A New Regioselective Synthesis of 1,2,5-Trisubstituted 1*H*-Imidazoles and Its Application to the Development of Eprosartan

Susan C. Shilcrat,* Mohamed K. Mokhallalati, Joseph M. D. Fortunak, and Lendon N. Pridgen*,†

Synthetic Chemistry Department, Chemical R&D, SmithKline Beecham Pharmaceuticals, P.O. Box 1539, King of Prussia, Pennsylvania 19406

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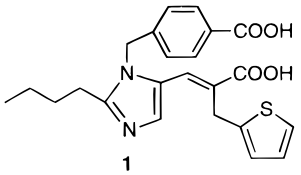
A new method is presented for the preparation of 1,2-disubstitued-1*H*-imidazole-5-carboxaldehydes by the reaction of *N*-monosubstituted amidines with 2-halo-3-alkoxy-2-propenals. The reaction is highly regioselective with ratios of 1,2,5:1,2,4-imidazolecarboxaldehydes ranging from 85:15 to 100:0. This methodology could be extended with similar results to the synthesis of imidazole-5-nitriles by the reaction of 2-bromo-3-methoxy-2-propenenitrile with *N*-monosubstituted amidines.

Introduction

Eprosartan (SK&F 108566, **1**) is one of a series of 1-(carboxybenzyl)imidazole-5-acrylic acids[1] that have been reported to be potent and selective angiotensin II receptor antagonists.[2] Key intermediates in the synthesis of this class of compounds are 1,2-disubstituted 1*H*-imidazole-5-carboxaldehydes **6a**−**l**. Two compounds, **6a** (R^1 = butyl; R^2 = CH_2Ph-4-COOMe) and **6k** (R^1 = butyl; R^2 = CH_2Ph-4-COOH), were of particular importance toward the preparation of SK&F 108566 and were required in multikilogram quantities.



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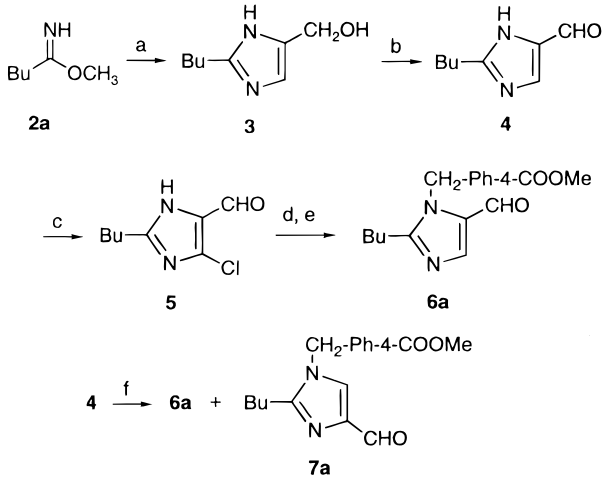
SK&F 108566 (Eprosartan)

Results and Discussion

The initial strategy toward synthesis of these molecules is shown in Scheme 1. This approach begins with the synthesis of 2-butyl-1*H*-imidazole-4-methanol (**3**) using methyl imidate **2a**. Imidazole **3** is oxidized and chlorinated to yield 2-butyl-4-chloro-1*H*-imidazole-5-carboxaldehyde[3] (**5**). A major drawback in this sequence of steps is the requirement to alkylate **5** in the 1-position with methyl 4-(bromomethyl)benzoate followed by dechlorination with 5% Pd/C to give **6a**. On scale-up, this sequence showed several inherent difficulties. The need to protect and subsequently deprotect the 4-position of the imidazole ring to ensure alkylation at the 1-position was inefficient and cumbersome. The chlorination/dechlorination sequence was addressed by the direct alkylation of 2-butyl-1*H*-imidazole-4-carboxaldehyde (**4**) with methyl 4-(bromomethyl)benzoate (Scheme 1). A chromatographically separable 1:1 mixture of regioisomers was obtained (**6a** and **7a**), resulting from nonselective alkylation at the 1 or 3 positions. On a pilot plant scale, **6a** and **7a** were separated by the formation of their respective bisulfite adducts. The less soluble, kinetically formed adduct **7a**, crystallized from the reaction medium, leaving behind a solution greatly enriched in **6a** that could be recovered in regiopurities greater than 98%. The synthesis of the early (hydroxymethyl)imidazole intermediate **3** involved reaction of high-pressure liquid ammonia with methyl valerimidate hydrochloride (**2a**) and 1,3-dihydroxyacetone dimer. Although the yields of **3** were generally good (70−75%), synthesis of large quantities of material by this procedure was not cost-effective. Overall, though nonregiospecific, this route still proved superior to the original one. Even though multikilogram quantities of **6a** were made in this manner, this procedure was still deemed unacceptable as a final

Scheme 1[a]



[a] Key: (a) 1,3-dihydroxyacetone dimer, NH_3, 60 °C; (b) MnO_2, CH_2Cl_2; (c) *N*-chlorosuccinimide; (d) methyl 4-(bromomethyl)benzoate, K_2CO_3, DMF; (e) H_2, Pd/C; (f) methyl 4-(bromomethyl)benzoate, tetraethylammonium hydroxide, DMF.

