A Simple and Practical Synthesis of 2-Aminoimidazoles

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A new and simple two-step procedure to synthesize 2-aminoimidazoles (2-AI's) from readily available materials has been developed. The cyclization reaction of α-halo ketones and *N*-acetylguanidine in acetonitrile (MeCN) at reflux, or in dimethylformamide (DMF) at ambient temperature, gives 4(5)-substituted and 4,5-disubstituted *N*-(1*H*-imidazol-2-yl)acetamides, which are then hydrolyzed to their respective 2-AI's. In general, the purified products were isolated in good yields. We have prepared several examples and have demonstrated the usefulness of this method by its application in the total synthesis of **8**, an interesting histamine analog, and oroidin, **15**, a marine natural product isolated from various sponges.

Introduction

The 2-aminoimidazole (2-AI) ring structure is of particular interest especially within the realms of medicinal chemistry. For example, several classes of marine natural products possessing this structure were recently discovered and identified.[1] Many of these compounds display a broad range of biological properties including antibacterial, antiinflammatory, anticancer, and antiviral activity. Synthetic 2-AI derivatives, including 2-aminohistamine have been shown to have H_1- and H_2-receptor agonist and antagonist activity.[2] Other unrelated 2-AI derivatives are selective 5-HT_3 receptor antagonists, which may be potentially useful in the treatment of chemotherapy induced emesis.[3] Novel cephalosporins with incorporated 2-AI rings display both Gram-positive and Gram-negative antibacterial activity as well as good β-lactamase stability.[4] In addition, 2-AI can serve as an important starting material in the preparation of 2-nitroimidazole (*azomycin*) a naturally occurring antibiotic.[5] Other synthetic analogs of 2-nitroimidazole have been found to be cytotoxic toward hypoxic tumor cells and act as hypoxic cell radiosensitizers.[6]

The methods reported to prepare imidazoles are numerous, although only a limited number describe the direct synthesis of the corresponding 2-amino derivatives. The preparation of 2-AI was accomplished by the intramolecular cyclization of *N*-(2,2-diethoxyethyl)guanidine upon acid hydrolysis.[7,8] The reaction of α-amino aldehydes or ketones with cyanamide appears to be the most commonly used direct approach.[1h,2c,5b,8,9] However, this reaction is pH sensitive and can lead to different products. In one case the formation of 1*H*-imidazo[1,2-*a*]imidazoles was observed.[8] The dimerization and cyclization of α-amino aldehydes or ketones to symmetrical pyrazines is also a common problem associated with this method.[9a,10] A classical, although indirect approach to 2-AI's relies upon the formation of 2-arylazo derivatives via diazonium coupling, followed by reduction.[2a,7,11] The phenyltriazene functionality can also serve as a masked amine surrogate. It has been introduced by the reaction of phenyl azide with the C-2 carbanion of N-1 protected imidazoles.[12] The synthesis of 2-amino-4,5-diarylimidazoles was accomplished by the reduction of symmetrical 2,2′-azoimidazoles.[13] These azoimidazoles were prepared by the condensation of 1,2-hydrazinedicarboxamidine with benzoins, followed by oxidation. A more recent procedure was reported where 2-AI's were formed by the reaction of α-diketones with guanidine, followed by catalytic hydrogenation.[14] Other indirect approaches to 2-AI's involve ipso type substitutions of appropriate C-2 substituted imidazoles, where the addition of a suitable nitrogen nucleophile is followed by the elimination of an activated leaving group such as a halogen or alkyl sulfoxide or sulfone. This method has been applied with limited success to electron-poor imidazoles or when

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fluorine is the leaving group.[4,15] An interesting synthetic route to functionalized 2-AI's, which were difficult to obtain by other methods, has been achieved using a base-catalyzed rearrangement of 3-amino-1,2,4-oxadiazoles.[16] Another type of heterocyclic rearrangement involves the reaction of 2-aminooxazoles with ammonia or formamide.[17] Most recently, the synthesis of 2-amino-4(5)-(α-hydroxyalkyl)imidazoles has been demonstrated where 2-AI was reacted with aldehydes under neutral conditions.[18]

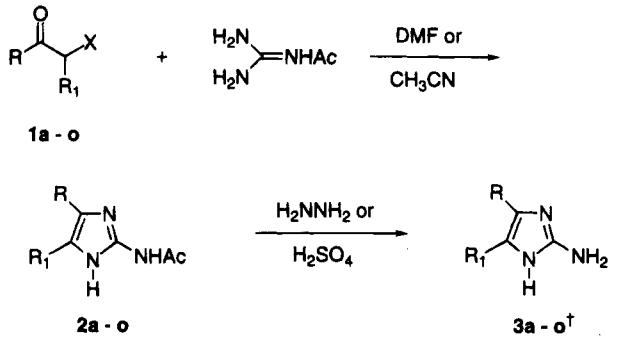
Analogous to the reaction of α-diketones with guanidine, an obvious conceptual synthesis of 2-AI's would be the reaction of α-halo ketones with guanidine. Surprisingly very little has been reported regarding this method.[16d,19,20] Since many α-halo ketones are readily available, we reasoned that this may represent a very practical approach to various 2-AI's.

Results and Discussion

Several attempts were made to synthesize 2-amino-4(5)-phenylimidazole (**3e**) by the reaction of α-bromoacetophenone (**1e**) with guanidine. In our initial trials, the free base of guanidine was liberated *in situ* from it's hydrochloride (HCl) salt with sodium hydroxide (NaOH) in ethanol (EtOH) followed by the addition of the bromide. Variations made to the reaction conditions were all unsuccessful. In general these experiments yielded intractable mixtures of compounds which we chose not to isolate or identify. Salt-free guanidine was also generated using strongly basic Amberlite IRA-400-(OH) ion exchange resin.[21] Once again, gross mixtures were observed by thin layer chromatography (TLC) when attempts were made to treat **1e** with the free base in anhydrous dimethyl sulfoxide (DMSO), DMF, or EtOH.

By substituting guanidine with an excess of *N*-acetylguanidine,[21,22] we observed a clean reaction when **1e** was stirred at room temperature in anhydrous DMF. The bromide was completely consumed after 96 h as indicated by TLC on silica using 10% methanol (MeOH) in chloroform ($CHCl_3$). The DMF solution was poured into water (H_2O) whereupon a precipitate formed which was collected and washed with cold H_2O. This method gave relatively clean material by TLC but a 20−30% loss in mass resulted. We were able to avoid this loss by slightly modifying the workup. Instead of pouring the DMF solution into H_2O, we first removed the solvent completely under high vacuum and then washed the solid. The product was recrystallized from MeOH and shown to be 4(5)-phenyl-*N*-(1*H*-imidazol-2-yl)acetamide, **2e** (58%), by NMR and elemental analysis. An additional product, that was originally seen by TLC while monitoring the reaction, completely disappeared. We later identified it as diacetylguanidine,[21,23] which is soluble in H_2O and MeOH and therefore removed upon workup.

