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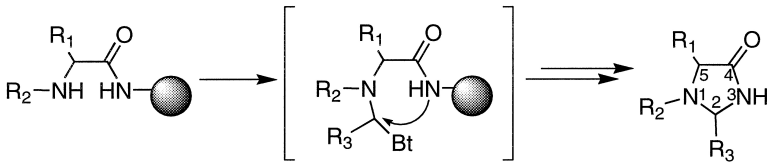

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Solid-Phase Synthesis of 1,2,5-Trisubstituted 4-Imidazolidinones

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An efficient method for the preparation of 1,2,5-trisubstituted 4-imidazolidinones is presented. The synthetic approach is based on the formation of an *N*-[1-(benzotriazol-1-yl)alkyl] moiety on the amino group of a MBHA resin-bound amino acid. The nucleophilic substitution of the benzotriazole group with an amidic nitrogen results in the formation of a five-membered imidazolidinone ring. The reaction is nonstereospecific and produces diastereomers in ratios that vary depending on the substituents on the ring. A variety of *N*-α-alkylated amino acids were cyclized with aromatic, aliphatic, and heterocyclic aldehydes to determine optimal reaction conditions and to select building blocks for the future preparation of a large, diverse range of individual trisubstituted imidazolidinones as well as a mixture-based combinatorial library.

Introduction

Solid-phase chemistry has proven itself to be an efficient route to the preparation of large numbers of diverse compounds, including heterocycles.[1] The solid-phase approach makes possible the synthesis of miscellaneous compounds by either parallel or combinatorial methods. Until now, for imidazolidinones, the reported solid-phase strategies were limited to the synthesis of 2-imidazolidinones.[2,3] 4-Imidazolidinones belong to a group of less explored and investigated imidazolidinones. Methods used for the solution synthesis of 2,5-disubstituted 4-imidazolidinones involve either Beckman rearrangement of 1-alkoxycarbonyl azetidin-3-one based intermediates,[4] condensation of α-aminonitriles with carbonyl compounds,[5] or cyclization of α-aminocarboxamides with aldehydes or ketones in the presence of catalysts such as *p*-toluenesulfonic acid[6] or zeolites.[7] The oldest method is based on dehydration and intramolecular cyclization of N-acylated dipeptides in the presence of strong mineral acids.[8] Similar products were also prepared by anodic oxidation of N-protected dipeptide esters.[9] Seebach et al.[10] introduced a 4-imidazolidinone ring as an excellent chiral synthon for the diastereoselective alkylation of the carbon at position 5 (α-carbon of the glycinyl group). Subsequent acidolysis of this heterocycle provides novel derivatives of α-amino acids. These heterocyclic compounds were also identified as products of the spontaneous cyclization of primary amino groups of peptides or proteins in the presence of formaldehyde, acetone, or acetaldehyde in aqueous solutions.[11] Similar modifications were used to form enzymatically stable prodrugs based on peptides.[12] 5-Substituted 2,2-dimethyl-4-imidazolidinones were found to be moderate inhibitors of tyrosine and histidine decarboxylases.[13] N-terminal 4-imidazolidinone-like modification was observed as a result of the reaction of the primary amino group of Leu-Enkephalin with the aldehydic form of monosaccharides.[14] 4-Imidazolidinone derivatives of proteins or peptides were also detected in the human liver during chronic ethanol oxidation.[15] Compounds based on this relatively small heterocyclic scaffold may have promising biological and pharmacological properties.

The synthetic approach reported here is based on the formation of a reactive adduct of benzotriazole and aldehyde described by Katritzky.[16] We found that the *N*-[1-(benzotriazol-1-yl)alkyl] derivative from the α-amino group of a resin-bound amino acid undergoes spontaneous intramolecular nucleophilic substitution with the nearest amide to form a five-membered 4-imidazolidinone ring (Scheme 1). This nonstereospecific reaction enables the synthesis of an array of diastereomeric mixtures of 1,2,5-trisubstituted imidazolidinones.

