A Regiospecific Synthesis of 1,4-Disubstituted Imidazoles

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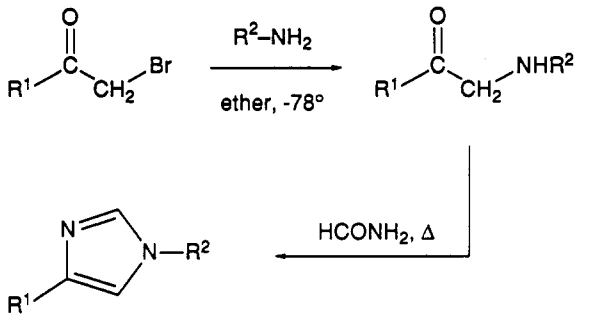
The imidazole ring appears in a variety of biologically active molecules, particularly as the functional nucleus of the amino acid histidine, which acts as a base to bind transition metal ions and protons. During the course of our work to prepare low-MW mimics of copper-containing proteins,[1] we required a versatile synthetic route to highly soluble, isomerically pure 1,4-disubstituted imidazoles. With few exceptions,[2] syntheses of such compounds have been accomplished by treating the conjugate base of 2,4-(5)-disubstituted imidazoles[3] and 4(5)-monosubstituted imidazoles[3c,4] with an electrophile such as $(CH_3)_2SO_4$ or $PhCH_2Br$. However, these prior studies show that *N*-alkylations of the imidazolate ion generally afford isomeric mixtures of products, complicating further transformations unless a separation step is included. Also, the introduction of *tert*-butyl or aryl groups on the nitrogen atom *via* nucleophilic alkylation is not possible, because the corresponding halides do not react by an S_N2 process. We report here a straightforward method for preparing isomerically pure 1,4-disubstituted imidazoles having methyl, isopropyl, or *tert*-butyl groups at the 4-position. Although the reactions proceed in only moderate yield, the products are not contaminated by the 1,5-regioisomer, and bulky groups are readily incorporated at the 1-position.

Previous work has shown that heating α-bromo- or α-amino ketones in formamide leads to the formation of the imidazole nucleus.[5] By that method, 4,5-diaryl-,[5] 4(5)-aryl-,[5] and 4(5)-*tert*-butylimidazole[6] have been prepared. Likewise, 4-*tert*-butyl-1-isopropyl-2-mercaptoimidazole has been made by condensing 1-(*N*-isopropylamino)-3,3-dimethyl-2-butanone with KSCN.[7] We reasoned that the reaction of α-alkylamino ketones with formamide should therefore produce 1,4-disubstituted imidazoles. Thus, solutions of primary amines in diethyl ether react with bromoacetone, 1-bromo-3-methyl-2-butanone, or 1-bromo-3,3-dimethyl-2-butanone to afford the corresponding unstable amino ketones by nucleophilic substitution. Subsequent heating in formamide causes the desired cyclization, producing crude 1,4-disubstituted imidazoles (Scheme 1), which could be purified by flash chromatography. Distillation or crystallization afforded the nine compounds shown in Table 1 in yields ranging from 20 to 82%.

Scheme 1



We are unaware of any other published routes to imidazoles **1**, **4**, **7**, and **9**; so the generality of the method reported here makes it the choice for preparing 1,4-disubstituted imidazoles. The nature of the substituent at the 4-position on the ring is restricted by the number of readily accessible bromomethyl ketones; but recent work, detailing the synthesis of α-halo ketones from halo alkenes, should circumvent this limitation.[8] There appears to be little restriction on the nature of the substituent that appears attached to the nitrogen atom, and we have obtained products using a variety of primary amines, except for hindered anilines.[9]

Experimental Section

1-Bromo-3-methyl-2-butanone was prepared according to the published procedure.[10] All other solvents and reagents were obtained from commercial sources and used without further purification. ^1H NMR spectra were recorded in $CDCl_3$ at 200.132 MHz, and peaks are reported in ppm relative to an internal standard of tetramethylsilane. Analtech precoated silica gel plates (0.25 mm) were used for thin-layer chromatography. Flash chromatography was carried out according to the general procedure of Still.[11] Melting points were determined using a Fisher-Johns apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Norcross, GA.

1,4-Disubstituted Imidazoles. General Procedure. Under an argon atmosphere, a pressure-equalizing dropping funnel charged with the bromomethyl ketone[12] (10.0 g) in diethyl ether (20 mL) was attached to a 300-mL round-bottomed flask, containing a magnetic stir bar and a solution of the primary amine (3 equiv for 1–7 or 2 equiv for 8 and 9) in diethyl ether (70 mL). The solution was stirred while cooling in a dry ice–acetone bath to −78 °C. The solution of the bromide was then added dropwise over 15 min, and the mixture was stirred for an

