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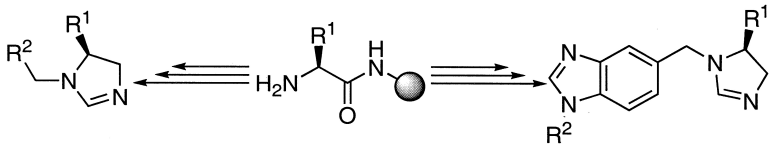

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Use of Vilsmeier Reagent for the Solid-Phase Synthesis of 1,5-Disubstituted 4,5-Dihydro-1*H*-imidazoles and Disubstituted 4,5-Dihydro-1*H*-imidazolylbenzimidazoles

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The solid-phase synthesis of novel imidazolines and dihydroimidazolylbenzimidazoles is described. Resin-bound diamines, derived from resin-bound N-acylated amino acid amides, were cyclized using Vilsmeier reagent to yield imidazolines following cleavage. Similarly, cyclization of resin-bound tetraamines having two secondary amines and an *o*-dianiline yielded dihydroimidazolylbenzimidazoles following cleavage.

Introduction

Considerable attention has been focused on the synthesis of heterocycles, and nitrogen heterocycles in particular, since they exhibit diverse biological and pharmacological activities.[1,2] Preparation of these heterocycles from amino acids or peptides has an added advantage that the well-defined chemistry of amino acids and peptides can be utilized to introduce diversity. Dihydroimidazoles are reported to exhibit a wide range of biological and pharmacological activities.[3−6] Examples of such activities include α-receptor stimulation, vasodepressor activity, α-adrenergic inhibition, and sympathomimetic, antihistaminic, histamine-like, and cholinomimetic activity[5] and as a potent antagonist of α_2-adrenoceptor.[6] The dihydroimidazole moiety is reported to be an essential pharmacophore for exhibiting antihyperglycemic activities.[3] Dihydroimidazoles, such as midaglizole, deriglidole, and efaroxan, have been found to be potent antihyperglycemic agents.[3] Benzimidazole derivatives are reported to be a unique, potent, and broad-spectrum class of antirhino/enteroviral agents.[7] Benzimidazoles have also been reported to exhibit significant antiviral activity against herpes viruses (HSV-1), human cytomegalovirus (HCMV),[8,9] influenza virus,[10] RNA virus,[11] anti-HIV activities,[9] and antimicrobial acvtivity against *Staphylococcus aureus*, *E. coli*, and *Candida albicans*.[11,12] Benzimidazoles have been reported to act as potent and selective topoisomerase I inhibitors,[13] selective neuropeptide Y Y1 receptor antagonists,[14] angiotensin II (AII) inhibitors,[15] inhibitors of HCMV replication,[9] and 5-HT_3 antagonists in the isolated guinea pig ileum.[16] The benzimidazole moiety is reported to be an important scaffold for binding to the cavity at the protein−protein interface of human growth hormone (hGH) and its receptor.[17]

Because of potential biological and pharmacological applications of dihydroimidazoles and benzimidazoles, the synthesis of substituted dihydroimidazoles and dihydroimidazolylbenzimidazoles is considered worthwhile. Herein, we report a facile one-pot cyclization of a diamine having two secondary amines and a tetraamine having two secondary amines and an *o*-dianiline using Vilsmeier reagent[18] to yield the 1,5-disubstituted 4,5-dihydro-1*H*-imidazoles and disubstituted 4,5-dihydro-1*H*-imidazolylbenzimidazoles, respectively. Vilsmeier reagent is a chloromethyleneiminium salt [$(CH_3)_2N^+ = CHCl$, $PO_2Cl_2^-$] derived from the reaction of *N*,*N*-dimethylformamide and phosphorus oxychloride ($POCl_3$).[18] This has mostly been used for synthesis of a large number of heterocyclic compounds, cyclodehydration of heterocycles,[19] formylation of activated aromatic compounds,[20] and carbonyl compounds.[21] This study highlights the introduction of diversity at the N1 position of the dihydroimidazole moiety, which has heretofore been an underutilized position to introduce diversity.

