An Expedient Synthesis of Ethyl 4(5)-Alkyl(aryl)thioimidazole-5(4)-carboxylate

Jean C. Caille,*[1] Stanislas Didierlaurent, Dominique Lefrançois, Marie H. Lelièvre, Christelle Sury, Jozsef Aszodi
Centre de Recherche Roussel-Uclaf, F-93235 Romainville Cedex, France
Fax + 33(41)427655

Received 19 October 1994; revised 3 January 1995

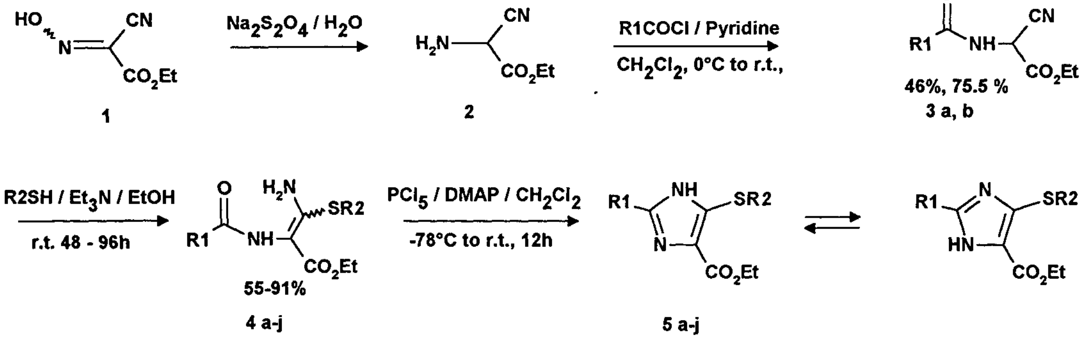
Various ethyl 4-alkyl(aryl)thioimidazole-5-carboxylates have been synthesized by the reaction of ethyl valeramidocyanoacetate with a variety of alkyl(aryl) thiols in the presence of triethylamine and subsequent phosphorus pentachloride/4-dimethylaminopyridine (DMAP) mediated cyclization of the acyclic intermediates.

In connection with our synthetic studies on biologically interesting imidazoles we have recently focused our attention on the multifunctional 4-alkyl(aryl)thioimidazole derivatives. Although there are a few known syntheses of this framework,[2-7] we decided to investigate a new convergent approach, starting from inexpensive and/or commercially available starting materials. In this paper, we wish to report our efforts towards the preparation of the aforementioned compounds which constitute useful intermediates in medicinal chemistry.

Commercially available ethyl isonitrocyanoacetate (**1**) was reduced to the corresponding amino derivative **2** according to Ref. 8. The crude amine was acylated with valeryl chloride to give the ethyl valeramidocyanoacetate (**3b**). Reactions of this nitrile **3b** with three equivalents of thiol in the presence of 10 % of triethylamine in ethanol at room temperature gave **4** as a mixture of inseparable isomers (Table 1) according to NMR. It was not possible to decide on the basis of the NMR spectrum which isomer was predominating.

The cyclization step was carried out on the *Z*/*E* mixture of **4** by treatment with two equivalents of phosphorus pentachloride in the presence of 4-dimethylaminopyridine and subsequent hydrolysis with a saturated solution of sodium hydrogen carbonate, to give **5** (Table 2).

It is worth mentioning that a preliminary attempt to cyclize the intermediate **4a** by using trifluoromethanesulfonic/triphenylphosphine oxide[9] led to a different compound of unknown structure having the same molecular weight.



3	R1	4-5	R1	R2
a	Me	a	Me	Et
b	Bu	b	Bu	Me
		c	Bu	Et
		d	Bu	CH_2-CH_2-OAc
		e	Bu	CH_2-CO_2tBu
		f	Bu	Ph
		g	Bu	CH_2-Ph
		h	Bu	CH_2-C_6H_4-(4)OMe
		i	Bu	C_6H_4-(4)OMe
		j	Bu	C_6H_4-(4)F

Downloaded by: Universite Laval. Copyrighted material.

