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# An Improved Method for the Synthesis of Dissymmetric N,N′-Disubstituted Imidazole-4,5-dicarboxamides

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**Abstract:** Symmetrically and dissymmetrically disubstituted imidazole-4,5-dicarboxamides (I45DCs) have diverse bioactivities and therefore represent useful small molecules for lead structure identification in drug discovery. For this reason, an improved synthesis was developed as a first step in the preparation of greater numbers of analogues. The method involves the transformation of imidazole-4,5-dicarboxylic acid into dissymmetrically disubstituted I45DCs in four steps and in a minimum yield of 51%. This reflects an overall reduction of one synthetic step and a greater than 30% improvement in yield over the known method.

Imidazole is a common structural unit found in many biologically active compounds. Substituted imidazoles have been synthesized by combinatorial fashion on solid-supports[1] as well as in the solution phase[2] and are promising scaffolds for drug design. We have previously reported the use of symmetric N,N′-disubstituted imidazole-4,5-dicarboxamides (I45DCs) in a study on heterocyclic HIV-1 protease inhibitors, finding modest inhibitory activity with this class of compounds.[3] The I45DCs are also known to affect memory,[4] to protect embryos from teratogens,[5] and as structural components of antibiotics.[6] Intramolecular hydrogen bonded conformations of I45DCs are structurally similar to purine bases, and select I45DCs are known to influence respiration[7] as well as bind to adenosine receptors.[8] The ability of some I45DCs to mimic adenosine is particularly suggestive that these compounds could have bioactivities at other signal transduction targets such as G-proteins, ion channels, or kinases. In addition to their biological significance, I45DCs have also been studied in the context of metal binding[9] and as a monomer incorporated into polyamides.[10]

In addition to the previously described syntheses of I45DCs in the literature,[6,9,11] examples of mixed acid-amide or ester-amide functional group combinations substituted at the 4- and 5-positions of the imidazole ring have been reported.[6a,11] We report herein an improved synthesis of the dissymmetrically disubstituted I45DCs undertaken as part of a research effort to further explore the structure and function of these compounds. Symmetrically disubstituted I45DCs are naturally dissymmetric both by the tautomeric form of the imidazole ring as well as by the consequence of an intramolecular hydrogen bonded conformation that forms preferentially in these compounds.[10,11e,12] However, for the purposes of this paper, the term dissymmetric refers to the relative identity of the two carboxamide substitutents.

The literature route to dissymmetric I45DCs utilizes imidazole-4,5-dicarboxylic acid (**1**) as the starting material to create the pyrazine diacid dichloride (**2**) in 89% yield by refluxing with $SOCl_2$ in benzene with catalytic DMF (Scheme 1).[6a] Addition of water hydrolyzes the two acid chlorides to give **3** in 97% yield. Amines are then added to **3** to open the acyl imidazole bond, thereby generating **4** in 73% yield. Intermediate **4** is subsequently cyclized to pyrazine **5** in the presence of $SOCl_2$ and catalytic DMF in 35% yield. A subsequent pyrazine ring-opening reaction with a different amine provides the dissymmetric I45DC (**6**) in as high as 87% isolated yield. The maximum overall yield reported for this five-step synthesis is 19.2%.[6a,11e] Dissymmetric I45DCs have been

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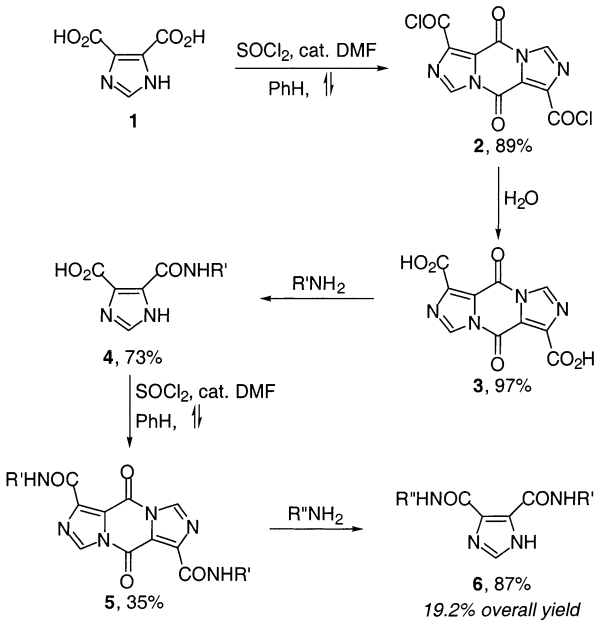
**SCHEME 1**