Results and Discussion

(i) Synthesis of 1,5-Disubstituted 4,5-Dihydroimidazoles. The synthetic approach for the solid-phase synthesis of 1,5-disubstituted 4,5-dihydroimidazoles is presented in Scheme 1. A Boc-L-amino acid was coupled to *p*-methylbenzhydrylamine (MBHA) resin, followed by deprotection of the Boc group to generate compound **1** (Scheme 1). The primary amine of the resin-bound amino acid was N-acylated with a carboxylic acid to generate compound **2**. Reduction of the resin-bound N-acylated amino acid amide using BH_3−THF[22] generated diamine **3** having two secondary amines. The resin-bound diamine **3** was treated with Vilsmeier reagent in anhydrous dioxane to generate compound **4**. The Vilsmeier reagent was formed in situ by the reaction of DMF and $POCl_3$.[18,23] Nucleophilic attack by one of two secondary amines of the resin-bound diamine to the chloromethyleneiminium salt then led to loss of chloride to form the iminium salt. Subsequent nucleophilic attack by the second secondary amine on the iminium salt with loss of dimethylamine led to intramolecular cyclization due to the formation of energetically favored five-membered ring. The final compound was cleaved from the solid support using anhydrous HF, followed by extraction with 95% acetic acid in H_2O to give compound **5**. Ten individual 1,5-disubstituted 4,5-

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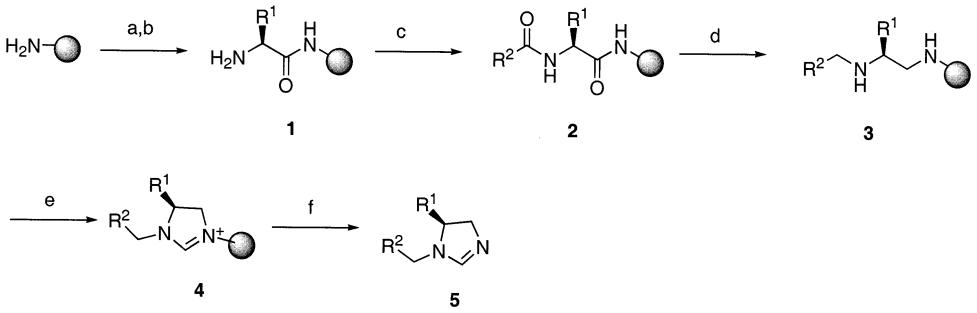
Scheme 1[a]



[a] (a) Boc-L-NHCH(R^1)CO_2H (6 equiv, 0.1 M, DMF), DIC (6 equiv), HOBt (6 equiv), 2 h, room temp; (b) 55% TFA/45% DCM, 30 min, room temp; (c) R^2CO_2H (10 equiv, 0.1 M, DMF), DIC (10 equiv), HOBt (10 equiv), overnight, room temp; (d) (i)BH_3−THF, 65 °C, 72 h, (ii) piperidine, 65 °C, 20 h; (e) DMF (10 equiv, 0.1 M, anhydrous dioxane), $POCl_3$ (10 equiv), 110 °C, 4 h; (f) HF, anisole, 0 °C, 7 h.

Table 1. MW and RP-HPLC Purity Found for 1,5-Disubstituted 4,5-Dihydro-1*H*-imidazoles

Product	R^1	R^2	Yield[a]	MW (calcd)	MW (found)	Purity (%)[b]
5a			65	188.1	188.9 ($M+H^+$)	76
5b			62	292.2	293.0 ($M+H^+$)	78
5c			60	294.2	295.1 ($M+H^+$)	79
5d			67	180.1	181.0 ($M+H^+$)	72
5e			68	182.2	183.0 ($M+H^+$)	76
5f			70	312.2	312.8 ($M+H^+$)	76
5g			65	210.2	211.0 ($M+H^+$)	80
5h			70	298.2	299.1 ($M+H^+$)	76
5i			65	168.2	169.0 ($M+H^+$)	80
5j			65	260.2	261.1 ($M+H^+$)	78

[a] The yields (by weight) obtained were greater than 60−70% with respect to the initial loading of the resin (1.10 mequiv/g). [b] Crude purity was determined from the relative peak areas (%) of RP-HPLC chromatograms run on a gradient of 5−95% acetonitrile in water (0.05% TFA) for 30 min at $\lambda = 214$ nm.

