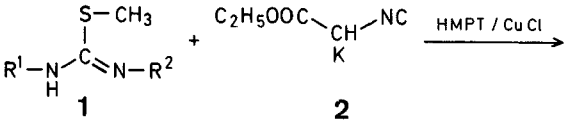
Regioselective Synthesis of 5-Amino-4-imidazolecarboxylates via Isonitrile Cycloaddition

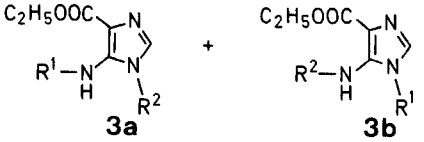
John T. Hunt, Paul A. Bartlett*

Department of Chemistry, University of California, Berkeley, California 94720, U.S.A.

Although 1,3-dipolar cycloaddition reactions of α-metallated isonitriles have gained prominence in heterocycle synthesis[1], their application to the preparation of imidazole derivatives has been limited, focusing primarily on nitriles and imidoyl chlorides as dipolarophiles[2]. We have developed a synthesis of 5-amino-4-imidazolecarboxylic esters **3** by the condensation of isothioureas **1** with the enolate of ethyl isocyanoacetate (**2**). Previously, derivatives of **3** have been prepared in a number of steps by the cyclization of α-formamidoamidines[3], and the condensation of primary amines with α-(ethoxymethyleneamino)-cyanoacetates[4]. The present method offers the advantage of a short, convergent route to the substituted ring system under mild conditions. Moreover, with unsymmetrical isothioureas, good regiocontrol is observed with a variety of different substituents (see Table).



1 **2**



3a **3b**

The condensation of the isothioureas with the potassium salt of ethyl isocyanoacetate (**2**) is carried out in hexamethylphosphoric triamide for several hours at room temperature with catalysis by copper(I) chloride. Copper(I) oxide in stoichiometric amounts will also effect the condensation, starting with the neutral ester. In the absence of copper(I) salts no reaction is observed. Copper(I) ion has been shown pre-

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Table. 5-Amino-4-imidazolecarboxylates **3** from Isothioureas **1** and **2**

Entry	R^1	R^2	Yield[a] [%]	Ratio[b] **3a**/**3b**	m.p. (solvent)	Molecular Formula[c]	I.R. ($CHCl_3$) ν_{max} [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	U.V. (ethanol) λ_{max} [nm] (log ε)
1	C_6H_5	C_6H_5	75	—	157–159° (C_2H_5OAc/hexane)	$C_{18}H_{17}N_3O_2$ (307.4)	3390 (NH); 1685 (CO); 1610, 1590	1.4 (t, 3H); 4.4 (q, 2H); 6.5–7.3 (m, 11H); 7.4 (s, 1H, NH)	210 (4.32); 248 (4.38); 291 (3.86)
2	C_6H_5—CH_2	C_6H_5	66	≥10:1	—[d]	$C_{19}H_{19}N_3O_2$ (321.4)	3385 (NH); 1680 (CO); 1610, 1590	1.2 (t, 3H); 3.8 (d, 2H); 4.3 (q, 2H); 6.2 (br t, 1H, NH); 6.8–7.5 (m, 11H)	213 (4.26); 226 (4.27); 281 (4.12)
3	H	C_6H_5—CH_2	30	≤1:20[e]	—[d]	$C_{13}H_{15}N_3O_2$ (245.3)	3250 (NH); 1675 (CO); 1605	1.2 (t, 3H); 4.3 (q, 2H); 4.7 (d, 2H); 5.7 (s, 1H, H-2); 7.3 (m, 6H)	212 (4.17); 227 (s); 292 (4.24)
4	C_6H_5—CH_2	C_6H_5—CO	70	1:4	144–145° [$(i\text{-}C_3H_7)_2O$/C_2H_5OAc]	$C_{20}H_{19}N_3O_3$ (349.4)	3400 (NH); 1695 (CO); 1600	1.3 (t, 3H); 4.3 (q, 2H); 5.2 (s, 2H); 7.0–8.0 (m, 11H); 9.2 (br s, 1H, NH)	213 (4.01); 231 (4.08); 265 (s)
5[f]	*c*-C_6H_{11}	*c*-C_6H_{11}	30	—	145–147° [$(i\text{-}C_3H_7)_2O$/C_2H_5OAc]	$C_{18}H_{29}N_3O_2$ (319.5)	3380 (NH); 1680 (CO); 1580	1.1–2.3 (m, 23H); 3.0 (m, 1H); 3.8 (m, 1H); 4.4 (q, 2H); 5.0 (br d, 1H, NH); 7.3 (s, 1H, H-2)	271 (3.87)

[a] Yield of recrystallized or chromatographed material.
[b] Ratios determined by ^{1}H-N.M.R. Physical properties reported for major isomer.
[c] All products gave satisfactory microanalyses (C ±0.39%; H ±0.13%; N ±0.30%).
[d] Obtained as an analytically pure gum after chromatography.
[e] **3a** (R^1 = H, R^2 = $C_6H_5CH_2$) detectable only by T.L.C. comparison with authentic material[5].
[f] Starting material: dicyclohexylcarbodiimide.

viously to catalyze the addition of nucleophiles to the carbenoid carbon of isonitriles[6], as well as the addition of alcohols to carbodiimides[7].

The intermediacy of carbodiimides in the reactions reported here cannot be completely ruled out: dicyclohexylcarbodiimide, for instance, reacts with **2** under the standard conditions to give a 30% yield of cycloadduct[2b] (entry 5, Table) in a sluggish reaction which also requires copper(I) ion. Nonetheless, neither copper(I) oxide nor **2** alone convert *N*,*N'*-diphenylisothiourea to the carbodiimide.

Whatever factors are responsible for the regioselectivity observed in the condensations of unsymmetrical isothioureas, there is no correlation between the substitution pattern of the imidazole and the position of the C=N double bond in the starting material[8]. These isonitrile carbanion cycloadditions therefore appear to be stepwise, as has been observed in a number of other systems[1,9].

Representative Procedure; Ethyl 1-Phenyl-5-phenylamino-4-imidazolecarboxylate:

A solution of **2** is prepared in hexamethylphosphoric triamide (0.5 ml) from ethyl isocyanoacetate[10] (1.7 mmol) and potassium hydride (1.7 mmol), and added to a mixture of *S*-methyl-*N*,*N'*-diphenylisothiourea[11], (**1**; $R^1 = R^2 = C_6H_5$; 190 mg, 0.8 mmol) and copper(I) chloride (30 mg, 0.3 mmol) in hexamethylphosphoric triamide (0.2 ml) at 0°[12]. After stirring for 4 h at 25°, the reaction is quenched with aqueous ammonium chloride, the mixture is extracted three times with ethyl acetate, and the combined organic layer is washed with water, dried with magnesium sulfate, and evaporated. Column chromatography (silica gel, 25% ether/ethyl acetate) affords **3** ($R^1 = R^2 = C_6H_5$); yield: 190 mg (75%).

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[12] Two equivalents of **2** are required for reaction with the benzoyl (entry 4, Table) and diphenyl (entry 1) isothioureas, because the products are sufficiently acidic to protonate **2**. For the other cases, more than one equiv of **2** was without effect.