Table 1. Ethyl (*E*)- and (*Z*)-3-Amino, 3-Alkyl(aryl)thio, 2[(1-Oxopentyl)amino]-prop-2-enoates **4a–j** Prepared

Product[a]	*Z*/*E* Ratio[b]	Yield (%)	mp (°C)	IR ($CHCl_3$) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)
4a	55 : 45	83[c]	123	3412, 3369, 3278, 1681, 1660	1.23, 1.26 (2t, 3H, *J* = 7, $CO_2CH_2C\underline{H}_3$), 1.33, 1.37 (2t, 3H, *J* = 7.5, $SCH_2C\underline{H}_3$), 1.88, 2.07 (2S, 3H, $COCH_3$), 2.84 (q, 2H, *J* = 7.5, SCH_2), 4.12 (q, 2H, *J* = 7, CO_2CH_2), 6.06, 6.33 (2s, 1H, NH), 6.89 (m, 2H, NH_2).
4b	65 : 35	80	110	3500, 3411, 3365, 3275, 1661	0.89, 0.94 [2t, 3H, *J* = 7.5, $C\underline{H}_3(CH_2)_3$], 1.23, 1.25 (2t, 3H, *J* = 7, $CO_2CH_2C\underline{H}_3$), 1.25–1.70 [m, 4H, $(CH)_2$], 2.12, 2.27 (m and t, 2H, *J* = 7.5, CH_2CO), 2.34, 2.35 (2s, 3H, SCH_3), 4.12, 4.14 (2q, 2H, *J* = 7, CO_2CH_2) 5.96, 6.15 (2 br s, 1H,. NH), 6.75 (br s, 2H, NH_2)
4c	70 : 30	72	111	3500, 3414, 3370, 3280, 1725, 1710	0.88, 0.94 [2t, 3H, *J* = 7.5, $C\underline{H}_3(CH_2)_3$], 1.23, 1.25 (2t, 3H, *J* = 7, $CO_2C\underline{H}_2CH_3$), 1.33, 1.36 (2t, 3H, *J* = 7.5, $SCH_2C\underline{H}_3$), 1.17–1.80 [m, 4H $(CH_2)_2$], 2.11, 2.27 (m and t, 2H, *J* = 7.5, CH_2CO), 2.83 (q, 2H, *J* = 7.5, SCH_2), 4.12 (q, 2H, *J* = 7, CO_2CH_2), 5.99, 6.19 (2br s, 1H, NH), 6.84 (br s, 2H, NH_2)
4d	65 : 35	60	84	3485, 3412, 3375, 3280, 1736, 1666	0.88, 0.94 [2t, 3H, *J* = 7 $(CH_2)_3C\underline{H}_3$], 1.23, 1.25 (2t, 32H, *J* = 7, $CO_2CH_2C\underline{H}_3$), 1.30–1.80 [m, 4H, $(CH_2)_2$], 2.10, 2.12 (2s, 3H, $COCH_3$), 2.12, 2.27 (m and t, 2H, *J* = 7.5, CH_2CO), 3.03 (t, 2H, *J* = 7, SCH_2), 4.12 (q, 2H, *J* = 7, CO_2CH_2), 4.22, 4.23 (2t, 2H, *J* = 7, OCH_2), 6.00, 6.20 (2br s, 1H, NH), 7.20, 7.44 (2 s, 2H, NH_2)