† To whom all inquiries should be addressed.

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(1) Weinstock, J.; Keenan, R. M.; Samanen, J.; Hempel, J.; Finkelstein, J. A.; Franz, R. G.; Gaitanopoulos, D. E.; Girard, G. R.; Gleason, J. G.; Hill, D. T.; Morgan, T. M.; Peishoff, C. E.; Aiyar, N.; Brooks, D. P.; Fredrickson, T. A.; Ohlstein, E. H.; Ruffolo Jr., R. R.; Stack, E. J.; Sulpizio, A. C.; Weidley, E. F.; Edwards, R. M.; Reiter, L. A. *J. Med. Chem.* **1991**, *34*, 1514.

(2) For other angiotensin II receptor antagonists, see (and references within): (a) Carini, D. J.; Duncia, J. V.; Johnson, A. L.; Chiu, A. T.; Price, W. A.; Wong, P. C.; Timmermans, P. B. *J. Med. Chem.* **1990**, *33*, 1330. (b) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B., III; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S. E.; Timmermans, P. B. *J. Med. Chem.* **1991**, *34*, 2525. (c) Pierce, M. E.; Carini, D. J.; Huhn, G. F.; Wells, G. J.; Arnett, J. F. *J. Org. Chem.* **1993**, *58*, 4642. (d) Furukawa, Y.; Kishimoto, S.; Nishikawa, K. U.S. Patent 4,355,040 1982.

(3) Watson, S. P. *Synth. Commun.* **1992**, *22*, 2971.

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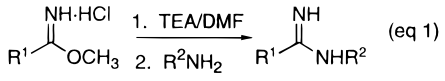
synthesis due to the inherent loss of one-half of available material, i.e., low to moderate yields, and to a dependence on **3** as a key intermediate.

We also examined the feasibility of hydroxymethylation of 2-butylimidazole in formalin. The reaction initially proceeded to give hydroxymethylation in the 5-position as desired. However, this material readily underwent further hydroxymethylation in the 4-position, giving a mixture of mono- and bis(hydroxymethylation) products. This is in agreement with other previous literature reports.[4] We were unable to obtain satisfactory yields of the 5-hydroxymethylated compound, and thus this route also was abandoned.

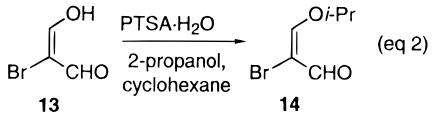
N-Monosubstituted amidines **12a**−**l** are readily synthesized in high yield by the reaction of the imidate **2a** or **2b** and a primary amine (eq 1).[5] Amidines have been

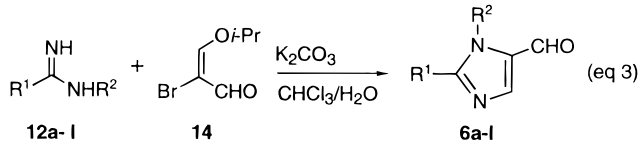


converted to imidazoles[6] and imidazolines[7] by condensation with a variety of 1,2 disubstituted synthons. One approach involved reaction of **12a** with either 2-bromo-3,3-diethoxypropanal[8] or 2-bromo-1,1,3,3-tetraethoxypropane.[9] However, we found both of these reagents to be relatively inaccessible. Our efforts to reproduce the literature preparations gave very low yields of material of questionable purity, making it difficult to evaluate their role in the formation of imidazoles.

In contrast to these molecules, halomalonaldehydes are stable, crystalline compounds.[10] Malonaldehyde bis(tetramethylacetal) can be readily converted in a single step to either 2-bromomalonaldehyde[11] (**13**) or 2-iodomalonaldehye.[12] Halomalonaldehydes have been reported as versatile synthons for a variety of heterocycles such as pyrazoles[13] and pyrimidines.[14] Amidinium salts have been reported to condense with a halomalonaldehyde to form halopyrimidines.[5b] However, treatment of 2-chloromalonaldehyde with thiobenzamide gave a good yield of 2-phenylthiazole-5-carboxaldehyde.[15] Thus, from these two observations, the question existed whether a halomalonaldehyde would undergo a 1,2-cyclization in our system to form the desired imidazolecarboxaldehyde or undergo 1,3-cyclization to form a halopyrimidine. Of particular interest was a report on the condensation of 2-bromomalonaldehyde with an *N*-arylamidine to form an imidazole-5-carboxaldehyde in good yield.[11] We were able to reproduce the literature results with *N*-arylamidine. However, when employing these reaction conditions using our *N*-benzylamidine **12a** (R^1 = butyl; R^2 = CH_2Ph-4-COOMe), we obtained a complex mixture of products in which the desired material was assayed (w/w) in only 10−20% yield. An extensive investigation of alternative reaction conditions did not appreciably improve this yield.