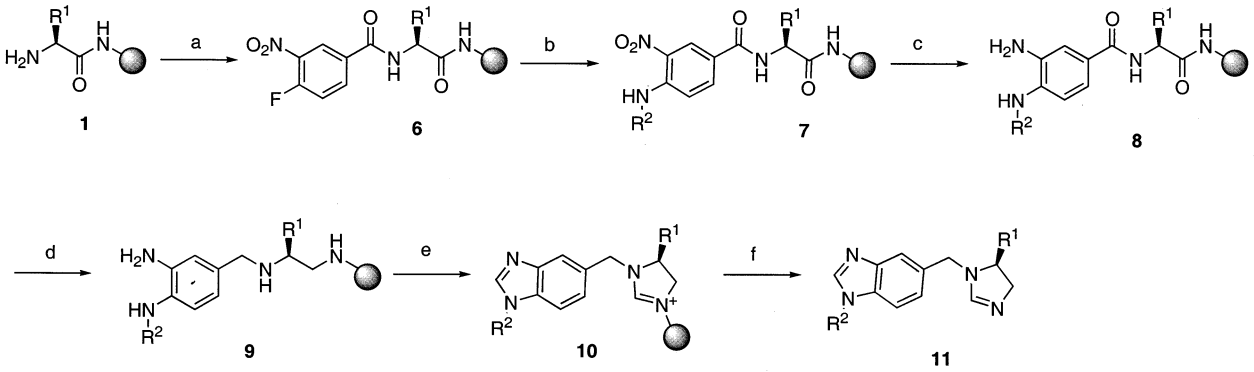
dihydro-1*H*-imidazoles were prepared derived from six amino acids (L-Ala, L-Ile, L-Phe, *p*-fluoro-L-phenylalanine, L-norvaline, and L-Val) at the first (R^1) position of diversity and eight different carboxylic acids (phenylacetic acid, 4,4′-biphenylcarboxylic acid, 3-methoxyphenylacetic acid, cyclopentylacetic acid, isobutyric acid, 4-methoxyphenylacetic acid, heptanoic acid, and cyclohexanebutyric acid) at the second (R^2) position of diversity (Table 1). Negligible amounts of starting material were observed by LC−MS and reverse-phase high-pressure liquid chromatography (RP-HPLC). The lower than expected yields (60−70%, see Table 1) are attributed to premature cleavage of the products due to generation of HCl during $POCl_3$ treatment.[24] The reaction stoichiometry of a 10 equiv excess of anhydrous DMF in the presence of a 10 equiv excess of $POCl_3$ in anhydrous dioxane (110 °C, 4 h) was found to yield the final products in high purity and reasonable yield (Table 1).

The compounds were purified by RP-HPLC and characterized by high-resolution mass spectra (HRMS), ^{1}H NMR, and ^{13}C NMR spectroscopy. Following purification (in 0.05% trifluoroacetic acid), the protonated dihydroimidazoles ($pK_a \approx 9.5$)[3] were characterized as their corresponding trifluoroacetate salts. The appearance of one strong downfield proton signal at δ ∼9.9−10.3 ppm in the ^{1}H NMR spectra corresponded to the −NH of the protonated dihydroimidazolyl moiety.[3] Negligible amounts of racemization (<1%) were observed as detected by ^{1}H NMR spectra during either BH_3−THF reduction[22] or $POCl_3$-mediated cyclization,[25] in conformity with our earlier observations.

(ii) Synthesis of Disubstituted 4,5-Dihydro-1*H*-imidazolylbenzimidazoles. The synthetic strategy for the solid-phase synthesis of disubstituted 4,5-dihydro-1*H*-imidazolylbenzimidazoles is outlined in Scheme 2. The primary amine of the resin-bound amino acid **1** was acylated using 4-fluoro-3-nitrobenzoic acid in the presence of *N*,*N*-diisopropylcarbodiimide (DIC) to generate compound **6**. The resin-bound fluoronitro derivative **6** was treated with a primary amine in the presence of *N*,*N*′-diisopropylethylamine (DIEA) to generate an *o*-nitroaniline **7** by displacement of the arylfluoro group.[26,27] Reduction of the aromatic nitro group using tin(II) chloride dihydrate ($SnCl_2 \cdot 2H_2O$)[27] generated an *o*-dianiline **8**. Exhaustive reduction of amide bonds of **8** with BH_3−THF[22] generated tetraamine **9**. The resin-bound tetraamine was treated with Vilsmeier reagent[18] (DMF in the presence of $POCl_3$) to generate compound **10**. Two aliphatic secondary amines cyclized to form the dihydroimidazole moiety as described above. Similarly, the *o*-dianilines also cyclized concomitantly to form a stable benzimidazole moiety. The compounds were cleaved from the solid support using anhydrous HF and extracted with 95% acetic acid in water to yield **11**.