Results and Discussion

For all reaction steps the "tea-bag" methodology[17] was used. This facilitated the handling of the many different resins under the various conditions examined. Starting material **1** (see Scheme 1) was prepared by standard condensation of a Boc-amino acid to the MBHA resin, followed by deprotection of the Boc group and neutralization. N-alkylated amino acid **3** was obtained by reductive alkylation using aldehyde **2** and $NaBH_3CN$. The completeness of the reaction was confirmed by a negative ninhydrin test. For compounds with $R_2 = H$, commercially available Boc-N-methylated precursors were coupled to the resin and deprotected. Proline-based compounds (**6b**) were prepared in which the alkylation step was omitted (see Scheme 1). The washed and dried resin **3** was refluxed in dry benzene in the presence of aldehyde **4** and benzotriazole (BtH). The resin was washed with dry benzene, and the reaction was repeated under the same conditions. Following washing and drying, the products were released from the resin by treatment with anhydrous HF. Products were obtained, following the extraction and lyophilization, as yellowish solids. All the products were characterized by LC−MS. Selected samples were purified, and their structures were confirmed by ^1H and/or ^{13}C NMR.

To determine if the ring closure could be facilitated by the presence of a Lewis acid, separate experiments using 3 equiv of $BF_3 \cdot Et_2O$ or $ZnBr_2$ in DCM or DMF/MeOH,

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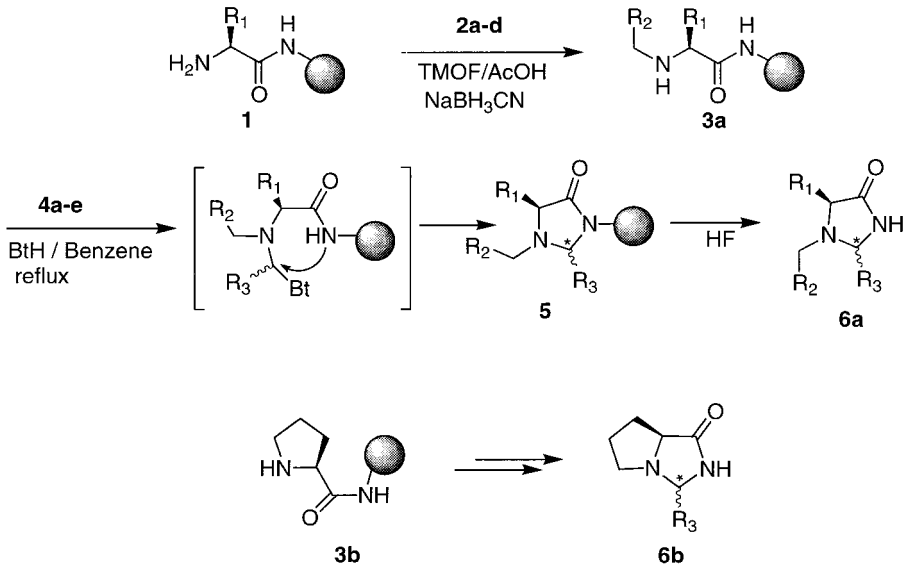
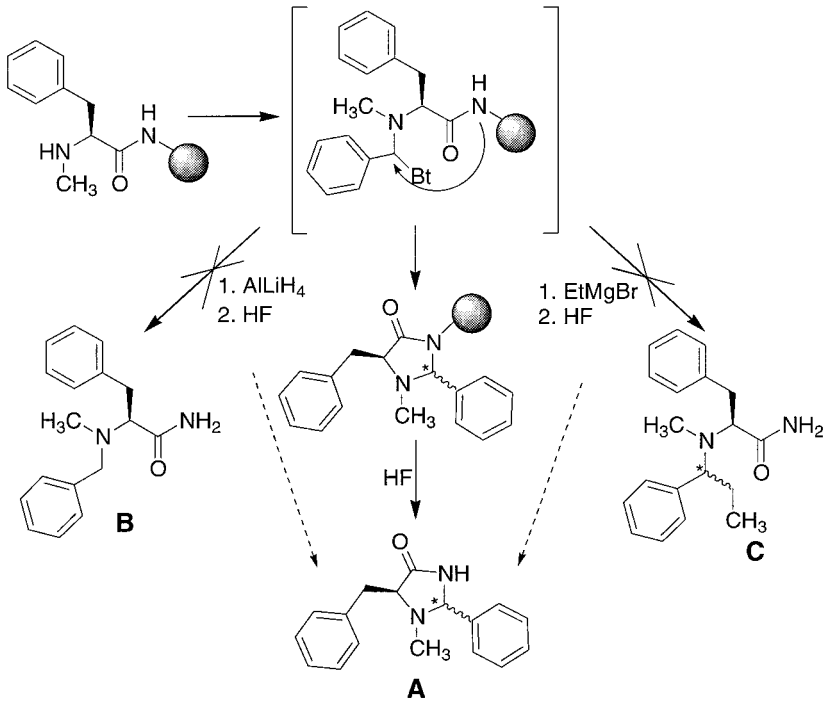
Scheme 1