4f	65 : 35	86	115	3471, 3411, 3360, 3287, 1662	0.93, 0.95 [2t, 3H, *J* = 7, $(CH_2)_3C\underline{H}_3$], 1.24, 1.26 (2t, 3H, *J* = 7, $CO_2CH_2C\underline{H}_3$), 1.30–1.80 [m, 4H, $(CH_2)_2$], 2.22, 2.33 (m and t, 2H, *J* = 7.5, CH_2CO), 4.44 (m, 2H, CO_2CH_2), 6.10, 6.25 (2 br s, 1H, NH), 6.40 (br s, 2H, NH_2), 7.40–7.65 (m, 5H_{arom})
4g	70 : 30	85	132	3470, 3410, 3370, 3280, 1665	0.89, 0.92 [2t, 3H, *J* = 7 $(CH_2)_3C\underline{H}_3$], 1.22, 1.23 (2t, 3H, *J* = 7, $CO_2CH_2C\underline{H}_3$), 1.30–1.75 [m, 4H $(CH_2)_2$], 2.12, 2.25 (br t and t, 2H, *J* = 7, 7.5, CH_2CO), 4.07 (s, 2H, SCH_2), 4.10 (q, 2H, *J* = 7, CO_2CH_2), 6.05, 6.15 (2s, 1H, NH), 6.71 (br s, 2H, NH_2), 7.30–7.40 (m, 5H_{arom})
4h	70 : 30	90	120	3488, 3458, 3411, 3360, 1665	0.89, 0.91 [2t, 3H, *J* = 7, $(CH_2)_3C\underline{H}_3$], 1.22, 1.23 (2t, 3H, *J* = 7, $CO_2CH_2C\underline{H}_3$), 1.25–1.70 [m, 4H $(CH_2)_2$], 2.11, 2.25 (br t and t, 2H, *J* = 7.5, CH_2CO), 3.80, 3.81 (2s, 3H, OCH_3), 4.03 (br s, 2H, SCH_2), 4.10 (q, 2H, *J* = 7, CO_2CH_2), 5.99, 6.15 (2s, 1H, NH), 6.87, 6.89, 7.30 (4H_{arom})
4i	60 : 40	91	122	3470, 3415, 3370, 3290, 1660	0.92, 0.95 [2t, 3H, *J* = 7, $(CH_2)_3C\underline{H}_3$], 1.24, 1.25 (2t, 3H, *J* = 7, $CO_2CH_2C\underline{H}_3$), 1.30–1.80 [m, 4H $(CH_2)_2$], 2.10–2.30, 2.32 (m and t, 2H, *J* = 7.5, CH_2CO), 3.85, 3.86 (2s, 3H, OCH_3), 4.12 (m, 2H, CO_2CH_2), 6.08, 6.22 (2s, 1H, NH), 6.98, 7.48 (2m, 4H_{arom})
4j	65 : 35	67	118	3475, 3410, 3370, 3290, 1663	0.93, 0.95 [2t, 3H, *J* = 7, $(CH_2)_3C\underline{H}_3$], 1.24, 1.26 (2t, 3H, *J* = 7, $CO_2CH_2C\underline{H}_3$), 1.30–1.80 [m, 4H $(CH_2)_2$], 2.22, 2.33 (m and t, 2H, *J* = 7.5, CH_2CO), 4.14) m, 2H, CO_2CH_2), 6.10, 6.25 (2 br s, 1H, NH), 6.40 (br s, 2H, NH_2), 7.40–7.65 (m, 5H_{arom})