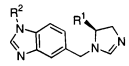
Twelve control compounds were prepared using nine amino acids (L-Val, L-norvaline, L-cyclohexylglycine, L-phenylglycine, L-norleucine, L-Ile, *p*-iodo-L-phenylalanine, *p*-chloro-L-phenylalanine, and cyclohexylalanine) at the first (R^1) position of diversity and seven primary amines (hexylamine, benzylamine, 3-fluorophenylethylamine, 4-methoxybenzylamine, 2,4-dichlorophenylethylamine, 4-chlorobenzylamine, and phenylethylamine) at the second (R^2) position of diversity. Negligible amounts (<1%) of uncyclized material were observed by LC−MS and RP-HPLC. The final compounds were obtained in moderate yield and good purity (see Table 2). The final compounds were purified and were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy.

Scheme 2[a]



[a] (a) 4-Fluoro-3-nitrobenzoic acid (10 equiv, 0.1 M, DMF), DIC (10 equiv), overnight, room temp; (b) R^2NH_2 (20 equiv, 0.2 M, DMF), DIEA (20 equiv), overnight, room temp; (c) $SnCl_2 \cdot 2H_2O$ (20 equiv, 0.5 M, DMF), 14 h, room temp; (d) (i) BH_3−THF, 65 °C, 72 h, (ii) piperidine, 65 °C, 20 h; (e) DMF (20 equiv, 0.2 M, anhydrous dioxane), $POCl_3$ (20 equiv), 110 °C, overnight; (f) HF, anisole, 0 °C, 7 h.

Table 2. MW and RP-HPLC Purity Found for Disubstituted 4,5-Dihydro-1*H*-imidazolylbenzimidazoles



Product	R^1	R^2	Yield[a]	MW (calcd)	MW (found)	Purity (%)[b]
11a			68	326.3	327.3 ($M+H^+$)	72
11b			68	346.2	346.7 ($M+H^+$)	78
11c			64	378.2	378.8 ($M+H^+$)	70
11d			66	402.2	402.8 ($M+H^+$)	65
11e			67	448.1	449.9 ($M+H^+$)	73
11f			68	326.3	326.8 ($M+H^+$)	76
11g			63	340.3	341.3 ($M+H^+$)	80
11h			65	366.3	366.9 ($M+H^+$)	76
11i			69	588.0	589.1 ($M+H^+$)	70
11j			65	428.2	429.2 ($M+H^+$)	70
11k			70	420.2	421.3 ($M+H^+$)	71

[a] The yields (by weight) obtained were greater than 60−70% with respect to the initial loading of the resin (1.10 mequiv/g). [b] Crude purity was determined from the relative peak areas (%) of HPLC chromatograms run with a gradient of 5−95% acetonitrile in water (0.05% TFA) for 30 min at $\lambda = 214$ nm.

Negligible amounts (<1%) of racemization were observed for the final compounds by ^{1}H NMR spectra.

Conclusion

The efficient synthesis of 1,5-disubstituted 4,5-dihydro-1*H*-imidazole and disubstituted 4,5-dihydro-1*H*-imidazolylbenzimidazole from resin-bound amino acids has been described. Vilsmeier reagent was successfully used to prepare these heterocycles from diamines and tetraamines without introduction of a formyl group. It is interesting to note that in the case of tetraamine, the two different sets of amines (i.e., two aliphatic secondary amines and *o*-dianilines) were cyclized concomitantly without any trace of undesirable byproducts. Because of the reasonable purity of the final products, this approach could be extended to prepare a combinatorial library[28] of thousands of compounds.

