JOURNAL OF combinatorial CHEMISTRY

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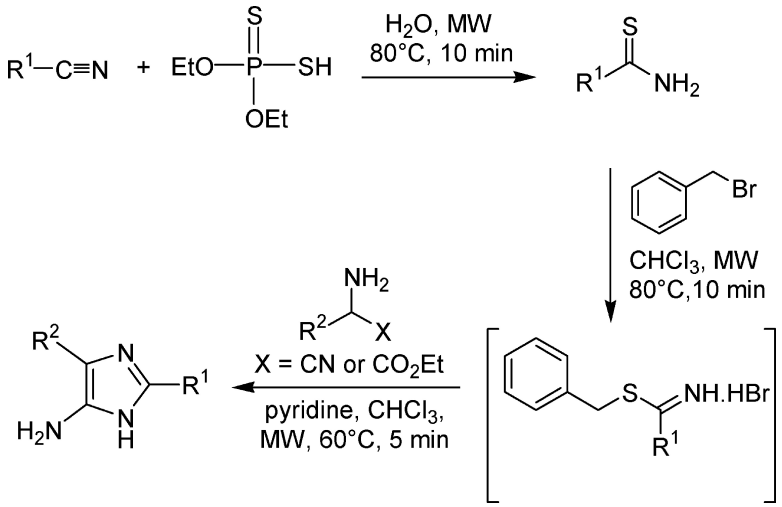
J. Comb. Chem., **2006**, 8 (4), 464-468• DOI: 10.1021/cc060030j • Publication Date (Web): 28 May 2006



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Articles

Synthesis of 2,4-Disubstituted 5-Aminoimidazoles Using Microwave Irradiation

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Received March 22, 2006

A microwave-assisted parallel synthesis of 2,4-disubstituted 5-aminoimidazoles has been developed. Significant rate enhancement was observed for all steps in the three-step protocol. The overall reaction time was shortened to 25 min, as compared to 53 h for the conventional procedures. A representative set of 2,4-disubstituted 5-aminoimidazoles was prepared using commercially available parallel reactors.

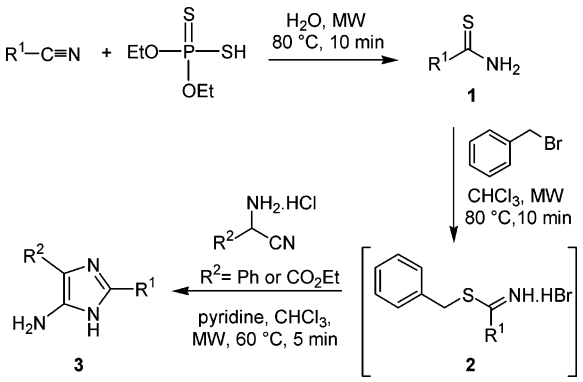
Introduction

5-Aminoimidazoles are attractive constructs in chemical synthesis because they are key components in many bioactive compounds of both natural and synthetic origin.[1] Examples include 5-aminoimidazole ribonucleotide (AIR), an ubiquitous precursor in the biosynthesis of purines and thiamine,[2] imidazolic pesticides,[3] gonadotropin-releasing hormone receptor antagonists;[4] and 5-amino-4-carboxamide-1-β-D-ribofuranoside, a commonly used AMP-kinase activator.[5] Despite the diversity of properties of these compounds, the chemistry of 5-aminoimidazoles has not received as much attention as they deserve. This may be attributed to its lower stability, as compared to other classes of aminoazoles; however, recent experimental findings[6] have sparked a renewed interest in 5-aminoimidazoles, and consequently, we became interested in developing an efficient procedure for the synthesis of these compounds.

Several reports on the synthesis of 2,4-disubstituted 5-aminoimidazoles have been published earlier;[7] however, in many cases, prolonged reaction times were necessary, and the yields obtained were often dependent on the substrates used. Thus, finding a facile synthesis of this class of compounds would be desirable.

A promising synthetic strategy (Scheme 1) is based on the reaction between thioamides **1** and benzyl bromide to form the intermediate thioiminoether hydrobromides **2**, which, in turn, undergo condensation with α-aminonitriles to give the respective 2,4-disubstituted 5-aminoimidazoles **3**.[7e] To our knowledge, this methodology has not been employed with microwave irradiation. We therefore investigated the use of microwaves to promote each step of the synthetic strategy and herein describe a rapid and high-yielding synthesis of 2,4-disubstituted 5-aminoimidazoles. Since a variety of reagents can be used in each step of the reaction, the overall strategy enables efficient library generation.

