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One-Pot Synthesis of Multisubstituted Benzimidazoles via Sequential Ugi and Catalytic Aza-Wittig Reaction Starting from 2-Aminobenzoyl Azides

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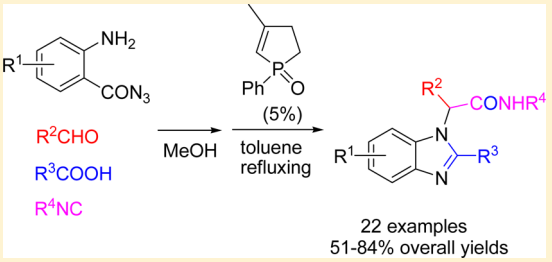
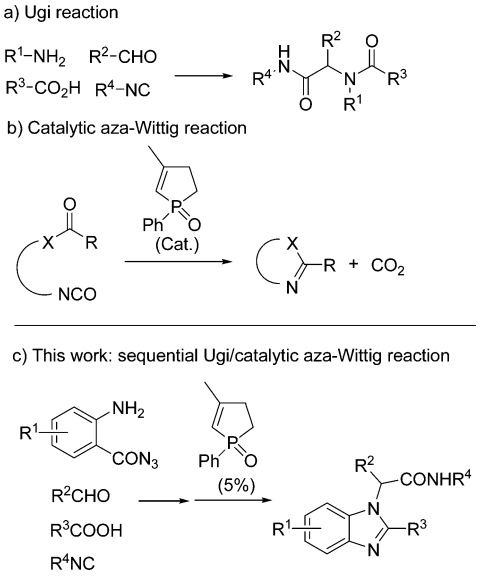
Supporting Information

ABSTRACT: A simple and one-pot synthesis of multisubstituted benzimidazoles by a Ugi 4CC/catalytic aza-Wittig sequence was developed. The reaction of 2-aminobenzoyl azide **2**, aldehyde **3**, acid **4**, and isocyanide **5** produced the benzimidazoles **8** in moderate to good yields via a sequential Ugi condensation and catalytic aza-Wittig in the presence of a catalytic amount of phospholene oxide.



Owing to their exceptional synthetic efficiency and high atom economy, multicomponent reactions (MCRs) have attracted considerable interest recently in organic and medicinal chemistry.[1] The Ugi reaction is one of the most important MCR which produces efficiently an α-acylamino-carboxamide adduct starting from four components of amine, aldehyde or ketone, acid, and isocyanide in a one-pot fashion (Scheme 1a). The sequential Ugi reaction and various postcondensation reactions constitute powerful synthetic tools for the preparation of many diverse organic molecules, especially heterocyclic compounds.[2−10] For example, the pharmacologically useful 1,4-benzodiazepin-2-ones were prepared by a sequential Ugi/deprotection/cyclization (UDC) strategy.[2] The sequential Ugi/cyclization/elimination reaction was utilized to produce various fused tetrazoles under mild reaction conditions.[3] The Ugi/reductive Heck strategy was described recently to generate 3-benzazepines in good to high yields.[4] The peptidomimetic 3-carboxamide-1,4-benzodiazepin-5-ones were also obtained by sequential Ugi/Staudinger/aza-Wittig reaction with good diastereoselectivity.[5]

Scheme 1. Sequential Ugi/Catalytic Aza-Wittig Reaction Approach to Benzimidazoles Synthesis



The aza-Wittig reactions of iminophosphoranes have received great attention in view of their utility in the synthesis of heterocyclic compounds under mild neutral conditions.[11] Recently, a catalytic aza-Wittig reaction was reported to prepare some heterocycles starting from carbonyl isocyanate derivatives with the 3-methyl-1-phenyl phospholene oxide as catalyst (Scheme 1b).[12] The above catalytic aza-Wittig process shows high atom efficiency by using a catalytic amount of organophosphorus reagents compared with the conventional aza-Wittig reaction. Thus, it is speculated that combining the efficiency of the Ugi reaction with a postcondensation catalytic aza-Wittig reaction would facilitate access to some biologically useful heterocycles in high atom efficiency. However, there is no report on the sequential Ugi and catalytic aza-Wittig reaction previously.

Multisubstituted benzimidazole derivatives are an important class of heterocyclic compounds with substantial biological activities. For example, some benzimidazoles have been found recently to be potent Janus kinases 1 inhibitors,[13] sphingosine 1-phosphate receptor 1 antagonists,[14] angiotensin II receptor type 1 (AT1) blockers,[15] poly(ADP-ribose) polymerases-1

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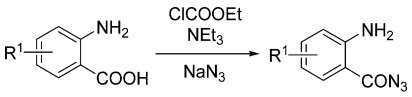
inhibitors,[16] anticancer agents,[17] antibacterial agents,[18] anti-HIV-1 agents,[19] and anti-inflammatory agents.[20] The broad utility of benzimidazoles has prompted significant efforts toward their synthesis. Benzimidazoles were generally prepared from the condensation of benzene-1,2-diamine with carboxylic acids under high temperature or dehydration conditions.[21] The reaction of benzene-1,2-diamine with aldehydes or alcohols was also utilized for synthesis of benzimidazoles in the presence of various catalysts.[22] Some 2-styrylbenzimidazoles were obtained successfully from reaction of benzene-1,2-diamine with α-aroylidineketene dithioacetals under copper catalysis conditions.[23] Hypervalent iodine-mediated synthesis of benzimidazoles was reported via an oxidative rearrangement starting from 2-aminophenylimines.[24] Some benzimidazole scaffolds have been synthesized using an Ugi/deprotection/cyclization strategy.[25] An efficient and facile assembly of various 2-substituted benzimidazoles has been developed through the domino reactions of *o*-haloarylcarbodiimides with active methylene species under copper catalysis conditions.[26] Recently, we have been interested in the synthesis of various heterocycles via multicomponent or aza-Wittig reactions.[27] Herein, we wish to report a new efficient synthesis of multisubstituted benzimidazoles by sequential Ugi and catalytic aza-Wittig reaction starting from 2-aminobenzoyl azide precursors (Scheme 1c).