Scheme 1. Synthesis of 2-Aminoimidazoles



#	X	R	R_1	Yields (%)‡
1a - 3a	Cl	CH_3	H	(32) 82
1b - 3b	Br	Et	H	(78) 86
1c - 3c	Br	^{t}Bu	H	(61) 84
1d - 3d	Br	CH_3	CH_3	(58) 72
1e - 3e	Br	Ph	H	(58) 68
1f - 3f	Br	4-Me-C_6H_4	H	(56) 67
1g - 3g	Br	4-Br-C_6H_4	H	(52) 58
1h - 3h	Br	4-OMe-C_6H_4	H	(57) 72
1i - 3i	Br	3-NO_2-C_6H_4	H	(41) 73
1j - 3j	Br	3-OPh-C_6H_4	H	(47) 70
1k - 3k	Br	Ph	CH_3	(65) 84
1l - 3l	Br	Ph	Ph	(61) 86
1m - 3m	Br	2-$C_{10}H_7$	H	(58) 83
1n - 2n	Cl	-$(CH_2)_3$-		(31)
1o - 3o	Cl	-$(CH_2)_4$-		(36) 78

† **3n** was not prepared; See text.

‡ Purified or recrystallized yields; Yields in ( )s are for **2a-o**.

The reaction has been successfully carried out with various available α-halo ketones as depicted in Scheme 1. Several attempts to prepare 4(5)-(trifluoromethyl)-*N*-(1*H*-imidazol-2-yl)acetamide from 3-bromo-1,1,1-trifluoroacetone failed. In this case only unidentifiable materials were obtained. A direct comparison was made between α-chloro- and α-bromo ketones in three examples. In general the bromides seem to work much better than the chlorides. The yield of **2e** was reduced to 40% when α-chloroacetophenone was substituted for **1e**. When **1d** was replaced with 3-chloro-2-butanone, **2d** was obtained in poor yield (13%). However, when 2-bromocyclopentanone[24] was used instead of the α-chloro ketone **1n**, essentially no improvement was observed.

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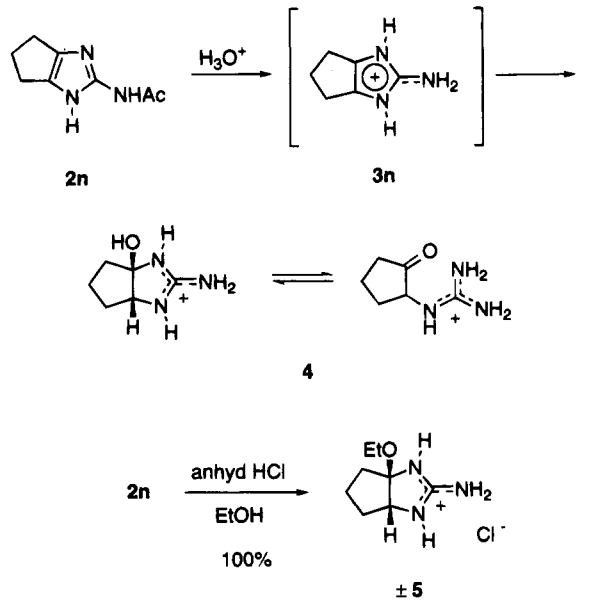
This result may be attributed to the instability of 2-bromocyclopentanone.

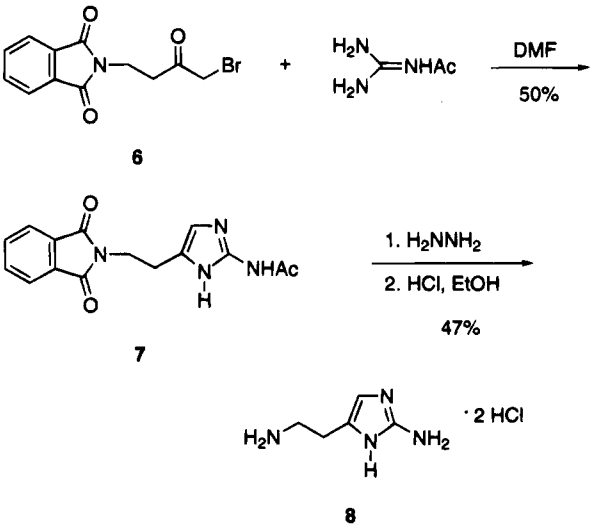
Several modifications of the reaction conditions, including temperature, solvents, and auxiliary bases, were also explored using compound **1e** as a model. At 60 and 90 °C new byproducts were observed. Inferior results were obtained when the reaction was run in $CHCl_3$, tetrahydrofuran (THF), dimethoxyethane (DME), or DMSO. However, the reaction could be performed in MeCN at reflux, although the yield of **2e** was reduced to 44%. We found MeCN to be the solvent of chose for entries **1n** and **1o**. The addition of bases such as triethylamine, diisopropylethylamine, or calcium carbonate was also investigated, but in general the reaction yields were significantly diminished. Therefore, these bases were omitted and an excess of acetylguanidine was used. Typically, a 3-fold excess was necessary since we always observed the formation of the diacetylguanidine side-product.

In general the 2-amino group was readily deacetylated under acidic conditions with sulfuric acid, H_2O, and MeOH at reflux or under basic conditions with neat hydrazine at 70 °C. When the *N*-(1*H*-imidazol-2-yl)-acetamides were subjected to hydrolysis with concd H_2SO_4 in 95% EtOH, the ethyl sulfate salts of 2-AI's were formed. An unexpected transformation was observed when the fused (acetylamino)imidazole **2n** was subjected to acid hydrolysis. The initial reaction of **2n** with H_2SO_4 produced what appeared to be several new compounds as judged by TLC (silica, 20% saturated methanolic NH_3 in $CHCl_3$). Unlike the other alkyl and dialkyl 2-AI's, a noticeable loss in fluorescence (TLC) was also observed. A much cleaner reaction took place when **2n** was heated to reflux in 50% aqueous trifluoroacetic acid (TFA) for 24 h, followed by the removal of excess TFA and H_2O under high vacuum. Once again a loss in fluorescence (TLC) was observed. At first we suspected that once amide hydrolysis occurred, H_2O subsequently attacked the 2-position of the aminoimidazolium cation, displacing ammonia to give the tetrahydrocyclopentaimidazolin-2-one. However, this was not the case as judged by evidence obtained from ^1H NMR and mass spectral data. Four exchangeable protons were observed from the ^1H NMR (DMSO-d_6) data at δ 7.82 (2), 8.38 and 8.95, possibly indicating a protonated 2-amino-2-imidazoline. Mass spectrometry of the product gave a strong M + H peak of 142. In addition, the product was stained very dark by ninhydrin. This data supports the proposed structures **4** as shown in Scheme 2. To verify these results the hydrolysis of **2n** was carried out with anhyd HCl in EtOH under reflux. We anticipated that under these conditions EtOH would replace H_2O as the nucleophile, and the more stable ethoxy-substituted bicyclic product **5** would be formed as illustrated in Scheme 2. Spectroscopic and analytical data confirmed the formation of imidazoline **5**. In unrelated work, similar carbinolamine-type structures have been isolated and characterized when 1,2-cyclohexanedione was treated with arginine peptides.[25] In another report, 2-amino-4,5-dimethoxy-4,5-diphenylimidazoline hydrochloride was prepared by the treatment of 2-amino-4,5-diphenyl-4-hydroxy-4*H*-imidazole with methanolic HCl.[14] Unfortunately, efforts to hydrolyze (acetylamino)imidazole **2n** with hydrazine gave a mixture of unidentifiable products,

Scheme 2. Hydrolysis of 2n



Scheme 3. Synthesis of 2-Aminohistamine



whereas other basic conditions (excess NaOH in MeOH at reflux) gave unreacted starting material. At elevated temperatures, using n-butanol instead of MeOH, the reaction mixture became dark after several hours, although TLC (silica, 20% saturated methanolic NH_3 in $CHCl_3$) indicated mostly unreacted starting material. Unlike **2n**, the cyclohexyl derivative **2o** could be converted to the corresponding imidazole **3o** when subjected to hydrolysis with anhyd ethanolic HCl. We propose that the formation of **4** and **5** occurs in order to alleviate ring strain. Although aromaticity is destroyed, the stable imidazolidinium cation is formed.