[a] All products **4a–j** refer to a mixture of *E*- and *Z*-isomers. Compound **4e** was not isolated. After carrying out the reaction in CH_2Cl_2, the crude product was used directly in the next step. Satisfactory microanalyses obtained: C ± 4.2, H ± 0.11, N ± 0.24, S ± 0.28.

[b] The predominance of either *Z*- or *E*-isomer could not be determined by ^1H NMR spectroscopy.

[c] The reaction was carried out in $EtOH/CH_2Cl_2$ (60 : 40).

The yield of cyclization depends slightly on the nature of the chosen base. 4-Dimethylaminopyridine turned out to be better than pyridine but 4-pyrrolidinopyridine did not improve the yield. Besides, similar results seem to be possible by using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), though fewer attempts have been made with this latter base.

The role of sodium hydrogen carbonate also seems to be crucial in hydrolyzing a putative phosphate complex. Practically, it is necessary to stir the crude mixture after addition of the base for half an hour before performing the extraction.

In summary, the method described here is a simple practical procedure for the preparation of ethyl 4-alkyl(aryl)thioimidazolecarboxylates **5** in fairly good yields.

All solvents and amines were dried and stored under a N_2 atmosphere. All other reagents were used as commercially available without further purification. The reactions were carried out under moisture-free conditions. Melting points were determined on a Köfler block and are uncorrected. Microanalyses were performed in our laboratories. ^1HNMR spectra were recorded either on a Bruker WP60 (60 MHz) or a Bruker WM 250 (250 MHz) spectrometer. IR spectra were recorded on a Perkin-Elmer 580 spectrometer.

Ethyl 2-Amino-2-cyanoacetate (2):

To a stirred solution of the oxime **1** (70 g, 490 mmol) in H_2O (700 mL) and sat. $NaHCO_3$ (560 mL) was added portionwise, throughout 30 min $Na_2S_2O_4$ (238 g). The solution effervesced and its temperature rose to about 22 °C. Then the temperature was raised to 35 °C and the mixture stirred at 35 °C for 1 h. After this time the solution was saturated with NaCl, extracted with CH_2Cl_2 (5 × 500 mL) and then the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give the crude product **2** as an oil which must be used immediately in the next step; yield: 36.7 g (58 %).

Ethyl 2-[(1-Oxopentyl)amino]-2-cyanoacetate (3b):

To a stirred solution of freshly prepared amine **2** (6.71 g, 52.36 mmol) in CH_2Cl_2 (100 mL) at 0–5 °C was added dropwise pyridine (4.24 mL, 52.36 mmol). Then, valeryl chloride (6.31 mL, 52.36 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 30 min,

Downloaded by: Universite Laval. Copyrighted material.

Table 2. Ethyl 4(5)-Alkyl-(aryl)thioimidazole-5(4)-carboxylates **5a–j** Prepared