(1) Sorrell, T. N. *Tetrahedron* **1989**, *45*, 3.
(2) (a) Martin, P. K.; Matthews, H. R.; Rapoport, H.; Thyagarajan, G. *J. Org. Chem.* **1968**, *33*, 3758. (b) Padwa, A.; Smolanoff, J.; Tremper, A. *Tetrahedron Lett.* **1974**, 29. (c) van Leusen, A. M.; Wildeman, J.; Oldenziel, O. H. *J. Org. Chem.* **1977**, *42*, 1153. (d) O'Connell, J. F.; Parquette, J.; Yelle, W. E.; Wang, W.; Rapoport, H. *Synthesis* **1988**, 767. (e) Turner, R. M.; Lindell, S. D.; Ley, S. V. *J. Org. Chem.* **1991**, *56*, 5739.
(3) See, for example: (a) Masui, M.; Miyata, H.; Suda, K.; Yamauchi, M. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1960. (b) Grimmett, M. R. *Adv. Heterocycl. Chem.* **1980**, *27*, 241 and references therein. (c) Lipshutz, B. H.; Morey, M. C. *J. Org. Chem.* **1983**, *48*, 3745. (d) Suarez, A.; Vila, J. M.; Pereira, M. T.; Gayoso, E.; Gayoso, M. *J. Organomet. Chem.* **1987**, *335*, 359.
(4) (a) Pyman, F. L. *J. Chem. Soc.* **1910**, *97*, 1814. (b) Pyman, F. L. *J. Chem. Soc.* **1922**, *121*, 2616. (c) Hazeldine, C. E.; Pyman, F. L.; Winchester, J. *J. Chem. Soc.* **1924**, *125*, 1431. (d) Pyman, F. L.; Forsyth, W. G. *J. Chem. Soc.* **1925**, *127*, 573. (e) Burtles, R.; Pyman, F. L.; Roylance, J. *J. Chem. Soc.* **1925**, *127*, 581. (f) Jones, J. B.; Hysert, D. W. *Can. J. Chem.* **1971**, *49*, 3012. (g) Rapoport, H.; Matthews, H. R. *J. Am. Chem. Soc.* **1973**, *95*, 2297. (h) Takeuchi, Y.; Yeh, H. J. C.; Kirk, K. L.; Cohen, L. A. *J. Org. Chem.* **1978**, *43*, 3565. (i) Begtrup, M.; Larsen, P. *Acta Chem. Scand.* **1990**, *44*, 1050.
(5) Bredereck, H.; Theilig, G. *Chem. Ber.* **1953**, *86*, 88.
(6) Jonsson, A. *Acta Chem. Scand.* **1954**, *8*, 1389.
(7) Corey, E. J.; Brunelle, D. J. *Tetrahedron Lett.* **1976**, 3409.
(8) Morton, H. E.; Leanna, M. R. *Tetrahedron Lett.* **1993**, *34*, 4481.
(9) We could not obtain products using 2,6-dimethylaniline and *o*-anisidine. The relatively low nucleophilicity of anilines, coupled with steric crowding near the site of cyclization, apparently hampers the reaction with formamide. Note that the yield of compound **9**, which has an unhindered aryl substituent on the nitrogen atom, is the lowest of the imidazoles reported here.
(10) Gaudry, M.; Marquet, A. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. 6, p 193. This material slowly isomerizes at room temperature to 3-bromo-3,3-dimethyl-2-butanone.
(11) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

0022-3263/94/1959-1589$04.50/0

Table 1. Physical and Spectroscopic Data for 1,4-Disubstituted Imidazoles

compd	R^1	R^2	yield[a] (%)	R_f	^{1}H NMR data
1	Me	^{t}Bu	21	0.29	1.53 (9H, s, C(CH_3)$_3$), 2.23 (3H, d, J = 0.9 Hz, CH_3), 6.77 (1H, t, J = 1.1 Hz, C_5-H), 7.49 (1H, d, J = 1.5 Hz, C_2-H)
2	^{i}Pr	Et	27	0.37	1.26 (6H, d, J = 6.9 Hz, CH(CH_3)$_2$), 1.43 (3H, t, J = 7.4 Hz, CH_2CH_3), 2.89 (1H, sept, J = 6.9 Hz, CH(CH$_3$)$_2$), 3.90 (2H, q, J = 7.4 Hz, CH_2CH_3), 6.62 (1H, t, J = 0.9 Hz, C_5-H), 7.37 (1H, d, J = 1.2 Hz, C_2-H)
3	^{i}Pr	^{i}Pr	47	0.39	1.26 (6H, d, J = 6.8 Hz, 4-CH(CH_3)$_2$), 1.46 (6H, d, J = 6.7 Hz, 1-CH(CH_3)$_2$), 2.88 (1H, sept, J = 6.8 Hz, 4-CH(CH$_3$)$_2$), 4.27 (1H, sept, J = 6.7 Hz, 1-CH(CH$_3$)$_2$), 6.65 (1H, t, J = 1.0 Hz, C_5-H), 7.43 (1H, d, J = 1.2 Hz, C_2-H)
4	^{i}Pr	^{t}Bu	34	0.43	1.25 (6H, d, J = 6.9 Hz, CH(CH_3)$_2$), 1.54 (9H, s, C(CH_3)$_3$), 2.87 (1H, sept, J = 6.9 Hz, CH(CH$_3$)$_2$), 6.73 (1H, t, J = 1.1 Hz, C_5-H), 7.50 (1H, d, J = 1.5 Hz, C_2-H)
5	^{t}Bu	Et	30	0.43	1.28 (9H, s, C(CH_3)$_3$), 1.41 (3H, t, J = 7.3 Hz, CH_2CH_3), 3.90 (2H, q, J = 7.3 Hz, CH_2CH_3), 6.61 (1H, d, J = 1.3 Hz, C_5-H), 7.39 (1H, d, J = 1.3 Hz, C_2-H)
6	^{t}Bu	^{i}Pr	39	0.48	1.28 (9H, s, C(CH_3)$_3$), 1.44 (6H, d, J = 6.7 Hz, CH(CH_3)$_2$), 4.25 (1H, sept, J = 6.7 Hz, CH(CH$_3$)$_2$), 6.64 (1H, d, J = 1.4 Hz, C_5-H), 7.42 (1H, d, J = 1.4 Hz, C_2-H)
7	^{t}Bu	^{t}Bu	28	0.53	1.29 (9H, s, 4-C(CH_3)$_3$), 1.54 (9H, s, 1-C(CH_3)$_3$), 6.71 (1H, d, J = 1.4 Hz, C_5-H), 7.52 (1H, d, J = 1.4 Hz, C_2-H)
8	^{t}Bu	benzyl	82	0.32	1.23 (9H, s, C(CH_3)$_3$), 5.00 (2H, s, NCH_2Ph), 6.55 (1H, d, J = 1.3 Hz, C_5-H), 7.05–7.45 (6H, m, ArH and C_2-H)
9	^{t}Bu	p-tolyl	20	0.54	1.35 (9H, s, C(CH_3)$_3$), 2.39 (3H, s, CH_3),6.95 (1H, d, J = 1.4 Hz, C_5-H),7.24 (4H, s, ArH), 7.75 (1H, d, J = 1.4 Hz, C_2-H)