To further demonstrate the overall utility of this methodology, the chemistry was successfully applied in the total synthesis of 2-aminohistamine, **8**,[2a] and the marine natural product oroidin, **15**.[11,26] For the total synthesis of **8** (Scheme 3), we preferred the *N*-phthaloyl protecting group, since it could be simultaneously removed along with the *N*-acetyl group using hydrazine. Beginning with the known 1-bromo-4-phthalimido-2-

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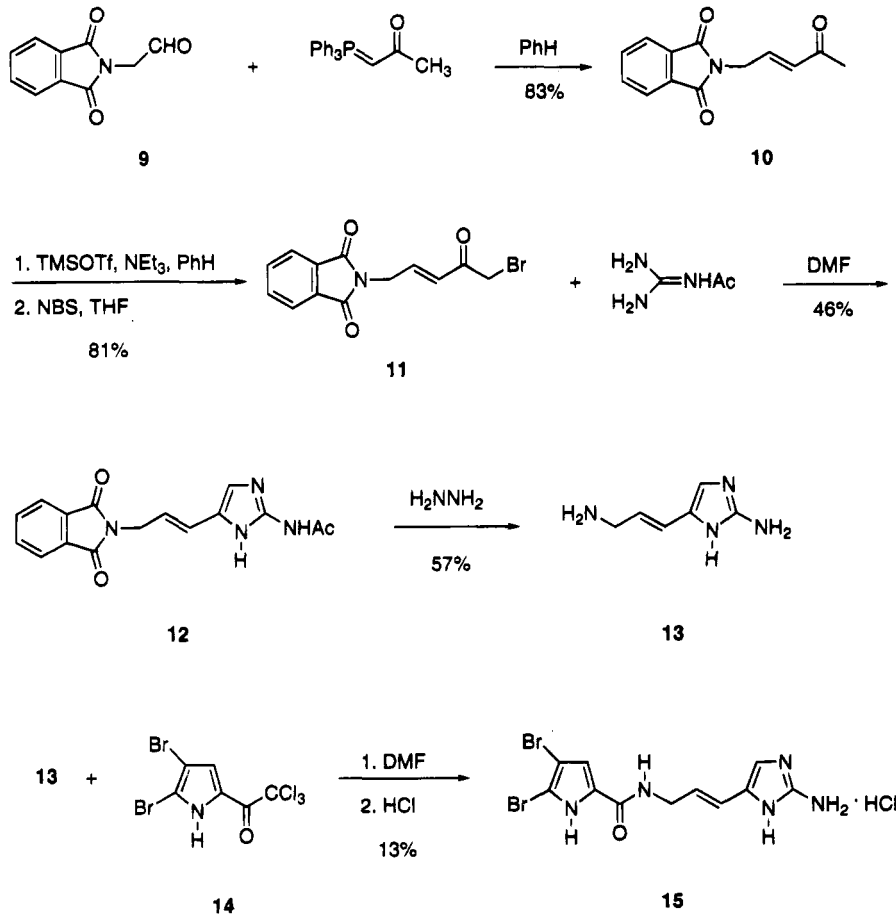
Scheme 4. Synthesis of Oroidin



butanone, **6**,[27] the dihydrochloride salt of **8** was easily prepared in 23% overall yield. The total synthesis of **15** is outlined in Scheme 4. Wittig reaction of 1-(triphenylphosphoranylidene)-2-propanone and phthalimidoacetaldehyde, **9**,[28] gave exclusively the *E*-isomer **10** in 83% yield. Compound **10** was subsequently converted to the trimethylsilyl enol ether which was immediately transformed to α-bromo ketone **11** using *N*-bromosuccinimide (NBS) in 81% yield. Under the established standard conditions, **11** was converted to 2-AI **12** in 46% yield which was deprotected with hydrazine and isolated as the dihydrochloride salt of **13**.[1i] The free base of **13** (generated *in situ*) was treated with trichloromethyl ketone **14**[29] to give oroidin **15** in 13% yield after repeated chromatography and salt formation.[30] The ^{1}H NMR data for synthetic and natural oroidin were identical in all respects. The synthetic material was also shown to be equivalent to the natural product by HPLC coinjection.

Conclusions

In summary, a new synthesis of 2-aminoimidazoles (2-AI's) has been developed. Attempts to form 2-AI's by the reaction of guanidine and α-halo ketones were unsuccessful, however, the use of *N*-acetylguanidine as a guanidine equivalent gave *N*-(1*H*-imidazol-2-yl)acetamides. A thorough, but not exhaustive, investigation of this reaction was performed. In general, the best results were obtained when 3 equiv of *N*-acetylguanidine and the α-bromo ketones were stirred in DMF at room temperature for 4 days. Several examples are reported in this paper. For reasons unknown, the reaction failed in the case of 3-bromo-1,1,1-trifluoroacetone. In all but one circumstance, the hydrolysis of the acetamides gave 2-AI's in good yields after purification. Interestingly, acetamide **2n** could not be hydrolyzed to its corresponding 2-AI, whereas imidazoline **4** was the product obtained. New, as well as previously reported, 2-AI derivatives have been synthesized. The total synthesis of 2-aminohistamine, **8**, and the marine natural product oroidin, **15**, were achieved using this methodology. This new method has some notable advantages as opposed to other synthetic routes and may be used as an effective alternative. For example, the starting materials are either available or readily accessible. Compared to classical procedures, this method avoids the use of diazonium chemistry and reductions.[2a,7,11-14] In addition, the methods pioneered by Lawson and Lancini require α-amino ketones, which may not be suitable because of problems relating to preparation, stability, or sensitivity to reaction conditions.[8-10]

Experimental Section

^{1}H and ^{13}C spectra were determined using a General Electric QE-300 spectrometer operating at a field strength of 300 and 75 MHz, respectively. Chemical shifts are reported in parts

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per million (δ) setting the references such that in DMSO-d_6 the DMSO is at 2.49 ppm and in CD_3OD the CH_3OH is at 3.30 ppm. Melting points were determined on a Meltemp apparatus and are not corrected. Decomposition points were characterized by color darkening. Infrared absorption spectra were taken on a MIDAC Corp. FTIR. Analytical HPLC was performed using a Zorbax C18 column (250 mm × 4.6 mm; 5 μm) with a gradient mobile phase consisting of 20–40% CH_3CN in 0.1 M HOAc and NEt_3: pH = 5.0. Flow rate = 1.5 mL/min; injection volume = 10 μL. High and low resolution FAB mass spectra were performed by the Scripps Research Institute Mass Spectrometry Facility, San Diego, CA. Elemental analysis were performed by Atlantic Microlabs, Inc., Norcross, GA. Column chromatography was performed using silica gel 60 (Merck Art 9385) and basic aluminum oxide (Brockmann 1, activated, ~150 mesh). All starting materials were obtained from commercially available sources unless otherwise indicated. Anhydrous DMF and MeCN was obtained from Aldrich Chemical Co. and used as is. Benzene (PhH) was dried over 3 Å molecular sieves prior to use. Anhydrous THF was prepared by distillation over sodium benzophenone ketyl under nitrogen atmosphere. Diethyl ether is referred to as ether. Sephadex LH-20 was obtained from Pharmacia, Uppsala, Sweden.