2a	benzaldehyde
2b	4-nitrobenzaldehyde
2c	4-fluorobenzaldehyde
2d	3-furaldehyde

4a	benzaldehyde
4b	4-nitrobenzaldehyde
4c	p-anisaldehyde
4d	butyraldehyde
4e	3-furaldehyde

Scheme 2



respectively, were used for the treatment of the resin with the preformed Bt derivative at room temperature for 3 h. No differences in product yields or purity were observed.

To prove that the cyclization occurs prior to HF treatment, we attempted to replace the Bt group by nucleophiles stronger than the amidic nitrogen. The standard conditions, described above for the formation of the Bt intermediate on the *N*-methylphenylalanine resin with benzaldehyde (Scheme 2), were used. In the next step, ethylmagnesium bromide (20 equiv excess in THF, room temp (rt), 3 h) was used to substitute the Bt with an ethyl group. In a parallel experiment, $LiAlH_4$ (10 equiv in THF, rt, 3 h) was used as a hydride anion donor.[18] Following HF treatment, we obtained, in both instances, exclusively the imidazolidinone (product A) in high purity and yield without any sign of the presence of products B and C (see Scheme 2).

We then designed an array of compounds choosing from a variety of distinctive groups to create three varying sites

Table 1. 1,2,5-Trisubstituted 4-Imidazolidinones

compd	R_1	R_2	R_3	yield[a] (%)	ratio[b] of diastereomers	MS (M + 1) expected/found
6a-1	Me	Ph	Ph	83	1:3.6	267.3/267.1
6a-2	Me	Ph	4-$NO_2C_6H_4$	77	1:2.9	312.3/312.1
6a-3	Me	Ph	4-$MeOC_6H_4$	61	1:1.6	297.3/297.1
6a-4	Me	Ph	Pr	65	1:2	233.3/233.1
6a-5	Me	4-$NO_2C_6H_4$	Ph	29	*c*	312.3/312.1
6a-6	Me	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	28	*c*	357.3/357.0
6a-7	Me	4-$NO_2C_6H_4$	4-$MeOC_6H_4$	35	*c*	342.3/342.1
6a-8	Me	4-$NO_2C_6H_4$	Pr	83	1:2.1	278.3/278.1
6a-9	Me	4-FC_6H_4	Ph	56	1:1.6	285.3/285.1
6a-10	Me	4-FC_6H_4	4-$NO_2C_6H_4$	33	*c*	330.3/330.1
6a-11	Me	4-FC_6H_4	4-$MeOC_6H_4$	48	1:4	315.3/315.1
6a-12	Me	4-FC_6H_4	Pr	72	1:2.5	251.3/251.2
6a-13	Me	3-furanyl	Ph	55	1:1.5	257.1/256.7
6a-14	Me	3-furanyl	Pr	45	1:5	223.1/222.7
6a-15	Me	3-furanyl	3-furanyl	33	1:1	247.1/246.6
6a-16	iBu	H	Ph	82	1:1.5	233.2/232.6
6a-17	$PhCH_2$	Ph	Ph	44	*c*	343.4/343.2
6a-18	$PhCH_2$	Ph	4-$NO_2C_6H_4$	31	*c*	388.4/388.1
6a-19	$PhCH_2$	Ph	4-$MeOC_6H_4$	27	*c*	373.4/373.2
6a-20	$PhCH_2$	Ph	Pr	49	1:2.3	309.4/309.2
6a-21	$PhCH_2$	Ph	3-furanyl	30	1 : 5	333.2/332.7
6a-22	$PhCH_2$	4-$NO_2C_6H_4$	Ph	31	1:1	388.4/388.2
6a-23	$PhCH_2$	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	19	1:2.8	433.4/433.1
6a-24	$PhCH_2$	4-$NO_2C_6H_4$	4-$MeOC_6H_4$	14	*c*	418.5/418.2
6a-25	$PhCH_2$	4-$NO_2C_6H_4$	Pr	51	1:2.8	354.4/354.1
6a-26	$PhCH_2$	4-FC_6H_4	Ph	42	*c*	361.4/361.2
6a-27	$PhCH_2$	4-FC_6H_4	4-$NO_2C_6H_4$	42	1:1.8	406.4/406.1
6a-28	$PhCH_2$	4-FC_6H_4	4-$MeOC_6H_4$	31	*c*	391.5/391.2
6a-29	$PhCH_2$	4-FC_6H_4	Pr	46	1:3	327.4/327.1
6a-30	$PhCH_2$	H	Ph	68	1:1	267.1/266.6
6a-31	$PhCH_2$	2,5-MeC_6H_4	Pr	54	1:2	337.2/336.7
6a-32	iPr	2,5-MeC_6H_4	Pr	49	1:5	289.2/288.7
6b-1	$-(CH_2)_2-$		Ph	84	*c*	203.1/202.6
6b-2	$-(CH_2)_2-$		4-$NO_2C_6H_4$	73	1:5	248.3/248.1