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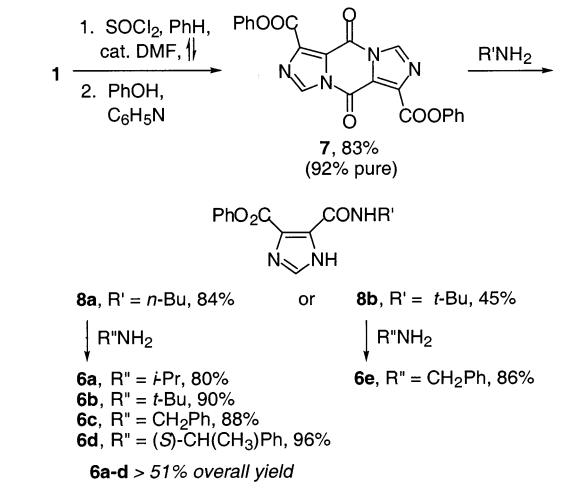
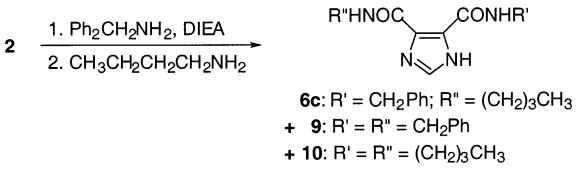



synthesized from analogues of **5** in 34−87% yield for this step alone.[6]

Our major modification to the known synthesis of dissymmetric I45DCs is to replace the water in Scheme 1 with phenol, thereby modulating the reactivity of the acid chloride as compared with the acyl imidazole bond for subsequent additions of two different primary amines. Thus, **1** is refluxed with $SOCl_2$ in benzene in the presence of catalytic DMF to yield **2** that is used without extensive purification. Addition of phenol and pyridine to **2** yields **7** (92% pure) contaminated with **3** or the partially hydrolyzed acid-ester combination or both (Scheme 2). Addition of *n*-butylamine to crude **7** at −40 °C opens the acyl imidazole bond to provide purified amide-ester **8a** (84% yield based on available **7**), whereas sterically hindered amines such as *tert*-butylamine require substantially longer reaction times at −20 °C for optimal conversion to ester-amide **8b** (45% yield based on available **7**). Either ester-amide (**8a** or **8b**) could then be converted to the dissymmetric I45DCs (**6a**−**e**) in good

**SCHEME 3**




isolated yields (80−96%) by the addition of a second amine. This modified synthesis to dissymmetric I45DCs requires only four steps from **1** and results in overall yields of analytically pure dissymmetric I45DCs of at least 51% by the pathway **1**→**6a**−**d**.

The preparation of **2** was slightly altered in this work as compared with the literature method,[6a] including modified reagent quantitites and the total time of the reflux. The reactivity of **2** and its relative insolubility in $CDCl_3$ made routine characterization difficult, as $^1$H NMR analysis in DMSO-$d_6$ results in partial hydrolysis due to the trace water present in the DMSO-$d_6$.

We initially attempted to make **6c** directly from **2** by adding 2 equiv each of benzylamine and diisopropylethylamine at −78 °C, followed by 2 equiv of *n*-butylamine (Scheme 3). However, only mixtures containing the symmetric I45DCs (**9** and **10**) and **6c** were obtained from this procedure, and our modified synthesis was chosen as an alternative method to control the relative reactivity of the acid chloride versus the acyl imidazole group.