General Procedure A: Synthesis of 2-*N*-Acetyl Substituted 2-Aminoimidazoles. To 3.0 equiv of acetylguanidine in anhyd DMF was added 1.0 equiv of the α-halo ketone (typically a 0.3 M solution of α-halo ketone). The reaction mixture was stirred at room temperature for 96 h whereupon it was evaporated to dryness and the residue was washed with H_2O, filtered, dried, and recrystallized. Alternatively, the residue was subjected to column chromatography.

General Procedure B: This procedure is identical to A, except MeCN was used as the solvent. The reaction mixtures were heated at reflux under argon for 16 h.

General Procedure C: Hydrolysis of 2-*N*-Acetyl Substituted 2-Aminoimidazoles. The 2-*N*-acetyl substituted 2-aminoimidazoles (0.1 g) was heated at reflux for 24 h in 5.0 mL of a 1:1 solution of MeOH:H_2O containing 5 drops of concd H_2SO_4. The reaction mixture was evaporated and the sulfate salt was recrystallized from H_2O. Alternatively, the base form was generated by adjusting the pH of the reaction mixture to ≈10 with 1% KOH in MeOH, and the product was purified by column chromatography.

***N*-[4(5)-Methyl-1*H*-imidazol-2-yl]acetamide (2a).** The general procedure A, applied to **1a**, gave **2a** (32%) after chromatography (silica, 5% $CHCl_3$/MeOH): mp 252–253 °C; ^{1}H NMR (DMSO-d_6) δ 2.01 (s, 3H), 2.04 (s, 3H), 6.36 (s, 1H), 10.91 (bs, 1H), 11.16 (bs, 1H). IR (KBr) 3455, 3318, 1674, 1624, 1296 cm^{-1}. Anal. Calcd for $C_6H_9N_3O$; C, 51.78; H, 6.52; N, 30.20. Found: C, 51.87; H, 6.55; N, 30.28.

2-Amino-4(5)-methylimidazole (3a).[9a] The general procedure C, applied to **2a**, gave **3a** (82%) as an oil after chromatography (Sephadex LH-20, MeOH): ^{1}H NMR (DMSO-d_6) δ 2.03 (s, 3H), 6.53 (s, 1H), 7.26 (bs, 2H), 11.59 (bs, 1H); IR (neat) 3362, 1682, 1242, 1213, 1013 cm^{-1}; HRMS calcd for $C_4H_7N_3$ (M + Na^+) 120.0538, found 120.0544. Anal. Calcd for $C_4H_7N_3$: C, 49.47; H, 7.27; N, 43.27. Found: C, 49.62; H, 7.13; N, 43.59.

***N*-[4(5)-Ethyl-1*H*-imidazol-2-yl]acetamide (2b).** The general procedure A, applied to **1b**, gave **2b** (78% crude). Recrystallized from EtOAc (52%): mp 207–208 °C; ^{1}H NMR (DMSO-d_6) δ 1.10 (t, 3H, J = 7.5 Hz), 2.00 (s, 3H), 2.41 (q, 2H, J = 7.5Hz), 6.38 (s, 1H), 10.96 (bs, 1H), 11.15 (bs, 1H). ^{13}C NMR (DMSO-d_6) δ 13.57, 19.97, 22.74, 140.23, 168.14; IR (neat) 3314, 1674, 1630, 1580, 1298 cm^{-1}. Anal. Calcd for $C_7H_{11}N_3O$: C, 54.88; H, 7.24; N, 27.43. Found: C, 54.98; H, 7.24; N, 27.32.

2-Amino-4(5)-ethylimidazole (3b). The general procedure C, applied to **2b**, gave **3b** (86%), as an oil after chromatography. (Sephadex LH-20, MeOH): ^{1}H NMR (DMSO-d_6) δ 1.10 (t, 3H, J = 7.5Hz), 2.39 (q, 2H, J = 7.6Hz), 6.51 (s, 1H), 7.29 (bs, 2H), 11.71 (bs, 1H). IR (neat) 3349, 1682, 1217, 1061, 1007 cm^{-1}; HRMS calcd for $C_5H_9N_3$ (M + H) 112.0875, found 112.0879. Anal. Calcd for $C_5H_9N_3$; C, 54.03; H, 8.16; N, 37.81. Found: C, 53.88; H, 8.10; N, 37.46.

***N*-[4(5)-*tert*-Butyl-1*H*-imidazol-2-yl]acetamide (2c).** The general procedure A, applied to **1c**, gave **2c** (93% crude). Recrystallized from EtOAc (61%): mp 190–191 °C; ^{1}H NMR (DMSO-d_6) δ 1.17 (S, 9H), 2.00 (s, 3H), 6.36 (s, 1H), 11.06 (bs, 2H); ^{13}C NMR (DMSO-d_6) δ 22.71, 30.03, 31.13, 140.20, 168.21; IR (KBr) 3337, 2955, 1678, 1624, 1277 cm^{-1}. Anal. Calcd for $C_9H_{15}N_3O$: C, 59.64; H, 8.34; N, 23.19. Found: C, 59.70; H, 8.43; N, 23.11.

2-Amino-4(5)-*tert*-butylimidazole (3c). The general procedure C, applied to **2c**, gave **3c** (84%), as an oil after chromatography (Sephadex LH-20, MeOH): ^{1}H NMR (DMSO-d_6) δ 1.17 (s, 9H), 6.45 (s, 1H), 7.28 (bs, 1H), 11.8 (bs, 1H). IR (neat) 3181, 2971, 1684, 1242, 1013 cm^{-1}; HRMS calcd for $C_7H_{13}N_3$ (M + H) 140.1188, found 140.1183. Anal. Calcd for $C_7H_{13}N_3$: C, 60.40; H, 9.41; N, 30.19. Found: C, 60.56; H, 9.29; N, 29.98.

***N*-[4(5)-Dimethyl-1*H*-imidazol-2-yl]acetamide (2d).** The general procedure A, applied to **1d**, gave **2d** (82% crude). Recrystallized from EtOAc (58%): mp 269–271 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.97 (s, 6H), 1.99 (s, 3H), 10.80 (bs, 1H), 10.96 (bs, 1H); ^{13}C NMR (DMSO-d_6) δ 10.65, 22.76, 138.62, 167.89; IR (KBr) 3324, 1678, 1597, 1514, 1267 cm^{-1}. Anal. Calcd for $C_7H_{11}N_3O$: C, 54.88; H, 7.24; N, 27.43. Found: C, 54.97; H, 7.27; N, 27.40.

