JOURNAL OF combinatorial CHEMISTRY

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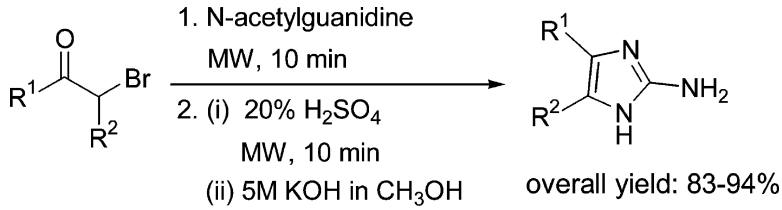
J. Comb. Chem., **2008**, 10 (1), 118-122• DOI: 10.1021/cc700143n • Publication Date (Web): 27 December 2007



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An Efficient and Expeditious Synthesis of Di- and Monosubstituted 2-Aminoimidazoles

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Received August 28, 2007

A microwave-assisted protocol was developed for the construction of di- and monosubstituted 2-aminoimidazoles. The two-step reaction involves the synthesis of *N*-(1H-imidazol-2-yl)acetamides from readily available α-haloketones and *N*-acetylguanidine, followed by deacetylation. Significant rate enhancement was observed for both steps of the protocol, and the overall reaction time was shortened to 20 min compared to 48 h of the conventional procedures. A representative set of di- and monosubstituted 2-aminoimidazoles was prepared using commercially available parallel reactors.

Introduction

2-Aminoimidazoles constitute an important class of heterocycles because they are found in many pharmacologically active substances[1]and in various marine metabolites,[2] some of which are potent antagonists of serotonergic and histaminergic receptors.[3] Because of these interesting biological properties, numerous synthetic routes to 2-aminoimidazoles have been reported.[4] Among them, however, only a few describe the direct synthesis of substituted 2-aminoimidazoles, in particular, 4,5-disubstituted-2-aminoimidazoles.[4b,e] The earliest method involves the condensation of α-aminocarbonyl compounds with cyanamide or isothioureas.[4d] However, this method is highly pH sensitive and can result in the self-condensation of the α-aminocarbonyl compounds. Another procedure is the cyclocondensation of aldehydes and guanidine nitrate using sodium cyanide and supported aluminum oxide,[4e] which provides 2-aminoimidazoles with identical substituents on positions 4 and 5 of the ring structure. Other alternative approaches involve the cyclocondensation between diketones with guanidine, followed by catalytic hydrogenation,[4b] the synthesis of 2-aminoimidazoles by the formation of imidazo[1,2-a]pyrimidines, followed by cleavage of the pyrimidine ring with hydrazine or amines,[4h] and the reaction of α-haloketones with *N*-acetylguanidine.[4c] Among these methodologies, the latter procedure appears to be the most straightforward and avoids the need for reduction or ring cleavage. However this methodology requires long reaction times for both steps of the reaction, and the yields of the substituted *N*-(1H-imidazol-2-yl)acetamides **1** obtained vary with the substrate used. Thus finding an improved procedure that is viable for library synthesis will be desirable.

Microwave-assisted organic synthesis (MAOS), a growing area in synthetic organic chemistry, is based on the empirical observation that some reactions proceed faster and result in higher yields under microwave irradiation than under conventional heating.[5] Although MAOS has been applied to the synthesis of various heterocyclic compounds,[5,6] to our knowledge, this technique has not been applied to the synthesis of substituted 2-aminoimidazoles **2** via the reaction of α-haloketones with *N*-acetylguanidines.[7] We therefore investigated the use of microwave irradiation to promote and activate each step of the synthetic strategy and herein describe a rapid and high yielding synthesis of **2** (Scheme 1).

Results and Discussion

Synthesis of Substituted *N*-(1H-Imidazol-2-yl)acetamides 1a−s. For comparison purposes, we began our investigation by carrying out the synthesis of **1** using the following procedure.[4c] A mixture of 2-bromoacetophenone (1.98 mmol, 1 equiv) and *N*-acetylguanidine (5.94 mmol, 3 equiv) in 30 mL of DMF was stirred at room temperature. The reaction (monitored by TLC) was found to be complete after 5 days. The reaction mixture was poured into 100 mL of cold water, and the precipitate was collected, washed with H_2O, and dried to give *N*-[4(5)-phenyl-1H-imidazol-2-yl]acetamide, **1a**, in 54% yield. Performing the reaction in acetonitrile shortened the reaction time to 24 h, but the product yield was only 42%. When the same reaction was heated in the microwave at 120 °C, using DMF as solvent, complete conversion was observed within 5 min, but the yield of **1a** was only 31%. Various other reaction conditions were studied (Table 1), and it was found that the cyclization reaction proceeded rapidly in CH_3CN at the ceiling temperature (100 °C), and **1a** was obtained in 96% yield. To illustrate the generality of this microwave condition, the reaction was carried out with various α-haloketones and *N*-acetylguanidine, and we were pleased to observe that the cyclization always proceeded smoothly to furnish both di- and monosubstituted *N*-(1H-imidazol-2-yl) acetamides in very high yields exceeding 90% (Table 2).