Experimental Section

Boc-amino acids and *N*-hydroxybenzotriazole (HOBt) were purchased from Calbiochem-Novabiochem Corp. (San Diego, CA) and Bachem Bioscience, Inc. (Philadelphia, PA). *p*-Methylbenzhydrylamine (MBHA) resin (1% divinylbenzene, 100−200 mesh, 1.1 mequiv/g substitution) and *N*,*N*′-diisopropylcarbodiimide (DIC) were purchased from Chem Impex, International (Wood Dale, IL). All other reagents and anhydrous solvents were purchased from Aldrich Chemical Co. (Milwaukee, WI). Analytical RP-HPLC was carried out on a Beckman system Gold instrument (Fullerton, CA). Samples were analyzed using a Vydac 218TP54 C18 column (0.46 cm × 25 cm). LC−MS (ESI) was recorded on a Finnigan Mat LCQ mass spectrometer (ThermoQuest Corporation, CA) at 214 nm using a Betasil C18, 3 μm, 100 Å, 3 mm × 50 mm column. Preparative RP-HPLC was performed on a Waters DeltaPrep preparative HPLC (Millipore) using a Vydac 218TP1022 C18 column (2.2 cm × 25 cm). High-resolution mass spectra (HRMS) were recorded at the Mass Spectrometry Facility of the University of California at Riverside.

(1) General Procedure for the Individual Synthesis of 1,5-Disubstituted 4,5-Dihydro-1*H*-imidazoles. A total of 100 mg of MBHA resin was sealed inside a polypropylene mesh packet.[29] Polypropylene bottles were used for all reactions. The resin was washed with dichloromethane (DCM), followed by neutralization with 5% diisopropylethylamine (DIEA) in DCM and washing with DCM.

(a) Coupling of Boc-L-amino Acid to MBHA Resin and N-Acylation. A Boc-L-amino acid (0.66 mequiv) in DMF (6.6 mL) was coupled to MBHA resin using DIC (103 μL, 0.66 mequiv) and HOBt (101 mg, 0.66 mequiv) for 2 h at room temperature, followed by washes with DMF (three times) and DCM (three times). The Boc group was deprotected using 55% TFA in DCM for 30 min, followed by neutralization using 5% DIEA in DCM. The primary amine was N-acylated using a carboxylic acid (1.1 mequiv) in DMF (11 mL) in the presence of DIC (172 μL, 1.1 mequiv) and HOBt (168 mg, 1.1 mequiv), followed by washes with DMF

(four times) and DCM (three times). A negative ninhydrin test[30] established the completeness of the coupling reactions.

(b) Exhaustive Reduction of Amide Groups by BH_3−THF. Exhaustive reduction of the N-acylated amino acid amide (0.22 mequiv of amide) was carried out in 50 mL glass conical tubes under nitrogen. To each tube was added the resin packet and boric acid (179 mg, 1.32 mequiv) followed by trimethyl borate (290 μL, 1.32 mequiv). Borane−THF complex (8.8 mL of 1 M, 4.4 mequiv) was added slowly. After cessation of hydrogen evolution, the capped tubes were heated at 65 °C for 72 h, followed by decantation of the reaction solution and quenching with methanol (MeOH). Following washes with DMF and MeOH (four times), the resin was treated with piperidine at 65 °C for 20 h to disproportionate the borane complexes.[22] The piperidine−borane complexes were removed by decantation of the solution, and the resin was washed with DMF (four times), DCM (four times), and MeOH (two times).

(c) Cyclization of the Diamine with Vilsmeier Reagent. Cyclization of the diamine was carried out in 50 mL conical tubes under nitrogen. To each tube the resin packet, DMF (85 μL, 1.1 mequiv), $POCl_3$ (103 μL, 1.1 mequiv), and anhydrous dioxane (11 mL) were added. The capped tubes were heated at 110 °C for 4 h, followed by decantation of the reaction solution. The resin was washed with dioxane (two times), DMF and MeOH (four times each), DCM (two times), IPA (two times), and DCM (four times).

The resin-bound 1,5-disubstituted 4,5-dihydro-1*H*-imidazoles were cleaved from the solid support using anhydrous HF in the presence of anisole at 0 °C for 7 h,[31] and the cleaved products were extracted with 95% acetic acid in H_2O and lyophilized.