2-Amino-4,5-dimethylimidazole Ethyl Sulfate (3d).[7,9a,14] The general procedure C, where EtOH was substituted for MeOH/H_2O, yielded **3d** from **2d**. Recrystallized from EtOH/ether (72%): mp 126–128 °C; ^{1}H NMR (DMSO-d_6) δ 1.09 (t, 3H, J = 7.1Hz), 1.96 (s, 6H), 3.72 (q, 2H, J = 7.1Hz), 7.21 (bs, 2H), 11.53 (bs, 2H). ^{13}C NMR (DMSO-d_6) δ 8.40, 15.11, 61.40, 116.84, 145.56; IR (KBr) 3439, 1688, 1238, 1013, 924 cm^{-1}. Anal. Calcd for $C_5H_9N_3$·$EtOSO_3H$: C, 35.43; H, 6.37; N, 17.71; S, 13.51. Found: C, 35.42; H, 6.20; N, 17.49; S, 13.32.

***N*-[4(5)-Phenyl-1*H*-imidazol-2-yl]acetamide (2e).**[20b] The general procedure A, applied to **1e**, gave **2e** (90% crude). Recrystallized from MeOH (58%): mp 230–231 °C; ^{1}H NMR (DMSO-d_6) δ 2.06 (s, 3H), 7.15 (t, 1H, J = 7.3 Hz), 7.24 (s, 1H), 7.31 (t, 2H, J = 7.5 Hz), 7.69 (d, 2H, J = 7.5 Hz), 11.23 (bs, 1H), 11.62 (bs, 1H); ^{13}C NMR (DMSO-d_6) δ 22.82, 109.24, 123.96, 124.29, 125.91, 128.44, 134.71, 136.12, 141.33, 168.55; IR (KBr) 3453, 3370, 1688, 1622, 1267 cm^{-1}. Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.65; H, 5.51; N, 20.89. Found: C, 65.78; H, 5.58; N, 20.96.

2-Amino-4(5)-phenylimidazole Sulfate (3e).[9a,19,20a] The general procedure C, applied to **2e**, gave **3e** from H_2O (68%): mp 275–278 °C; ^{1}H NMR (DMSO-d_6) δ 7.07 (bs, 2H), 7.22 (t, 1H, J = 7.3 Hz), 7.24 (s, 1H), 7.35 (t, 2H, J = 7.7 Hz), 7.62 (d, 2H, J = 7.4 Hz), 12.09 (bs, 1H); IR (KBr) 3358, 3154, 1682, 1136, 619 cm^{-1}. Anal. Calcd for $C_9H_9N_3$·$0.5H_2SO_4$: C, 51.91; H, 4.84; N, 20.18; S, 7.70. Found: C, 51.84; H, 4.83; N, 20.06; S, 7.80.

***N*-[4(5)-*p*-Tolyl-1*H*-imidazol-2-yl]acetamide (2f).** The general procedure A, applied to **1f**, gave **2f** (88% crude). Recrystallized from EtOH (56%): mp 210–211 °C; ^{1}H NMR (DMSO-d_6) δ 2.05 (s, 3H), 2.27 (s, 3H), 7.12 (d, 2H, J = 7.9 Hz), 7.16 (s, 1H), 7.58 (d, 2H, J = 7.9 Hz), 11.21 (bs, 1H), 11.56 (bs, 1H); IR (KBr) 3372, 1692, 1624, 1528, 1271 cm^{-1}. Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 67.07; H, 6.18; N, 19.57.

2-Amino-4(5)-*p*-tolylimidazole Sulfate (3f).[19] The general procedure C, applied to **2f**, gave **3f** from H_2O (67%): mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 2.29 (s, 3H), 6.78 (bs, 2H), 7.13 (s, 1H), 7.16 (d, 2H, J = 8.0 Hz), 7.56 (d, 2H, J = 8.0 Hz), 11.62 (bs, 1H); IR (KBr) 3353, 3144, 1690, 1512, 1101 cm^{-1}. Anal. Calcd for $C_{10}H_{11}N_3$·$0.5H_2SO_4$: C, 54.04; H, 5.44; N, 18.91; S, 7.21. Found: C, 54.19; H, 5.47; N, 18.85; S, 7.14.

***N*-[4(5)-*p*-Bromophenyl-1*H*-imidazol-21-yl]acetamide (2g).** The general procedure A, applied to **1g**, gave **2g** (90% crude). Recrystallized twice from EtOH (52%): mp 259–260 °C; ^{1}H NMR (DMSO-d_6) δ 2.05 (s, 3H), 7.31 (s, 1H), 7.48 (d, 2H, J = 8.5 Hz), 7.65 (d, 2H, J = 8.5 Hz), 11.23 (bs, 1H), 11.69 (bs, 1H); IR (KBr) 3449, 3343, 1694, 1622, 1267 cm^{-1}. Anal. Calcd for $C_{11}H_{10}BrN_3O$: C, 47.16; H, 3.60; Br, 28.53; N, 15.00. Found: C, 46.95; H, 3.66; Br, 28.64; N, 14.87.

2-Amino-4(5)-(*p*-bromophenyl)imidazole Sulfate (3g).[20a] The general procedure C, applied to **2g**, gave **3g** from H_2O

(58%): mp 257–260 °C; ^{1}H NMR (DMSO-d_6) δ 6.80 (bs, 2H), 7.29 (s, 1H), 7.52–7.59 (m, 4H), 11.78 (bs, 1H); IR (KBr) 3152, 2781, 1680, 1491, 1101 cm^{-1}. Anal. Calcd for $C_9H_8BrN_3 \cdot 0.5H_2SO_4$: C, 34.73; H, 2.91; Br, 25.68; N, 13.50; S, 20.61. Found: C, 34.86; H, 2.88; Br, 25.49; N, 13.55; S, 20.72.

***N*-[4(5)-(*p*-Methoxyphenyl)-1*H*-imidazol-2-yl]acetamide (2h).** The general procedure A, applied to **1h**, gave **2h** (92% crude). Recrystallized from EtOH (57%): mp 220–221 °C; ^{1}H NMR (DMSO-d_6) δ 2.05 (s, 3H), 3.73 (s, 3H), 6.88 (d, 2H, J = 8.7 Hz), 7.10 (s, 1H), 7.61 (d, 2H, J = 8.7 Hz), 11.19 (bs, 1H), 11.53 (bs, 1H); IR (KBr) 3449, 3349, 1684, 1626, 1273, 1165 cm^{-1}. Anal. Calcd for $C_{12}H_{13}N_3O_2$: C, 62.32; H, 5.67; N, 18.17. Found: C, 62.42; H, 5.68; N, 18.23.