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10.1021/cc700143n CCC: $40.75
Published on Web 12/27/2007

Scheme 1. Synthesis of Substituted 2-Aminoimidazoles **2**

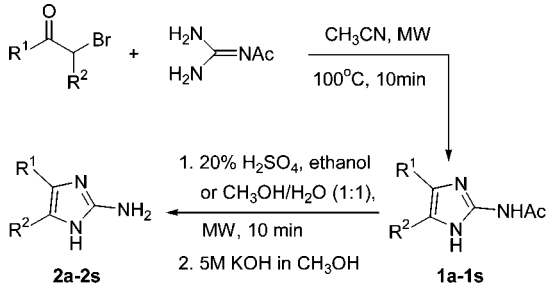

Table 1. Microwave-Assisted Synthesis of *N*-[4(5)-Phenyl-1H-imidazol-2-yl]acetamide **1a**

solvent	temp (°C)	reaction time (min)	yield (%)[a]
DMF	120	5	31
DMF	100	10	43
CH_3CN	80	10	62
CH_3CN	90	10	84
CH_3CN	100	10	96
$CHCl_3$	70	10	25
$CHCl_3$	80	10	40

[a] Refers to purified yield.

Table 2. Conventional Versus Microwave-Assisted Synthesis of Substituted *N*-(1H-Imidazol-2-yl)acetamides **1a**−**s**

			yield (%)[a]	
entry	R^1	R^2	RT[b]	MW
1a	C_6H_5	H	58[c], 54	96
1b	*m*-$NO_2C_6H_4$	H	41[c]	93
1c	*p*-$NO_2C_6H_4$	H		94
1d	*p*-ClC_6H_4	H		99
1e	*o*-$MeOC_6H_4$	H		93
1f	*p*-FC_6H_4	H		93
1g	C_6H_5	C_6H_5	61[c]	98
1h	*m*-$MeOC_6H_4$	H		92
1i	$C_{10}H_7$	H		94
1j	CH_3	CH_3	58[c]	93
1k	*p*-$CH_3C_6H_4$	H	56[c]	98
1l	C_6H_5	CH_3	58[c]	96
1m	*p*-CNC_6H_4	H		97
1n	$(CH_3)_3C$	H	61[c]	93
1o	$C_6H_5C_6H_4$	H		94
1p	*p*-BrC_6H_4	H	52[c]	98
1q	*p*-$MeOC_6H_4$	H	57[c]	96
1r	3,4-$Cl_2C_6H_3$	H		98
1s	*p*-BrC_6H_4	CH_3		98

[a] Refers to purified yield. Compound purity is >95% as determined by NMR. [b] RT refers to room temperature. [c] Ref 4c.

Synthesis of Substituted 2-Aminoimidazoles 2a−s. Because the microwave synthesis gave **1a** in high purity, the compound was used directly in the next step without purification. Prior to the microwave synthesis of **2a**, a preliminary study of the deacetylation reaction was carried out under conventional heating conditions.[4c] Compound **1a** (1.5 mmol) was refluxed using 30 mL of 20% H_2SO_4 in CH_3OH/H_2O (1:1), and complete deacetylation was observed after 24 h. The reaction mixture was evaporated under vacuum, and 2-amino-4(5)-phenylimidazole **2a** precipitated as a sulfate salt in 63% yield. However, under microwave irradiation at 100 °C, the same reaction was found to be completed within 10 min, and the sulfate salt of **2a** was obtained in 98% yield. In general, the acetamide group on compound **1** was readily deacetylated under sulfuric acid and CH_3OH/H_2O (1:1) to give the sulfate salt of **2** in high yield (Table 3). The only exceptions were compounds **1j** and **1n** which did not give any products under this reaction condition. Hence ethanol was used as the hydrolysis solvent in place of methanol and water, and the ethyl sulfate salts of **2j** and **2n** were formed, respectively, in high yields. In all cases, the salt of **2**, be it a sulfate or ethyl sulfate salt, could be quantitatively converted to a free base by adjusting the reaction mixture to pH ~10 with 5 M KOH in CH_3OH.