The 2-aminobenzoyl azide precursors **2** (Scheme 2) were prepared by reaction of 2-aminobenzoic acids with ethyl

Scheme 2. Preparation of 2-Aminobenzoyl Azide 2



chloroformate/NEt_3, followed by sodium azide in acetone, according to a literature report,[28] and the acyl azides **2** were produced in good yields (72−85%). The obtained acyl azides **2** were found to be stable and can be stored for about 2 weeks at room temperature.

Although many primary amines were utilized in the Ugi reaction, 2-aminobenzoyl azide **2** was not used previously in the reaction to prepare corresponding Ugi products. We selected initially the 2-amino-5-methylbenzoyl azide **2a**, 3-bromobenzaldehyde **3a**, 4-trifluoromethylbenzoic acid **4a**, and *t*-butylisocyanide **5a** as the Ugi reactants to optimize the reaction condition (Scheme 3). As the above four compounds were stirred in methanol at room temperature for 24 h, the Ugi product **6a** was produced smoothly, and it can be isolated in 84% yield. However, the obtained acyl azides **6a** were found not stable when stored. Therefore, the best result was obtained when the reaction was carried out in a one-pot fashion: after detecting the complete formation of the acyl azide **6a**, the solvent was changed from methanol to toluene. Heating the toluene solution resulted in transformation of **6a** to isocyanate intermediate **7a** via Curtius rearrangement. Then, a catalytic amount of phospholene oxide (**A**) was added and the resulted solution was refluxed. The final product obtained was verified to be benzimidazole **8a** (in 83% overall yield, Table 1, entry 1). If the above reaction was carried out after isolation of Ugi product **6a**, a relative lower overall yield (74%) of **8a** was obtained. In the reaction of **7a** with the phospholene oxide catalyst, no carbodimide was isolated from the reaction mixture.

Scheme 3. Preparation of Compounds 8a

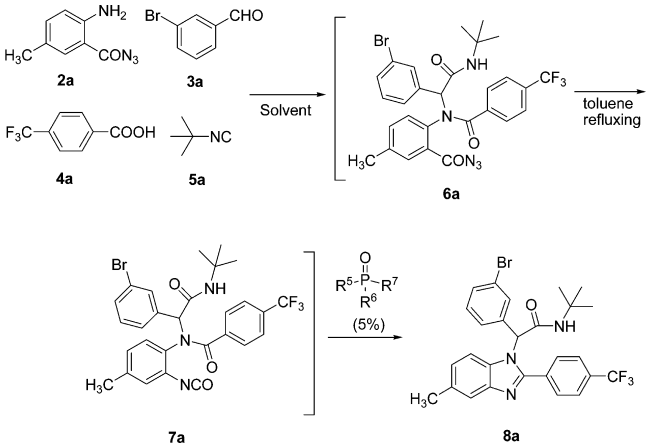


Table 1. Optimization of the Reaction Conditions

Entry	Solvent[a]	R^5-P(=O)-R^7 (R^6)	Yield[b] (%)
1	MeOH	 (**A**)	83
2	EtOH	(**A**)	65
3	THF	(**A**)	0
4	CH_2Cl_2	(**A**)	0
5	CH_3CN	(**A**)	0
6	Toluene	(**A**)	0
7	Acetone	(**A**)	0
8	EtOAc	(**A**)	0
9	DMF	(**A**)	0
10	MeOH	Ph_3PO	0
11	MeOH	Ph_2MePO	0
12	MeOH	$PhMe_2PO$	0

[a]Solvent used in Ugi reaction. [b]Isolated yields of **8a** based on the acyl azides **2a**.

This means that the intramolecular aza-Wittig reaction takes place quickly to give **8a**. The solvent for the Ugi reaction has a remarkable effect on the reaction. A relatively lower yield was reached as EtOH was utilized as solvent (65%, Table 1, entry 2). When THF, CH_2Cl_2, CH_3CN, toluene, DMF, or acetone was used in the Ugi reaction instead of methanol, no product was obtained from the reaction mixture (Table 1, entries 3−9). This might be due to the easy formation of a Schiff base intermediate only as methanol or ethanol were used as solvent. The reaction also failed to produce benzimidazole **8a** when triphenylphosphine oxide, diphenylmethylphosphine oxide, or dimethylphenylphosphine oxide was used as the catalyst in the catalytic aza-Wittig reaction (Table 1, entries 10−12), probably due to their low reactivity. The result implies that the acyclic phosphine oxides are not effective catalysts for the catalytic aza-Wittig reaction.