Concurrently, we attempted to synthesize 2-bromo-1,1,3,3-tetraethoxypropane as the 1,2-disubstituted synthon by the exhaustive acetalization of **13**. Our initial reaction produced a mixture of 2-bromo-1,1,3,3-tetraethoxypropane and 2-bromo-3-ethoxy-2-propenal. This mixture, in reaction with amidine **12a**, gave the imidazolecarboxaldehyde **6a** as the major product with 2-bromo-1,1,3,3-tetraethoxypropane recovered in total. Thus, it is the enol ether of **13** that is the active synthon in this reaction. We found that **13** can be converted in essentially quantitative yield to an enol ether derivative by reaction with an alcohol in an inert solvent such as chloroform or cyclohexane with acid catalyst and azeotropic removal of water (eq 2). A number of alcohols,



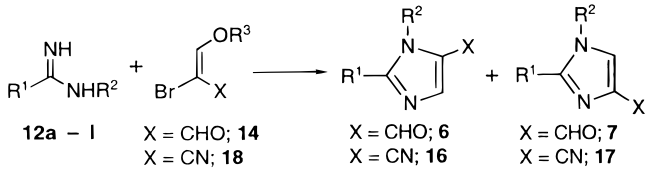


including ethanol, 2-propanol, *sec*-butanol, and 2-methyl-2-propanol, formed enol ethers that successfully participated in the imidazole-forming reaction. The best result, in terms of the long-term stability of the enol ether and the yield of imidazole, was obtained using the 2-propanol derivative, 2-bromo-3-(1-methylethoxy)-2-propenal (**14**). Identical reaction results were obtained using the halogenated enol ethers formed from 2-chloromalonaldehyde and 2-iodomalonaldehyde. However, because of its ease of synthesis and long-range stability, the bromo enol ether **14** was selected for use in large-scale synthesis.

Bromo enol ether **14** when reacted with a range of monosubstituted amidines gave imidazolecarboxaldehydes in moderate yields (eq 3) with no evidence of pyrimidine formation. More importantly, the reactions were regioselective. Table 1 shows the ratio of 1,2,5:1,2,4-imidazolecarboxaldehydes in the crude product, as determined by GC/MS (peak area ratio). Bulky substituents (e.g., Table 1, entries 7 and 8, R^2 = CH_2-1-naphthyl) at the 1-position generally ensured very high regioselectivity. The nature of the R^1 substituent, whether alkyl or aryl, did not seem to effect the yield of the imidazole product but showed a slight preference for **6** or **16** (see Table 1, entries 1 vs 2 and 7 vs 8). The best yields were obtained when R^2 was either alkyl or benzylic rather than aryl. When R^2 = Ph, better yields were obtained using the original procedure of Field *et al.*[11] utilizing 2-bromomalonaldehyde itself. The reaction was best run in a mixture of water and organic solvent. Several solvents (e.g., acetonitrile, THF, chloroform, and 1,2-dichloroethane) were found to be amenable to this reaction. The results herein were done using tetrahydrofuran or chloroform. The optimum ratio of organic solvent:water was 8:1 (v:v). Significant deviation of the solvent ratio in

(4) Godefroi, E. F.; Loozen, H. J. J.; Luderer-Platje, J. *Rec. Trav. Chim. Pays-Bas* **1972**, *91*, 1383.
(5) For a general review see: (a) Shriner, R. L.; Neumann, F. W. *Chem. Rev. (Washington, D.C.)* **1944**, *35*, 351. (b) Miocque, M.; Fauran, C.; Le Cloarec, A. Y. *Ann. Chim.* **1972**, *7*, 89.
(6) (a) Lipinski, C. A.; Blizniak, T. E.; Craig, R. H. *J. Org. Chem.* **1984**, *49*, 566. (b) Reiter, L. A. *J. Org. Chem.* **1984**, *49*, 3494. (c) Reiter, L. A. *J. Org. Chem.* **1987**, *52*, 2714.
(7) Marsura, A.; Luu-Duc, C.; Gellon, G. *Synthesis* **1985**, 537.
(8) (a) Wells, J. N.; Strahl, M. S. *J. Pharm. Sci.* **1971**, *60*, 533. (b) Sletzinger, M.; Reinhold, D.; Grier, J.; Beachem, M.; Tishler, M. *J. Am. Chem. Soc.* **1955**, *77*, 6365.
(9) Kirby, J. A. U.S. Patent 3,824,292, 1974.
(10) For a general review of the preparation and chemistry of halomalonaldehydes, see: Reichardt, C.; Halbritter, K. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 86.
(11) Field, G. F.; Zally, W. J. U.S. Patent 4,194,049, 1980.
(12) Reichardt, C.; Halbritter, K. *Liebigs Ann. Chem.* **1970**, *737*, 99.
(13) Reichardt, C.; Halbritter, K. *Liebigs Ann. Chem.* **1975**, 470.
(14) Roblin Jr., R. O.; Winnek, P. S.; English, J. P. *J. Am. Chem. Soc.* **1942**, *64*, 570.
(15) Silberg, A.; Benko, A.; Csavassy, G. *Chem. Ber.* **1964**, *97*, 1684.