Table 3. Conventional Versus Microwave-Assisted Synthesis of Substituted 2-Aminoimidazoles **2a**−**s**

			yield (%)[a]	
entry	R_1	R_2	reflux	MW
2a	C_6H_5	H	68[b], 63	98
2b	*m*-$NO_2C_6H_4$	H	73[b]	91
2c	*p*-$NO_2C_6H_4$	H		90
2d	*p*-ClC_6H_4	H		92
2e	*o*-$MeOC_6H_4$	H		91
2f	*p*-FC_6H_4	H		91
2g	C_6H_5	C_6H_5-	86[b]	94
2h	*m*-$MeOC_6H_4$	H		90
2i	$C_{10}H_7$	H		93
2j[c]	CH_3	CH_3	72[b]	91
2k	*p*-$CH_3C_6H_4$	H		95
2l	C_6H_5	CH_3	84[b]	95
2m	*p*-CNC_6H_4	H		91
2n[c]	$(CH_3)_3C$	H	84[b]	93
2o	$C_6H_5C_6H_4$	H		92
2p	*p*-BrC_6H_4	H	58[b]	94
2q	*p*-$MeOC_6H_4$	H	72[b]	89
2r	3,4-$Cl_2C_6H_3$	H		88
2s	*p*-BrC_6H_4	CH_3-		93

[a] Refers to purified yield. Compound purity is >95% as determined by NMR. [b] Ref 4c. [c] Ethyl sulfate salt.

In conclusion, we have developed an efficient and high yielding microwave-assisted protocol for the synthesis of di- and monosubstituted 2-aminoimidazoles. We have demonstrated that under microwave irradiation, the total reaction time was shortened from a couple of days to only 20 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 either 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).

^1H and ^{13}C NMR spectra were measured at 298 K on either a Bruker AMX500 or a 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 (EI).

General Procedure for the Synthesis of Substituted *N*-(1H-imidazol-2-yl)acetamides 1a−s. The respective α-haloketone (1.98 mmol, 1 equiv) was added to acetylguanidine (5.94 mmol, 3 equiv) in anhydrous acetonitrile (40 mL), and the reaction mixture was heated at 100 °C using 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. Thereafter, the reaction mixture was dried under vacuum, and the residue was washed with H_2O, filtered, and dried to give **1**. Alternatively, the residue was subjected to column chromatography using $MeOH/CH_2Cl_2$ (1:20) as eluent.

***N*-[4(5)-Phenyl-1H-imidazol-2-yl]acetamide, 1a.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.62 (bs, 1H, N*H*), 11.24 (bs, 1H, N*H*), 7.71 (d, 2H, Ar*H*, $J = 7.5$ Hz), 7.32 (t, 2H, Ar*H*, $J = 7.5$ Hz), 7.25 (s, 1H, imidazole-*H*), 7.16 (t, 1H, Ar*H*, $J = 7.1$ Hz), 2.07 (s, 3H, Ac*H*). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.5, 141.2, 136.1, 134.7, 128.9, 128.6, 128.3, 125.8, 123.9, 109.1, 22.7.

***N*-[4(5)-(3-Nitrophenyl)-1H-imidazol-2-yl]acetamide, 1b.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.82 (bs, 1H, N*H*), 11.29 (bs, 1H, N*H*), 8.53 (s, 1H, Ar*H*), 8.15 (d, 1H, Ar*H*, $J = 7.7$ Hz), 8.0 (dd, 1H, Ar*H*, $J_{dd} = 1.7$ Hz, $J_d = 8.0$ Hz), 7.61 (t, 1H, Ar*H*, $J = 8.1$ Hz), 7.53 (s, 1H, imidazole-*H*), 2.08 (s, 3H, Ac*H*). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.6, 148.3, 141.7, 136.5, 134.0, 130.1, 129.9, 120.3, 118.0, 111.3, 22.8.

***N*-[4(5)-(4-Nitrophenyl)-1H-imidazol-2-yl]acetamide, 1c.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.94 (bs, 1H, N*H*), 11.32 (bs, 1H, N*H*), 8.19 (d, 2H, Ar*H*, $J = 9.1$ Hz), 7.96 (d, 2H, Ar*H*, $J = 9.0$ Hz), 7.61 (s, 1H, imidazole-*H*), 2.08 (s, 3H, Ac*H*). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.7, 145.0, 142.1, 141.4, 134.3, 124.3 (×2), 124.0 (×2), 113.3, 22.8.

