ORGANIC LETTERS

2002
Vol. 4, No. 23
4133−4134

A Concise and Regioselective Synthesis of 1-Alkyl-4-imidazolecarboxylates

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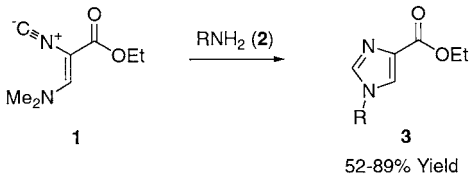
Received September 12, 2002

ABSTRACT



Reaction between ethyl 3-*N*,*N*-(dimethylamino)-2-isocyanoacrylate (1) and a primary amine (2) regioselectively affords 1-alkyl-4-imidazolecarboxylates (3) in good yields (52−89%). The method is applicable to unhindered and hindered amine substrates, as well as those containing reactive functionality such as alcohols and secondary and tertiary amines.

The imidazole nucleus is a common structural unit found in compounds of biological interest. As a result, a number of methods have been developed to prepare variously substituted imidazoles.[1] Despite the availability of such methods, the ability to efficiently access certain specific substitution patterns is limited and requires the design of new synthetic strategies.

A particular example of this is 1-alkyl-4-imidazolecarboxylates. Stereoselective routes are known for the synthesis of 1-aryl-4-imidazolecarboxylates,[2] 1-aryl-5-imidazolecarboxylates,[3] 1-alkyl-5-amino-4-imidazolecarboxylates,[4] and 1,5-dialkyl-4-imidazolecarboxylates.[5] Yet the only direct route to 1-alkyl-4-imidazolecarboxylates is via the alkylation of ethyl 4(5)-imidazolecarboxylate, which affords regioisomeric mixtures of alkylation products.[6] To overcome these issues, we have developed a simple and regioselective synthesis of 1-alkyl-4-imidazolecarboxylates (**3**) from a primary amine and readily prepared ethyl 3-*N*,*N*-(dimethylamino)-2-isocyanoacrylate (**1**).[7,8]

Representative examples of substituted imidazoles that are accessible via this chemistry and demonstrate the generality of the process are shown in Table 1. A range of steric substitution patterns about the primary amine is tolerated, and all afford the expected products in good yield, exemplified using *n*-alkylamines (**2a**, **2b**) and more hindered *sec*-

(1) For a review of some general methods of imidazole synthesis, see: (a) Gilchrist, T. L. *Heterocyclic Chemistry*; Longman: Essex, 1997; Chapter 8.1, pp 298−300. (b) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Thieme: New York, 1995; Chapter 5.33, pp 170−172. (c) Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry II*; Shinkai, I., Ed.; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds. in Chief; Elsevier: Tarrytown, 1996; Vol. 3, pp 185−209. (d) Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Katritzky, A. R., Rees, C. W., Eds. in Chief; Pergamon: Elmsford, 1984; Vol 5, pp 457−482.

(2) Combs, A. P.; Saubern, S.; Rafalski, M.; Lam, P. Y. S. *Tetrahedron Lett.* **1999**, *40*, 1623−1626.

(3) Chen, B.-C.; Bednarz, M. S.; Zhao, R.; Sunden, J. E.; Chen, P.; Shen, Z.; Skoumbourdis, A. P.; Barrish, J. C. *Tetrahedron Lett.* **2000**, *41*, 5453−5456.

(4) Hunt, J. T.; Bartlett, P. A. *Synthesis* **1978**, 741−742.

(5) (a) Nunami, K.-i.; Yamada, M.; Fukui, T.; Matsumoto, K. *J. Org. Chem.* **1994**, *59*, 7635−7642. (b) Hiramatsu, K.; Nunami, K.-i.; Hayashi, K.; Matsumoto, K. *Synthesis* **1990**, 781−782.

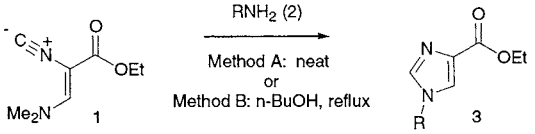
(6) Corelli, F.; Summa, V.; Brogi, A.; Monteagudo, E.; Botta, M. *J. Org. Chem.* **1995**, *60*, 2008−2015.

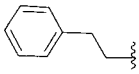
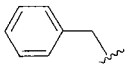
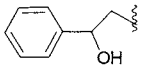
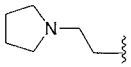
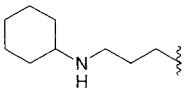
(7) For the first report of ethyl 3-*N*,*N*-(dimethylamino)-2-isocyanoacrylate (**1**), see: Kantlehner, W.; Wagner, F.; Bredereck, H. *Liebegs Ann. Chem.* **1980**, 344−357. **General procedure for preparation of 1.** Ethyl isocyanoacetate (5.4 mL, 49.5 mmol) and *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent, 20.4 mL, 99 mmol) were stirred at 23 °C for 24 h. Dimethylamine and *tert*-butyl alcohol were then removed in vacuo (90 °C, 1 Torr). The resulting residue could then be distilled following the literature procedure (100−102 °C, 0.001 Torr) or purified via silica gel chromatography (from 3:1 to 1:1 hexanes−ethyl acetate) to afford 4.7 g of **1** (57% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.18 (s, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.4−2.9 (brs, 6H), 1.30 (t, J = 7.1 Hz, 3H).