(5*S*)-5-Methyl-1-(2-phenylethyl)-4,5-dihydro-1*H*-imidazole (5a). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.28−1.29 (d, J = 6.5 Hz, 3H), 2.87−2.99 (m, 2H), 3.42−3.46 (dd, J = 8.2 Hz, J = 11.6 Hz, 1H), 3.60−3.66 (m, 1H), 3.71−3.77 (m, 1H), 3.95−3.99 (t, J = 11.5 Hz, 1H), 4.25−4.31 (m, 1H), 7.23−7.35 (m, 5H), 8.29 (s, 1H), 9.98 (s, 1H).). ^{13}C NMR (125 MHz, DMSO-d_6): δ 17.6, 39.2, 45.5, 51.0, 55.4, 126.7, 128.6, 128.8, 137.6, 156.9, 157.0. HRMS (DEI) m/z: 189.1385 found ([M + H]$^+$), 189.1392 calculated for $C_{12}H_{17}N_2$ ([M + H]$^+$).

(2) General Procedure for the Individual Synthesis of Disubstituted 4,5-Dihydro-1*H*-imidazolylbenzimidazoles. Coupling of a Boc-L-amino acid to MBHA resin and deprotection of the Boc group is described above in section 1a.

(a) N-Acylation Using 4-Fluoro-3-nitrobenzoic Acid. The primary amine of the resin-bound amino acid was N-acylated using 4-fluoro-3-nitrobenzoic acid (204 mg, 1.1 mequiv) in the presence of DIC (172 μL, 1.1 mequiv) in DMF (11 mL), followed by washes with DMF (three times), IPA (two times), and DCM (three times). The completeness of the coupling reaction was monitored by the ninhydrin test.[30]

(b) Displacement of the Arylfluoro Group. The resin-bound fluoronitro derivative was treated with a primary amine (2.2 mequiv) in the presence of DIEA (384 μL, 2.2 mequiv) in DMF (11 mL), followed by washes with DMF (four times), IPA (two times), and DCM (three times).

(c) Reduction of Aromatic Nitro Group. The resin-bound *o*-nitroaniline derivative was treated with tin(II) chloride dihydrate (20 equiv, 0.5 M) in DMF for 14 h at room temperature, followed by washes with DMF (eight times), MeOH (two times), and DCM (two times).

(d) Exhaustive Reduction of Amide Groups with BH_3−THF. Exhaustive reduction of the resin-bound N-acylated amino acid amide was carried out in the same manner as described above in section 1b.

(e) Cyclization Using Vilsmeier Reagent. Cyclization of the tetraamine was performed as described above in section 1c with DMF (170 μL, 1.1 mequiv), $POCl_3$ (206 μL, 1.1 mequiv), and anhydrous dioxane (11 mL) and heating at 110 °C overnight.

The resin-bound 1,5-disubstituted 4,5-dihydro-1*H*-imidazole benzimidazoles were cleaved from the solid support using anhydrous HF in the presence of anisole at 0 °C for 7 h,[31] and the cleaved products were extracted with 95% acetic acid in H_2O and lyophilized.

1-Hexyl-5-{[(5*S*)-5-isopropyl-4,5-dihydro-1*H*-imidazol-1-yl]methyl}-1*H*-benzimidazole (11a). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.78−0.86 (m, 9H), 1.23−1.27 (m, 6H), 1.83−1.86 (m, 2H), 2.25−2.27 (m, 1H), 3.70−3.73 (dd, J = 8.0 Hz, J = 12.2 Hz, 1H), 3.82 (t, J = 12.1 Hz, 1H), 3.92−3.96 (m, 1H), 4.38 (t, J = 7.1 Hz, 2H), 4.64−4.67 (d, J = 14.9 Hz, 1H), 5.00−5.03 (d, J = 15.0 Hz, 1H), 7.53−7.54 (d, J = 9.2 Hz, 1H), 7.91−7.92 (m, 2H), 8.75 (s, 1H), 9.10 (s, 1H), 10.52 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.6, 13.8, 17.3, 21.9, 25.5, 26.1, 28.9, 30.6, 42.2, 45.5, 48.1, 63.1, 112.5, 117.3, 124.9, 130.3, 132.3, 136.7, 143.4, 157.9.

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Supporting Information Available. LC-MS, HRMS, ^{1}H NMR, and ^{13}C NMR data of 1,5-disubstituted 4,5-dihydro-1*H*-imidazoles and disubstituted 4,5-dihydro-1*H*-imidazolylbenzimidazoles. This material is available free of charge via the Internet at http://pubs.acs.org.

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