Table 1. Results of Reaction of Amidines 12a−l with 2-Bromo-3-(1-methylethoxy)-2-propenal (14) (Eq 3) and 2-Bromo-3-methoxy-2-propenenitrile (18) (Eq 4)

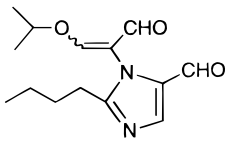


						isomer ratio[a]	
entry	amidine	R^1	R^2	yield (%),[b] **6**	yield (%),[b] **16**	**6**:**7**	**16**:**17**
1	**12a**	Bu	CH_2Ph-4-COOMe	52	43	85:15[e]	79:21
2	**12b**	Ph	CH_2Ph-4-COOMe	51	25	88:12	95:5
3	**12c**	Bu	CH_2-Ph	50	53	91:9	87:13
4	**12d**	Ph	CH_2-Ph	33	51	86:14	93:7
5	**12e**	Bu	Bu	42	45	94:6	100:0
6	**12f**	Ph	Bu	61	70	87:13	99:1
7	**12g**	Bu	CH_2-1-naphthyl	47	*c*	94:6	*c*
8	**12h**	Ph	CH_2-1-naphthyl	35	36	100:0	95:5
9	**12i**	Bu	Ph	38	*c*	87:13	*c*
10	**12j**	Ph	Ph	52	*d*	100:0	*d*
11	**12k**	Bu	CH_2Ph-4-COOH	83	*d*	90:10[e]	*d*
12	**12l**	Ph	CH_2Ph-4-COOH	51	*d*	*f*	*d*

[a] All yields are unoptimized except for **12k**. All compounds were stable except where indicated. GC/MS peak area ratios were used to determine isomer ratios from the crude product. All ratios reported could be improved to >99% by recrystallization from *tert*-butyl methyl ether or MEK/hexanes. [b] Yield of the desired regioisomer after chromatographic separation. [c] The nitrilo products were less stable than the aldehydes toward chromatography. As a consequence, we were unable to isolate and fully characterize minor isomers. [d] No reaction. [e] Determined by ^{1}H NMR (400 MHz) integration. [f] Not determined.

either direction resulted in much lower yields. Water is necessary to partially solubilize the acid-scavenging potassium carbonate, while an excess of water caused the hydrolysis of **14** to **13**. The reaction also proceeded well under anhydrous conditions using 18-crown-6 as a phase-transfer catalyst. Most amidines reacted readily at ambient temperature within 2−4 h. A more insoluble, unreactive amidine such as **12k** required reflux temperatures over 6−8 h for the reaction to proceed to completion. A variety of bases, both organic and inorganic, were tested in the reaction. Inorganic bases such as potassium carbonate performed best. When the reaction to form **6a** was performed in the presence of tetramethyl guanidine, a 6:1 ratio of 1,2,5:1,2,4-imidazolecarboxaldehydes was obtained. A 3:1 ratio was obtained for DBU.

An unsuccessful attempt was made to employ *unsubstituted* amidines (R^1 = butyl; R^2 = H) to synthesize imidazolecarboxaldehydes. The major product was postulated to be **15**, resulting from the alkylation of **14** onto the unprotected imidazole nitrogen. The regiochemistry of addition of this compound was not determined.



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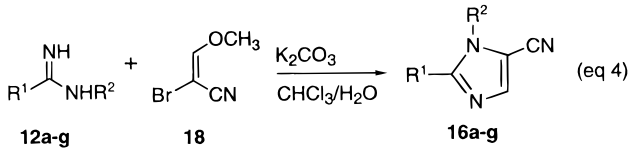
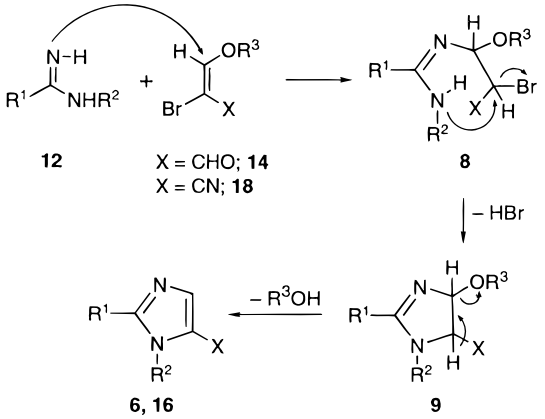
Having developed these reaction conditions, we found that we could extend the scope of this reaction to the synthesis of analogous 1,2-disubstituted imidazole-5-nitriles **16a**−**h** with good regioselectivity employing 2-bromo-3-methoxy-2-propenenitrile (**18**) (eq 4). This