With the optimized conditions, various 2-aminobenzoyl azides **2**, aldehydes **3**, acids **4**, and isocyanides **5** were employed for the one-pot reaction (Scheme 4). The reactions were carried out smoothly to give the corresponding multisubstituted benzimidazoles **8**, and moderate to good yields were often reached with different substituents of the reactants (Table 2). Various aldehydes and acids can be used in the above one-pot cyclization to prepare benzimidazoles **8**. As ortho-substituted

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Scheme 4. Preparation of Benzimidazoles 8

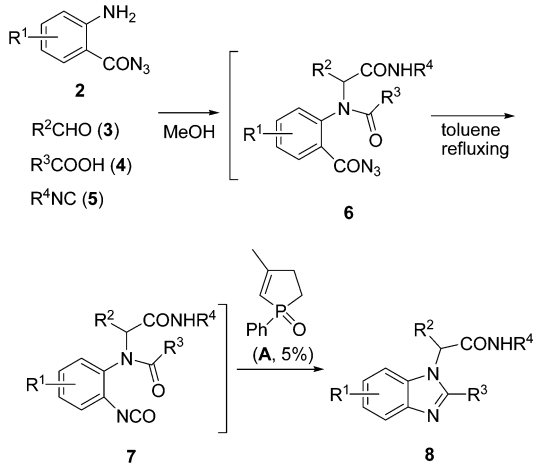

Table 2. Preparation of Compounds 8

	R^1	R^2	R^3	R^4	Yield[a] (%)
8a	5-CH_3	3-BrC_6H_4	4-$CF_3C_6H_4$	*t*-Bu	83
8b	5-CH_3	2-ClC_6H_4	4-ClC_6H_4	*c*-C_6H_{11}	51
8c	4-Cl	4-$CH_3OC_6H_4$	Ph	*t*-Bu	78
8d	4-Cl	2-$CH_3OC_6H_4$	Ph	*t*-Bu	65
8e	4-Cl	2-$CH_3C_6H_4$	Ph	*t*-Bu	60
8f	4-Cl	4-$CF_3C_6H_4$	Ph	*t*-Bu	70
8g	H	2-FC_6H_4	H	*t*-Bu	52
8h	H	4-(*t*-Bu)C_6H_4	CH_3	*c*-C_6H_{11}	82
8i	4-Cl	3-ClC_6H_4	Ph	*t*-Bu	71
8j	5-Cl	4-$CH_3OC_6H_4$	Ph	*t*-Bu	76
8k	5-Cl	4-$CH_3OC_6H_4$	Ph	*c*-C_6H_{11}	84
8l	5-Cl	4-$CH_3OC_6H_4$	Ph	*n*-Bu	76
8m	5-CH_3	4-ClC_6H_4	3-IC_6H_4	*c*-C_6H_{11}	70
8n	5-OCH_3	4-BrC_6H_4	4-$CF_3C_6H_4$	*t*-Bu	73
8o	4-Cl	Ph	Ph	*t*-Bu	79
8p	5-CH_3	Ph	4-$CH_3C_6H_4$	*t*-Bu	78
8q	5-CH_3	Ph	4-$CH_3OC_6H_4$	*t*-Bu	75
8r	H	*n*-Pr	CH_3	*t*-Bu	80
8s	H	Et	2-$CH_3C_6H_4$	*t*-Bu	77
8t	H	Ph	Et	*t*-Bu	72
8u	H	4-$CH_3OC_6H_4$		*t*-Bu	74
8v	H	2-$CH_3C_6H_4$		*t*-Bu	77

[a]Isolated yields based on the acyl azides **2**.

aromatic aldehydes (compounds **8b**, **8d**, **8e**, and **8g**, R^2 = 2-ClC_6H_4, 2-$CH_3OC_6H_4$, 2-$CH_3C_6H_4$, and 2-FC_6H_4) were used, moderate yields (51−65%) were obtained, whereas good yields (70−84%) of the products were reached when other aromatic or aliphatic aldehydes were utilized. However, no products were obtained when the aldehydes substituted with a strong electron-withdrawing group (R^2 = 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, and 3-$NO_2C_6H_4$) were used. The aromatic or aliphatic acids used have little effect on the yields. It is noteworthy that the reaction proceeds under mild conditions to give various multisubstituted benzimidazoles **8**, and the overall transformation is run in a simple one-pot procedure from four-component reactants in moderate to good overall yields.

In summary, we have developed a new method utilizing sequential Ugi reaction/catalytic aza-Wittig cyclization to synthesize multisubstituted benzimidazoles in a one-pot fashion, starting from the corresponding 2-aminobenzoyl azides as the amino component. The used 2-aminobenzoyl azides, aldehydes, acids, and isocyanides can be varied broadly, producing products with four potential points of diversity, which, in combination with the easy availability of the synthetic approach and the large scope of the reaction, makes it useful in synthetic and medicinal chemistry.

EXPERIMENTAL SECTION

One-Pot Synthesis of Benzimidazoles 8 via Sequential Ugi and Catalytic Aza-Wittig Reaction. A mixture of 2-aminobenzoyl azide **2**[28] (1 mmol), aldehyde **3** (1 mmol), acid **4** (1 mmol), and isocyanide **5** (1 mmol) was stirred in methanol (5 mL) at room temperature for 24−48 h, and then the solvent was evaporated completely under reduced pressure at room temperature. Toluene (5 mL) was added to the reaction system, and the reaction mixture was heated to 60−70 °C for 0.5 h to form isocyanate intermediate **7**. Then, 3-methyl-1-phenyl phospholene-1-oxide **A** (0.01 g, 0.05 mmol) was added, and the mixture was stirred at 110 °C for 5−10 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (ether/petroleum ether = 1:2, V/V) to give **8**.

