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Synthesis and Reactivity of *N*-Alkyl Carbamoylimidazoles: Development of *N*-Methyl Carbamoylimidazole as a Methyl Isocyanate Equivalent

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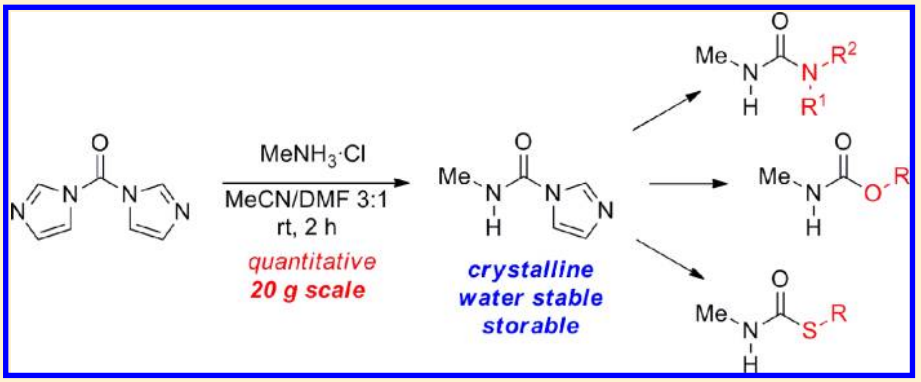
Supporting Information



ABSTRACT: A high-yielding synthesis of *N*-methyl carbamoylimidazole from 1,1-carbonyldiimidazole (CDI) and $MeNH_3Cl$ is described. The product is a crystalline, readily storable, water-stable compound that reacts as a methyl isocyanate (MIC) substitute. Reaction of *N*-methyl carbamoylimidazole in the presence of a base such as triethylamine occurs with nucleophiles such as amines, protected and unprotected amino acids, thiols and alcohols. The product *N*-methylureas, carbamates and thiocarbamates are obtained in good to excellent yields, with reactions occurring in either organic solvents or water. The protocol for the synthesis of *N*-methyl carbamoylimidazole is both scalable and general, occurring in quantitative yield at scales ranging from 300 mg to 20 g. The success of this method relies upon the reaction of CDI with the ammonium salt rather than the free amine, resulting in a significant improvement in the yield of *N*-methyl carbamoylimidazole. The reaction presumably involves a proton transfer from $MeNH_3Cl$ to the CDI, which results in the release of $MeNH_2$ with simultaneous activation of the CDI as its protonated form. Other primary ammonium hydrochloride salts, including protected α-amino acid salts, give excellent yields of the corresponding *N*-alkyl carbamoylimidazoles and serve as alkyl isocyanate surrogates. The resultant *N*-alkyl carbamoylimidazoles can be converted to ureas in high yields without the formation of intermediary isocyanates.

INTRODUCTION

Methyl isocyanate (**1**, MIC) is an important small molecule building block for the synthesis of a variety of *N*-methyl carbamoyl species such as ureas, carbamates and thiocarbamates. These functionalities can be found in a number of bioactive natural products and medicinally relevant targets, as well as pesticides and herbicides. However, the toxicity of MIC,[1,2] coupled with its handling difficulties, the requirement for its use in excess for many reactions and shipping restrictions, make its use undesirable. More generally alkyl and aryl isocyanates can also be used in an analogous fashion to MIC.[3]

In conjunction with our efforts toward the total synthesis of agelastatin A, a safe and readily accessible substitute for MIC was desired for the formation of a urea functionality.[4] A literature search, however, yielded few examples of such reagents (Figure 1). *N*,*S*-Dimethyl thiocarbamate (**2**) reacts as a MIC substitute,[5] although the requirement of an excess of amine for *N*-methylurea formation and the concomitant release of methanethiol are significant drawbacks. *N*-(Methylcarbamoyloxy)succinimide (**3**) has successfully been used for *N*-methylurea incorporation into complex molecules.[6] Problems associated with **3** include a low yield for its synthesis,[7] and reaction yields for its use typically ranging from 40% to 70% in most cases.[6,8]

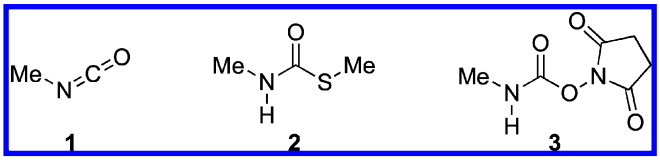


Figure 1. Methyl isocyanate and chemical substitutes.