(eq 4)

Scheme 2

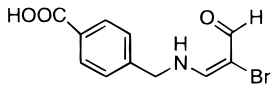


synthon proved to be less reactive than 2-bromo-3-(1-methylethoxy)-2-propenal (**14**). Reflux temperatures were necessary for the reaction to proceed. For those amidines that were relatively bulky or insoluble (e.g., Table 1, entries 10−12, R^1 = Ph, R^2 = Ph; R^1 = butyl, R^2 = CH_2-PhCOOH; R^1 = Ph, R^2 = CH_2PhCOOH, respectively), little or no product formation was achieved. Nevertheless, a wide range of amidines **12a**−**h** successfully reacted with **18** to form the desired imidazole-5-nitriles **16a**−**h** in good regioselectivity and moderate yields (Table 1).

One mechanism that would explain the high regioselectivity of this reaction is shown in Scheme 2. The unsubstituted nitrogen (an imino nitrogen except for **12i**, **j**) adds in a Michael fashion to the β-carbon bearing the alkoxy moiety. Attack by amidines at the β-carbon of analogous α,β-unsaturated esters, nitriles, and carbonyl compounds has been demonstrated.[16] This intermediate **8** cyclizes with extrusion of HBr to form **9**. Subsequent

(16) For a general review of the reactions of amidines with α,β-unsaturated esters, nitriles, and carbonyl derivatives, see Gautier, J.; Miocque, M.; Farnoux, C. C. In *The Chemistry of Amidines and Imidates*; Patai, S., Ed.; John Wiley & Sons; New York, 1975; Chapter 7, p 324−331.

loss of ROH results in either **6** or **16**. Initial attack by the monosubstituted nitrogen is disfavored, particularly in cases where R^2 is a bulky group (e.g., Table 1, entries 5−8, R^2 = butyl, CH_2-1-naphthyl). This Michael-type reaction is suggested by a minor byproduct **19** identified



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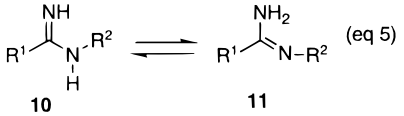
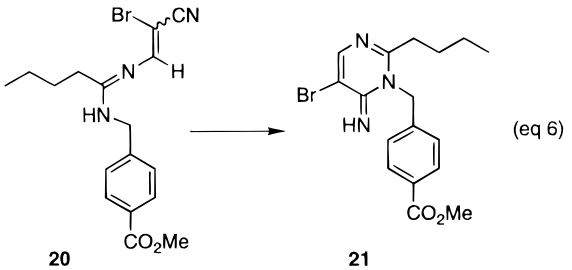
in the crude reaction product of **6k**, presumably formed from the reaction of *p*-aminomethylbenzoic acid (residual material from the synthesis of **12k**) with **14**. Initial attack onto the β-carbon of **14** is followed by loss of ROH in the absence of a mode of cyclization. For *N*-monosubstituted amidines, the literature implies that the amidine should exist in the imide form **10** when R^2 is alkyl, while other studies show that *N*-phenylamidines prevail in the amino form **11** (eq 5).[17] This may account for the poor yield obtained for the reaction of **12i**, as **14** may have difficulty reacting with an amidine in this tautomeric form.



10 **11**

Some additional support for this reaction mechanism is given by the isolation of the minor byproduct **21** from the reaction of **12a** with **18** to form **16a** (eq 6). The



20 **21**

pyrimidine structure of **21** was unambiguously determined by X-ray crystallography. The precursor of this molecule was conceivably an *N*,*N*′-disubstituted amidine **20** formed after the Michael reaction from an alternative loss of ROH rather than HBr. This molecule **20** then prefers to close in a 1,3-fashion onto the nitrile-forming pyrimidine **21**, rather than displace a vinylic bromide to form an imidazole. The reaction of amidines with β-difunctional compounds to form pyrimidines is known.[16] The rarity of observed pyrimidine formation in this transformation supports the prevalence of a mechanism in which HBr loss precedes the loss of ROH (Scheme 2).

In conclusion, *N*-monosubstitued amidines reacted in a regioselective manner with 2-halo-3-alkoxy-2-propenals and 2-bromo-3-methoxy-2-propenenitrile to form 1,2-disubstitued imidazole-5-carboxaldehydes and 1,2-disubstituted imidazole-5-nitriles in moderate yields. This reaction was scaled to produce multikilogram quantities of imidazole **6a**, a key intermediate in the synthesis the angiotensin II receptor antagonist SK&F 108566. This novel imidazole synthesis represents a significant improvement in the existing technology and provides a useful tool to design regioselective syntheses of 1,2,5-trisubstituted imidazoles.