Scheme 1. Microwave-Assisted Synthesis of 2,4-Disubstituted 5-Aminoimidazoles **3**



Results and Discussion

Synthesis of Thioamides 1a−j. For comparison purposes, we began our investigation by carrying out the synthesis of thioamides using the conventional heating procedure.[8a] A mixture of phenylacetonitrile (0.85 mmol) and diethyldithiophosphoric acid (1.02 mmol) in water was heated at 80 °C. The reaction (monitored by TLC) was found to be completed after 24 h. The crude mixture was purified by flash chromatography (silica (70−230 mesh), $CH_2Cl_2/Et_2O = 1:1$) to provide 2-phenylthioacetamide **1a** in 81% yield. When the same reaction was heated in the microwave at 80 °C, complete conversion was observed within 10 min, and **1a** was obtained in quantitative yield. A library of thioamides **1a−j** (Table 1) was subsequently generated from a single

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10.1021/cc060030j CCC: $33.50
Published on Web 05/28/2006

Table 1. Conventional versus Microwave-Assisted Synthesis of Thioamides **1a**−**j**

		yield (%)	
entry	R^1	reflux	MW
1a	$C_6H_5CH_2$−	81, 89[a]	99
1b	*p*-$NO_2C_6H_4$−	91[a]	96
1c	*m*-$NO_2C_6H_4$−	44[b]	91
1d	*m*$NO_2C_6H_4CH_2$−-	76[c]	93
1e	*m*-$ClC_6H_4CH_2$−	48[b]	87
1f	*p*-ClC_6H_4−	83[d]	96
1g	*p*-$MeOC_6H_4$−	81[d]	97
1h	$(CH_3)_2CH$-−	42[a]	96
1i	*p*-$NO_2C_6H_4CH_2$−	42[a]	83
1j	*p*-$ClC_6H_4CH_2$−	78[a]	82

[a] Ref 8a. [b] Ref 8b. [c] Ref 8c. [d] Ref 8d.

Table 2. Conventional versus Microwave-Assisted Synthesis of Thioiminoether Hydrobromides **2a**−**l**

		yield (%)	
entry	R^1	reflux	MW
2a	$C_6H_5CH_2$−	69	95
2b	*p*-$NO_2C_6H_4$−	60[a]	90, 73[b]
2c	*m*-$NO_2C_6H_4$−		85
2d	*m*-$NO_2C_6H_4CH_2$−	82[a]	90
2e	*m*-$ClC_6H_4CH_2$−		81
2f	*p*-ClC_6H_4−	64[a]	91, 56[b]
2g	*p*-$MeOC_6H_4$−		85
2h	$(CH_3)_2CH$−		92
2i	*p*-$NO_2C_6H_4CH_2$−	100[a]	100
2j	*p*-$ClC_6H_4CH_2$−		95
2k	C_6H_5−	94[a]	100
2l	CH_3−		100

[a] Ref 7e. [b] Yield of the hydrochloride salt obtained using benzyl chloride.

microwave irradiation experiment (80 °C, 10 min), employing a multivessel rotor system (CEM Mars X). Complete conversion (>99%) was achieved in all cases.

Synthesis of Thioiminoether Hydrobromides 2a−l. Thioiminoether salts are traditionally prepared by two general routes, the first of which involves the treatment of a mixture of nitrile and thiol compounds with anhydrous hydrogen halide (X = Cl or Br) gas,[7e,9] whereas the second method is based on the S-alkylation of thioamide with an alkyl halide.[10] Since gases could not be conveniently applied under microwave conditions, we adopted the latter synthetic route for the synthesis of thioiminoether salts **2a**−**l**. In our initial experiment using conventional synthesis, **1a** was treated with benzyl bromide in $CHCl_3$ at 80 °C for 3 h. The white precipitate that formed was isolated by filtration to give the desired thioiminoether hydrobromide **2a** in 69% yield. However, under microwave irradiation, the same reaction was found to be completed within 10 min, and **2a** was isolated in good yield (95%) and purity. Analogous S-alkylations with various thioamides were also performed successfully in high or quantitative yields (Table 2). It was also observed that benzyl bromide provided a significantly better yield than benzyl chloride (**2b** and **2f** in Table 2).