(8) For other chemistry using ethyl 3-*N*,*N*-(dimethylamino)-2-isocyanoacrylate (**1**) in heterocycle synthesis, see: (a) Lau, H.; Schollkopf, U. *Liebegs Ann. Chem.* **1982**, 2093−2095. (b) Heck, S.; Domling, A. *Synlett* **2000**, 424−426.

10.1021/ol026892k CCC: $22.00
Published on Web 10/18/2002

Table 1. Synthesis of 1-Alkyl-4-imidazolecarboxylates



	R	temp (°C)	time (h)	% yield (method)
a		70	1.5	74 (A)
b		70 150	2 15	80 (A) 68 (B)
c		70	2	89 (A)
d		140	48	62 (A)
e		70	1.5	61 (A)
f		70	2	85 (A)
g		70	2	52 (A)
h		70	72	31 (A)

alkyl (**2c**) and *tert*-alkylamines (**2d**). This is a key attribute of the method, as imidazole alkylation generally proceeds efficiently for unencumbered and/or activated alkylating agents. It should be noted that reaction times are roughly equivalent for the *n*-alkyl and *sec*-alkylamines (ca. 2 h, 70 °C), whereas the *tert*-alkylamine substrate necessitates a considerably longer reaction time and higher temperature (48 h, 140 °C).

Another salient feature of this chemistry is the chemoselectivity. Unprotected alcohols within the primary amine substrate are tolerated (**2e**) as are tertiary and secondary amine groups (**2f**, **2g**), all providing the desired imidazoles in good to high yields.

Aniline can also be used to prepare ethyl 1-phenyl-4-imidazolecarboxylate (**3h**), but a long reaction time is required and the yield is modest (72 h, 31%; Table 1, h).[9]

The reactions proceed most rapidly when run neat in 3 equiv of the primary amine (method A). Alternatively, *n*-butanol can be used as a solvent to improve amine solubility or reduce amine equivalents (Method B).

In summary, we have developed an operationally simple, regioselective, and efficient route for the synthesis of 1-alkyl-4-imidazolecarboxylates (**3**) utilizing the readily available starting material ethyl 3-*N*,*N*-(dimethylamino)-2-isocyanoacrylate (**1**). The method works well with unhindered and hindered amines as well as those containing alcohol and secondary and tertiary amine functionality.[10]

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(9) For an example of a related 1-heteroaryl-4-imidazolecarboxylate synthesis, see: Selic, L.; Stanovnik, B. *J. Heterocycl. Chem.* **1998**, *35*, 1527−1529.

(10) Representative procedures. **Method A: Ethyl-1-cyclopentyl-4-imidazolecarboxylate (3c).** Ethyl 3-*N*,*N*-(dimethylamino)-2-isocyanoacrylate (**1**) (875 mg, 5.2 mmol) and cyclopentylamine (1.33 mL, 15.6 mmol) were heated at 70 °C for 2 h. The excess amine was removed in vacuo, and the resulting residue was purified by silica gel chromatography (30:1 $CHCl_3$−MeOH) to afford 962 mg (89% yield) of **3c**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (s, 1H), 7.61 (s, 1H), 4.48 (m, 1H), 4.36 (q, J = 7.0 Hz, 2H), 2.23 (m, 2H), 1.9−1.7 (m, 6H), 1.38 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.1, 136.99, 133.96, 123.81, 60.48, 58.94, 33.81, 23.82, 14.55. IR (cm^{-1}): 2960, 1721, 1543, 1378, 1214, 1187, 1117, 1025, 760, 665. MS (CI): $(M + H)^+$ calcd, 209; $(M + H)^+$ found, 209.2. **Method B: Ethyl 1-benzyl-4-imidazolecarboxylate (3b).** A solution of ethyl 3-*N*,*N*-(dimethylamino)-2-isocyanoacrylate (**1**) (552 mg, 3.3 mmol) and benzylamine (432 uL, 4.0 mmol) in *n*-butanol (2.5 mL) was heated at reflux for 15 h. The solvent was removed in vacuo, and the residue was purified by silica gel chromatography ($CHCl_3$) to afford 515 mg (68% yield) of **3b**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (s, 1H), 7.47 (s, 1H), 7.25 (m, 3H), 7.08 (m, 2H), 5.04 (s, 2H), 4.23 (q, J = 7.05 Hz, 2H), 1.25 (t, J = 7.05 Hz, 3H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 162.97, 138.31, 135.31, 134.45, 129.32, 128.80, 127.71, 125.53, 60.64, 51.54, 14.56. IR (cm^{-1}): 2924, 1716, 1545, 1380, 1220, 1181, 1114, 1022, 971, 766, 711, 662. MS (CI): $(M + H)^+$ calcd, 231; $(M + H)^+$ found, 231.1