(17) For a general discussion of amidine tautomerism, see: Hafelinger, G.; Fodor, G.; Phillips, B. A. In *The Chemistry of Amidines and Imidates*; Patai, S., Ed.; John Wiley & Sons; New York, 1975; Chapters 1 and 2.

Experimental Section

General Procedure. Melting points are uncorrected. Gas chromatography/mass spectroscopy (GC/MS) was done on a Hewlett-Packard capillary gas chromatograph Model 5790A with a mass selective detector Model 5790A using a DB-1, 15 m × 0.252 mm capillary column. Flash column chromatography was done using Baker silica for flash columns (~40 μm average particle diameter) as stated. Thin-layer chromatography (TLC) separations were accomplished on silica precoated plates (Analtech, Inc.) and were detected with UV light.

Starting Materials. 2-Bromomalonaldehyde (**13**) was synthesized from malonaldehyde bis(dimethylacetal) (Aldrich) according to the procedure of Field *et al.*[11] 2-Bromo-3-methoxy-2-propenenitrile (**18**) was purchased from EBU Chemical, Japan. Methyl benzimidate hydrochloride was either purchased from Aldrich or produced from benzonitrile in 60% yield in a manner similar to the synthesis of methyl valerimidate hydrochloride outlined below.

Methyl Valerimidate Hydrochloride (2a). A solution of valeronitrile (101.4 g, 1.22 mol) in methanol (42.6 g, 1.33 mol) was cooled to 0 °C under nitrogen. Hydrogen chloride (53.0 g, 1.45 mol) was bubbled below the surface of the liquid at a rate such that the reaction temperature remained below 15 °C. Stirring was continued over 18 h, producing a thick, white slurry. *tert*-Butyl methyl ether (250 mL) was added, and stirring was continued for an additional 3 h. The suspension was filtered under a flow of nitrogen and washed with additional *tert*-butyl methyl ether (150 mL). The filter cake was vacuum-dried for 2 h under a rubber dam. The product was obtained as a white, fuming, hygroscopic solid (132.2 g, 72%), which was stored under nitrogen in the freezer (−20 °C): mp 91−92 °C; IR (film) 3361, 3194, 3100−2800, 1662, 1415, 1315, 1242, 1142 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.90 (t, 3H, J = 7.4 Hz), 1.28−1.35 (m, 2H), 1.57−1.65 (m, 2H), 2.70 (t, 2H, J = 7.6 Hz), 4.13 (s, 3H), 6.55 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 9.7, 17.6, 23.2, 28.0, 56.0, 176.3.

2-Bromo-3-(1-methylethoxy)-2-propenal (14). 2-Bromomalonaldehyde (45.3 g, 0.30 mol) and *p*-toluenesulfonic acid monohydrate (0.86 g, 4.50 mmol) in a mixture of 2-propanol (92 mL, 1.20 mol) and cyclohexane (650 mL) were heated to reflux under nitrogen. The resultant azeotrope was removed from the reaction via a Dean−Stark trap. Distillation was continued until approximately 40% (300 mL) of the original solvent volume had been removed. The reaction was then cooled to ambient temperature in an ice bath. The remaining solvent was removed on a rotary evaporator, leaving the crude product as a slightly orange oil, which was stored under nitrogen at reduced temperature (−20 °C). Occasionally, the oily product solidified under these conditions. NMR analysis of the crude material formed by this procedure generally showed less than 5% of either 2-bromomalonaldehyde (δ 8.56 ppm) or the tetracetal (CH_3 doublet at 1.24 ppm, J = 6.2 Hz) formed from overreaction. 2-Bromo-3-(1-methylethoxy)-2-propenal was used without further purification: IR (film) 3200−2300, 1560, 1378, 1317, 1173, 847, 712, 697 cm^{-1}; ^1H NMR

($CDCl_3$) δ 1.41 (d, 6H, J = 6.3 Hz), 4.48 (septet, 1H, J = 6.3 Hz), 7.67 (s, 1H), 9.09 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.4, 80.9, 105.2, 166.7, 184.3.

