH_3), 6.97 (d, 2H_{arom}, J = 4), 7.13 (d, 2H_{arom}, J = 4)
4g	59	153–155 (EtOAc/*i*-Pr_2O)	$C_{17}H_{14}N_2O_2$ (278.3)	3090, 1715	3.83	7.70	6.98–7.43 (m, 5H_{arom}), 7.26 (s, 5H_{arom})

[a] Satisfactory microanalyses obtained: C ±0.36, H ±0.26, N ±0.28.
[b] IR spectrum obtained as film.

All melting points were measured with a Yamato MP-21 melting point apparatus and are uncorrected. IR spectra were determined on a Shimadzu IR-420 spectrophotometer. ^{1}H-NMR spectra were recorded on a Hitachi R-20A (90 MHz) and Bruker AC-200 (200 MHz) spectrometers. Column chromatography was carried out on silica gel, Kieselgel 0.040–0.063 mm Merck.

Methyl (*E*)- and (*Z*)-3-Bromo-2-isocyanocinnamate (3a); Typical Procedure:

$POCl_3$ (5.1 g, 33 mmol) is added dropwise to a mixture of methyl (*E*)- and (*Z*)-3-bromo-2-formylaminocinnamate[3] (**2a**; 8.52 g, 30 mmol) and Et_3N (8.41 g, 83 mmol) in CH_2Cl_2 (30 mL) at −10 °C to −20 °C under vigorous stirring. The mixture is stirred at r.t. for 2 h and then poured into 20% aq K_2CO_3 (30 mL). The organic layer is washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. The resultant oil is chromatographed on a silica gel column using $CHCl_3$ as an eluent to give a mixture of (*E*)- and (*Z*)-**3a** as a colorless oil; yield: 7.2 g (90%).

IR (film): ν = 2110, 1740 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 3.65, 3.92 (2 s, 3H, OCH_3), 7.23–7.63 (m, 5H_{arom}).

Methyl (E)- and -(Z)-3-Bromo-4-ethyl-2-isocyano-2-hexenoate (**3b**): colorless oil; yield: 94%.

IR (film): ν = 2110, 1735 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 0.82 (t, 6H, J = 7.4 Hz, CH_3CH_2), 1.34–1.74 (m, 4H, CH_3CH_2), 3.56–3.96 (m, 1H, CH), 3.82 (s, 3H, OCH_3).

Methyl 1-Phenethyl-5-phenylimidazole-4-carboxylate (4c); Typical Procedure:

Phenethylamine (0.53 g, 4.4 mmol) is added dropwise to a solution of **3a** (1.06 g, 4 mmol) and Et_3N (0.62 mL, 4.4 mmol) in HMPT (4 mL) under ice cooling. After stirring is continued at r.t. for 6 h, the mixture is poured into a mixture of Et_2O and sat. aq $NaHCO_3$. The organic layer is dried ($MgSO_4$) and concentrated *in vacuo*. The residue is chromatographed on a silica gel column using EtOAc/hexane (1:1) as an eluent to afford methyl 1-phenethyl-5-phenylimidazole-4-carboxylate (**4c**) as a colorless oil; yield: 0.96 g (78%).

Received: 8 January 1990; revised: 17 April 1990

(1) Synthesis of Amino Acids and Related Compounds, Part 39. Part 38:
Takiguchi, K.; Yamada, K.; Suzuki, M.; Nunami, K.; Hayashi, K.; Matsumoto, K. *Agric. Biol. Chem.* **1989**, *53*, 77.
(2) Matsumoto, K.; Moriya, T.; Suzuki, M. *Yuki Gosei Kagaku Kyokaishi* **1985**, *43*, 764; *C.A.* **1985**, *103*, 160064.
(3) Nunami, K.; Hiramatsu, K.; Hayashi, K.; Matsumoto, K. *Tetrahedron* **1988**, *44*, 5467.
(4) Hunt, J.T.; Bartlett, A.P. *Synthesis* **1978**, 741.
(5) Suzuki, M.; Nunami, K.; Moriya, T.; Matsumoto, K.; Yoneda, N. *J. Org. Chem.* **1978**, *43*, 4933.