Synthesis of 2,4-Disubstituted 5-Aminoimidazoles 3a−o. Since the microwave synthesis of **2** gave the desired product in high purity, **2** was used directly in the next step without purification. Prior to the microwave synthesis of **3**, a preliminary study of the reaction was carried out under conventional heating conditions. Compound **2a** was treated with α-aminobenzyl cyanide in the presence of pyridine at 80 °C. The reaction was found to be completed after 26 h (monitored by TLC), and **3a** was obtained in 78% yield. First attempts to translate this reaction into a microwave protocol resulted in complete decomposition. This led us to investigate the reaction more closely. Subsequent variation of the temperature and reaction time showed that the condensation reaction proceeded sufficiently quickly and a nearly complete conversion was obtained after 5 min at 60 °C (Table 3). To illustrate the generality of this microwave condition, a diverse set of **3** was prepared via parallel synthesis using **2** and α-aminobenzyl cyanide or aminocyanoacetic acid ethyl ester.[11] In all cases, the condensation proceeded smoothly to furnish the desired 2,4-disubstituted 5-aminoimidazole in high yields (Table 4).

Table 3. Temperature−Time Study of the Microwave-Assisted Synthesis of **3a**

temp (°C)	time (min)	yield (%)
80	10	0
	5	12
75	10	10
	5	34
70	10	21
	5	51
65	10	32
	5	68
60	10	46
	5	98
55	5	69

Table 4. Conventional versus Microwave-Assisted Synthesis of 2,4-Disubstituted 5-Aminoimidazoles **3a**−**o**

			yield (%)	
entry	R^1	R^2	reflux	MW
3a	$C_6H_5CH_2$−	C_6H_5−	78, 80[a]	98
3b	*p*-$NO_2C_6H_4$−	C_6H_5−	67[a]	94
3c	*m*-$NO_2C_6H_4$−	C_6H_5−		93
3d	*m*-$NO_2C_6H_4CH_2$−	C_6H_5−	79[a]	91
3e	*m*-$ClC_6H_4CH_2$−	C_6H_5−	85[a]	96
3f	*p*-ClC_6H_4−	C_6H_5−	90[a]	98
3g	*p*-$MeOC_6H_4$−	C_6H_5−		83
3h	$(CH_3)_2CH$−	C_6H_5−		93
3i	CH_3−	C_6H_5−		87
3j	C_6H_5−	C_6H_5−	95[a]	98
3k	C_6H_5−	−CO_2Et	82[a]	91
3l	$C_6H_5CH_2$−	−CO_2Et	94[a]	98
3m	*p*-$NO_2C_6H_4$−	−CO_2Et	98[a]	98
3n	*p*-$NO_2C_6H_4CH_2$−	−CO_2Et	90[a]	97
3o	CH_3−	−CO_2Et		92

[a] Ref 7e.

In conclusion, an efficient and high-yielding synthesis of 2,4-disubstituted 5-aminoimidazoles has been devised. Using microwave irradiation, we have shown that the total reaction time for the synthesis of one compound could be shortened from a couple of days to only 25 min. These results further demonstrate the value of microwave-assisted synthesis in increasing yields, shortening reaction times, and streamlining high-throughput chemistry.

Experimental Section

General Procedures. All chemical reagents were obtained from Aldrich, Merck, Lancaster, or Fluka and were used

without further purification. The microwave-assisted reactions were performed using a CEM Mars X microwave oven equipped with an EST-300 plus temperature probe as sensor. Ramp time was 5 min for all the reactions. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and visualized with UV light or stained with ninhydrin. Flash column chromatograph was performed with silica (Merck, 70−230 mesh). CC refers to flash column chromatography.

^{1}H NMR and ^{13}C NMR spectra were measured at 298 K on Bruker ACF 300 Fourier transform spectrometer and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). The number of protons (*n*) for a given resonance was indicated as *n*H. Mass spectra were performed on Finnigan MAT 95/XL-T spectrometer under electron impact.