***N*-[4(5)-(4-Chlorophenyl)-1H-imidazol-2-yl]acetamide, 1d.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.67 (bs, 1H, N*H*), 11.22 (bs, 1H, N*H*), 7.72 (d, 2H, Ar*H*, $J = 8.6$ Hz), 7.36 (d, 2H, Ar*H*, $J = 8.6$ Hz), 7.30 (s, 1H, Imidazole-*H*), 2.07 (s, 3H, Ac*H*). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.6, 141.4, 135.0, 133.7, 130.1, 128.4 (×2), 125.6 (×2), 109.9, 22.8.

***N*-[4(5)-(2-Methoxyphenyl)-1H-imidazol-2-yl]acetamide, 1e.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.56 (bs, 1H, N*H*), 11.21(bs, 1H, N*H*), 7.53–6.93 (m, 5H, Ar*H*, imidazole-*H*), 3.89 (s, 3H, −OC*H*$_3$), 2.08 (s, 3H, Ac*H*). ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.7, 156.6, 141.6, 136.2, 136.0, 131.1, 127.1, 121.4, 113.8, 112.1, 56.4, 23.9.

***N*-[4(5)-(4-Fluorophenyl)-1H-imidazol-2-yl]acetamide, 1f.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.62 (bs, 1H, N*H*), 11.21 (bs, 1H, N*H*), 7.75–7.70 (m, 2H, Ar*H*), 7.24 (s, 1H, imidazole-*H*), 7.14 (t, 2H, Ar*H*, $J = 9.1$ Hz), 2.06 (s, 3H, Ac*H*). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.5, 162.3, 141.3, 135.2, 131.3, 125.7, 125.6, 115.3, 115.0, 108.9, 22.7.

***N*-[4,5-Diphenyl-1H-imidazol-2-yl]acetamide, 1g.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.59 (bs, 1H, N*H*), 11.17 (bs, 1H, N*H*), 7.47–7.25 (m, 10H, Ar*H*), 2.09 (s, 3H, Ac*H*). ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.0, 141.0, 135.1, 132.6, 131.0, 128.9 (×2), 128.5, 128.1 (×2), 128.0 (×2), 127.3, 126.8 (×2), 122.9, 22.7.

***N*-[4(5)-(3-Methoxyphenyl)-1H-imidazol-2-yl]acetamide, 1h.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.62 (bs, 1H, N*H*), 11.25 (bs, 1H, N*H*), 7.28–7.21 (m, 4H, Ar*H*), 6.74–6.71 (m, 1H, Imidazole-*H*), 3.76 (s, 3H, -OC*H*$_3$), 2.06 (s, 3H, Ac*H*). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.4, 159.4, 141.1, 136.1, 130.1, 129.3, 116.4, 111.7, 109.4, 109.0, 54.8, 22.7.

***N*-[4(5)-Naphthalen-2-yl-1H-imidazol-2-yl]acetamide, 1i.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.70 (bs, 1H, N*H*), 11.28 (bs, 1H, N*H*), 8.19 (s,1H, imidaazole*H*), 7.88–7.83(m, 4H, Nap*H*), 7.47–7.40 (m, 3H, Nap*H*), 2.08 (s, 3H, Ac*H*). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.6, 141.6, 133.4, 132.2, 131.8, 129.6, 127.8, 127.6, 127.5, 126.1, 125.1, 123.4, 121.4, 110.0, 22.8.

***N*-[4,5-Dimethyl-1H-imidazol-2-yl]acetamide 1j.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.51 (bs, 2H, N*H*), 1.81 (s, 6H, −C*H*$_3$), 1.63 (s, 3H, Ac*H*). ^{13}C NMR (125 MHz, DMSO-d_6): δ 181.9 175.4, 162.1, 158.9, 27.6, 25.0 (×2).

***N*-[4(5)-p-Tolyl-1H-imidazol-2-yl]acetamide, 1k.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.55 (bs, 1H, N*H*), 11.19 (bs, 1H, N*H*), 7.59 (d, 2H, Ar*H*, $J = 8.0$ Hz), 7.17–7.11 (m, 3H, Ar*H* and Imidazole-*H*), 2.28 (s, 3H, C*H*$_3$), 2.06 (s, 3H, Ac*H*). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.4, 141.1, 136.2, 134.8, 131.9, 128.9 (×2), 123.9 (×2), 108.4, 22.7, 20.7.

***N*-[5(4)-Methyl-4(5)-phenyl-1H-imidazol-2-yl]acetamide, 1l.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.56 (bs, 1H, N*H*), 11.21 (bs, 1H, N*H*), 7.59 (d, 2H, Ar*H*, $J = 7.9$ Hz), 7.18–7.12 (m, 3H, Ar*H*), 2.28 (s, 3H, −C*H*$_3$), 2.07 (s, 3H, Ac*H*). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.7, 141.2, 135.1, 129.4, 129.1 (×2), 128.6, 124.0 (×2), 108.7, 22.8, 20.8.