The addition of phenol and pyridine to **2** in dichloromethane results in a rapid reaction to yield **7**. The reaction proceeds in apparent quantitative yield as determined by $^1$H NMR analysis of a reaction aliquot; however, the initial solid obtained by filtration often yields **7** contaminated with trace pyridine. The elemental analysis of **7** yields CHN ratios consistent with the presence of 8% of diacid **3**, explaining why the initial solid requires multiple washes to remove trace pyridine.

The conditions for the ring opening of **7** by different primary amines were first determined by comparing small-scale reactions at varying temperatures and removing aliquots from these reactions as a function of time for subsequent $^1$H NMR analysis. Addition of *n*-butylamine to **7** was determined to be complete within 30 min at −60 °C. We observed phenol displacement in the $^1$H NMR spectrum over the entire range of temperatures tested (from −60 to 20 °C), although this appeared to be most significant (∼6%) above −20 °C. Though pyridine is known as a general acylation catalyst, no difference in the reactivity of **7** was observed in the absence of pyridine under otherwise similar conditions.

The ring opening of **7** by *tert*-butylamine was expected to be slower as compared to *n*-butylamine due to the steric constraints of the former. Indeed, the reaction was only 85% complete after 50 h at −20 °C as determined by the relative integration of signals for **7** vs **8b** in the $^1$H NMR spectrum. There were also signals evident for competing displacement of the phenyl ester.

The dissymmetrically disubstituted I45DCs are of interest as a promising drug design scaffold, and this improved synthetic procedure is an important first step to the preparation of multiple I45DCs for screening against a variety of biological targets.

## Experimental Section

**General Methods.** All apparatus were oven-dried and cooled in a desiccator. Reagent-grade THF and $CH_2Cl_2$ were distilled from sodium benzophenone ketyl and $CaH_2$, respectively, before use. All other reagents were purchased from commercial suppliers and used without purification. Thin-layer chromatography was done on 250 $\mu$m silica gel plates containing a fluorescent indicator and visualized by using UV and $I_2$ as well as ninhydrin spray for amines. Melting points are uncorrected, and elemental analyses were done by a contracting lab. $^1$H and $^{13}$C NMR spectra were measured in DMSO-$d_6$ at 400 and 75.5 MHz, respectively, and are referenced to DMSO [$^1$H ($\delta$ 2.50) and $^{13}$C ($\delta$ 39.5)].

**5,10-Dioxo-5*H*,10*H*-diimidazo[1,5-a:1′-5′-d]pyrazine-1,6-dicarboxylic Acid Diphenyl Ester (7).** To a dry round-bottom flask were added 10.01 g of imidazole-4,5-dicarboxylic acid (64.13 mmol) and 50 mL of benzene. To this stirred suspension were added 28.0 mL of thionyl chloride (384 mmol) and 2.5 mL of DMF (32 mmol), and the resulting mixture was refluxed for 16 h. After the mixture was cooled to room temperature, the solid product was collected by vacuum filtration, washed with two 20 mL portions of benzene, and dried under vacuum to yield 9.80 g of crude **2** (98% recovery) as a tan solid. This product was used without characterization.