General Procedure for the Microwave-Assisted Synthesis of Thioamides (1). To the respective nitrile (0.85 mmol) in water was added diethyldithiophosphoric acid (1.02 mmol), and the mixture was heated at 80 °C under microwave irradiation (300 W). The reaction, monitored by TLC ($MeOH/CH_2Cl_2$ = 1:20), was found to be completed after 10 min, following which the reaction mixture was extracted with diethyl ether (3 × 50 mL) and then washed with saturated $NaHCO_3$. The combined organic layer was dried with $MgSO_4$ and purified by CC (CH_2Cl_2/Et_2O = 1:1) to give **1**.

2-Phenylthioacetamide (1a). ^{1}H NMR (MeOH-d_4): δ 7.36−7.22 (m, 5H, Ar*H*), 3.92 (s, 2H, CH_2). 99% yield.

4-Nitrothiobenzamide (1b). ^{1}H NMR (MeOH-d_4): δ 8.24−8.22 (d, 2H, C*H*═C(NO_2) of aromatic ring, J = 8.0 Hz), 8.02−8.0 (d, 2H, C*H*═CH of aromatic ring, J = 8.0 Hz). 96% yield.

3-Nitrothiobenzamide (1c). ^{1}H NMR (MeOH-d_4): δ 8.73 (s, C*H*═C(NO_2) of aromatic ring), 8.35−8.23 (m, 2H, Ar*H*), 7.67−7.61 (t, 1H, CH−C*H*═CH of aromatic ring, J = 8.0 Hz). 91% yield.

2-(3-Nitrophenyl)-thioacetamide (1d). ^{1}H NMR (MeOH-d_4): δ 8.26 (s, 1H, C*H*═C(NO_2) of aromatic ring), 8.14−8.10 (d, 1H, C(NO_2)═C*H* of aromatic ring, J = 8.0 Hz), 7.78−7.75 (d, 1H, C*H*−CH═CH of aromatic ring, J = 7.7 Hz), 7.58−7.52 (t, 1H, CH−C*H*═CH of aromatic ring, J = 8.0 Hz), 4.02 (s, 2H, CH_2). 93% yield.

2-(3-Chlorophenyl)-thioacetamide (1e). ^{1}H NMR (MeOH-d_4): δ 7.39−7.25 (m, 4H, Ar*H*), 3.90(s, 2H, CH_2). 87% yield.

4-Chlorothiobenzamide (1f). ^{1}H NMR (MeOH-d_4): δ 7.88−7.86 (d, 2H, C*H*═C(Cl) of aromatic ring, J = 8.0 Hz), 7.40−7.37 (d, 2H, C*H*═CH of aromatic ring, J = 8.0 Hz). 96% yield.

4-Methoxythiobenzamide (1g). ^{1}H NMR (MeOH-d_4): δ 7.94−7.91 (d, 2H, C*H*═C(OMe) of aromatic ring, J = 9.1 Hz), 6.92−6.89 (d, 2H, C*H*═CH of aromatic ring, J = 8.7 Hz), 3.83 (s, 3H, OCH_3). 97% yield.

Thioisobutyramide (1h). ^{1}H NMR (MeOH-d_4): δ 2.89−2.85 (m, 1H, C*H*), 1.20 (s, 3H, CH_3), 1.18 (s, 3H, CH_3). 96% yield.

2-(4-Nitrophenyl)-thioacetamide (1i). ^{1}H NMR (MeOH-d_4): δ 8.19−8.16 (d, 2H, C*H*═C(NO_2) of aromatic ring, J = 8.7 Hz), 7.61−7.58 (d, 2H, C*H*═CH of aromatic ring, J = 8.7 Hz), 4.04 (s, 2H, CH_2). 83% yield.

2-(4-Chlorophenyl)-thioacetamide (1j). ^{1}H NMR (MeOH-d_4): δ 7.33−7.27 (m, 4H, Ar*H*), 3.89 (s, 2H, CH_2). 82% yield.

General Procedure for the Microwave-Assisted Synthesis of Thioiminoether Hydrobromides (2). The respective thioamide **1** (0.73 mmol) was added to a solution of bromomethylbenzene (2.9 mmol) in anhydrous chloroform, and the mixture was heated at 80 °C under microwave irradiation (300 W). The reaction was monitored by TLC ($MeOH/CH_2Cl_2$ = 1:20) and was found to be completed after 10 min. The reaction mixture was evaporated to near dryness in vacuo, and diethyl ether was added in large excess to precipitate the thioiminoether hydrobromide **2.** The white precipitate formed was filtered, dried under vacuum, and used for the next step of the synthesis.