***N*-[4(5)-(4-Cyanophenyl)-1H-imidazol-2-yl]acetamide, 1m.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.87 (bs, 1H, N*H*), 11.29 (bs, 1H, N*H*), 7.89 (d, 2H, Ar*H*, $J = 8.7$ Hz), 7.76 (d, 2H, Ar*H*, $J = 8.3$ Hz), 7.53 (s, 1H, Imidazole-*H*), 2.08 (s, 3H, Ac*H*). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.7, 141.8, 139.2, 134.5 (×2), 132.4, 124.3 (×2), 119.2, 112.3, 107.7, 22.7.

***N*-[4(5)-tert-Butyl-1H-imidazol-2-yl]acetamide, 1n.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.06 (bs, 2H, N*H*), 6.37 (s, 1H, Imidazole-*H*), 2.01 (s, 3H, Ac*H*), 1.18 (s, 9H, −(C*H*$_3$)$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.2, 140.1, 139.7, 105.2, 103.5, 30.0 (×3), 22.7.

***N*-[4(5)-Biphenyl-4-yl-1H-imidazol-2-yl]acetamide, 1o.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.65(bs,1H, N*H*), 11.26(bs, 1H, N*H*), 7.80 (d, 2H, Ar*H*, $J = 8.3$ Hz), 7.70–7.62 (m, 4H, Ar*H*), 7.46 (t, 2H, Ar*H*, $J = 7.5$ Hz), 7.37–7.32 (m, 2H, Ar*H* and Imidazole-*H*), 2.08 (s, 3H, Ac*H*). ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.6, 142.5, 141.1, 138.6, 135.0, 129.9 (×2), 128.2, 127.7 (×2), 127.3 (×2), 125.6 (×2), 110.6, 31.7, 23.8.

***N*-[4(5)-(4-Bromophenyl)-1H-imidazol-2-yl]-acetamide, 1p.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.69 (bs, 1H, N*H*), 11.23 (bs, 1H, N*H*), 7.67 (d, 2H, Ar*H*, $J = 8.3$ Hz), 7.50 (d, 2H, Ar*H*, $J = 8.6$ Hz), 7.32 (s, 1H, Imidazole-*H*), 2.07 (s, 3H, Ac*H*). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.6, 141.4, 134.0, 132.0, 131.3 (×2), 126.0 (×2), 118.5, 109.9, 22.8.

***N*-[4(5)-(4-Methoxyphenyl)-1H-imidazol-2-yl]-acetamide, 1q.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.50 (bs, 1H, N*H*), 11.19 (bs, 1H, N*H*), 7.62 (d, 2H, Ar*H*, J = 8.3 Hz), 7.11 (s, 1H, Imidazole-*H*), 6.89(d, 2H, Ar*H*, J = 8.4 Hz), 3.75 (s, 3H, $-$OC*H*$_3$), 2.06 (s, 3H, Ac*H*). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.5, 157.7, 141.2, 130.4, 127.6, 125.2 ($\times$2), 113.9 ($\times$2), 107.8, 55.0, 22.8.

***N*-[4(5)-(3,4-Dichlorophenyl)-1H-imidazol-2-yl]-acetamide, 1r.** ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.74 (bs, 1H, N*H*), 11.23 (bs, 1H, N*H*), 7.93–7.44 (m, 4H, Ar*H* Imidazole-*H*), 2.07 (s, 3H, Ac*H*). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.6, 141.5, 135.5, 131.2, 130.5, 127.7 ($\times$2), 125.4, 123.9, 111.0, 22.7.

***N*-[4(5)-(4-Bromo-phenyl)-5(4)-methyl-1H-imidazol-2-yl]-acetamide, 1s.** ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.55 (bs, 1H, N*H*), 11.08 (bs, 1H, N*H*), 7.54 (s, 4H, Ar*H*), 2.38(s, 3H, C*H*$_3$), 2.06 (s, 3H, Ac*H*). ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.7, 135.4, 131.6 ($\times$2), 130.3, 127.9 ($\times$2), 120.3,120.2,118.5, 23.2,11.6.