Previous efforts in our lab toward the synthesis of ureas via carbamoylimidazolium salts[9] led us to explore the potential of a

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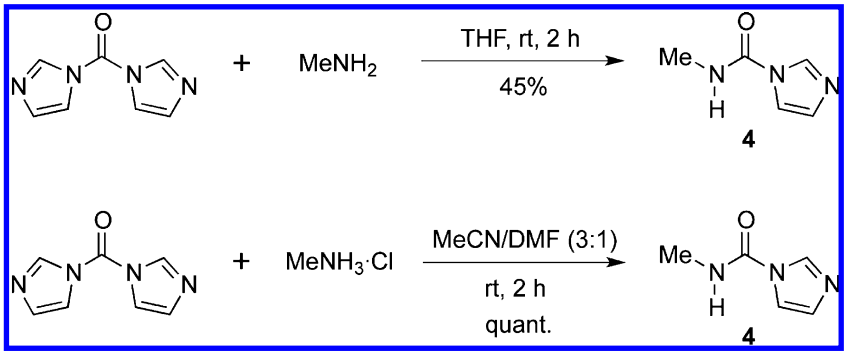
Scheme 1. Synthesis of *N*-Methyl Carbamoylimidazole (4) from Methylamine and Methylammonium Chloride



methylamine adduct of 1,1-carbonyldiimidazole (CDI)[10] as a suitable MIC substitute. Secondary amines have long been known to react with CDI to give stable carbamoylimidazoles in high yields.[11] Conversely the reaction of CDI with primary alkyl amines is prone to symmetrical urea formation, likely resulting from the dissociation of the adduct to imidazole and the corresponding isocyanate.[11,12] Although near quantitative yields of the monoaddition products can be obtained, these stem exclusively from the use of branched amines,[13] with the associated steric bulk likely slowing symmetrical urea formation. Linear primary amines, which lack this steric bulk, lead to products in lower yields, ranging from 55% to 85% in most cases.[14] Although these reports do not mention the fate of the remaining material, symmetrical urea formation is likely.

RESULTS AND DISCUSSION

As *N*-methyl carbamoylimidazole (**4**) would be expected to dissociate in solution, it was hoped that the compound could be formed and dissociated *in situ* as a source of MIC for the synthesis of *N*-methylureas. To explore this possibility, CDI and $MeNH_2$ were dissolved in $CDCl_3$, and the reaction was monitored by ^1H NMR. Although both **4** and 1,3-dimethylurea were evident, no trace of MIC could be observed. It was also discovered that no mass loss occurred on concentration, contrary to what would be expected if **4** dissociated to the volatile MIC. Furthermore, it was determined that **4** could be isolated through silica gel flash chromatography in 45% yield as a white, crystalline solid, giving additional evidence of the stability of the compound (Scheme 1; see Supporting Information for X-ray crystal structure).

For **4** to be useful as a MIC substitute, however, a more efficient synthesis was required. While the equimolar quantity of 1,3-dimethylurea observed in its synthesis indicates that **4** would be reactive enough for *N*-methylurea formation, it also results in poor isolated yields of the reagent (Scheme 1). To this end, the synthesis of **4** was attempted with $MeNH_3Cl$ in the absence of base. Although $MeNH_3Cl$ itself is not nucleophilic, CDI could act as a base, providing both a small concentration of $MeNH_2$ and leading to CDI activation through protonation. While the activation of carbonylimidazoles through protonation is known,[15] the direct reaction of ammonium salts with CDI in the absence of an exogenous base has not been previously reported. Gratifyingly this method proved effective, affording **4** in quantitative isolated yield at scales ranging from 300 mg to 20 g (Scheme 1). This is the highest yielding synthesis of an *N*-alkyl carbamoylimidazole from CDI reported to date.

As expected, **4** proved very effective as a carbamoylating reagent when used with 1.0 equiv of Et_3N (Table 1). A variety of *N*-methylureas **5** were obtained in both excellent conversions and isolated yields from primary and secondary amines, as well as primary (Table 1, entries 9, 11 and 12) and secondary (entry 10) ammonium salts, using as little as 1.0 equiv of **4** in most cases. The reagent also displayed excellent chemoselectivity, reacting exclusively with amines in the presence of alcohols (Table 1, entry 8) and carboxylates (entry 12). More impressively, **4** also gave excellent conversions in water (Table 1, entry 12),[16] allowing for the carbamoylation of highly polar and otherwise insoluble reactants such as free amino acids.[17] This may prove useful for the incorporation of *N*-methyl and related *N*-alkyl groups into proteins and other large biomolecules.

The utility of **4** in water highlights the stability of the molecule. Although the use of isocyanates can lead to the formation of symmetrical ureas through the hydrolysis of the reagent, no trace of 1,3-dimethylurea is observed. In fact, only trace imidazole could be detected by ^1H NMR in a sample of **4** after 12 months of storage at room temperature with no effort made to exclude moisture. Even under reaction conditions that give poor conversions, the product *N*-methylurea is always equimolar to imidazole by ^1H NMR analysis, indicating an absence of hydrolysis of unreacted **4**. ^1H NMR analysis in D_2O confirmed that hydrolysis of **4** is slow, with only 6% conversion to imidazole observed after 18 h and 10% after 3 days. Furthermore, dissociation of **4** is not evident even after 5 days in $CDCl_3$ with 1.0 equiv of Et_3N.

There is a single report of **4** in the literature, synthesized by Williams and co-workers through the addition of imidazole to MIC.[18] A reported melting point of 113−115 °C confirmed that adduct formation is more thermodynamically favored than dissociation, which is supported by our stability studies. Dissociation of carbamoylimidazoles is believed to occur through a zwitterionic intermediate.[19] Unlike *N*-aryl carbamoylimidazoles, however, the opportunity for resonance stabilization does not exist with the zwitterion of **4**.[14e] In combination with the high reactivity between MIC and imidazole reported by Williams, this is the likely cause for its lack of detectable dissociation and hydrolysis under the reaction conditions for *N*-methylurea formation. While the hydrolysis of the molecule was studied and determined to occur through an *E*1cB mechanism,[18] no attempt was made at using **4** for *N*-methylurea syntheses. Moreover, no subsequent report has examined the utility of **4** as a methyl isocyanate substitute. This is not surprising, however, as prior to this work MIC was required for a high-yielding synthesis of **4**, making its use as a MIC substitute redundant.