*2-(4-Bromophenyl)-N-(tert-butyl)-2-(5-methyl-2-(4-(trifluoromethyl)phenyl)-1H-benzimidazol-1-yl)acetamide (**8a**).* White solid (yield 0.45 g, 83%); mp: 226−228 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.79−7.75 (m, 4H, Ar-H), 7.64 (s, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.38 (s, 1H), 7.23−6.99 (m, 4H), 6.06 (s, 1H), 5.54 (s, 1H), 2.48 (s, 3H), 1.30 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 165.2, 152.7, 143.5, 136.6, 133.3, 133.1, 132.1, 132.0, 131.8, 131.5, 130.7, 130.4, 129.8, 126.2, 125.8, 125.4, 123.0, 120.2, 111.9, 63.4, 52.4, 28.4, 21.4; MS (EI, 70 eV) m/z (%) 545 (M^+, 9), 444 (100), 364 (21). Anal. Calcd for $C_{27}H_{25}BrF_3N_3O$: C, 59.57; H, 4.63; N, 7.72. Found: C, 59.62; H, 4.60; N, 7.88. HRMS (ESI) m/z calcd for $C_{27}H_{26}BrF_3N_3O$ $[M + H]^+$: 544.1206; found: 544.1211.

*2-(2-Chlorophenyl)-2-(2-(4-chlorophenyl)-5-methyl-1H-benzimidazol-1-yl)-N-cyclohexylacetamide (**8b**).* White solid (yield 0.25 g, 51%); mp: 186−188 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.59−7.30 (m, 9H), 7.01−6.96 (m, 2H), 6.30 (s, 1H), 5.83 (s, 1H), 3.98−3.92 (m, 1H), 2.45 (s, 3H), 1.90−0.86 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 165.3, 153.9, 143.5, 136.2, 134.5, 132.7, 132.3, 130.5, 130.3, 130.2, 129.4, 129.0, 128.9, 128.3, 127.1, 125.0, 120.0, 111.2, 62.5, 49.0, 32.7, 25.1, 24.6, 21.4; MS (EI, 70 eV) m/z (%) 491 (M^+, 30), 365 (52), 331 (100), 165 (13). Anal. Calcd for $C_{28}H_{27}Cl_2N_3O$: C, 68.29; H, 5.53; N, 8.53. Found: C, 68.26; H, 5.64; N, 8.44. HRMS (ESI) m/z calcd for $C_{28}H_{28}Cl_2N_3O$ $[M + H]^+$: 492.1604; found: 492.1615.

*N-(tert-Butyl)-2-(6-chloro-2-phenyl-1H-benzimidazol-1-yl)-2-(4-methoxyphenyl)acetamide (**8c**).* White solid (yield 0.35 g, 78%); mp: 207−209 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.70−7.46 (m, 6H), 7.23−7.10 (m, 4H), 6.89 (d, J = 8.4 Hz, 2H), 6.03 (s, 1H), 5.64 (s, 1H), 3.80 (s, 3H), 1.33 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 166.0, 159.7, 155.4, 141.8, 135.1, 130.2, 129.6, 129.4, 128.8, 128.5, 126.1, 123.3, 120.9, 114.6, 112.6, 64.0, 55.2, 52.3, 28.4; MS (EI, 70 eV) m/z (%) 447 (M^+, 10), 347 (100), 239 (16), 192 (13), 136 (17). Anal. Calcd for $C_{26}H_{26}ClN_3O_2$: C, 69.71; H, 5.85; N, 9.38. Found: C, 69.59; H, 5.64; N, 9.42. HRMS (ESI) m/z calcd for $C_{26}H_{27}ClN_3O_2$ $[M + H]^+$: 448.1786; found: 448.1800.

*N-(tert-Butyl)-2-(6-chloro-2-phenyl-1H-benzimidazol-1-yl)-2-(2-methoxyphenyl)acetamide (**8d**).* White solid (yield 0.29 g, 65%); mp: 228−230 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.65 (d, J = 8.4 Hz, 1H), 7.59−6.99 (m, 10H), 6.80 (d, J = 7.8 Hz, 1H), 6.27 (s, 1H), 5.66 (s, 1H), 3.55 (s, 3H), 1.36 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 166.3, 157.1, 156.0, 141.9, 135.4, 130.6, 130.1, 130.0, 129.3, 128.6, 128.4, 128.3, 123.0, 122.5, 120.8, 120.6, 112.5, 111.0, 60.5, 55.2, 52.1, 28.5; MS (EI, 70 eV) m/z (%) 447 (M^+, 19), 347 (100), 317 (31), 229 (27). Anal. Calcd for $C_{26}H_{26}ClN_3O_2$: C, 69.71; H, 5.85; N, 9.38. Found: C, 69.96; H, 5.60; N, 9.40. HRMS (ESI) m/z calcd for $C_{26}H_{27}ClN_3O_2$ $[M + H]^+$: 448.1786; found: 448.1794.

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*N-(tert-Butyl)-2-(6-chloro-2-phenyl-1H-benzimidazol-1-yl)-2-(o-tolyl)acetamide (**8e**).* White solid (yield 0.26 g, 60%); mp: 225−227 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.72−7.15 (m, 12H), 6.01 (s, 1H), 5.58 (s, 1H), 1.88 (s, 3H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 166.1, 155.6, 141.7, 136.7, 135.4, 132.6, 131.4, 130.2, 129.6, 129.3, 129.2, 128.7, 128.5, 127.3, 126.8, 123.2, 120.8, 112.2, 63.2, 52.2, 28.3, 18.9; MS (EI, 70 eV) m/z (%) 431 (M^+, 19), 331 (100), 317 (33), 239 (17), 104 (25). Anal. Calcd for $C_{26}H_{26}ClN_3O$: C, 72.29; H, 6.07; N, 9.73. Found: C, 72.00; H, 6.14; N, 9.70. HRMS (ESI) m/z calcd for $C_{26}H_{27}ClN_3O$ $[M + H]^+$: 432.1837; found: 432.1843.