General Procedure for the Synthesis of Substituted 2-Aminoimidazoles 2a$-$s. Method 1. The respective compound **1** (1.5mmol) was added to 30 mL of MeOH/H_2O (1:1) solution containing 20% (6 mL) of concentrated H_2SO_4 and heated at 100 °C under microwave irradiation (300 W). The reaction was monitored by TLC (MeOH/CH_2Cl_2 = 1:20) and was found to be complete after 10 min The reaction mixture was concentrated, and the precipitate that formed was filtered and recrystallized from an appropriate solvent to give **2** as a sulfate salt. The sulfate salt of **2** was converted to a free base by adjusting the reaction mixture to pH ~10 with 5 M KOH in MeOH, concentrating the reaction mixture, and then purifying the residue by recrystallization or column chromatography using MeOH/CH_2Cl_2 (1:20) as eluent.

Method 2: Using Concentrated H_2SO_4 in Ethanol. The respective compound **1** was added to 30 mL of ethanol containing 20% (6 mL) of concentrated H_2SO_4 and heated at 100 °C under microwave irradiation (300 W). The reaction was monitored by TLC (MeOH/CH_2Cl_2 = 1:20) and was found to be complete after 10 min The reaction mixture was concentrated, and the precipitate that formed was filtered and recrystallized from an appropriate solvent to give **2** as a ethyl sulfate salt. The ethyl sulfate salt of **2** could be converted to a free base by adjusting the reaction mixture to pH ~10 with 5 M KOH in MeOH, concentrating the reaction mixture, and then purifying the residue by column chromatography using MeOH/CH_2Cl_2 (1:20) as eluent.

2-Amino-4(5)-phenylimidazole, 2a. ^{1}H NMR (300 MHz, MeOH-d_4): δ 7.57–7.33 (m, 5H, Ar*H*), 7.14 (s, 1H imidazole-*H*). ^{13}C NMR (75 MHz, MeOH-d_4): δ 151.32, 133.4, 129.7 ($\times$2), 129.3, 127.8, 127.5, 125.0, 112.2. Exact Mass Calcd for $C_9H_9N_3$: 159.0796. Found: 159.0794.

2-Amino-4(5)-3-nitrophenylimidazole, 2b. ^{1}H NMR (300 MHz, MeOH-d_4): δ 8.40 (s, 1H, Ar*H*), 7.98–7.92 (m, 2H, Ar*H*), 7.51 (t, 1H, Ar*H*, J = 8.0 Hz), 7.10 (s, 1H, imidazole-*H*). ^{13}C NMR (75 MHz, MeOH-d_4): δ 152.5, 150.2, 137.2, 134.2, 130.7 ($\times$2), 121.2, 119.2, 112.9. Exact Mass Calcd for $C_9H_8N_4O_2$: 204.0647. Found: 204.0650.

2-Amino-4(5)-4-nitrophenylimidazole, 2c. ^{1}H NMR (300 MHz, MeOH-d_4): δ 8.16 (d, 2H, Ar*H*, J = 9.1 Hz), 7.75 (d, 2H, Ar*H*, J = 9.1 Hz), 7.20 (s, 1H, imidazole-*H*). ^{13}C NMR (75 MHz, MeOH-d_4): δ 150.1, 148.6, 135.2, 127.2, 126.2 ($\times$2), 125.5 ($\times$2), 113.4. Exact Mass Calcd for $C_9H_8N_4O_2$: 204.0647. Found: 204.0648.

2-Amino-4(5)-4-chlorophenylimidazole, 2d. ^{1}H NMR (300 MHz, MeOH-d_4): δ 7.52 (d, 2H, Ar*H*, J = 8.7 Hz), 7.29 (d, 2H, Ar*H*, J = 8.7 Hz), 6.95 (s, 1H, imidazole-*H*). ^{13}C NMR (75 MHz, MeOH-d_4): δ 151.5, 133.0, 132.9, 132.4, 129.7 ($\times$2), 126.5 ($\times$2), 111.9. Exact Mass Calcd for $C_9H_8ClN_3$: 193.0407. Found: 193.0608.

2-Amino-4(5)-2-methoxyphenylimidazole, 2e. ^{1}H NMR (300 MHz, MeOH-d_4): δ 7.52–7.51 (m, 1H, Ar*H*), 7.32–7.29 (m, 1H, Ar*H*), 7.16–7.09 (m, 2H, Ar*H* and Imidazole-*H*), 7.01 (t, 1H, Ar*H*, J = 7.7 Hz), 3.95 (s, 3H, $-$OC*H*$_3$). ^{13}C NMR (75 MHz, MeOH-d_4): δ 156.0, 149.4, 127.8, 125.9 ($\times$2), 121.0, 119.8, 115.7, 111.5, 55.0. Exact Mass Calcd for $C_{10}H_{11}N_3O$: 189.0902. Found: 189.0903.