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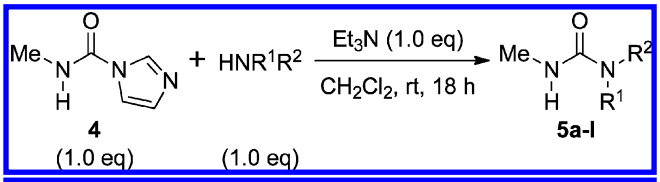
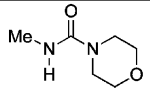
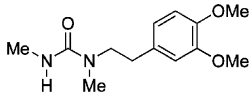
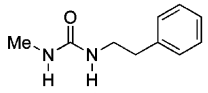
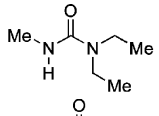
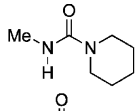
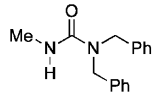
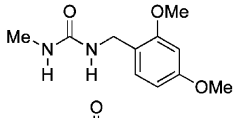
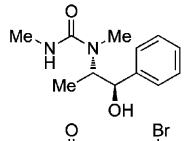
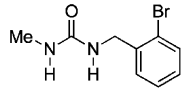
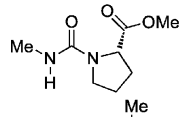
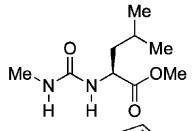
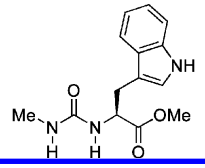
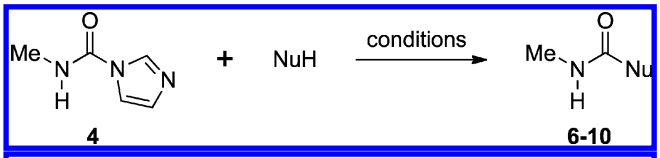
Table 1. Synthesis of *N*-Methyl Ureas 5a–l from 4[a]

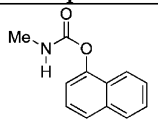
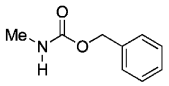
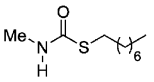
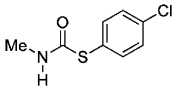
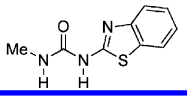


entry	product		yield (%)
1		**5a**	quant.
2		**5b**	88
3		**5c**	quant.
4		**5d**	89
5		**5e**	91
6		**5f**	97
7		**5g**	quant.
8		**5h**	92
9[b]		**5i**	99
10[b]		**5j**	81
11[bc]		**5k**	97
12[cd]		**5l**	89

[a]Et_3N (0.20 mmol) added to a solution of **4** (0.20 mmol) and amine (0.20 mmol) in CH_2Cl_2 (1.0 mL). [b]HCl salt of amines and 2.0 equiv of Et_3N used. [c]2.0 equiv of **4** used. [d]Reaction conducted in H_2O.

Table 2. Synthesis of *N*-Methyl Carbamoyl Derivatives 6–10



entry	product		conditions[a]	yield (%)
1		**6**	A	65
2		**6**	B	26
3		**6**	C	65
4		**7**	B	82
5		**8**	A	quant.
6		**9**	D	76
7		**10**	B	94

[a]Conditions. Method A: Et_3N (0.40 mmol) added to a solution of the nucleophile (0.20 mmol) and **4** (0.40 mmol) in CH_2Cl_2 (1.0 mL); mixture stirred at room temperature for 18 h. Method B: NaH (0.22 mmol) added to a solution of the nucleophile (0.20 mmol) and **4** (0.20 mmol) in DMF (1.0 mL); mixture stirred at room temperature for 18 h. Method C: Et_3N (0.40 mmol) added to a solution of the nucleophile (0.20 mmol) and **4** (0.40 mmol) in CH_2Cl_2 (1.0 mL); mixture heated under microwave irradiation at 120 °C for 10 min. Method D: Et_3N (0.40 mmol) added to a solution of the nucleophile (0.20 mmol) and **4** (0.40 mmol) in THF (1.0 mL); mixture stirred at 65 °C for 18 h.

There is also considerable interest in the synthesis of *N*-methyl carbamates as a variety of pesticides contain this moiety. Most prominent among these is carbaryl (Sevin) (**6**), the production of which led to the Bhopal disaster. Although MIC has largely been replaced by phosgene for the synthesis of *O*-aryl *N*-methylcarbamate pesticides,[20] this can hardly be considered an improvement from a safety standpoint. With innocuous imidazole as its only byproduct, **4** could be a safer alternative for the synthesis of this class of molecules. Treatment of 1-naphthol with **4** and Et_3N led to the formation of **6** (Table 2), although 2.0 equiv of the reagent was required to obtain adequate yields (entry 1). Altering the base (entry 2) or using more forcing conditions (entry 3) failed to increase the yield. Addition of imidazole to **6**, however, resulted in the formation of 1-naphthol and carbamoylimidazole **4**, confirming that these depressed yields result from an equilibrium between **6** and 1-naphthol under the reaction conditions. Methods to sequester imidazole during the reaction are currently being investigated.