[a] Calculation of the yield is based on actual weight of purified compounds and the initial loading of the resin. [b] Ratio and purity data are based on the integration of the HPLC traces at 214 nm. The diastereomers were not resolved. [c] Not determined.

of diversity. We included typical aliphatic and diversely substituted aromatic groups as well as one heterocyclic group (3-furanyl) (see Table 1). Different reaction conditions were examined using these model compounds in order to optimize the cyclization. This enabled the selection of appropriate building blocks to be included in the later preparation of a mixture-based combinatorial library of imidazolidinones. In preliminary experiments, we observed significant differences in product yield and purity, which varied depending on the various substituents. Table 1 shows the data obtained under uniform conditions (see Experimental Section) that provided the best results for the selected reactants. The combination of two or three aromatic groups on the imidazolidinone skeleton required significant prolongation of the reaction time, and in some cases, no significant improvement was observed even after prolonged treatment with a larger excess of aldehyde and BtH (**6a-6**, **6a-15**, **6a-19**, **6a-23**, **6a-24**, **6a-28**). In these cases we were still able to isolate unreacted starting material **3a**. This observation suggests that the key step is the formation of a Bt intermediate. The least tendency to form this intermediate was found when $R_2 = R_3 =$ 4-$NO_2C_6H_4$ (**6a-6**, **6a-23**). The cyclization itself proceeded spontaneously without significant side products. For **6a-5**, **6a-7**, **6a-9**, **6a-12**, **6a-20**, and **6a-29**, we observed a "non-cyclized" side product (less than 5%), identified by mass spectra to be an N,N′-dialkylated amide of an amino acid with $R_2 \neq R_3$. Several samples were treated without any change using anhydrous HF for 7 h at −5 °C to verify that this side product was not the result of decomposition in HF. All of the alanine-based imidazolidinones had a higher purity and yield than those based on phenylalanine. The introduction of sterically hindered groups (compounds **6a-5-7**, **6a-18, 19**, **6a-23**, **24**, and **6a-27,28**) resulted in a low or moderate yield even with repeated treatments with fresh reagents. The compounds containing a 3-furanyl group were contaminated by several side products that were not characterized but that were most likely formed because of the significant reactivity of position 2 of the furanyl moiety. N-1-methylated imidazolidinones, as well as those based on proline, were prepared in high purity and close to quantitative yield. The reaction provides, in most instances, both diastereomers in a ratio dependent on the other substituents on the imidazolidinone ring.