2-Amino-4(5)-(*p*-methoxyphenyl)imidazole Sulfate (3h).[19] The general procedure C, applied to **2h**, gave **3h** from H_2O (72%): mp 291–293 °C; ^{1}H NMR (DMSO-d_6) δ 3.74 (s, 1H), 6.85 (bs, 2H), 6.92 (d, 2H, J = 8.8 Hz), 7.55 (d,2H, J = 8.8 Hz), 11.8 (bs, 1H); IR (KBr) 3393, 1680, 1514, 1260, 1132 cm^{-1}. Anal. Calcd for $C_{10}H_{11}N_3O \cdot 0.5H_2SO_4$: C, 50.41; H, 5.08; N, 17.64; S, 6.73. Found: C, 50.59; H, 5.12; N, 17.59; S, 6.87.

***N*-[4(5)-(*m*-Nitrophenyl)-1*H*-imidazol-2-yl]acetamide (2i).** The general procedure A, applied to **1i**, gave **2i** (41%) after chromatography (silica 5% MeOH/$CHCl_3$): mp 262–263 °C; ^{1}H NMR (DMSO-d_6) δ 2.07 (s, 3H), 7.53 (s, 1H), 7.60 (t, 1H, J = 8.0 Hz), 7.99 (dt, 1H, J = 8.0, 1.5 Hz), 8.14 (d, 1H, J = 7.9 Hz), 8.52 (s, 1H), 11.31 (bs, 1H), 11.83 (bs, 1H); ^{13}C NMR (DMSO-d_6) δ 22.83, 111.43, 117.94, 118.11, 120.28, 120.34, 129.97, 130.08, 130.20, 134.01, 136.54, 141.72, 148.32, 168.63; IR (KBr) 3428, 3150, 1663, 1615, 1520 cm^{-1}. Anal. Calcd for $C_{11}H_{10}N_4O_3$: C, 53.66; H, 4.08; N, 22.76. Found: C, 53.60; H, 4.09; N, 22.69.

2-Amino-4(5)-(*m*-nitrophenyl)imidazole Sulfate (3i).[19] The general procedure C, applied to **2i** gave **3i** from H_2O (73%): mp 258–259 °C; ^{1}H NMR (DMSO-d_6) δ 6.84 (bs, 2H), 7.51 (s, 1H), 7.63 (t, 1H, J = 8.0 Hz), 8.01–8.04 (m, 2H), 8.47 (s, 1H), 11.78 (bs, 1H); ^{13}C NMR (DMSO-d_6) d 111.64, 118.00, 118.16, 121.44, 126.09, 129.80, 130.28, 131.16, 148.28, 149.19; IR (KBr) 3360, 3153, 1690, 1528, 1348 cm^{-1}. Anal. Calcd for $C_9H_8N_4O_2 \cdot 0.5\ H_2SO_4 \cdot 1.5H_2O$: C, 40.52; H, 3.97; N, 21.01, S, 6.01. Found: C, 40.50; H, 3.93; N, 20.91; S, 5.89.

***N*-[4(5)-(*m*-Phenoxyphenyl)-1*H*-imidazol-2-yl]acetamide (2j).** The general procedure A, applied to **1j**,[31] gave **2j** (47%) after chromatography (silica, 5% MeOH, $CHCl_3$): mp 139–140 °C; ^{1}H NMR (DMSO-d_6) δ 2.03 (s, 3H), 6.82 (dd, 1H, J = 2.6, 7.9 Hz), 7.04 (d, 2H, J = 8.6 Hz), 7.14 (t, 1H, J = 7.3Hz), 7.27–7.48 (m, 6H), 11.19 (bs, 1H), 11.65 (bs, 1H); IR (KBr) 3480, 3414, 1676, 1614, 1489 cm^{-1}. Anal. Calcd for $C_{17}H_{15}N_3O$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.42; H, 5.22; N, 14.08.

2-Amino-4(5)-(*m*-phenoxyphenyl)imidazole (3j). The general procedure C, applied to **2j**, gave **3j** as a semisolid which failed to crystallize. Purification was accomplished by addition of methanolic ammonia, filtration and evaporation. The residue was subjected to chromatography (5% MeOH saturated with NH_3/EtOAc) yielding 70% of **3j** as an oil: ^{1}H NMR (DMSO-d_6) δ 5.29 (bs, 2H), 6.72 (dd, 1H, J = 2.7, 8.0 Hz), 6.99–7.02 (m, 3H), 7.12 (t, 1H, J = 7.6 Hz), 7.22–7.40 (m, 5H), 10.42 (bs, 1H); IR (KBr) 3380, 1638, 1586, 1487, 1225 cm^{-1}. Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.69; H, 5.22; N, 16.72. Found: C, 71.95; H, 5.30; N, 16.87.

***N*-[4(5)-Methyl-4(5)-phenyl-1*H*-imidazol-2-yl]acetamide (2k).** The general procedure A, applied to **1k**, gave **2k** (96% crude). Recrystallized from EtOH (65%): mp 191–193 °C; ^{1}H NMR (DMSO-d_6) δ 2.04 (s, 3H), 2.37 (s, 3H), 7.18 (t, 1H, J = 7.2 Hz), 7.34 (t, 2H, J = 7.5 Hz), 7.58 (d, 2H, J = 7.4 Hz), 11.07 (bs, 1H), 11.46 (bs, 1H). ^{13}C NMR (DMSO-d_6) δ 22.81, 122.97, 126.41, 126.87, 127.18, 127.36, 127.54, 127.79 128.07, 128.21, 128.56, 131.00, 132.61, 132.65, 135.11, 141.05, 168.94; IR (KBr) 3372, 3316, 1659, 1611, 1281 cm^{-1}. Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.93; H, 6.07; N, 19.51.

2-Amino-4(5)-methyl-4(5)-phenylimidazole Sulfate (3k).[9a,14] The general procedure C, applied to **2k**, gave **3k** from H_2O (84%): mp = 161–164 °C; ^{1}H NMR (DMSO-d_6) δ 2.21 (s, 3H), 7.27 (t, 1H, J = 7.4 Hz), 7.36 (bs, 2H), 7.41 (t, 2H, J = 7.4 Hz), 7.48 (d, 2H, J = 7.5 Hz), 11.42 (bs, 1H); IR (KBr) 3164, 1686, 1107, 764, 694 cm^{-1}. Anal. Calcd for $C_{10}H_{11}N_3 \cdot 0.5H_2SO_4 \cdot 0.75H_2O$: C, 52.44; H, 5.61; N, 18.35; S, 7.00. Found: C, 52.54; H, 5.59; N, 18.37; S, 6.91.

***N*-[4(5)-Diphenyl-1*H*-imidazol-2-yl]acetamide (2l).** The general procedure A, aplied to **1l**, gave **2l** (96% crude). Recrystallized from EtOH (61%): mp = 259–260 °C; ^{1}H NMR (DMSO-d_6) δ 2.07 (s, 3H), 7.18–7.42 (m, 10H), 11.17 (bs, 1H), 11.60 (bs, 1H); ^{13}C NMR (DMSO-d_6) d 22.81, 122.95, 126.41, 126.88, 127.35, 128.06, 128.21, 128.55, 131.00, 132.61, 135.10, 141.06, 168.94; IR (KBr) 3449, 3293, 1678, 1618, 1273 cm^{-1}. Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.62; H, 5.45; N, 1515. Found: C, 73.69; H, 5.46; N, 15.22.