2-Amino-4(5)-4-Fluorophenylimidazole, 2f. Recrystallized from EtOH as a white solid. ^{1}H NMR (500 MHz, MeOH-d_4): δ 7.62–7.61 (m, 2H, Ar*H*), 7.22 (t, 2H, Ar*H*, J = 8.9 Hz), 7.15 (s, 1H, Imidazole-*H*). ^{13}C NMR (75 MHz, MeOH-d_4): δ 165.8, 162.5, 128.4, 127.9, 127.8, 125.5, 117.3, 117.0, 109.9. Exact Mass Calcd for C_9H_8 FN_3: 177.0702. Found: 177.0702.

2-Amino-4,5-diphenylimidazole, 2g. ^{1}H NMR (300 MHz, MeOH-d_4): δ 7.41–7.26 (m, 10H, Ar*H*). ^{13}C NMR (75 MHz, MeOH-d_4): δ 149.4, 131.4, 129.8 ($\times$2), 129.3 ($\times$2), 128.9, 128.5 ($\times$2), 128.3 ($\times$2), 128.2 ($\times$2), 127.8, 125.5. Exact Mass Calcd for $C_{15}H_{13}N_3$: 235.1109. Found: 235.1108.

2-Amino-4(5)-3-methoxyphenylimidazole, 2h. ^{1}H NMR (300 MHz, MeOH-d_4): δ 7.25 (t, 1H, Ar*H*, J = 8.0 Hz), 7.12–7.11 (m, 2H, Ar*H*), 7.01 (s, 1H, imidazole-*H*), 6.82–6.79 (m, 1H, Ar*H*), 3.80 (s, 3H, $-$OC*H*$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.9, 139.7, 130.0, 129.8, 127.1, 120.7, 116.5, 112.0, 107.4, 55.7. Exact Mass Calcd for $C_{10}H_{11}N_3O$: 189.0902. Found: 189.0903.

2-Amino-4(5)-naphthalenimidazole, 2i. Recrystallized from EtOH. ^{1}H NMR (300 MHz, MeOH-d$_4$): δ 9.20 (s,1H, Napt*H*), 9.12 (s, 1H, Napt*H*), 8.89–8.76 (m, 4H, Napt*H* and Imidazole-*H*), 8.43–8.38 (m, 2H, Napt*H*). ^{13}C NMR (75 MHz, DMSO-d_6): δ 143.3, 133.9, 133.7, 133.2, 130.2, 129.8, 128.9, 128.8, 128.1, 127.7, 124.5, 124.1, 106.3. Exact Mass Calcd for $C_{13}H_{11}N_3$: 209.0953. Found: 209.0951.

2-Amino-4,5-dimethylimidazole ethyl sulfate, 2j. Recrystallized from EtOH/ether. ^{1}H NMR (300 MHz, MeOH-d_4): δ 4.04 (q, 2H, $-$C*H*$_2-$CH$_3$, J = 7.0 Hz), 1.90 (s, 6H, C*H*$_3$), 1.27 (t, 3H, $-$CH$_2-$C*H*$_3$, J = 7.0 Hz). ^{13}C NMR (125 MHz, MeOH-d_4): δ 183.0, 81.8, 65.2, 30.6, 23.7 ($\times$ 2),15.2. Exact Mass Calcd for $C_5H_9N_3$: 111.0796. Found: 111.0802.

2-Amino-4-*p*-tolylimidazole, 2k. ^{1}H NMR (300 MHz, MeOH-d_4): δ 7.41 (d, 2H, Ar*H*, J = 8.0 Hz), 7.11 (d, 2H, Ar*H*, J = 8.0 Hz), 6.81 (s, 1H, imidazole-*H*), 2.30 (s, 3H, $-$C*H*$_3$). ^{13}C NMR (75 MHz, MeOH-d_4): δ 136.7, 130.1 ($\times$2), 129.5, 127.5, 126.4, 124.9 ($\times$2), 112.3, 21.1. Exact Mass Calcd for $C_{10}H_{11}N_3$: 173.0953. Found: 173.0950.

2-Amino-5(4)-methyl-4(5)-phenylimidazole, 2l. ^{1}H NMR (300 MHz, MeOH-d_4): δ 7.45 (s, 5H, Ar*H*), 2.29 (s, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, MeOH-d_4): δ 148.0, 130.1 ($\times$2), 129.6, 129.3, 127.9 ($\times$2), 123.5, 120.0, 10.0. Exact Mass

Calcd for $C_{10}H_{11}N_3$: 173.0953. Found: 173.0950. **2l** was converted to its more stable chloride salt by treatment with concentrated HCl. Single crystals of the chloride salt of **2l** were grown from water and characterized by X-ray crystallography.