To a dry round-bottom flask was added crude **2** (0.524 g, 1.67 mmol) followed by 10 mL of dichloromethane and phenol (0.332 g, 3.53 mmol) under $N_2$. The suspension was cooled to 0 °C, and 285 $\mu$L of pyridine (3.53 mmol) was added dropwise over two min. After 1 h, the solid was collected by vacuum filtration and washed with two 10 mL portions of dichloromethane. Pyridine is the most frequent contaminant of this solid as determined by $^1$H NMR analysis. The pyridine can be completely removed by suspending the solid in 20 mL of refluxing dichloromethane for 10 min, cooling to room temperature, collecting the solid by vacuum filtration, rinsing the solid with two 10 mL portions of dichloromethane, and drying the solid under vacuum. This procedure yielded 0.612 g of **7** (83% from **1**): $^1$H NMR (DMSO-$d_6$) $\delta$ 9.12 (s, 2 H), 7.52−7.56 (m, 4 H), 7.34−7.40 (m, 6 H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 159.0, 150.0, 148.2, 139.2, 139.0, 129.9, 126.6, 123.3, 121.5; FAB MS *m*/*z* 429 [M + H]$^+$. Anal. Calcd for $C_{21.04}H_{11.36}N_4O_6$ (**7**, 92%:**3**, 8%): C, 60.72; H, 2.75; N, 13.47. Found: C, 60.32; H, 2.64; N, 13.16.

**4-Phenoxycarbonyl-5-*n*-butylaminocarbonylimidazole (8a).** To a dry round-bottom flask were added **7** (3.945 g, 9.21 mmol, 92% pure) and 60 mL of THF under $N_2$. To this suspension at −40 °C was added *n*-butylamine (1.82 mL, 18.4 mmol) dropwise over 2 min before stirring for 1.5 h. The THF was removed under vacuum to yield a solid that was crystallized and subsequently recrystallized from methanol until pure. The final product was dried under vacuum to yield 4.11 g of **8a** (84% from available **7**): mp 142−144 °C; TLC $R_f$ (85:10:5 $CH_2Cl_2$/MeOH/AcOH) = 0.38; $^1$H NMR (DMSO-$d_6$) $\delta$ 13.52 (bs, 1 H), 9.37 (bs, 1 H), 7.93 (s, 1 H), 7.46−7.50 (m, 2 H), 7.26−7.34 (m, 3 H), 3.26−3.29 (m, 2 H), 1.43−1.49 (m, 2 H), 1.26−1.30 (m, 2 H), 0.81−0.85 (m, 3 H). Carbonyl resonances and one of the substituted imidazole carbons were observed only as weak and broad signals in the $^{13}$C NMR spectrum recorded in DMSO-$d_6$. The peak maximum for each is estimated to the nearest whole ppm: $^{13}$C NMR (DMSO-$d_6$) $\delta$ 163, 158, 150.2, 137.3, 133, 129.6, 126.1, 121.9, 38.5, 31.0, 19.5, 13.5; FAB MS *m*/*z* 288 [M + H]$^+$; Anal. Calcd for $C_{15}H_{17}N_3O_3$: C, 62.71; H, 5.96; N, 14.63. Found: C, 62.51; H, 5.70; N, 14.59.

**4-Phenoxycarbonyl-5-*t*-butylaminocarbonylimidazole (8b).** To a dry round-bottom flask were added **7** (3.218 g, 7.51 mmol, 92% pure) and 100 mL of THF under $N_2$. To this suspension at −20 °C was added *tert*-butylamine (1.58 mL, 15.0 mmol) dropwise over 2 min, and the reaction was stirred for 50 h. The reaction mixture was diluted with 200 mL of ethyl ether and filtered to remove solids. Concentration under vacuum resulted in an oily residue that was redissolved in 10 mL of THF. Addition of 200 mL of water resulted in precipitation of a light-yellow solid that was collected by filtration. This solid was crystallized from methanol to yield 1.792 g of **8b** (45% from available **7**) after drying: mp 177−178 °C; TLC $R_f$ (85:10:5 $CH_2Cl_2$/MeOH/AcOH) = 0.29; $^1$H NMR (DMSO-$d_6$) $\delta$ 13.48 (bs, 1 H), 9.36 (bs, 1 H), 7.91 (s, 1 H), 7.46−7.50 (m, 2 H), 7.27−7.34 (m, 3 H), 1.33 (m, 9 H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 163.8, 157.0, 150.3, 137.1, 134.0, 129.7, 128.1, 126.2, 122.0, 50.9, 28.6; FAB MS *m*/*z* 288 [M + H]$^+$. Anal. Calcd for $C_{15}H_{17}N_3O_3$: C, 62.71; H, 5.96; N, 14.63. Found: C, 62.92; H, 6.18; N, 14.74.