2-Amino-4,5-diphenylimidazole Hemisulfate (3l).[7,13,14,20a] The general procedure C, applied to **2l**, gave **3l** from H_2O (86%): mp 242–245 °C; ^{1}H NMR (DMSO-d_6) δ 7.35–7.44 (m, 10H), 7.54 (bs, 2H), 12.68 (bs, 1H); IR (KBr) 3184, 1696, 1223, 1022, 885 cm^{-1}. Anal. Calcd for $C_{15}H_{13}N_3 \cdot H_2SO_4$: C, 54.04; H, 4.54; N, 12.61; S, 9.62. Found: C, 54.11; H, 4.54; N, 12.54; S, 9.74.

***N*-[4(5)-β-Naphthyl-1*H*-imidazol-2-yl]acetamide (2m).** The general procedure A, applied to **1m**, gave **2m** (93% crude). Recrystallized from EtOH (58%): mp 225–226 °C; ^{1}H NMR (DMSO-d_6) δ 2.08 (s, 3H), 7.40–7.48 (m, 3H), 7.82–7.91 (m, 4H), 8.18 (s, 1H), 11.30 (bs, 1H), 11.70 (bs, 1H); IR (KBr) 3385, 1669, 1614, 1528, 1275 cm^{-1}. Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.69; H, 5.22; N, 16.72. Found: C, 71.65; H, 5.25; N, 16.73.

2-Amino-4(5)-β-naphthlylimidazole Sulfate (3m).[19] The general procedure C, applied to **2m**, gave **3m** from H_2O (83%): mp 280–283 °C; ^{1}H NMR (DMSO-d_6) δ 6.96 (bs, 2H), 7.37 (s, 1H), 7.42–7.51 (m, 2H), 7.76–7.89 (m, 4H), 8.11 (s, 1H), 11.95 (bs, 1H); IR (KBr) 3397, 3160, 1686, 1636, 1134 cm^{-1}. Anal. Calcd for $C_{13}H_{11}N_3 \cdot 0.5H_2SO_4 \cdot 1.25H_2O$: C, 57.92; H, 4.96; N, 15.59; S, 5.95. Found: C, 57.95; H, 4.82; N, 15.34; S, 6.12.

***N*-(1,4,5,6-Tetrahydro-1*H*-cyclopentaimidazol-2-yl)acetamide (2n).** The general procedure B, applied to **1n**, gave **2n** (39% crude). Recrystallized from MeOH (31%): mp > 300 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.00 (s, 3H), 2.30 (m, 2H), 2.49 (m, 4H, overlaps DMSO), 10.89 (bs, 1H), 11.20 (bs, 1H); IR (KBr) 3308, 1676, 1618, 1287, 1167 cm^{-1}. Anal. Calcd for $C_8H_{11}N_3O$: C, 58.16; H, 6.71; N, 25.44. Found: C, 58.27; H, 6.79; N, 25.43.

***N*-(4,5,6,7-Tetrahydro-1*H*-benzimidazol-2-yl)acetamide (2o).** The general procedure B, applied to **1o**, gave **2o** (36%) after chromatography (silica, 5% MeOH, $CHCl_3$): mp = 295–298 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.67 (bs, 4H), 2.00 (s, 3H), 2.37 (bs, 4H), 10.86 (bs, 1H), 11.03 (bs, 1H); IR (KBr) 3341, 1674, 1620, 1597, 1277 cm^{-1}. Anal. Calcd for $C_9H_{13}N_3O \cdot 0.3H_2O$: C, 58.55; H, 7.43; N, 22.76. Found: C, 58.44; H, 7.19; N, 22.49.

2-Amino-4,5,6,7-tetrahydrobenzimidazole Ethyl Sulfate (3o). The general procedure C, where EtOH was substituted for MeOH/H_2O, yielded **3o** in 78% from **2o** after the solvent was removed, and the crystalline residue was washed with ether and dried. Recrystallized from EtOH/ether: mp 136–138 °C; ^{1}H NMR (DMSO-d_6) δ 1.09 (t, 3H, J = 7.2 Hz), 1.68 (bs, 4H), 2.33 (bs, 4H), 3.72 (q, 2H, J = 7.2 Hz), 7.29 (bs, 2H), 11.59 (bs, 2H); IR (KBr) 3393, 1676, 1257, 1018, 924 cm^{-1}. Anal. Calcd for $C_7H_{11}N_3 \cdot EtOSO_3H$: C, 41.05; H, 6.51; N, 15.96; S, 12.18. Found: C, 40.93; H, 6.53; N, 15.85; S, 12.29.

2-Amino-3a-ethoxy-1,3a,4,5,6,6a-hexahydrocyclopentaimidazolidine Hydrochloride (5). Compound **2n** (50 mg; 0.30 mmol) was reluxed 16 h in 5 mL of anhyd EtOH saturated with dry HCl. The mixture was concentrated to a clear viscous oil which failed to crystallize. ^{1}H NMR (DMSO-d_6) δ 1.12 (t, 3H, J = 7.0Hz), 1.46 (m, 1H), 1.59–1.86 (m, 4H), 2.06 (m, 1H), 3.39 (dq-partially overlapped by H_2O, 2H, J = 7.0, 2.8 Hz), 4.04 (d, 1H, J = 6.8 Hz), 7.92 (bs, 2H), 8.41 (bs, 1H), 8.95 (bs, 1H); IR (KBr) 3210, 1684, 1574, 1190, 1090 cm^{-1}; LRMS calcd for $C_8H_{15}N_3O$ (M + H) 170, found 170. Anal. Calcd for $C_8H_{16}ClN_3O \cdot 0.5H_2O$: C, 44.75; H, 7.98; Cl, 16.51; N, 19.57. Found: C, 44.42; H, 7.63; Cl, 16.63; N, 19.92.

***N*-{5-[2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)ethyl]-1*H*-imidazol-2-yl}acetamide (7).** The α-bromo ketone **6**,[27] (700 mg, 2.36 mmol) was added to a stirred solution of 717 mg (7.10 mmol) of acetylguanidine in 5 mL of anhyd DMF. After 96 h

evaporation of the reaction mixture gave a brown solid which was washed with H_2O (3 × 20 mL), filtered, and dried. Recrystallization from a minimal amount of hot EtOH with cooling at −5 °C for 1 h afforded 352 mg (50%) as tan crystals: mp 252−254 °C; ^{1}H NMR (DMSO-d_6) δ 2.01 (s, 3H), 2.71 (bs, 2H), 3.76 (t, 2H, J = 7.0 Hz), 6.51 (s, 1H), 7.82 (m, 4H), 11.04 (bs, 1H), 11.18 (bs, 1H); IR (KBr) 3372, 3320, 1707, 1680, 1610 cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_4O_3$: C, 60.39; H, 4.73; N, 18.78. Found: C, 60.29; H, 4.80; N, 18.60.