2-Amino-4(5)-4-cyanophenylimidazole, 2m. ^{1}H NMR (300 MHz, MeOH-d_4): δ 7.74 (d, 2H, Ar*H*, J = 8.3 Hz), 7.65 (d, 2H, Ar*H*, J = 8.6 Hz), 7.17 (s, 1H, imidazole-*H*). ^{13}C NMR (75 MHz, MeOH-d_4): δ 152.6, 139.5, 133.5 (×2), 133.0, 125.2 (×2), 120.2, 114.7, 109.5. Exact Mass Calcd for $C_{10}H_8N_4$: 184.0749. Found: 184.0749.

2-Amino-4(5)-*tert*-butyl-imidazole ethyl sulfate, 2n. Recrystallized from EtOH/ether. ^{1}H NMR (300 MHz, MeOH-d_4): δ 6.46 (s, 1H, imidazole-*H*), 4.07 (q, 2H, $-CH_2-CH_3$, J = 6.8 Hz), 1.32–1.28 (m, 9H, $-(CH_3)_3$), 1.06–1.02 (m, 3H, $-CH_2-CH_3$). ^{13}C NMR (75 MHz, MeOH-d_4): δ 113.7, 112.2, 106.8, 101.3, 64.3, 28.5, 25.3, 23.7, 14.5. Exact Mass Calcd for $C_7H_{13}N_3$: 139.1109. Found: 139.1107.

2-Amino-(4-biphenyl)imidazole, 2o. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.74–7.68 (m, 6H, Ar*H*), 7.46 (t, 2H, Ar*H*, J = 7.0 Hz), 7.38–7.33 (m, 1 H, Ar*H*), 7.30 (s, 1H, imidazole-*H*), 6.72 (bs, 2H, NH_2). ^{13}C NMR (75 MHz, DMSO-d_6): δ 148.2, 139.3, 139.0, 128.9 (×2), 128.7, 127.6, 127.0 (×2), 126.4 (×2), 124.5 (×2), 109.8, 30.7. Exact Mass Calcd for $C_{15}H_{13}N_3$: 235.1109. Found: 235.1108.

2-Amino-4(5)-4-bromophenylimidazole, 2p. ^{1}H NMR (300 MHz, MeOH-d_4): δ 7.47 (s, 4H, Ar*H*), 7.01 (s, 1H, imidazole-*H*). ^{13}C NMR (75 MHz, MeOH-d_4): δ 151.3, 132.8 (×2), 132.5, 132.3, 126.9 (×2), 121.0, 111.9. Exact Mass Calcd for $C_9H_8BrN_3$: 236.9902. Found: 236.9903.

2-Amino-4(5)-4-methoxyphenylimidazole, 2q. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.85 (s, 1H, imidazole-*H*), 7.72 (d, 2H, Ar*H*, J = 8.9 Hz), 7.05 (d, 2H, Ar*H*, J = 8.9 Hz), 3.81 (s, 3H, $-OCH_3$). ^{13}C NMR (75 MHz, MeOD-d_4): δ 160.1, 129.1, 127.3, 127.2 (×2), 115.2 (×2), 115.1, 103.5, 56.0. Exact Mass Calcd for $C_{10}H_{11}N_3O$: 189.0902. Found: 189.0906.

2-Amino-4(5)-3,4-dichlorophenylimidazole, 2r. ^{1}H NMR (300 MHz, MeOH-d_4): δ 7.71 (s, 1H, Ar*H*), 7.70–7.38 (m, 2H, Ar*H*), 6.99 (s, 1H, imidazole-*H*). ^{13}C NMR (75 MHz, MeOH-d_4): δ 149.7, 134.3, 133.1, 132.3, 129.4, 127.4, 126.9, 125.3, 111.7. Exact Mass Calcd for $C_9H_7Cl_2N_3$: 227.0017. Found: 227.0018.

2-Amino-4(5)-(4-bromo-phenyl)-5(4)-methyl-imidazole, 2s. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.77 (bs, 2H, NH_2), 7.59 (d, 2H, Ar*H*, J = 8.8 Hz), 7.41 (d, 2H, Ar*H*, J = 8.9 Hz), 2.22 (s, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 147.5, 132.2 (×2), 128.6, 128.2 (×2), 120.6, 120.5, 119.8, 10.8. Exact Mass Calcd for $C_{10}H_{10}BrN_3$: 251.0058. Found: 251.0169.

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 **1a**−**s** and **2a**−**s**, and X-ray crystal structure of the chloride salt of **2l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC700143N