Methyl 4-[(2-Butyl-5-formyl-1*H*-imidazol-1-yl)methyl]benzoate (6a) and Its Regioisomer Methyl 4-[(2-Butyl-4-formyl-1*H*-imidazol-1-yl)methyl]benzoate (7a) via the Alkylation of 2-Butyl-1*H*-imidazole-4-carboxaldehyde (4). A solution of 2-butyl-1*H*-imidazole-4-carboxaldehyde (**4**)[3] (30.4 g, 200 mmol) in DMF (90 mL) was treated with a 40% aqueous solution of tetraethylammonium hydroxide (76.7 g, 220 mmol). After being stirred for 1 h, the reaction was cooled to 0 °C and treated dropwise with a solution of methyl 4-(bromomethyl)benzoate (50.5 g, 220 mmol) in DMF (60 mL) so that the internal temperature did not exceed 10 °C. Stirring was continued for 1 h at 0 °C and 2 h at ambient temperature. The reaction mixture was quenched into 5% aqueous sodium chloride solution (150 mL) and extracted with ethyl acetate (2 × 150 mL). The combined ethyl acetate layers were washed with water (150 mL). Isomers **6a** and **7a** were separated by forming their bisulfite salts in ethyl acetate. The less soluble bisulfite adduct of **7a** crystallized from the reaction medium first. It was converted back to **7a** in 54% overall yield with saturated sodium carbonate solution. Imidazole **7a** was converted to its carboxylic acid derivative **7k** for characterization: mp 197−198 °C; IR (KBr) 3430, 3100−3000, 3000−2800, 2789, 1702, 1680, 1612, 1546, 1517, 1463, 1416, 1313, 1270, 1159, 1092, 1016, 824 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 0.84 (t, 3H, J = 7.4 Hz), 1.22−1.31 (m, 2H), 1.47−1.57 (m, 2H), 2.63 (t, 2H, J = 7.8 Hz), 4.81 (s, 1H), 5.34 (s, 2H), 7.25 (d, 2H, J = 8.3 Hz), 7.92 (s, 1H), 8.00 (d, 2H, J = 8.3 Hz), 9.68 (s, 1H); ^{13}C NMR (acetone-d_6) δ 12.5, 21.9, 25.9, 29.3, 51.0, 126.7 (2), 129.6, 130.1 (2), 130.9, 139.8, 140.8, 152.0, 168.0, 184.2; MS (CI, CH_4) m/z 287 (M + H). Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.09; H, 6.41; N, 9.54.

A 40% yield of **6a** was obtained as a white solid. Its spectral data and mp are reported below.

General Procedure for the Preparation *N*-Monosubstituted Amidines 12a−l). Under nitrogen, a solution of the imidate hydrochloride **2a** or **2b** (140 mmol) in DMF (100 mL) at 0 °C was treated with triethylamine (19.6 mL, 140 mmol). The resultant suspension was stirred for 1 h at ambient temperature and then filtered. The filter cake of triethylamine hydrochloride was washed with DMF (10 mL). The combined filtrates were transferred to a clean vessel under nitrogen and treated with the amine (100 mmol) and triethylamine (14.0 mL, 100 mmol). The reaction was heated at 60 °C for 16 h. After cooling, the reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with water and brine and dried ($MgSO_4$). Volatile solvents were removed in vacuo. The resulting amidines were generally used in the next step without further purification. In the cases of **12k** and **12l** the reaction mixture remained heterogeneous throughout. After cooling to 20 °C, the amidine product was isolated by filtration and dried.

Methyl 4-[[*N*-(1-iminopentyl)amino]methyl]benzoate (12a) was obtained as a colorless oil in 93% yield: IR (neat) 3250, 3100−3000, 3000−2800, 1724, 1642, 1614, 1572, 1402, 1281, 1110, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J = 7.3 Hz), 1.29−1.38 (m, 2H), 1.54−1.61 (m, 2H), 2.28 (t, 2H, J = 7.7 Hz), 3.88 (s, 3H), 4.43 (s, 2H), 6.07 (br, 2H), 7.35 (d, 2H, J = 7.9 Hz), 7.94 (d, 2H, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 13.5, 22.3, 28.1, 29.5, 46.0, 52.2, 126.7 (2), 129.8, 130.3 (2), 141.9, 166.6, 171.0; HRMS calcd for $C_{14}H_{21}N_2O_2$ (M + H)$^+$, 249.1603, found 249.1596.

General Procedure for the Preparation of 1,2-Disubstituted 5-Formyl-1*H*-imidazoles 6a−j. A solution of amidine **12a−j** (30.0 mmol) and **14** (8.69 g, 45.0 mmol) in chloroform (60 mL) and water (7.5 mL) was treated with solid potassium carbonate (6.22 g, 45.0 mmol) and stirred at ambient temperature for 18 h. The reaction mixture was partitioned between methylene chloride and water. The organic phase was washed with water and brine and dried ($MgSO_4$). The product was isolated by flash chromatography on silica with 5% (v/v) acetonitrile/methylene chloride as eluant.

Methyl 4-[(2-butyl-5-formyl-1*H*-imidazol-1-yl)methyl]benzoate (6a) was obtained as a white solid in 52% yield after recrystallization from *tert*-butyl methyl ether: mp 72−74 °C; IR (KBr) 3400, 3100−3000, 3000−2800, 2750, 1715, 1663, 1614, 1527, 1465, 1286, 1161, 1107, 804, 749, 717 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 7.4 Hz), 1.30−1.39 (m, 2H), 1.65−1.73 (m, 2H), 2.64 (t, 2H, J = 7.8 Hz), 3.90 (s, 3H), 5.63 (s, 2H), 7.07 (d, 2H, J = 8.3 Hz), 7.82 (s, 1H), 7.99 (d, 2H, J = 8.3 Hz), 9.67 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.4, 26.5, 29.3, 47.9, 52.2, 126.2 (2), 129.8, 130.2 (2), 131.3, 141.2, 143.7, 156.7, 166.6, 178.8. Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.90; H, 6.77; N, 9.17.