General Procedure for the Microwave-Assisted Synthesis of 2,4-Disubstituted 5-Aminoimidazole (3a−3j). To a solution of **2** (0.47 mmol) in anhydrous dichloromethane (10 mL) was added pyridine (0.47 mmol). In another round-bottomed flask containing the respective α-aminoacetonitrile hydrochloride (0.56 mmol) in anhydrous dichloromethane (10 mL) was added NH_3 in methanol (2 M, 0.56 mL). Both reaction mixtures were filtered into the microwave vessel, and anhydrous chloroform (30 mL) was added. The reaction mixture was heated to 60 °C in a microwave reactor (300 W) and monitored using TLC. The reaction was completed within 5 min, after which the reaction mixture was evaporated to near dryness in vacuo, and diethyl ether was added to precipitate the final product, **3**. The product was filtered, washed with diethyl ether, and dried under vacuum.

2-Benzyl-5-phenyl-3*H*-imidazol-4-ylamine (3a). ^{1}H NMR (MeOH-d_4): δ 7.48−7.11 (m, 10H, Ar*H*), 3.95(s, 2H, CH_2).^{13}C NMR (MeOH-d_4): δ 144.5, 139.4 (×2), 130.1, 129.8 (×2), 129.6 (×2), 129.5, 127.9 (×2), 127.6 (×2), 125.9, 125.2, 35.2. Exact mass calcd for $C_{16}H_{15}N_3$: 249.1266; found: 249.1266. 98% yield.

2-(4-Nitrophenyl)-5-phenyl-3*H*-imidazol-4-ylamine (3b). ^{1}H NMR (MeOH-d_4): δ 8.35−8.32 (d, 2H, Ar*H*, J = 9.0 Hz), 8.10−8.06 (d, 2H, Ar*H*, J = 8.7 Hz), 7.66−7.64 (d, 2H, Ar*H*, J = 7.7 Hz), 7.49−7.44 (t, 2H, Ar*H*, J = 7.7 Hz), 7.32−7.26 (t, 1H, Ar*H*, J = 7.3 Hz). ^{13}C NMR (MeOH-d_4): δ 131.3, 131.1, 130.4, 129.4 (×2), 128.9 (×2), 128.7, 128.0 (×2), 127.6 (×2), 125.7 (×2), 125.3. Exact mass calcd for $C_{15}H_{12}N_4O_2$, 280.0960; found, 280.0966. 94% yield.

2-(3-Nitrophenyl)-5-phenyl-3*H*-imidazol-4-ylamine (3c). ^{1}H NMR (MeOH-d_4): δ 8.99−8.30 (m, 4H, Ar*H*), 8.02−7.50 (m, 5H, Ar*H*). ^{13}C NMR (MeOH-d_4): δ 135.4, 134.2, 133.7, 132.9, 131.7, 130.5 (×2), 129.5, 128.6, 127.1 (×2), 125.4, 123.6 (×2), 121.9. Exact mass calcd for $C_{15}H_{12}N_4O_2$, 280.0960; found, 280.0961. 93% yield.

2-(3-Nitrobenzyl)-5-phenyl-3*H*-imidazol-4-ylamine (3d). ^{1}H NMR (MeOH-d_4): δ 8.27−8.22 (m, 2H, Ar*H*), 7.76−7.34 (m, 7H, Ar*H*), 4.41 (s, 2H, CH_2). ^{13}C NMR (MeOH-d_4): δ 155.4, 139.9, 137.7, 136.2, 131.6, 130.3 (×2), 129.2,

128.7 (×2), 126.6, 124.8, 123.9 (×2), 52.3, 32.1. Exact mass calcd for $C_{16}H_{14}N_4O_2$, 294.1117; found, 294.1114. 91% yield.