Product[a]	Yield (%)	mp (°C)	IR ($CHCl_3$) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
5a	43	114	3438, 3257, 1671, 1546, 1501	1.38, 1.39 (2t, 6H, $J = 7$, $CH_2C\underline{H}_3$), 2.44 (s, 3H, $CH_3C=C$), 3.18 (q, 2H, $J = SCH_2$), 4.34 (q, 2H, $J = 7$, CO_2CH_2)
5b	72	74	3437, 3257, 1673	0.93 [t, 3H, $J = 7$, $C\underline{H}_3(CH_2)_3$], 1.39 (t, 3H, $J = 7$, $OH_2C\underline{H}_3$), 1.39, 1.74 [2m, 4H, $C\underline{H}_3(CH_2)_2$], 2.64 (s, 3H, SCH_3), 2.82 (t, 2H, $J = 7.5$, $CH_2C=C$), 4.35 (q, 2H, $J = 7$, CO_2CH_2)
5c	76	syrup	3437, 3260, 1672	0.93 [t, 3H, $J = 7.5$, $C\underline{H}_3(CH_2)_3$], 1.37, 1.39 (2t, 6H, $J = 7$, $OCH_2C\underline{H}_3$), 1.39, 1.72 [2m, 4H, $CH_3(C\underline{H}_2)_2$], 2.72 (t, 2H, $J = 7.5$, $CH_2C=C$), 3.17 (q, 2H, $J = 7$, SCH_2), 4.35 (q, 2H, $J = 7$, CO_2CH_2)
5d	55	68	3443, 3260, 1733, 1675	0.94 [t, 3H, $J = 7$, $C\underline{H}_3(CH_2)_3$], 1.39 (t, 3H, $J = 7$, $OCH_2C\underline{H}_3$), 1.39, 1.71 (2m, 4H, $CH_3(C\underline{H}_2)_2$), 2.08 (s, 3H, $OCOCH_3$), 2.71 (t, 2H, $J = 7.5$, $CH_2C=C$), 3.41 (m, 2H, SCH_2), 4.35 (m, 4H, CO_2CH_2)
5e	43[b]	63	3438, 3260, 1726, 1672, 1544, 1498, 1369	0.93 [t, 3H, $J = 7$, $C\underline{H}_3(CH_2)_3$], 1.38 (t, 3H, $J = 7$, $OCH_2C\underline{H}_3$), 1.38, 1.72 [2m, 4H, $CH_3(C\underline{H}_2)_2$], 1.47 (s, 9H, $t\text{-}C_4H_9$), 2.73 (t, 2H, $J = 7{,}5$, $CH_2C=C$), 3.82 (s, 2H, SCH_2CO), 4.35 (q, 2H, $J = 7$, CO_2CH_2)
5f	84	74	3431, 3267, 1887, 1675	0.89 [t, 3H, $J = 7$, $C\underline{H}_3(CH_2)_3$], 1.31 (t, 3H, $J = 7$, $OCH_2C\underline{H}_3$), 1.33, 1.67 [2m, 4H, $CH_3(C\underline{H}_2)_2$], 2.68 (t, 2H, $J = 7.5$, $CH_2C=C$), 4.32 (q, 2H, $J = 7$, CO_2CH_2), 7.15–7.14 (m, 5H_{arom})
5g	83	120	3438, 3255, 1674	0.94 (t, 3H, $J = 7$, $C\underline{H}_3(CH_2)_3$), 1.36 (t, 3H, $J = 7$, $OCH_2C\underline{H}_3$), 1.36, 1.72 [2m, 4H, $CH_3(C\underline{H}_2)_2$], 2.73 (t, 2H, $J = 7.5$, $CH_2C=C$), 4.33 (q, 2H, $J = 7$, CO_2CH_2), 4.41 (s, 2H, SCH_2), 7.20–7.45 (m, 5H_{arom})
5k	72	105	3435, 3257, 1672	0.94 [t, 3H, $J = 7$, $C\underline{H}_3(CH_2)_3$], 1.36 (t, 3H, $J = 7$, $OCH_2C\underline{H}_3$), 1.36, 1.72 [2m, 4H, $CH_3(C\underline{H}_2)_2$], 2.73 (t, 2H, $J = 7.5$, $CH_2C=C$), 3.78 (s, 3H, OCH_3), 4.32 (q, 2H, $J = 7$, CO_2CH_3), 4.36 (m, 2H, SCH_2), 6.83, 7.32 (2m, 4H_{arom})
5i	71	96	3433, 1688	0.88 [t, 3H, $J = 7$, $C\underline{H}_3(CH_2)_3$], 1.37 (t, 3H, $J = 7$, $OCH_2C\underline{H}_3$), 1.33, 1.63 (2m, 4H, $CH_3(CH_2)_2$], 2.64 (t, 2H, $J = 7.5$, $CH_2C=C$), 3.80 (s, 3H, OCH_3), 4.36 (q, 2H, $J = 7$, CO_2CH_2), 6.87, 7.44 (2m, 4H_{arom})
5j	82	100	3432, 1688, 1676	0.89 [t, 3H, $J = 7$, $C\underline{H}_3(CH_2)_3$], 1.35 (t, 3H, $J = 7$, $OCH_2C\underline{H}_3$), 1.32, 1.66 (2m, 4H, $CH_3(C\underline{H}_2)_2$], 2.68 (t, 2H, $J = 7.5$, $CH_2C=C$), 4.34 (q, 2H, $J = 7$, CO_2CH_2), 6.99, 7.42 (2m, 4H_{arom})

[a] All products **5a–j** refer to a mixture of tautomers.
Satisfactory microanalyses obtained: C ± 0.33, H ± 0.13, N ± 0.19, S ± 0.33.

[b] Overall yield from **3b**.

the temperature being kept below 8 °C. The mixture was allowed to warm up to r.t. and stirred for an additional hour. When no more starting material remained as judged by TLC, the mixture was poured into a separatory funnel. The organic layer was washed successively with H_2O, brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to give a solid which was triturated with isopropyl ether to give a white solid; yield: 8.4 g (75.5 %); mp 88 °C.