**4(5)-*n*-Butylaminocarbonyl-5(4)-isopropylaminocarbonylimidazole (6a).** To a dry round-bottom flask were added **8a** (0.862 g, 3.00 mmol) and isopropylamine (0.51 mL, 6.00 mmol) in 10 mL of THF under $N_2$. The solution was refluxed for 5 h before concentration of the solution under vacuum to yield an oil. The oil was dissolved in 20 mL of 9:1 hexane−chloroform. This solution was extracted with two 50 mL portions of 0.1 M HCl followed by three 100 mL portions of $H_2O$. The organic fraction was concentrated and the resulting solid crystallized from methanol to yield 0.608 g of **6a** (80%) after drying: mp 141−143 °C; TLC $R_f$ (85:10:5 $CH_2Cl_2$/MeOH/AcOH) = 0.69. The $^1$H spectrum indicated the presence of conformers: $^1$H NMR (DMSO-$d_6$) $\delta$ 13.16 (bs, 1 H), 11.11 (bs, 1 H), 8.53 (bs, 0.6 H), 8.24 (bs, 0.4 H), 7.78 (s, 1 H), 3.95−4.16 (m, 2 H), 3.17−3.30 (m, 2 H), 1.46−1.54 (m, 2 H), 1.32−1.34 (m, 2 H), 1.17 (s, 3.6 H), 1.18 (s, 5.4 H), 0.87−0.91 (m, 3 H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 163.3, 157.1, 135.8, 132.7, 128.3, 40.66, 38.33, 31.16, 22.30, 19.64, 13.67; FAB MS *m*/*z* 253 [M + H]$^+$. Anal. Calcd for $C_{12}H_{20}N_4O_2$: C, 57.13; H, 7.99; N, 22.21. Found: C, 57.11; H, 8.16; N, 22.30.

**4(5)-*n*-Butylaminocarbonyl-5(4)-*t*-butylaminocarbonylimidazole (6b).** To a dry round-bottom flask were added **8a** (0.862 g, 3.00 mmol) and *tert*-butylamine (0.63 mL, 6.00 mmol) in 10 mL of THF under $N_2$. The solution was refluxed for 12 h before workup as described for **6a**. The organic fraction was concentrated and the resulting oil azeotroped (three times) with 10 mL portions of chloroform to yield 0.716 g of **6b** (90%) as an oil after drying: TLC $R_f$ (85:10:5 $CH_2Cl_2$/MeOH/AcOH) = 0.72. The $^1$H and $^{13}$C NMR spectrum indicated the presence of conformers: $^1$H NMR (DMSO-$d_6$) $\delta$ 13.19 (bs, 0.4 H), 13.06 (bs, 0.6 H), 11.49 (bs, 0.6 H), 11.21 (bs, 0.4 H), 8.50 (bs, 1 H), 7.76 (s, 1 H), 3.23−3.42 (m, 2 H), 1.42−1.53 (m, 2 H), 1.38 (s, 9 H), 1.22−1.32 (m, 2 H), 0.87−0.99 (m, 3 H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 163.4, 162.9, 157.9, 157.2, 135.5, 133.0, 132.2, 129.1, 128.0, 50.7, 50.2, 31.1, 28.4, 19.6, 13.6; FAB MS *m*/*z* 267 [M + H]$^+$. Anal. Calcd for $C_{13}H_{22}N_4O_2$: C, 58.63; H, 8.33; N, 21.04. Found: C, 58.72; H, 8.53; N, 21.07.