[a] Refers to isolated products that were pure by TLC. Satisfactory analyses were obtained for all new compounds. These data were supplied to the referees.

additional 1 h at −78 °C. The cooling bath was removed and the mixture allowed to warm to room temperature and to stir for several hours, until precipitation of the HBr salts appeared complete. The contents of the flask were poured into a separatory funnel and shaken with a small amount of 15% aqueous NaOH until the while solids dissolved. The ether layer was washed with water and brine and dried over $MgSO_4$. Filtration and concentration of the solution afforded the crude α-amino ketone as a light yellow oil or solid. This material could be isolated by vacuum distillation or flash chromatography (yield 80–90%), but typically it was used immediately in its crude form.

A 300-mL two-necked flask with an attached air-cooled condenser was charged with formamide (35 mL), which was heated to 180 °C under argon with stirring. A pressure-equalizing dropping funnel containing the amino ketone was fitted to the reaction vessel, and the amino ketone was added dropwise over 1 h.[13] The mixture was then allowed to react for an additional 2–3 h (for **2**, **5**, and **8**) or 4–8 h (all others) at 180 °C. After cooling, the dark reaction mixture was treated with an equal volume of water and 20 mL of 15% aqueous NaOH. The mixture was extracted twice with 200-mL portions of toluene, which were combined, washed with water and brine, and dried over Na_2SO_4. The drying agent was removed by filtration, and the toluene was evaporated at reduced pressure to yield a yellow-brown oil, which was purified by flash chromatography.[14] For imidazoles **1**–**7**, 9:1 (v:v) ethyl acetate–methanol was used as the eluent; for **8** and **9**, ethyl acetate was used. Short-path distillation under reduced pressure with use of a Kugelrohr apparatus (entries **1**–**6** and **8**) or recrystallization from hexanes (**7**, mp 98–99 °C, and **9**, mp 71–72 °C) afforded the colorless, hygroscopic[15] 1,4-disubstituted imidazoles. Proton NMR analysis confirmed the 1,4-disubstitution pattern by the size of the "cross-ring" coupling constants, i.e. $J_{(C2H-C5H)} > 1.1$ Hz.[4g] Also, the proton on C_5 of **1**–**4** appears as a triplet because it is coupled to C_2–H *and* the methyl or methine proton(s) of the group on C_4.[4g]

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(12) Similar yields of **1** and **6** were obtained using chloroacetone and 1-chloro-3,3-dimethyl-2-butanone, respectively. The substitution of chloride ion by primary amines is extremely slow, and the reaction does not require cooling to −78 °C.

(13) Solid amino ketones were added in portions over the course of 1 h.

(14) There are several toluene-soluble side products detectable by TLC, although the desired imidazole is generally the largest component (by mass) of the toluene extracts. The corresponding tetraalkyl-1,2-dihydropyrazine (from the self-condensation of the α-amino ketone) was found to be one of the side products formed in the preparation of **1**, **2**, and **8**; an analysis of side reactions for the other imidazoles was not performed. The dihydropyrazines are readily identified by their complex ^{1}H NMR spectra. See: Lown, J. W.; Akhtar, M. H. *J. Chem. Soc., Perkin Trans. 1* **1973**, 683.

(15) If the products are not kept in a dry atmosphere, a peak from absorbed water can be detected in the ^{1}H NMR spectrum within hours.