*N-(tert-Butyl)-2-(6-chloro-2-phenyl-1H-benzimidazol-1-yl)-2-(4-(trifluoromethyl)phenyl)acetamide (**8f**).* White solid (yield 0.34 g, 70%); mp: 180−182 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.72 (d, J = 8.4 Hz, 1H), 7.64−7.26 (m, 10H), 7.20 (s, 1H), 6.15 (s, 1H), 5.56 (br, 1H), 1.30 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 164.9, 155.2, 141.8, 138.0, 134.6, 131.1, 130.6, 130.4, 129.4, 129.3, 129.1, 127.9, 127.7, 126.0, 123.9, 122.3, 121.2, 112.5, 63.5, 52.6, 28.4; MS (EI, 70 eV) m/z (%) 485 (M^+, 17), 385 (100), 86 (40), 84 (67). Anal. Calcd for $C_{26}H_{23}ClF_3N_3O$: C, 64.26; H, 4.77; N, 8.65. Found: C, 64.01; H, 4.67; N, 8.46. HRMS (ESI) m/z calcd for $C_{26}H_{24}ClF_3N_3O$ $[M + H]^+$: 486.1555; found: 486.1552.

*2-(1H-Benzimidazol-1-yl)-N-(tert-butyl)-2-(2-fluorophenyl)-acetamide (**8g**).* White solid (yield 0.17 g, 52%); mp: 205−207 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.98 (s, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.35−7.04 (m, 7H), 6.70 (s, 1H), 6.32 (s, 1H), 1.31 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 165.6, 161.6, 159.2, 143.2, 142.2, 133.4, 131.1, 131.0, 129.0, 124.9, 123.2, 122.6, 120.1, 116.0, 115.8, 109.7, 56.7, 52.2, 28.3; MS (EI, 70 eV) m/z (%) 325 (M^+, 6), 226 (100), 207 (9). Anal. Calcd for $C_{19}H_{20}FN_3O$: C, 70.13; H, 6.20; N, 12.91. Found: C, 70.00; H, 6.00; N, 12.95. HRMS (ESI) m/z calcd for $C_{19}H_{21}FN_3O$ $[M + H]^+$: 326.1663; found: 326.1661.

*2-(4-(tert-Butyl)phenyl)-N-cyclohexyl-2-(2-methyl-1H-benzimidazol-1-yl)acetamide (**8h**).* White solid (yield 0.33 g, 82%); mp: 136−138 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.67 (d, J = 7.2 Hz, 1H), 7.35−7.05 (m, 7H), 6.22 (br, 1H), 6.10 (s, 1H), 3.92−3.87 (m, 1H), 2.42 (s, 3H), 1.88−0.87 (m, 19H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 166.0, 152.3, 151.8, 142.6, 134.3, 131.1, 127.5, 125.9, 122.4, 122.2, 119.2, 111.0, 62.5, 48.9, 34.5, 32.6, 31.1, 25.2, 24.6, 14.7; MS (EI, 70 eV) m/z (%) 403 (M^+, 12), 277 (100), 263 (12), 221 (10). Anal. Calcd for $C_{26}H_{33}N_3O$: C, 77.38; H, 8.24; N, 10.41. Found: C, 77.36; H, 8.20; N, 10.25. HRMS (ESI) m/z calcd for $C_{26}H_{34}N_3O$ $[M + H]^+$: 404.2696; found: 404.2701.

*N-(tert-Butyl)-2-(6-chloro-2-phenyl-1H-benzimidazol-1-yl)-2-(3-chlorophenyl)acetamide (**8i**).* White solid (yield 0.32 g, 71%); mp: 191−193 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.72 (d, J = 9.0 Hz, 1H), 7.56−7.17 (m, 10H), 7.07 (d, J = 7.8 Hz, 1H), 6.05 (s, 1H), 5.51 (s, 1H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 165.1, 155.3, 141.8, 136.1, 135.1, 134.7, 130.5, 130.4, 129.3, 129.2, 129.0, 127.8, 125.6, 123.8, 121.1, 112.5, 63.6, 52.5, 28.4; MS (EI, 70 eV) m/z (%) 451 (M^+, 14), 351 (100), 317 (9), 239 (9). Anal. Calcd for $C_{25}H_{23}Cl_2N_3O$: C, 66.38; H, 5.12; N, 9.29. Found: C, 66.11; H, 4.97; N, 9.46. HRMS (ESI) m/z calcd for $C_{25}H_{24}Cl_2N_3O$ $[M + H]^+$: 452.1291; found: 452.1290.