The scope of the reactivity of **4** has also been extended to a variety of other nucleophile classes to give biologically relevant molecules in good to excellent yields (Table 2). Among these are anticonvulsant carbamate **7**,[21] thiocarbamates **8** and **9** investigated for their nematicidal[22] and antimycotic[23] activities, respectively, and benzthiazuron (**10**), a potent broad leaf and grass herbicide[24] derived from 2-aminobenzthiazole. The lack of reactivity of **4** with alcohols had previously been displayed in the reaction of ephedrine (Table 1, entry 8). However, the use of a stronger base such as sodium hydride provides a method for the formation of carbamates (Table 2, entry 4).

With the synthesis and reactivity of **4** established, the chemistry was extended to additional systems (Scheme 2). The reaction of other ammonium hydrochloride salts with CDI proved as effective as $MeNH_3Cl$, with excellent yields of *N*-alkyl

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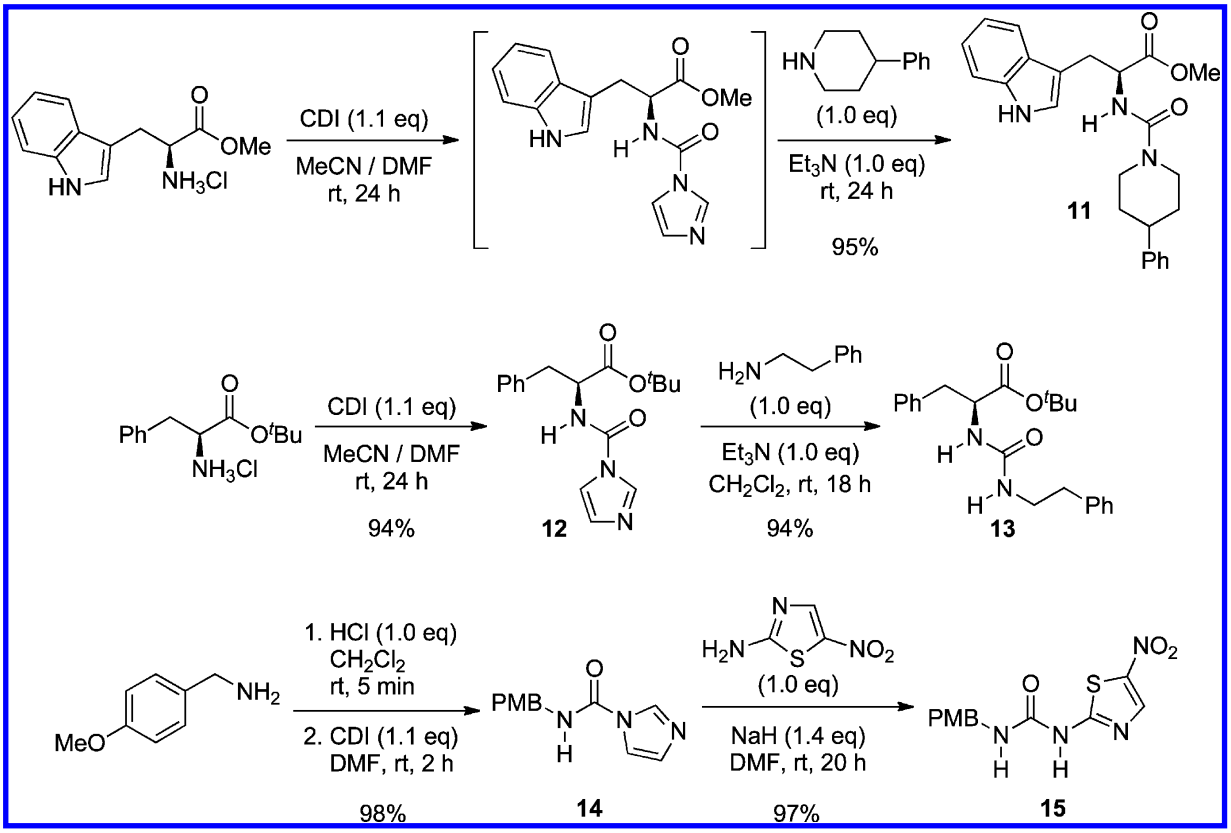
Scheme 2. Synthesis and Utility of Other Primary *N*-Alkyl Carbamoylimidazoles via Ammonium Salts



carbamoylimidazoles obtained whether starting from the salt or protonating *in situ*. Subsequent urea formation was also high-yielding and accessible in a one-pot protocol for derivatives where the carbamoylimidazole could not be isolated cleanly. Biologically relevant compounds were readily synthesized through this method, including somatostatin agonist **11**[25] and AR-A014418 (**15**), a GSK-3β inhibitor investigated for the treatment of Alzheimer's disease[26] and depression.[27] The very high-yielding two-step synthesis of **15** is noteworthy as the reported yield for this compound from PMB isocyanate is 22%.[26]