2-(3-Chlorobenzyl)-5-phenyl-3*H*-imidazol-4-ylamine (3e). ^{1}H NMR (MeOH-d_4): δ 7.49−7.10 (m, 9H, Ar*H*), 3.96 (s, 2H, CH_2). ^{13}C NMR (MeOH-d_4): δ 141.8, 131.1, 130.3, 129.9 (×2), 129.5, 129.0, 127.9 (×2), 127.7, 126.9, 126.0, 125.2 (×2), 124.4, 34.7. Exact mass calcd for $C_{16}H_{14}ClN_3$, 283.0876; found, 283.0875. 96% yield.

2-(4-Chlorophenyl)-5-phenyl-3*H*-imidazol-4-ylamine (3f). ^{1}H NMR (MeOH-d_4): δ 7.89−7.86 (d, 2H, C*H*═C(Cl) of aromatic ring, J = 8.7 Hz), 7.66−7.62 (m, 4H, Ar*H*), 7.55−7.50 (t, 2H, Ar*H*, J = 7.7 Hz), 7.42−7.37 (t, 1H, Ar*H*, J = 7.3 Hz). ^{13}C NMR (MeOH-d_4): δ 138.7, 138.2, 137.1, 130.9 (×2), 130.3 (×2), 129.0, 128.9 (×2), 127.3 (×2), 124.9, 123.3 (×2). Exact mass calcd for $C_{15}H_{12}ClN_3$, 269.0720; found, 269.0720. 98% yield.

2-(4-Methoxyphenyl)-5-phenyl-3*H*-imidazol-4-ylamine (3g). ^{1}H NMR (MeOH-d_4): δ 7.85−7.82 (d, 2H, Ar*H*, J = 9.1 Hz), 7.64−7.61 (d, 2H, Ar*H*, J = 7.7 Hz), 7.52−7.47 (t, 2H, Ar*H*, J = 7.7 Hz), 7.35 (t, 1H, Ar*H*, J = 7.3 Hz), 7.15−7.12 (d, 2H, C*H*═C(OMe) of aromatic ring, J = 8.7 Hz), 3.89 (s, 3H, OCH_3). ^{13}C NMR (MeOH-d_4): δ 164.0, 140.0, 130.3 (×2), 129.3 (×2), 129.2, 128.8, 127.1(×2), 116.8 (×2), 116.2 (×2), 113.1, 56.2. Exact mass calcd for $C_{16}H_{15}N_3O$, 265.1215; found, 265.1213. 83% yield.

2-Isopropyl-5-phenyl-3*H*-imidazol-4-ylamine (3h). ^{1}H NMR (MeOH-d_4): δ 7.59−7.31 (m, 5H, Ar*H*), 1.43−1.27 (m, 7H, CH_3 and C*H*). ^{13}C NMR (MeOH-d_4): δ 135.1, 131.5, 130.7 (×2), 130.2 (×2), 128.6 (×2), 126.8, 34.8, 28.1, 20.9. Exact mass calcd for $C_{12}H_{15}N_3$, 201.1266; found, 201.1263. 93% yield.

2-Methyl-5-phenyl-3*H*-imidazol-4-ylamine (3i). ^{1}H NMR (MeOH-d_4): δ 7.55−7.31 (m, 5H, Ar*H*), 2.57 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 138.3, 134.1 (×2), 128.8 (×2), 128.5, 126.3, 124.4 (×2), 11.1. Exact mass calcd for $C_{10}H_{11}N_3$, 173.0953; found, 173.0955. 87% yield.

2,5-Diphenyl-3*H*-imidazol-4-ylamine (3j). ^{1}H NMR (MeOH-d_4): δ 8.05−8.02 (d, 2H, Ar*H*, J = 6.6 Hz), 7.73−7.70 (d, 2H, Ar*H*, J = 7.7 Hz), 7.64−7.49 (m, 5H, Ar*H*), 7.39−7.33 (t, 1H, Ar*H*, J = 7.7 Hz). ^{13}C NMR (MeOH-d_4): δ 139.5, 137.1, 132.7, 130.8 (×2), 130.3 (×2), 129.1, 129.0 (×2), 127.3 (×2), 124.6 (×2), 114.0. Exact mass calcd for $C_{15}H_{13}N_3$, 235.1109; found, 235.1105. 98% yield.