**4(5)-Benzylaminocarbonyl-5(4)-*n*-butylaminocarbonylimidazole (6c). Method A, via Stoichiometric Additions.** To a dry round-bottom flask was added **2** (1.002 g, 3.19 mmol) in 100 mL of THF under Ar, and the suspension was cooled to −78 °C. A solution of benzylamine (698 $\mu$L, 6.38 mmol) and diisopropylethylamine (1.11 mL, 6.38 mmol) in 25 mL of THF was added dropwise with stirring over 30 min. The solution was held 24 h at −78 °C before a solution of *n*-butylamine (0.631 $\mu$L, 6.38 mmol) in 20 mL of THF was added dropwise, and the reaction mixture was stirred for another 8 h at −78 °C and then allowed to warm to room temperature. After 12 h at room temperature, the THF was removed under vacuum and the resulting material partitioned between ethyl acetate and 10% citric acid. The organic fraction was washed with 1 M $NaHCO_3$, water, and brine. The solution was dried over $MgSO_4$, filtered, and concentrated to a solid containing both symmetric I45DCs and **6c**. TLC and $^1$H NMR analysis of the reaction following workup indicated the presence of significant quantities (∼25% of the isolated total) of the symmetric I45DCs **9** and **10** along with **6c**. The three products were separable by column chromatography, although this synthetic method to dissymmetric I45DCs was not further pursued. TLC: **9**, $R_f$ (19:1 $CH_2Cl_2$/MeOH) = 0.54; **10**, $R_f$ (19:1 $CH_2Cl_2$/MeOH) = 0.44; **6c**, $R_f$ ( 19:1 $CH_2Cl_2$/MeOH) = 0.58.

**Method B, via 8a.** To a dry round-bottom flask were added **8a** (0.863 g, 3.00 mmol) and benzylamine (0.66 mL, 6.00 mmol) in 10 mL of THF under $N_2$. The solution was refluxed for 5 h before concentration under vacuum. The solid was suspended in 50 mL of water, stirred for 10 min, filtered, and washed with an additional 50 mL of water. Crystallization from methanol provided 0.559 g of **6c** (88%) after drying: mp 126−128 °C; TLC

$R_f$ (85:10:5 $CH_2Cl_2$/MeOH/AcOH) = 0.75. The $^1H$ and $^{13}C$ NMR spectrum indicated the presence of conformers: $^1H$ NMR (DMSO-$d_6$) $\delta$ 13.25 (bs, 1 H), 11.64 (bs, 0.5 H), 11.06 (bs, 0.5 H), 9.16 (bs, 0.5 H), 8.61 (bs, 0.5 H), 7.83 (bs, 1 H), 7.22−7.32 (m, 5 H), 4.47−4.56 (m, 2H), 3.22−3.32 (m, 2 H), 1.45−1.52 (m, 2 H), 1.25−1.37 (m, 2 H), 0.85−0.90 (m, 3 H); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 163.6, 163.3, 158.2, 157.9, 139.2, 139.0, 136.1, 136.0, 133.0, 132.5, 128.5, 128.3, 127.9, 127.2, 127.0, 126.8, 42.2, 38.7, 31.2, 19.6, 13.6; FAB MS *m*/*z* 301 $[M + H]^+$. Anal. Calcd for $C_{16}H_{20}N_4O_2$: C, 63.99; H, 6.71; N, 18.66. Found: C, 63.99; H, 6.45; N, 18.75.