CONCLUSION

In summary, an easily handled, water-stable, crystalline MIC substitute has been shown to be an excellent reagent for the synthesis of *N*-methylureas, carbamates and thiocarbamates. This constitutes a significant practical advance given the significance of these functional groups in biologically relevant targets and the toxicity of MIC. Moreover, in most cases only 1 equiv of the reagent is required while avoiding the drawbacks associated with other reported MIC substitutes. Although the reaction of primary, linear amines with CDI generally gives carbamoylimidazoles in low yields due to competing symmetrical urea formation, *N*-methyl carbamoylimidazole (**4**) was isolated in quantitative yield from the reaction of CDI with $MeNH_3Cl$. This is the first reported synthesis of a carbamoylimidazole from an ammonium salt in the absence of base, and it is also the highest-yielding synthesis of a carbamoylimidazole from a primary, linear amine reported to date. The approach was shown to be general, with direct reaction of ammonium hydrochloride salts with CDI occurring in the absence of exogenous base to give linear *N*-alkyl carbamoylimidazoles in high yield, without competing symmetrical urea formation.

EXPERIMENTAL SECTION

General Procedure. Unless carried out in water, all reactions were performed under nitrogen in flame-dried glassware.[28] Tetrahydrofuran was freshly distilled from sodium/benzophenone ketyl under nitrogen. Dichloromethane and acetonitrile were freshly distilled from calcium hydride under nitrogen. Dimethylformamide was obtained as ≥99.9% pure and stored under argon. All other solvents were obtained as ACS grade or better from commercial suppliers and used as received. All reagents were used as received from commercial suppliers. Purity of CDI was determined to be 90% by ^{1}H NMR analysis in $CDCl_3$ and used as such. Flash chromatography on silica gel (60 Å, 230−400 mesh) was performed with reagent grade solvents. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel plates, visualized with a UV_{254} lamp, and stained with ninhydrin. Solvent ratios for chromatography and R_f values are reported as v/v ratios. Melting points are uncorrected and obtained on compounds purified through flash chromatography without any further recrystallization. ^{1}H and ^{13}C NMR spectra were obtained as solutions in deuterated solvents. Chemical shifts are reported in δ ppm values. Proton chemical shifts were internally referenced to tetramethylsilane (δ 0.00 ppm) or to the residual proton resonance in CD_3OD (δ 3.31 ppm) or DMSO-d_6 (δ 2.50 ppm). Carbon chemical shifts were internally referenced to the solvent resonances in $CDCl_3$ (δ 77.00 ppm), CD_3OD (δ 49.15 ppm), or DMSO-d_6 (δ 39.51 ppm). Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; *J*, coupling constant in Hz.

***N*-Methyl Carbamoylimidazole[18] (4).** CDI (20.0 g, 111 mmol, 1.10 equiv) and $MeNH_3Cl$ (6.82 g, 101 mmol, 1.0 equiv) were dissolved in DMF (20 mL) and acetonitrile (60 mL). The solution was stirred at room temperature for 2 h before being concentrated under an air stream to a thick oil. Flash chromatography (4% MeOH/

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CH_2Cl_2) gave **4** as a white solid (12.6 g, quantitative yield). R_f = 0.24 (4% MeOH/CH_2Cl_2); mp = 109−111 °C (lit.[18] 113−115 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.35 (t, J = 1.5 Hz, 1H), 7.09 (br s, 1H), 6.82 (br s, 1H), 3.02 (d, J = 4.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 135.7, 130.0, 116.3, 27.4; IR (solid) ν_{max} 3201, 3147, 3112, 3036, 1713, 1552, 1481, 1422, 1364, 1330, 1291, 1252, 1192, 1069, 1046, 910, 837, 807 720 cm^{-1}; MS (ESI) m/z (rel intensity) 148 (8), 126 (14), 69 (100); HRMS (ESI) m/z calcd for $C_5H_8N_3O$ (MH^+) 126.0661, found 126.0656.

General Procedure for the Synthesis of *N*-Methyl Ureas 5a−l. To a solution of carbamoylimidazole **4** (25.0 mg, 0.200 mmol, 1.0 equiv) and amine (0.200 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) was added Et_3N (0.03 mL, 0.215 mmol, 1.1 equiv). The solution was stirred for 18 h and concentrated under reduced pressure. Flash chromatography yielded *N*-methylureas **5a−l**.

***N*-Methylmorpholine-4-carboxamide[29] (5a).** 28.8 mg, quantitative yield; white solid; R_f = 0.24 (8% MeOH/CH_2Cl_2); mp = 81−83 °C (lit.[29] 85−87 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (br s, 1H), 3.68−3.66 (m, 4H), 3.37−3.34 (m, 4H), 2.79 (d, J = 4.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 66.4, 43.8, 27.4.