General Procedure for the Microwave-Assisted Synthesis of 2-Substituted 5-Amino-1*H*-imidazole-4-carboxylic Acid Ethyl Ester (3k−3o). To a mixture of the respective thioiminoether hydrobromide **2** (0.47 mmol) in anhydrous chloroform (50 mL) was added pyridine (0.47 mmol) and aminocyanoacetic acid ethyl ester (0.56 mmol). The reaction mixture was heated at 60 °C in a microwave reactor (300 W) and monitored using TLC. The reaction was completed within 5 min, after which the reaction mixture was evaporated to dryness in vacuo, and diethyl ether was added to precipitate the final product, **3**. The precipitate was filtered, washed with diethyl ether, and dried under vacuum. For **3l**−**3n**, the compound could not be precipitated, so the compound was purified via CC (5% MeOH in CH_2Cl_2).

5-Amino-2-phenyl-1*H*-imidazole-4-carboxylic Acid Ethyl Ester (3k). ^{1}H NMR (DMSO-d_6): δ 7.89−7.42 (m, 5H, Ar*H*), 4.36−4.29 (q, 2H, CH_2, J = 7.0 Hz), 1.40−1.34 (t, 3H, CH_3, J = 7.0 Hz). ^{13}C NMR (MeOH-d_4): δ 163.3, 131.1, 130.6, 130.5, 129.9 (×2), 127.1 (×2), 121.9, 63.8, 60.8, 15.0. Exact mass calcd for $C_{12}H_{13}N_3O_2$, 231.1008; found, 231.1009. 91% yield.

5-Amino-2-benzyl-1*H*-imidazole-4-carboxylic Acid Ethyl Ester (3l). ^{1}H NMR (DMSO-d_6): δ 7.38−7.36 (m, 5H, Ar*H*), 4.30−4.27 (q, 2H, CH_2, J = 6.9 Hz), 4.16 (s, 2H, CH_2), 1.32−1.27 (t, 3H, CH_3, J = 7.1 Hz). ^{13}C NMR (MeOH-d_4): δ 162.2, 152.5, 147.3, 137.2, 129.3 (×2), 129.0, 127.5 (×2), 102.2, 60.4, 34.2, 14.4. Exact mass calcd for $C_{13}H_{15}N_3O_2$, 245.1164; found, 245.1163. 98% yield.

5-Amino-2-(4-nitrophenyl)-1*H*-imidazole-4-carboxylic Acid Ethyl Ester (3m). ^{1}H NMR (DMSO-d_6): δ 8.29 (s, 4H, Ar*H*), 4.28−4.20 (q, 2H, CH_2, J = 7.3 Hz), 1.33−1.28 (t, 3H, CH_3, J = 7.0 Hz). ^{13}C NMR (DMSO-d_6): δ 160.5, 147.1, 135.2, 126.8 (×2), 124.9, 124.2 (×2), 124.0, 102.9, 59.3, 14.6. Exact mass calcd for $C_{12}H_{12}N_4O_4$, 276.0859; found, 276.0866. 98% yield.

5-Amino-2-(4-nitrobenzyl)-1*H*-imidazole-4-carboxylic Acid Ethyl Ester (3n). ^{1}H NMR (MeOH-d_4): δ 8.19−8.16 (d, 2H, C*H*═C(NO_2) of aromatic ring, J = 8.7 Hz), 7.49−7.46 (d, 2H, C*H*═CH of aromatic ring, J = 8.7 Hz), 4.30−4.23 (q, 2H, CH_2, J = 7.0 Hz), 4.03 (s, 2H, CH_2), 1.35−1.31 (t, 3H, CH_3, J = 7.0 Hz). ^{13}C NMR (DMSO-d_6): δ 160.7, 155.2, 154.0, 146.2, 145.7 (×2), 129.9 (×2), 123.5 (×2), 58.6, 33.7, 14.7. Exact mass calcd for $C_{13}H_{14}N_4O_4$, 290.1015; found, 291.1018. 97% yield.

5-Amino-2-methyl-1*H*-imidazole-4-carboxylic Acid Ethyl Ester (3o). ^{1}H NMR (MeOH-d_4): δ 4.29−4.22 (q, 2H, CH_2, J = 7.0 Hz), 2.23 (s, 3H, CH_3), 1.35−1.30 (t, 3H, CH_3, J = 7.0 Hz). ^{13}C NMR (MeOH-d_4): δ 162.8, 154.6, 146.7, 102.4, 60.6, 15.0, 13.6. Exact mass calcd for $C_7H_{11}N_3O_2$, 169.0851; found, 169.0852. 92% yield.