**4(5)-(*S*)-α-Methylbenzylaminocarbonyl-5(4)-*n*-butylaminocarbonylimidazole (6d).** To a dry round-bottom flask were added **8a** (0.862 g, 3.00 mmol) and (*S*)-α-methylbenzylamine (0.77 mL, 6.00 mmol) in 10 mL of THF under $N_2$. The solution was refluxed for 5 h before workup as described for **6a**. The organic fraction was concentrated and the resulting oil azeotroped (three times) with 10 mL portions of chloroform to yield 0.919 g of **6d** (96%) as an oil after drying: TLC $R_f$ (85:10:5 $CH_2Cl_2$/MeOH/AcOH) = 0.78. The $^1H$ and $^{13}C$ NMR spectrum indicated the presence of conformers: $^1H$ NMR (DMSO-$d_6$) $\delta$ 13.18 (bs, 1 H), 11.70 (bs, 0.6 H), 10.97 (bs, 0.4 H), 8.81 (bs, 0.4 H), 8.60 (bs, 0.6 H), 7.81 (bs, 1 H), 7.22−7.40 (m, 5 H), 5.12−5.14 (m, 2 H), 3.28−3.32 (m, 2 H), 1.45−1.52 (m, 5 H), 1.29−1.34 (m, 2 H), 0.89−0.91 (m, 3 H). Carbonyl resonances were only observed as a weak and broad signal near 160 ppm in the $^{13}C$ NMR in DMSO-$d_6$: $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 144.2, 136.0, 128.4, 126.8, 126.0, 48.2, 38.7, 31.1, 22.6, 19.6, 13.7; $^{13}C$ NMR ($CDCl_3$) $\delta$ 163.3, 162.6, 158.7, 144.6, 135.1, 133.6, 128.8, 128.2, 127.2, 126.2, 97.4, 50.4, 48.9, 39.4, 31.6, 23.1, 22.4, 20.3, 13.9; ES MS *m*/*z* 315 $[M + H]^+$. Anal. Calcd for $C_{17}H_{22}N_4O_2$: C, 64.95; H, 7.05; N, 17.82. Found: C, 64.55; H, 6.88; N, 17.78.

**4(5)-Benzylaminocarbonyl-5(4)-*t*-butylaminocarbonylimidazole (6e).** To a dry round-bottom flask were added **8b** (0.863 g, 3.00 mmol) and *tert*-butylamine (0.66 mL, 6.00 mmol) in 10 mL of THF under $N_2$. The solution was refluxed for 5 h before as described for **6c**. Crystallization from methanol provided 0.771 g of **6e** (86%) after drying: mp 177−178 °C; TLC $R_f$ (85:10:5 $CH_2Cl_2$/MeOH/AcOH) = 0.74. The $^1H$ NMR spectrum indicated the presence of conformers: $^1H$ NMR (DMSO-$d_6$) $\delta$ 13.13 (bs, 1 H), 11.47 (bs, 0.3 H, N−H), 10.98 (bs, 0.7 H), 9.09 (bs, 1 H), 7.81 (s, 1 H), 7.22−7.37 (m, 5 H), 4.48−4.57 (m, 2 H), 1.38 (s, 9 H); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 163.6, 157.2, 139.2, 135.8, 132.1, 129.4, 128.4, 127.2, 126.9, 50.4, 42.1, 28.4; FAB MS *m*/*z* 301 $[M + H]^+$. Anal. Calcd for $C_{16}H_{20}N_4O_2$: C, 63.99; H, 6.71; N, 18.66. Found: C, 64.10; H, 6.75; N, 18.73.

**Determining Conditions for the Synthesis of 8a by $^1H$ NMR Analysis.** Conditions for the formation of **8a** from **7** were determined by monitoring reactions as a function of temperature and time. The reactions were set up similar to those described for the synthesis of **8a** but with 0.60 mmol of **7** and 1.2 mmol of *n*-butylamine in 10 mL of THF under $N_2$ at the various temperatures. In addition, pyridine was added (1.2 mmol) to each reaction as a general acylation catalyst. The reaction was stirred, and aliquots were removed at 30 min, 1 h, and 2 h. Each aliquot was concentrated under vacuum and dissolved in DMSO-$d_6$ for analysis by $^1H$ NMR spectroscopy. The presence or absence of C2-H/C2′-H from **7** (9.12 ppm) was taken as an indication of the reaction progress, while the relative integration of the C2-H in **8a** (7.92 ppm) along with the phenol signals furthest upfield (6.73−6.77 ppm) provided an indication of how much product formed versus how much phenol was displaced under the given reaction condition.

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