1-(3,4-Dimethoxyphenethyl)-1,3-dimethylurea (5b). 44.4 mg, 88% yield; colorless oil; R_f = 0.36 (8% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81−6.79 (m, 1H), 6.76−6.73 (m, 2H), 4.22 (br q, J = 4.5 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.47 (t, J = 7.5 Hz, 2H), 2.81 (s, 3H), 2.77 (t, J = 7.5 Hz, 2H), 2.76 (d, J = 4.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 148.9, 147.5, 131.9, 120.7, 112.0, 111.3, 55.87, 55.86, 51.1, 34.7, 34.2, 27.6; IR (thin film in CH_2Cl_2) ν_{max} 3416, 3350, 2997, 2937, 2835, 1635, 1514, 1464, 1416, 1379, 1262, 1235, 1155, 1029, 807, 765 cm^{-1}; MS (DART) m/z (rel intensity) 254 (13), 253 (100); HRMS (DART) m/z calcd for $C_{13}H_{21}N_2O_3$ (MH^+) 253.1552, found 253.1548.

1-Methyl-3-phenethylurea[30] (5c). 35.6 mg, quantitative yield; white solid; R_f = 0.21 (6% MeOH/CH_2Cl_2); mp = 75−77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.26 (m, 2H), 7.23−7.17 (m, 3H), 4.69 (br t, J = 7.0 Hz, 1H), 4.64 (br s, 1H), 3.41 (td, J = 7.0, 7.0 Hz, 2H), 2.79 (t, J = 7.0 Hz, 2H), 2.70 (d, J = 5.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 139.2, 128.8, 128.5, 126.3, 41.6, 36.4, 27.0.

1,1-Diethyl-3-methylurea[31] (5d). 23.2 mg, 89% yield; colorless oil; R_f = 0.26 (6% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (br s, 1H), 3.25 (q, J = 7.0 Hz, 4H), 2.81 (d, J = 4.5 Hz, 3H), 1.13 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 41.2, 27.5, 13.8.

***N*-Methylpiperidine-1-carboxamide[32] (5e).** 25.9 mg, 91% yield; white solid; R_f = 0.52 (7% MeOH/CH_2Cl_2); mp = 68−70 °C (lit.[32] 72−74 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (br s, 1H), 3.33−3.30 (m, 4H), 2.80 (d, J = 4.5 Hz, 3H), 1.62−1.51 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 44.8, 27.6, 25.6, 24.4.

1,1-Dibenzyl-3-methylurea (5f). 49.3 mg, 97% yield; white solid; R_f = 0.36 (4% MeOH/CH_2Cl_2); mp = 75−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.31 (m, 4H), 7.29−7.23 (m, 6H), 4.48 (s, 4H), 4.36 (br q, J = 4.5 Hz, 1H), 2.78 (d, J = 4.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 137.6, 128.7, 127.4, 127.1, 50.2, 27.8; IR (solid) ν_{max} 3505, 3355, 3028, 2918, 1602, 1550, 1493, 1395, 1266, 1156, 971, 949, 736, 692 cm^{-1}; MS (DART) m/z (rel intensity) 256 (17), 255 (100); HRMS (DART) m/z calcd for $C_{16}H_{19}N_2O$ (MH^+) 255.1497, found 255.1496.

1-(2,4-Dimethoxybenzyl)-3-methylurea (5g). 44.8 mg, quantitative yield; white solid; R_f = 0.30 (5% MeOH/CH_2Cl_2); mp = 145−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8.5 Hz, 1H), 6.43−6.40 (m, 2H), 5.01 (br t, J = 5.5 Hz, 1H), 4.66 (br q, J = 4.5 Hz, 1H), 4.24 (d, J = 5.5 Hz, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 2.72 (d, J = 4.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 159.0, 158.3, 130.0, 119.8, 103.9, 98.5, 55.34, 55.26, 39.7, 27.1; IR (solid) ν_{max} 3325, 2940, 1742, 1616, 1580, 1509, 1206, 1155, 1131, 1034, 830 cm^{-1}; MS (ESI) m/z (rel intensity) 247 (13), 225 (5), 152 (9), 151 (100); HRMS (ESI) m/z calcd for $C_{11}H_{17}N_2O_3$ (MH^+) 225.1233, found 225.1227.

1-((1*R*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-1,3-dimethylurea[33] (5h). 40.9 mg, 92% yield; colorless oil; R_f = 0.28 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.23 (m, 5H), 4.87 (br s, 1H), 4.79 (dd, J = 3.0, 3.0 Hz, 1H), 4.59 (br s, 1H), 4.28 (qd, J = 7.0, 3.0 Hz, 1H), 2.79 (d, J = 4.5 Hz, 3H), 2.46 (s, 3H), 1.16 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 141.7, 128.0, 127.4, 126.5, 77.7, 58.5, 31.7, 27.6, 13.1.

1-(2-Bromobenzyl)-3-methylurea[34] (5i). Ammonium HCl salt used as starting material, with 2 equiv of Et_3N (0.06 mL, 0.430 mmol); 48.1 mg, 99% yield; white solid; R_f = 0.30 (5% MeOH/CH_2Cl_2); mp = 151−153 °C (lit.[34] 154−155 °C); ^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (dd, J = 8.0, 1.0 Hz, 1H), 7.37−7.29 (m, 2H), 7.15 (td, J = 8.0, 2.0 Hz, 1H), 4.85 (s, 2H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 161.8, 140.2, 133.8, 130.6, 129.9, 128.8, 124.1, 45.3, 27.2.