*N-(tert-Butyl)-2-(5-chloro-2-phenyl-1H-benzimidazol-1-yl)-2-(4-methoxyphenyl)acetamide (**8j**).* White solid (yield 0.34 g, 76%); mp: 223−225 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.77 (s, 1H), 7.61 (d, J = 6.6 Hz, 2H), 7.53−7.49 (m, 3H), 7.12−7.07 (m, 4H), 6.86 (d, J = 8.4 Hz, 2H), 6.06 (s, 1H), 5.60 (s, 1H), 3.79 (s, 3H), 1.33 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 166.2, 159.7, 155.8, 144.2, 133.0, 130.4, 129.6, 129.4, 128.9, 128.2, 126.1, 123.4, 119.9, 114.4, 113.5, 63.9, 55.3, 52.3, 28.5; MS (EI, 70 eV) m/z (%) 447 (M^+, 6), 347 (100), 239 (14), 136 (10). Anal. Calcd for $C_{26}H_{26}ClN_3O_2$: C, 69.71; H, 5.85; N, 9.38. Found: C, 69.53; H, 5.80; N, 9.60. HRMS (ESI) m/z calcd for $C_{26}H_{27}ClN_3O_2$ $[M + H]^+$: 448.1786; found: 448.1776.

*2-(5-Chloro-2-phenyl-1H-benzimidazol-1-yl)-N-cyclohexyl-2-(4-methoxyphenyl)acetamide (**8k**).* White solid (yield 0.40 g, 84%); mp: 153−155 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.70 (d, J = 6.0 Hz, 1H), 7.57 (d, J = 6.6 Hz, 2H), 7.49−7.44 (m, 3H), 7.10−7.05 (m, 4H), 6.83 (d, J = 9.0 Hz, 2H), 6.15 (s, 1H), 5.95 (br, 1H), 3.86−3.77 (m, 4H), 1.89−1.03 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 166.0, 159.6, 155.7, 144.1, 132.8, 130.3, 129.3, 129.1, 128.9, 128.8, 128.2, 126.0, 123.4, 119.7, 114.3, 113.5, 63.3, 55.2, 48.8, 32.6, 25.1, 24.5; MS (EI, 70 eV) m/z (%) 473 (M^+, 10), 347 (100), 239 (14), 218 (14), 98 (17). Anal. Calcd for $C_{28}H_{28}ClN_3O_2$: C, 70.95; H, 5.95; N, 8.87. Found: C, 70.97; H, 5.82; N, 8.69. HRMS (ESI) m/z calcd for $C_{28}H_{29}ClN_3O_2$ $[M + H]^+$: 474.1943; found: 474.1942.

*N-Butyl-2-(5-chloro-2-phenyl-1H-benzimidazol-1-yl)-2-(4-methoxyphenyl)acetamide (**8l**).* White solid (yield 0.34 g, 76%); mp: 207−209 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.77 (s, 1H), 7.61 (d, J = 7.8 Hz, 2H), 7.53−7.50 (m, 3H), 7.13−7.04 (m, 4H), 6.85 (d, J = 8.4 Hz, 2H), 6.20 (s, 1H), 5.86 (s, 1H), 3.79 (s, 3H), 3.39−3.25 (m, 2H), 1.47−1.43 (m, 2H), 1.27−1.24 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 167.0, 159.7, 155.8, 144.1, 132.8, 130.4, 129.4, 128.9, 128.3, 125.9, 123.5, 119.8, 114.4, 113.5, 63.3, 55.3, 39.7, 31.3, 19.9, 13.6; MS (EI, 70 eV) m/z (%) 447 (M^+, 14), 347 (100), 220 (34), 192 (45). Anal. Calcd for $C_{26}H_{26}ClN_3O_2$: C, 69.71; H, 5.85; N, 9.38. Found: C, 69.90; H, 5.87; N, 9.30. HRMS (ESI) m/z calcd for $C_{26}H_{27}ClN_3O_2$ $[M + H]^+$: 448.1786; found: 448.1785.

*2-(4-Chlorophenyl)-N-cyclohexyl-2-(2-(3-iodophenyl)-5-methyl-1H-benzimidazol-1-yl)acetamide (**8m**).* White solid (yield 0.41 g, 70%); mp: 189−191 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.03 (s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.60 (s, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.30−6.93 (m, 7H), 6.16 (s, 1H), 5.69 (d, J = 8.4 Hz, 1H), 3.92−3.87 (m, 1H), 2.46 (s, 3H), 1.91−0.83 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 165.3, 152.6, 143.4, 139.0, 138.1, 134.5, 133.0, 132.7, 131.9, 131.5, 130.3, 129.0, 128.2, 125.2, 120.1, 111.9, 94.6, 62.9, 49.0, 32.6, 25.1, 24.6, 21.4; MS (EI, 70 eV) m/z (%) 583 (M^+, 36), 457 (100), 330 (65). Anal. Calcd for $C_{28}H_{27}ClIN_3O$: C, 57.60; H, 4.66; N, 7.20. Found: C, 57.46; H, 4.78; N, 7.37. HRMS (ESI) m/z calcd for $C_{28}H_{28}ClIN_3O$ $[M + H]^+$: 584.0960; found: 584.0961.

*2-(4-Bromophenyl)-N-(tert-butyl)-2-(5-methoxy-2-(4-(trifluoromethyl)phenyl)-1H-benzimidazol-1-yl)acetamide (**8n**).* White solid (yield 0.41 g, 73%); mp: 252−253 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.79−7.75 (m, 4H), 7.49 (d, J = 8.4 Hz, 1H), 7.37 (s, 1H), 7.32−6.86 (m, 5H), 6.05 (s, 1H), 5.52 (s, 1H), 3.87 (s, 3H), 1.30 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 165.2, 156.8, 153.1, 144.2, 136.4, 133.2, 132.2, 132.0, 130.7, 130.5, 129.7, 128.4, 126.2, 126.0, 123.1, 114.2, 112.9, 102.4, 63.5, 55.7, 52.5, 28.5; MS (EI, 70 eV) m/z (%) 561 (M^+, 25), 461 (100), 203 (31). Anal. Calcd for $C_{27}H_{25}BrF_3N_3O_2$: C, 57.87; H, 4.50; N, 7.50. Found: C, 57.60; H, 4.73; N, 7.25. HRMS (ESI) m/z calcd for $C_{27}H_{26}BrF_3N_3O_2$ $[M + H]^+$: 560.1155; found: 560.1159.