Summary

The method presented in this study is the first solid-phase approach enabling the preparation of an array of trisubstituted 4-imidazolidinones using many widely available amino acid building blocks as well as a large number of aldehydes. This strategy can also be utilized in the assembly of other pharmacophores. The reaction conditions used permit the incorporation of a wide range of diverse substituents. The

compounds were found to be stable under normal conditions (as reported by Seebach et al.,[19] hydrolysis of 4-imidazolidinone ring requires refluxing with 6 M HCl). The potential of these compounds in various in vitro assay systems will be reported elsewhere. This study provides useful information regarding the reactivity of various building blocks and possible side reactions used with this synthetic approach.

Experimental Section

Boc-L-amino acids and 1-hydroxybenzotriazole (HOBt) were purchased from Calbiochem-Novabiochem Corp. (San Diego, CA). Boc-L-*N*-methylphenyalanine and Boc-L-*N*-methylleucine were purchased from Peninsula laboratories, Inc. (Belmont, CA). MBHA resin (1% DVB, 100−200 mesh, 1.1 mmol/g) and *N*,*N*′-diisopropylcarbodiimide (DIC) were purchased from Chem Impex International (Wood Dale, IL), trifluoroacetic acid (TFA) from Halocarbon (River Edge, NJ), and hydrogen fluoride from Air Products (San Marcos, CA). All the other solvents (dichloromethane, *N*,*N*′-dimethylformamide, benzene, MeOH, acetonitrile) and reagents (aldehydes, benzotriazole, trimethyl orthoformate (TMOF), $NaBH_3CN$, $ZnBr_2$, $BF_3 \cdot Et_2O$, 1 M $AlLiH_4$ in THF, 1 M EtMgBr in THF, AcOH, DIEA, 4 Å sieves) were purchased from Aldrich Chemical Co. (Milwaukee, WI).

General Solid-Phase Methods. The MBHA resin was sealed in "tea bags" (100 mg of resin per bag, 1.1 mmol of available amino groups per gram). Following neutralization with 5% DIEA in DCM (10 mL/bag, 2 × 2 min) and washing (10 mL DCM/bag, 6×) of the resin, Boc-amino acids were coupled using HOBt and DIC (6 equiv excess each) in DMF (6 mL/bag) for 2 h. The resin was then washed (2 × DMF, 3 × DCM, each wash 10 mL/bag), and the Boc group was cleaved with 55% TFA in DCM (10 mL/bag, 20 min), followed by subsequent neutralization with 5% DIEA in DCM (10 mL/bag, 2 × 2 min).

Reductive Alkylation. Resin **1** was washed with DCM (10 mL/bag, 6×) and dried. Reductive alkylation was accomplished under argon. In a typical procedure, "tea bags" containing the resin were shaken under anhydrous conditions in 10 mL of DMF/DCM/MeOH (1:8:2) per bag, with 10 equiv of the aldehyde (**2a**−**d**), 5 equiv of trimethyl orthoformate, 10 equiv of AcOH, 10 equiv of $NaBH_3CN$, at room temperature, for 1 h. The resin was then washed (3 × DMF, 2 × MeOH, 4 × DCM, 3 × 5% DIEA in DCM, 6 × DCM, 10 mL of solvent per bag) and dried under vacuum.

4-Imidazolidinone Formation. "Tea bags" with a dry resin **3** were refluxed in dry benzene (6 mL/bag) with 10 equiv of aldehyde (**4a**−**e**) and 10 equiv of benzotriazole for 16 h; 4 Å sieves (1 g/bag) were used to ensure dry conditions. Following decantation, this step was repeated with fresh solvents and reagents. Following washing (3 × DCM, 3 × DMF, 3 × MeOH, 5 × DCM) and drying, products were separately cleaved from the resin by treatment with HF (5 mL/bag, 1.5 h, −5 °C). The resin was extracted with 95% AcOH (2 × 5 mL/bag), and the resulting product was lyophilized. Before further characterization, all the compounds were lyophilized again from 50% aqueous acetonitrile (2 × 5 mL/product).