Acknowledgment. We thank the National University of Singapore for financial support of this work.

Supporting Information Available. ^{1}H and ^{13}C NMR spectra of compounds **3a**−**3o**. ^{1}H NMR spectra of compounds **1a**−**1j**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Shealy, Y. F. *J. Pharm. Sci.* **1970**, *59*, 1533−1558.
(2) (a) Schrimsher, J. L.; Schendel, F. J.; Stubbe, J.; Smith, J. M. *Biochemistry* **1986**, *25*, 4366−4371. (b) Estramareix, B.; David, S. *Biochem. Biophys. Res. Commun.* **1986**, *134*, 1136−1141.
(3) Cramp, S. M.; Hatton, L. R. *Eur. Pat. Appl.* EP 283173, 1988.
(4) Zhu, Y.; Gross, T. D.; Gao, Y.; Connors, P. J., Jr.; Guo, Z.; Chen, C. *PCT Int. Appl.* WO 01 29,044. *Chem. Abstr.* **2001**, *134*, 311224.
(5) Samari, H. R.; Seglen, P. O. *J. Biol. Chem.* **1998**, *273*, 23758−23763.
(6) (a) Jorgensen, S. B.; Viollet, B.; Andreelli, F.; Frosig, C.; Birk, J. B.; Schjerling, P.; Vaulont, S.; Richter, E. A.; Wojtaszewski, J. F. P. *J. Biol. Chem.* **2004**, *279*, 1070−1079. (b) Scott, J. W.; Hawley, S. A.; Green, K. A.; Anis, M.; Stewart, G.; Scullion, G. A.; Norman, D. G.; Hardie, D. G. *J. Clin. Invest.* **2004**, *113*, 274−284. (c) Gadalla, A. E.; Pearson, T.; Currie, A. J.; Dale, N.; Hawley, S. A.; Sheehan,

M.; Hirst, W.; Michel, A. D.; Randall, A.; Hardie, D. G.; Frenguelli, B. G. *J. Neurochem.* **2004**, *88*, 1272−1282. (d) Nath, N.; Giri, S.; Prasad, R.; Salem, M. L.; Singh, A. K.; Singh, I. *J. Immunol.* **2005**, *175*, 566−574. (e) Rattan, R.; Giri, S.; Singh, A. K.; Singh, I. *J. Biol. Chem.* **2005**, *280*, 39582−39593.

(7) (a) Vuilhorgne, M.; Malpart, J.; Mutti, S.; Mignani, S. *J. Heterocycl. Chem.* **2003**, *40*, 150−162. (b) Gomez, E.; Avendano, C.; McKillop, A. *Tetrahedron* **1986**, *42*, 2625−2634. (c) Rose, C. J.; Rainsworth, A. T. West German Pat., 2 358 509, 1974; *Chem. Abstr.* **1974**, *81*, 63630y. (d) Miller, C. S.; Gurin, S.; Wilson, D. W. *J. Am. Chem. Soc.* **1952**, *74*, 2892−2894. (e) Bader, H.; Downer, J. D.; Driver, P. *J. Chem. Soc.* **1950**, 2775−2784. (f) Cook, A. H.; Heilbron, I.; Smith, E. *J. Chem. Soc. Abstr.* **1949**, 1440−1442.

(8) (a) Yousif, N. M.; *Tetrahedron* **1989**, *45*, 4599−4604. (b) Walczynski, K.; Timmerman, H.; Zuiderveld, P. O.; Zhang, M. Q.; Glinka, R. *Farmaco* **1999**, *54*, 533−541. (c) Brillon, D. *Synth. Commun.* **1992**, *22*, 1397−1401. (d) Benner, S. A. *Tetrahedron Lett.* **1981**, *22*, 1851−1854.

(9) (a) Baati, R.; Gouverneur, V.; Mioskowski, C. *Synthesis* **1999**, 927−929.

(10) (a) Takido, T.; Itabashi, K. *Synthesis* **1987**, 817−819. (b) Walter, W.; Krohn, J. *Chem. Ber.* **1969**, *102*, 3786−3794.

(11) Logemann, F. I.; Gordon, S. *Chem. Ind.* **1980**, *5*, 541−542.

CC060030J