4-[(2-Butyl-5-formyl-1*H*-imidazol-1-yl)methyl]benzoic Acid (6k). A solution of **12k** (30.0 mmol) and **14** (8.69 g, 45.0 mmol) in chloroform (60 mL) and water (7.5 mL) was treated with solid potassium carbonate (6.22 g, 45.0 mmol) and refluxed under nitrogen for 8 h. As the reaction proceeded, the initially heterogeneous reaction mixture became homogeneous. After cooling, water (30 mL) was added. The aqueous phase was washed with methylene chloride (2 × 30 mL). The pH of the aqueous phase (typically 9.0−10.5) was adjusted to 5.0−5.3 by the addition of 10% aqueous HCl and then extracted with methylene chloride (3 × 30 mL). The combined organic phases were washed with water (30 mL) and brine (30 mL) and dried ($MgSO_4$). After concentration and recrystallization from 2-butanone:ethyl acetate, the product was obtained as a white solid in 83% yield: mp 147−148 °C; IR (KBr) 3400, 3100−3000, 3000−2800, 2750, 2600, 1684, 1663, 1612, 1578, 1539, 1488, 1468, 1319−1244, 1157, 805, 779, 754 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.81 (t, 3H, J = 7.4 Hz), 1.23−1.32 (m, 2H), 1.52−1.59 (m, 2H), 2.65 (t, H, J = 7.6 Hz), 5.67 (s, 2H), 7.11 (d, 2H, J = 8.2 Hz), 7.91 (d, 2H, J = 8.2 Hz), 7.96 (s, 1H), 9.67 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 13.4, 21.5, 25.3, 28.7, 47.0, 126.1 (2), 129.6 (2), 129.8, 131.0, 141.7, 143.4, 156.0, 166.8, 179.3. Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.11; H, 6.45; N, 9.71.

General Procedure for the Preparation of 1,2-Disubstituted 5-Cyano-1*H*-imidazoles 16a−h. A solution of amidine **12a−h** (30.0 mmol) and 2-bromo-3-methoxy-2-propenenitrile (**18**) (7.29 g, 45.0 mmol) in chloroform (60 mL) and water (7.5 mL) was treated with solid potassium carbonate (6.22 g, 45.0 mmol) and heated to reflux for 18 h. After cooling, the reaction mixture was partitioned between methylene chloride and water. The organic phase was washed with water and brine and dried ($MgSO_4$). The product was isolated by flash chromatography on silica with 1:1 ether:petroleum ether as eluant.

Methyl 4-[(2-butyl-5-cyano-1*H*-imidazol-1yl)methyl]benzoate (16a) was obtained as a white solid in 43% yield after recrystallization from *tert*-butyl methyl ether/hexanes: mp 58−60 °C; IR (KBr) 3400, 3129−3000, 3000−2865, 2223, 1717, 1420, 1416, 1284, 1108, 756, 722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 7.4 Hz), 1.31−1.39 (m, 2H), 1.64−1.72 (m, 2H), 2.63 (t, 2H, J = 7.7 Hz), 3.92 (s, 3H), 5.28 (s, 2H), 7.14 (d, 2H, J = 8.3 Hz), 7.67 (s, 1H), 8.05 (d, 2H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.3, 27.0, 29.4, 48.3, 52.3, 105.5, 111.4, 126.4 (2), 128.4, 130.5 (2), 138.6, 139.4, 153.3, 166.3. Anal. Calcd for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.37; H, 6.41; N, 14.14.

Methyl 4-[(2-butyl-3,4-dihydro-4-imido-5-bromopyrimid-3-yl)methyl]benzoate (21) was obtained as a yellow solid in 3% yield from the reaction of **12a** and **18**: mp 108−110 °C; IR (KBr) 3400, 3318, 3100−3000, 1942, 1725, 1617, 1563, 1528, 1411, 1286, 1114, 869, 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 7.3 Hz), 1.27−1.36 (m, 2H), 1.59−1.67 (m, 2H), 2.51 (t, 2H, J = 7.8 Hz), 3.90 (s, 3H), 5.50 (br, 2H), 7.25 (d, 2H, J = 8.3 Hz), 7.69 (s, 1H), 8.02 (d, 2H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 13.4, 21.3, 27.8, 33.2, 48.2, 52.0, 109.7, 126.3 (2), 128.5, 129.4 (2), 141.4, 146.8, 155.2, 161.4, 165.8. Anal. Calcd for $C_{17}H_{20}BrN_3O_2$: C, 53.98; H, 5.33; N, 11.11; Br, 21.12. Found: C, 54.02; H, 5.37; N, 10.96; Br, 20.94.

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Supporting Information Available: Spectral data for **12b**−**j**,**l**, **6b**−**j**,**l**, and **16b**−**f**,**h** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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