***N*-(*N*′-Methylurea)-L-proline Methyl Ester (5j).** Ammonium HCl salt used as starting material, with 2 equiv of Et_3N (0.06 mL, 0.430 mmol); 30.2 mg, 81% yield; colorless oil; R_f = 0.35 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (br s, 1H), 4.44 (dd, J = 8.0, 3.0 Hz, 1H), 3.74 (s, 3H), 3.49−3.44 (m, 1H), 3.37−3.31 (m, 1H), 2.81 (d, J = 5.0 Hz, 3H), 2.19−1.95 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 157.2, 58.9, 52.1, 45.7, 29.7, 27.3, 24.5; IR (thin film in CH_2Cl_2) ν_{max} 3336, 2953, 2879, 1729, 1652, 1558, 1436, 1372, 1198, 1095, 1015, 769 cm^{-1}; MS (ESI) m/z (rel intensity) 209 (63), 187 (81), 155 (16), 130 (100), 128 (49), 127 (22); HRMS (ESI) m/z calcd for $C_8H_{15}N_2O_3$ (MH^+) 187.1077, found 187.1084.

***N*-(*N*′-Methylurea)-L-leucine Methyl Ester (5k).** Ammonium HCl salt used as starting material, with 2 equiv each of **4** (50.0 mg, 0.400 mmol) and Et_3N (0.06 mL, 0.430 mmol); 39.2 mg, 97% yield; white solid; R_f = 0.29 (8% MeOH/CH_2Cl_2); mp = 85−87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (br d, J = 8.5 Hz, 1H), 5.05 (br q, J = 4.5 Hz, 1H), 4.48 (ddd, J = 8.5, 5.5, 5.5 Hz, 1H), 3.73 (s, 3H), 2.76 (d, J = 4.5 Hz, 3H), 1.77−1.66 (m, 1H), 1.59 (ddd, J = 13.5, 8.5, 5.5 Hz, 1H), 1.48 (ddd, J = 13.5, 9.5, 5.5 Hz, 1H), 0.94 (d, J = 6.5 Hz, 3H), 0.93 (d, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 158.6, 52.1, 51.6, 41.8, 27.0, 24.8, 22.8, 21.8; IR (solid) ν_{max} 3324, 2957, 2873, 1742, 1630, 1583, 1435, 1341, 1273, 1227, 1193, 1141, 981 cm^{-1}; MS (ESI) m/z (rel intensity) 225 (10), 203 (16), 146 (100); HRMS (ESI) m/z calcd for $C_9H_{19}N_2O_3$ (MH^+) 203.1390, found 203.1391.

***N*-(*N*′-Methylurea)-L-tryptophan (5l).** Two equivalents each of **4** (50.0 mg, 0.400 mmol) and Et_3N (0.06 mL, 0.430 mmol) were used. The reaction was quenched with 0.5 M HCl in methanol prior to concentrating under an air stream; 46.5 mg, 89% yield; white solid; R_f = 0.60 (80% EtOAc/hexanes); mp = 182−184 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (dt, J = 8.0, 1.0 Hz, 1H), 7.31 (dt, J = 8.0, 1.0 Hz, 1H), 7.08 (s, 1H), 7.06 (td, J = 8.0, 1.0 Hz, 1H), 6.98 (td, J = 8.0, 1.0 Hz, 1H), 4.53 (dd, J = 6.5, 6.5 Hz, 1H), 3.29 (dd, J = 14.0, 6.5 Hz, 1H), 3.16 (dd, J = 14.0, 6.5 Hz, 1H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 178.6, 161.5, 138.1, 129.3, 124.5, 122.4, 119.8, 119.6, 112.3, 111.5, 56.2, 29.2, 27.0; IR (solid) ν_{max} 3396, 2922, 2852, 1708, 1558, 1457, 1416, 1339, 1230, 1093, 1010, 740 cm^{-1}; MS (ESI) m/z (rel intensity) 284 (100), 262 (69), 256 (78), 205 (48), 188 (68), 149 (73); HRMS (ESI) m/z calcd for $C_{13}H_{16}N_3O_3$ (MH^+) 262.1186, found 262.1181.

General Procedure for the Synthesis of *N*-methyl Carbamates, Thiocarbamates and Aryl Ureas 6−10. Procedure A. To a solution of carbamoylimidazole **4** (50.0 mg, 0.400 mmol, 2.0 equiv) and a nucleophile (0.200 mmol, 1.0 equiv) dissolved in CH_2Cl_2 (1.0 mL) was added Et_3N (55 μL, 0.395 mmol, 2.0 equiv). The solution was stirred at room temperature for 18 h and concentrated under reduced pressure. The products were isolated by flash chromatography.

Procedure B. To a solution of carbamoylimidazole **4** (25.0 mg, 0.200 mmol, 1.0 equiv) and a nucleophile (0.200 mmol, 1.0 equiv) dissolved in DMF (1.0 mL) was added 60% NaH in mineral oil (8.8 mg, 0.220 mmol, 1.1 equiv). The solution was stirred at room temperature for 18 h and concentrated under an air stream. The products were isolated by flash chromatography.

Procedure D. To a solution of carbamoylimidazole **4** (50.0 mg, 0.400 mmol, 2.0 equiv) and a nucleophile (0.200 mmol, 1.0 equiv) dissolved in THF (1.0 mL) was added Et_3N (55 μL, 0.395 mmol, 2.0 equiv). The solution was stirred at 65 °C for 18 h and concentrated

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under reduced pressure. The products were isolated by flash chromatography.