Analytical Methods. All the products were analyzed by LC−MS (electrospray ionization) using Finnigan Mat LCQ (Thermo Quest Corporation, CA) on a Betasil C18 column, at 214 nm. Analytical and preparative RP HPLC was carried out on a Beckman System Gold instrument (Fullerton, CA) on a Vydac C18 column, at 214 nm. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Varian 500 instrument in DMSO-d_6. Proton and carbon chemical shifts are reported in ppm; diastereoisomers were not resolved.

5-Methyl-1-(4-nitrobenzyl)-2-propylimidazolidin-4-one (6a-8). ^{1}H NMR: δ 0.79−0.85 (t, J = 7.4 Hz, 3H, H15), 1.02−1.04 (d, J = 6.8 Hz, 3H, H17), 1.19−1.22 (m, 2H, H14), 1.36−1.51 (m, 2H, H13), 3.26−3.27 (q, J = 6.8 Hz, 1 H, H5), 3.89−3.99 (2d, J = 15.6 Hz, 2H, H6), 4.24−4.25 (d, J = 6.3 Hz, 1H, H2), 7.64−7.66 (d, J = 8.7 Hz, 2H, H 11, H9). ^{13}C NMR: δ 13.0 (C17), 13.9 (C15), 16.7 (C14), 34.2 (C13), 49.0 (C6), 56.7 (C5), 71.3 (C2), 123.3−147.4 (C7, C8, C9, C10, C11, C12), 174.8 (C4).

2-Furan-3-yl-1-furan-3-ylmethyl-5-imidazolidin-4-one (6a-15). ^{1}H NMR: δ 1.09−1.1 (m, 3H, H17), 5.30 (s, 1H, H6), 6.37−6.40 (d, J = 14.3 Hz, 1H, H16), 6.48−6.51 (d, J = 18.0 Hz, 1H, H4), 7.52−7.84 (m, 5H, H16, NH, H5, H13, H2), 8.46 (s, 1H, NH^+). ^{13}C NMR: δ 16.3 (C17), 42.7 (C11), 56.5 (C8), 57.7 (C8′), 66.3 (C6), 66.7 (C6′), 109.2−109.3 (C4), 110.8 (C16), 111.9 (C3, C12), 141.5−144.1 (C2, C5, C13, C15), 165.0 (C9).

5-Isobutyl-1-methyl-2-phenylimidazolidin-4-one (6a-16). ^{1}H NMR: δ 0.91 (d, J = 2.8 Hz, 3H, H17), 0.93 (d, J = 3.0 Hz, 3H, H13), 1.41−1.54 (m, 1H, H14′), 1.59 (s, 3H, H6), 1.55−1.66 (m, 1H, H14), 1.86−1.98 (m, 1H, H15), 3.37−3.39 (m, 1H, H5), 5.45 (s, 1H, H2), 7.38−7.42 (m, 2H, H8, H12), 7.43−7.46 (m, 3H, H9, H10, H11). ^{13}C NMR: δ 22.1 (C17), 23.1 (C16), 24.0 (C15), 35.9 (C16), 38.2 (C14), 60.7 (C5), 75.0 (C2), 127.9 (C8, C12), 128.5 (C9, C11), 129.3 (C10), 136.3 (C7), 173.6 (C1).

1,5-Dibenzyl-2-phenylimidazolididin-4-one (6a-17). ^{1}H NMR: δ 2.77−2.81 (dd, J = 5.1 Hz, 3.8 Hz, 2H, H20), 2.89−2.93 (dd, J = 3.8 Hz, H20), 3.60−3.77 (m, 3H, H5, H6), 4.93 (d, J = 1.4 Hz, 1H, H2), 6.84−6.86 (d, J = 7.3 Hz, 2H, NH), 7.05−7.30 (m, 15H, H8−H12, H14−H18, H22−H26), 8.47 (s, 1H, NH^+). ^{13}C NMR: δ 35.7 (C20), 54.8 (C6), 64.4 (C5), 75.3 (C2), 125.9 (m, C8−C12, C22−C26, C14−C18), 136.7 (C13), 138.10 (C21), 140.8 (C7), 172.5 (C4).