*N-(tert-Butyl)-2-(6-chloro-2-phenyl-1H-benzimidazol-1-yl)-2-phenylacetamide (**8o**).* White solid (yield 0.33 g, 79%); mp: 180−181 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.70−7.20 (m, 13H), 6.09 (s, 1H), 5.67 (s, 1H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 165.7, 155.4, 141.7, 135.1, 134.2, 130.3, 129.4, 129.2, 128.9, 128.8, 128.6, 127.4, 123.4, 120.8, 112.6, 64.3, 52.3, 28.4; MS (EI, 70 eV) m/z (%) 417 (M^+, 11), 317 (100), 239 (21), 152 (8). Anal. Calcd for $C_{25}H_{24}ClN_3O$: C, 71.85; H, 5.79; N, 10.05. Found: C, 71.64; H, 5.54; N, 10.00. HRMS (ESI) m/z calcd for $C_{25}H_{24}ClN_3NaO$ $[M + Na]^+$: 440.1500; found: 440.1503.

*N-(tert-Butyl)-2-(5-methyl-2-(p-tolyl)-1H-benzimidazol-1-yl)-2-phenylacetamide (**8p**).* White solid (yield 0.32 g, 78%); mp: 198−200 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.59 (s, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.31−7.19 (m, 7H), 6.98−6.94 (m, 2H), 6.16 (s, 1H), 5.62 (s, 1H), 2.44 (s, 3H), 2.42 (s, 3H), 1.30 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 166.2, 154.8, 143.7, 140.3, 134.7, 132.4, 132.0, 129.6, 129.3, 128.8, 128.4, 127.6, 126.9, 124.5, 119.9, 112.0, 64.1, 52.1, 28.5, 21.4; MS (EI, 70 eV) m/z (%) 411 (M^+, 3), 311 (100). Anal. Calcd for $C_{27}H_{29}N_3O$: C, 78.80; H, 7.10; N, 10.21. Found: C, 78.84; H, 7.32; N, 10.34. HRMS (ESI) m/z calcd for $C_{27}H_{29}N_3NaO$ $[M + Na]^+$: 434.2203; found: 434.2201.

*N-(tert-Butyl)-2-(2-(4-methoxyphenyl)-5-methyl-1H-benzimidazol-1-yl)-2-phenylacetamide (**8q**).* White solid (yield 0.32 g, 75%); mp: 197−199 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.58−6.96 (m, 12H), 6.17 (s, 1H), 5.67 (s, 1H), 3.85 (s, 3H), 2.44 (s, 3H), 1.30

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(s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 166.2, 160.9, 154.7, 143.6, 134.7, 132.4, 132.0, 130.8, 128.8, 128.4, 127.6, 124.4, 122.0, 119.8, 114.3, 111.9, 64.1, 55.3, 52.1, 28.5, 21.4; MS (EI, 70 eV) m/z (%) 427 (M^+, 16), 327 (100). Anal. Calcd for $C_{27}H_{29}N_3O_2$: C, 75.85; H, 6.84; N, 9.83. Found: C, 75.96; H, 6.90; N, 9.65. HRMS (ESI) m/z calcd for $C_{27}H_{29}N_3NaO_2$ $[M + Na]^+$: 450.2152; found: 450.2146.

*N-(tert-Butyl)-2-(2-methyl-1H-benzimidazol-1-yl)pentanamide (**8r**).* White solid (yield 0.23 g, 80%); mp: 154−156 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.73 (d, J = 7.8 Hz, 1H), 7.31−7.24 (m, 3H), 5.27 (s, 1H), 4.80−4.77 (m, 1H), 2.62 (s, 3H), 2.44−2.11 (m, 2H), 1.44−1.22 (m, 11H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.7, 152.0, 142.9, 133.2, 122.5, 119.5, 110.8, 59.5, 51.7, 31.5, 28.4, 19.7, 14.7, 13.6; MS (EI, 70 eV) m/z (%) 287 (M^+, 22), 187 (100), 159 (50). Anal. Calcd for $C_{17}H_{25}N_3O$: C, 71.04; H, 8.77; N, 14.62. Found: C, 71.22; H, 8.70; N, 14.60. HRMS (ESI) m/z calcd for $C_{17}H_{26}N_3O$ $[M + H]^+$: 288.2070; found: 288.2075.

*N-(tert-Butyl)-2-(2-(o-tolyl)-1H-benzimidazol-1-yl)butanamide (**8s**).* White solid (yield 0.27 g, 77%); mp: 132−134 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.87 (d, J = 7.8 Hz, 1H), 7.51−7.27 (m, 7H), 5.50 (s, 1H), 4.49−4.47 (m, 1H), 2.38−2.18 (m, 5H), 1.27 (s, 9H), 0.58 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.7, 154.3, 143.2, 132.1, 130.7, 130.1, 129.1, 125.7, 123.0, 122.8, 120.2, 112.1, 62.1, 51.6, 28.4, 22.8, 19.7, 10.8; MS (EI, 70 eV) m/z (%) 349 (M^+, 10), 249 (100), 119 (35). Anal. Calcd for $C_{22}H_{27}N_3O$: C, 75.61; H, 7.79; N, 12.02; Found: C, 75.82; H, 7.60; N, 12.10. HRMS (ESI) m/z calcd for $C_{22}H_{27}N_3NaO$ $[M + Na]^+$: 372.2046; found: 372.2045.