2-Aminohistamine Dihydrochloride (8).[2a] To 200 mg (0.67 mmol) of compound **7** was added 5 mL of anhyd hydrazine. The mixture was stirred at 70 °C for 4 h under argon. Evaporation afforded an oil which was subjected to column chromatography [basic alumina, 5−20% MeOH (saturated with NH_3) in $CHCl_3$]. The fractions containing the product were combined and evaporated yielding a light brown oil which was dissolved in ethanolic HCl (5 mL). Evaporation gave a brown solid which was recrystallized from EtOH/ether affording 62mg (47%) as tan crystals: mp 178−180 °C; ^{1}H NMR (DMSO-d_6) δ 2.78 (t, 2H, J = 7.3 Hz), 3.01 (bs, 2H), 6.67 (s, 1H), 7.45 (bs, 2H), 8.25 (bs, 3H), 11.78 (bs, 1H), 12.36 (bs, 1H); IR (KBr) 3341, 1674, 1468, 1138, 953 cm^{-1}. Anal. Calcd for $C_5H_{10}N_4$·2HCl: C, 30.16; H, 6.08; Cl, 35.62; N, 28.14. Found: C, 30.07; H, 6.01; Cl, 35.44; N, 27.87.

2-(4-Oxopent-2-enyl)isoindole-1,3-dione (10). To 10.0g (52.9 mmol) of the aldehyde **9**[28] and 16.8g (52.9 mmol) of (triphenylphosphoranylidene)-2-propanone was added 200 mL of anhyd PhH. The mixture was heated at reflux for 4 h. Evaporation of the solvent followed by recrystallization from a minimal amount of MeOH with cooling at −5 °C for 1 h afforded 10.1 g (83%) as white crystals: mp 87−88 °C; ^{1}H NMR (DMSO-d_6) δ 2.18 (s, 3H), 4.38 (dd, 2H, J = 1.3, 4.6Hz), 6.03 (dt, 1H, J = 1.3,16.2Hz), 6.87 (dt, 1H, J = 4.6, 16.2Hz), 7.83−7.92 (m, 2H); IR (KBr) 3462, 1707, 1678, 1416, 1262 cm^{-1}. Anal. Calcd for $C_{13}H_{11}NO_3$·0.1H_2O: C, 67.58; H, 4.89; N, 6.05. Found: C, 67.48; H, 4.85; N, 6.05.

2-(5-Bromo-4-oxopent-2-enyl)isoindole-1,3-dione (11). To 5.4 g (23.6 mmol) of **10** was added 125 mL of anhyd PhH containing 3.6 g (35.6 mmol) of NEt_3. Trimethylsilyl triflate, 5.7 g (25.9 mmol), was added over a 10 min period with stirring at room temp under argon. After 15 h, 50 mL of saturated aqueous $NaHCO_3$ was added and this mixture was extracted with 500 mL of ether. The organic layer was washed with 50 mL of H_2O, dried (Na_2SO_4), and evaporated. The yellow residual oil was triturated with petroleum ether (3 × 50 mL) and evaporated yielding 7.1 g (100%) of a yellow crystalline solid which was used as is: ^{1}H NMR (DMSO-d_6) δ 0.16 (s, 9H), 4.24 (d, 2H, J = 5.4 Hz), 4.32 (d, 2H, J = 28.4 Hz), 5.85 (dt, 1H, J = 5.4, 15.4 Hz), 6.03 (d, 1H, J = 15.4 Hz), 7.81−7.90 (m, 4H). The silyl enol ether was dissolved in 75 mL of anhyd THF, and 2.94 g (35.4 mmol) of $NaHCO_3$ was added while the mixture was cooled to 0 °C. To the mixture was added NBS 3.87g (23.6 mmol) and stirring was continued for 2 h after which time it was allowed to warm to rt and 10 mL of saturated aqueous $NaHCO_3$ was added. The mixture was then extracted with 500 mL of ether. The organic layer was washed with H_2O, dried (Na_2SO_4), and concentrated to give a solid which was recrystallized from MeOH (5.9 g, 81%) as white crystals: mp 123−124 °C; ^{1}H NMR (DMSO-d_6) δ 4.40−4.42 (m, 4H, overlapping methylene groups), 6.27 (dt, 1H, J = 1.3, 16.1 Hz), 6.98 (dt, 1H, J = 4.5, 16.1 Hz), 7.84−7.92 (m, 4H); IR (KBr) 3449, 1725, 1638, 1391, 953 cm^{-1}. Anal. Calcd for $C_{13}H_{10}BrNO_3$: C, 50.67; H, 3.27; Br, 25.93; N, 4.55. Found: C, 50.55; H, 3.33; Br, 25.90; N, 4.49.

***N*-{5-[3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)propenyl]-1*H*-imidazol-2-yl}acetamide (12).** The general procedure A, applied to **11**, gave 46% of **12** as yellow crystals from EtOH: mp 279−281 °C; ^{1}H NMR (DMSO-d_6) δ 2.01 (s, 3H), 4.26 (d, 2H, J = 5.8 Hz), 6.05 (dt, 1H, J = 5.8, 15.6 Hz), 6.29 (d, 1H, J = 15.6 Hz), 6.74 (s, 1H), 7.81−7.90 (m, 4H), 11.11 (bs, 1H), 11.40 (bs, 1H); IR (KBr) 3468, 3308, 1721, 1634, 1167 cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_4O_3$·0.1H_2O: C, 61.57; H, 4.59; N, 17.95. Found: C, 61.36; H, 4.52; N, 17.67.

5-(3-Aminopropenyl)-1*H*-imidazol-2-ylamine (13).[1i] Compound **13** was prepared as described for **8**, starting from **12**, and characterized as the dihydrochloride salt: brown crystals (57%); mp 211−213 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.53 (m, 2H), 6.10 (dt, 1H, J = 6.6, 16.1 Hz), 6.46 (d, 1H, J = 16.1 Hz), 7.00 (s, 1H), 7.54 (bs, 2H), 8.29 (bs, 3H), 12.14 (s, 1H), 12.92 (bs, 1H); IR (KBr) 3399, 1692, 1674, 1483, 959 cm^{-1}. Anal. Calcd for $C_6H_{12}Cl_2N_4$: C, 34.14; H, 5.73; Cl, 33.59; N, 26.54. Found: C, 34.22; H, 5.69; Cl, 33.51; N, 26.49.

Oroidin (15).[1l,26] To 150 mg of **13** (1.09 mmol as the free base), in 5 mL of anhyd DMF under argon, was added 1.2 g (3.26 mmol) of **14**[29] which was stirred for 16 h. Evaporation to dryness (low heat, 25 °C) under vacuum followed by column chromatography (silica, 15% saturated methanolic NH_3, 85% $CHCl_3$) afforded a yellow solid. This material was dissolved in EtOH and treated with EtOH/HCl. Evaporation to dryness followed by column chromatography (Sephadex LH-20, MeOH) afforded 59 mg (13%) as a yellow orange solid determined to be >92% pure by analytical HPLC: mp 202−205 °C dec (starts to evolve gas at 80−90 °C); ^{1}H NMR (CD_3OD) δ 4.04 (d, 2H, J = 5.2 Hz), 6.09 (dt, 1H, J = 5.5, 16.1 Hz), 6.30 (d, 1H, J = 16.1 Hz), 6.75 (s, 1H), 6.85 (s, 1H); IR (KBr) 3408, 3167, 1686, 1628, 1397 cm^{-1}; HRMS calcd for $C_{11}H_{11}Br_2N_5O$ (M + H) 387.9409, found 387.9400.

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