1,5-Dibenzyl-2-propylimidazolidin-4-one (6a-20). ^{1}H NMR: δ 0.59−0.62 (t, J = 7.1 Hz, 1H, H15), 0.74−0.76 (t, J = 7.2 Hz, 3H, H15′), 0.97−1.05 (m, 2H, H14, H14′), 1.23−1.41 (m, 3H, H13, H13′), 2.69−2.72 (m, 1H, H17, H17′), 2.94−2.97 (m, H5, H5′), 2.98−3.06 (m, H6, H6′), 3.18−3.19 (d, J = 5.7 Hz, 1H, H2), 3.19−3.20 (d, J = 5.7 Hz, H2′), 7.15−7.56 (m, 15H, H8−H12, H19−H23, NH).

1,5-Dibenzyl-2-furan-3-yl-imidazolidin-4-one (6a-21). ^{1}H NMR: δ 2.70−2.74 (dd, J = 5.1 Hz, 1H, H18), 2.84−2.88 (dd, J = 3.8 Hz, 1H, H18), 3.53−3.55 (m, 1H, H8), 3.64−3.79 (2d, J = 13.7 Hz, H11), 5.00 (s, 1H, H6), 5.65 (s, 1H, H10), 6.38 (s, H4), 7.10−7.43 (m, 18H, H2, H4), 7.10−7.43 (m, H2, H5, H13−H17, H20−H24), 8.40 (s, 1, NH^+). ^{13}C NMR: δ 35.6 (C18), 54.8 (C11), 64.1 (C6), 67.5

(C8), 108.8 (C4), 108.8 (C3), 125.9−130.2 (m, C13−C17, C20−C24), 136.9 (C12), 138.1 (C19), 141.4 (C5), 143.3 (C2), 172.5 (C9).

5-Benzyl-1-methyl-2-phenylimidazolidin-4-one (6a-30). ^{1}H NMR: δ 2.10 (s, 3H, H6), 2.92 (dd, J = 4.6 Hz, J = 13.9 Hz, 1H, H14), 3.02 (dd, J = 4.8 Hz, J = 13.9 Hz, 1H, H14′), 3.26−3.34 (m, 1H, H5), 4.62 (d, J = 2.0 Hz, 1H, H2), 7.01−7.51 (m, 10H, H8, H9, H10, H11, H12, H16, H17, H18, H19, H20), 8.46 (s, 1H, NH). ^{13}C NMR: δ 35.4 (C6), 36.8 (C14), 66.5 (C5), 77.3.1 (C2), 127.8 (C8, C12), 127.2−128.8 (C9, C10, C11, C17, C18, C19), 129.9 (C16, C20), 134.3 (C7), 138.4 (C15), 172.7 (C4).

3-Phenyl-4*H*-pyrrolo[1,2-*c*]-2*H*-imidazol-1-one (6b-1). ^{1}H NMR: δ 1.84−2.0 (m, 2H, H7), 2.03−2.18 (m, 2H, H6), 3.38−3.56 (m, 2H, H8), 4.33−4.53 (m, 1H, H5), 5.76 (s, 1H, H2), 7.47−7.51 (m, 2H, H11, H13), 7.51−7.57 (m, 3H, H10, H12, H14), 9.34 (s, 1H, NH). ^{13}C NMR: δ 24.0 (C7), 26.9 (C6), 55.8 (C8), 62.8 (C5), 77.0 (C2), 127.1 (C10, C14), 128.8 (C11, C13), 129.9 (C12), 136.8 (C9), 171.5 (C4)

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Supporting Information Available. Examples of LC−MS and/or RP HPLC of crude products, ^{1}H NMR and/or ^{13}C NMR spectra for selected imidazolidinones, and an example of a detailed protocol for "tea-bag" synthesis of a 4-imidazolidinone. This material is available free of charge via the Internet at http://pubs.acs.org.

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