*N-(tert-Butyl)-2-(2-ethyl-1H-benzoimidazol-1-yl)-2-phenylacetamide (**8t**).* White solid (yield 0.24 g, 72%); mp: 157−159 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.73 (d, J = 7.8 Hz, 1H), 7.34−6.96 (m, 8H), 6.11 (s, 1H), 5.91 (br, 1H), 2.84 (q, J = 7.8 Hz, 2H), 1.42−1.31 (m, 12H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 166.1, 156.6, 142.4, 134.4, 134.1, 128.8, 128.5, 127.5, 122.3, 122.0, 119.1, 111.3, 62.6, 52.0, 28.3, 21.3, 11.6; HRMS (ESI) m/z calcd for $C_{21}H_{25}N_3NaO$ $[M + Na]^+$: 358.1890; found: 358.1892.

*N-(tert-Butyl)-2-(2-(furan-2-yl)-1H-benzoimidazol-1-yl)-2-(4-methoxyphenyl)acetamide (**8u**).* White solid (yield 0.30 g, 74%); mp: 161−163 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.80 (d, J = 8.4 Hz, 1H), 7.62−6.67 (m, 10H), 6.60 (s, 1H), 5.66 (s, 1H), 3.78 (s, 3H), 1.31 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 166.5, 159.5, 144.7, 144.6, 144.2, 143.2, 134.0, 129.2, 126.4, 123.3, 123.0, 120.0, 114.1, 113.6, 112.6, 112.0, 63.5, 55.2, 52.1, 28.4; HRMS (ESI) m/z calcd for $C_{24}H_{25}N_3NaO_3$ $[M + Na]^+$: 426.1788; found: 426.1784.

*N-(tert-Butyl)-2-(2-(thiophen-2-yl)-1H-benzoimidazol-1-yl)-2-(o-tolyl)acetamide (**8v**).* White solid (yield 0.31 g, 77%); mp: 221−223 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.80 (d, J = 7.8 Hz, 1H), 7.55−6.99 (m, 10H), 6.37 (s, 1H), 5.73 (s, 1H), 1.87 (s, 3H), 1.35(s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 166.4, 148.6, 143.0, 137.0, 134.4, 132.7, 131.2, 129.2, 129.0, 128.4, 127.8, 127.4, 126.4, 123.2, 122.8, 120.0, 111.8, 63.3, 52.1, 28.3, 18.9; HRMS (ESI) m/z calcd for $C_{24}H_{25}N_3NaOS$ $[M + Na]^+$: 426.1611; found: 426.1630.

Isolation of Some Ugi Intermediates 6a and 6p. A mixture of 2-aminobenzoyl azide **2** (1 mmol), aldehyde **3** (1 mmol), acid **4** (1 mmol), and isocyanide **5** (1 mmol) was stirred in methanol (5 mL) at room temperature for 24−48 h, and then the solvent was evaporated under reduced pressure at room temperature. The residue was purified by flash chromatography on silica gel (ether/petroleum ether = 1:4, V/V) to give **6**.

*2-(N-(1-(3-Bromophenyl)-2-(tert-butylamino)-2-oxoethyl)-4-(trifluoromethyl)benzamido)-5-methylbenzoyl Azide (**6a**).* White solid (yield 0.52 g, 84%); mp: 103−105 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.87−6.67 (m, 11H), 6.45−6.32 (m, 1H), 6.23−6.06 (m, 1H), 2.26−2.15 (m, 3H), 1.37−0.87 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.3, 169.4, 168.6, 139.8, 138.4, 137.2, 135.7, 134.5, 134.0, 133.9, 131.5, 131.1, 131.0, 130.8, 129.4, 129.2, 128.7, 128.6, 128.3, 124.5, 122.0, 65.1, 51.7, 29.0, 28.0, 20.7; IR (KBr): 2140, 1690, 1640 cm^{-1}. Anal. Calcd for $C_{28}H_{25}BrF_3N_5O_3$: C, 54.56; H, 4.09; N, 11.36. Found: C, 54.50; H, 4.00; N, 11.58.

*2-(N-(2-(tert-Butylamino)-2-oxo-1-phenylethyl)-4-methylbenzamido)-5-methylbenzoyl Azide (**6p**).* White solid (yield 0.39 g, 81%); mp: 115−117 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.84−7.41 (m, 2H), 7.30−6.66 (m, 10H), 6.37−6.04 (m, 2H), 2.24−2.12 (m, 6H), 1.38−1.22 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.2, 170.7, 169.2, 139.4, 138.3, 137.3, 134.1, 133.9, 133.2, 130.7, 130.6, 129.1, 128.8, 128.3, 128.2, 128.1, 127.9, 66.2, 51.6, 28.6, 21.3, 20.8; IR (KBr): 2138, 1691, 1632 cm^{-1}. Anal. Calcd for $C_{28}H_{29}N_5O_3$: C, 69.55; H, 6.04; N, 14.48. Found: C, 69.60; H, 6.00; N, 14.24.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02575.

^{1}H and ^{13}C NMR spectra of compounds **6a**, **6p**, and **8a−v** (PDF)

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Notes

The authors declare no competing financial interest.

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