$C_{10}H_{16}N_2O_3$	calc.	C 56.59	H 7.60	N 13.2
(212.2)	found	56.8	7.7	13.1

IR ($CHCl_3$): $\nu = 3429, 2250, 1758, 1692, 1493\ cm^{-1}$.

^1H NMR ($CDCl_3$/TMS): $\delta = 0.93$ (t, 3H, $J = 7$ Hz, $CH_2C\underline{H}_3$), 1.37 (t, 3H, $J =$ Hz, $OCH_2C\underline{H}_3$), 1.37 (m, 2H, $C\underline{H}_2CH_2$), 1.66 (m, 2H, $CH_2C\underline{H}_2$), 2.32 (m, 2H, $CH_2C=N$), 4.34 (m, 2H, $OC\underline{H}_2CH_3$), 5.54 (1H, d, $J = 7.5$ Hz, CH), 6.36 (1H, br, NH).

Ethyl (*E*)- and (*Z*)-3-Amino-3-ethylthio-2-[(1-oxopentyl)amino]-prop-2-enoate (4c); Typical Procedure:

To a stirred solution of amide **3b** (11.6 g, 54.6 mmol) in EtOH (250 mL) was added dropwise Et_3N (0.76 mL, 5.5 mmol) and ethanethiol (8 mL, 109 mmol). The mixture was stirred for 4 or 5 d at r.t. while small portions of ethanethiol were added until the starting material had disappeared as judged by TLC. The solvent and the excess of ethanethiol were removed by distillation to give a yellow solid which was triturated in isopropyl ether to give **4c** as a white solid; yield: 10.8 g (72 %); mp 111 °C (Table 1).

Ethyl 2-Butyl-4(5)-ethylthioimidazole-5(4)-carboxylate (5c); Typical Procedure:

To a stirred suspension of PCl_5 (3.03 g, 14.6 mmol) in CH_2Cl_2 (10 mL) was added dropwise under N_2 at –78 °C, a solution of 4-DMAP (1.96 g, 16 mmol). After the reaction mixture was kept at this temperature for 5 min, the enamine **4c** (2 g, 7.3 mmol) was added dropwise in CH_2Cl_2 (20 mL). The mixture was allowed to warm up to r.t. and stirred overnight. Sat. $NaHCO_3$ (200 mL) was added and the mixture was stirred for 1 h and poured into a separatory funnel. The aqueous layer was extracted with EtOAc (4 x 30 mL), the organic layers were washed successively with water, brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography on silica gel (EtOAc/CH_2Cl_2, 10:90) to give **5c** as a syrup; yield: 1.42 g (76 %) (Table 2).

The authors thank Dr. Catherine Lang for recording and interpretation of NMR spectra and Dr. Jean-Paul Vevert for fruitful discussions.

(1) Present address: Sipsy Laboratories, route de Beaucouzé, F-49240 Avrillé, France.

(2) Sen, A. K.; Mukhopadhyay, A. K. *Indian J. Chem. Sec. B.* **1981**, *20*, 275.

(3) Sen, A. K.; Sengupta, D. K. *Indian J. Chem. Sec. B.* **1983**, *22*, 30.

(4) Rahman, A.; Ila, H.; Junjappa, H. *J. Chem. Soc., Chem. Commun.* **1984**, 430.

(5) European Patent Appl. EP 168950; *Chem. Abstr.* **1986**, *105*, 78933.

(6) Spaltenstein, A.; Holler, T. P.; Hopkins, P. B. *J. Org. Chem.* **1987**, *52*, 2977.

(7) Van Leusen, A. M.; Schut, J. *Tetrahedron Lett.* **1976**, 285.

(8) Logemann, F. I.; Shaw, G. *Chem. Ind. (London)* **1980**, 541.

(9) Hendrickson, J. B.; Hussoin, Md. S. *J. Org. Chem.* **1987**, 52, 4137.

Downloaded by: Universite Laval. Copyrighted material.