Carbaryl[31] (6). Prepared using Procedure A; 26.2 mg, 65% yield; off-white solid; R_f = 0.42 (25% EtOAc/toluene); mp = 137−139 °C (lit.[31] 140−142 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97−7.94 (m, 1H), 7.86−7.83 (m, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.52−7.48 (m, 2H), 7.45 (t, J = 8.0 Hz, 1H), 7.29 (d, 8.0 Hz, 1H), 5.18 (br s, 1H), 3.12 (d, J = 5.0 Hz, 0.3H), 2.92 (d, J = 5.0 Hz, 2.7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 146.8, 134.6, 127.9, 127.4, 126.3, 126.2, 125.5, 125.4, 121.3, 118.1, 27.9.

Benzyl Methylcarbamate[21] (7). Prepared using Procedure B; 27.1 mg, 82% yield; colorless oil; R_f = 0.62 (4% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.29 (m, 5H), 5.10 (s, 2H), 4.72 (br s, 1H), 2.80 (d, J = 5.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 136.6, 128.5, 128.1, 128.0, 66.6, 27.5.

***S*-Octyl Methylcarbamothioate[22] (8).** Prepared using Procedure A; 40.7 mg, quantitative yield; colorless oil; R_f = 0.46 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (br s, 1H), 2.90 (t, J = 7.5 Hz, 2H), 2.87 (d, J = 5.0 Hz, 3H), 1.61 (quintet, J = 7.5 Hz, 2H), 1.38−1.27 (m, 10H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 31.8, 30.4, 30.0, 29.13, 29.07, 28.7, 27.8, 22.6, 14.0.

***S*-(4-Chlorophenyl) methylcarbamothioate[23] (9).** Prepared using Procedure D; 30.7 mg, 76% yield; white solid; R_f = 0.30 (CH_2Cl_2); mp = 125−126 °C (lit.[23] 127−129 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dt, J = 8.5, 2.0 Hz, 2H), 7.38 (dt, J = 8.5, 2.0 Hz, 2H), 5.40 (br s, 1H), 2.87 (d, J = 4.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 136.6, 136.0, 129.5, 126.9, 28.2.

Benzthiazuron[24] (10). Prepared using Procedure B. Crude solid washed with CH_2Cl_2 to give **10**; 39.0 mg, 94% yield; white solid; mp = 263−265 °C (lit.[24] 265 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (br s, 1H), 7.85 (dd, J = 8.0, 1.0 Hz, 1H), 7.59 (br d, J = 8.0 Hz, 1H), 7.34 (td, J = 7.5, 1.0 Hz, 1H), 7.19 (td, J = 7.5, 1.0 Hz, 1H), 6.77 (br s, 1H), 2.73 (d, J = 4.5 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.2, 154.6, 149.1, 131.3, 125.7, 122.4, 121.2, 119.4, 26.3.

(*S*)-Methyl 3-(1*H*-Indol-3-yl)-2-(4-phenylpiperidine-1-carboxamido)propanoate[25] (11). CDI (48.9 mg, 0.271 mmol, 1.1 equiv) and L-tryptophan methyl ester HCl (62.0 mg, 0.243 mmol, 1.0 equiv) were dissolved in DMF (0.2 mL) and acetonitrile (1.0 mL). The solution was stirred at room temperature for 2 h before the addition of 4-phenylpiperidine (38.7 mg, 0.240 mmol, 1.0 equiv) and Et_3N (35.0 μL, 0.251 mmol, 1.0 equiv). The solution was stirred for 24 h and concentrated under an air stream. Flash chromatography with ethyl acetate gave **11** as a colorless oil (92.4 mg, 95% yield). R_f = 0.71 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (br s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.30 (t, J = 7.5 Hz, 2H), 7.23−7.14 (m, 4H), 7.10 (td, J = 7.5, 1.0 Hz, 1H), 6.98 (d, J = 2.5 Hz, 1H), 5.02 (br d, J = 7.5 Hz, 1H), 4.89 (ddd, J = 7.5, 5.5, 5.5 Hz, 1H), 4.02 (br d, J = 13.0 Hz, 1H), 3.91 (br d, J = 13.0 Hz, 1H), 3.70 (s, 3H), 3.36 (dd, J = 15.0, 5.5 Hz, 1H), 3.31 (dd, J = 15.0, 5.5 Hz, 1H), 2.82 (ddd, J = 13.0, 2.5, 2.5 Hz, 1H), 2.77 (ddd, J = 13.0, 2.5, 2.5 Hz, 1H), 2.61 (tt, J = 12.0, 3.5 Hz, 1H), 1.80−1.75 (m, 2H), 1.67−1.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 156.7, 145.4, 136.1, 128.5, 127.9, 126.7, 126.4, 122.6, 122.2, 119.6, 118.7, 111.3, 110.5, 54.5, 52.2, 44.6, 44.5, 42.7, 32.94, 32.87, 28.0.

(*S*)-*tert*-Butyl 2-(1*H*-Imidazole-1-carboxamido)-3-phenylpropanoate (12). CDI (53.7 mg, 0.298 mmol, 1.1 equiv) and L-phenylalanine *tert*-butyl ester HCl (70.1 mg, 0.272 mmol, 1.0 equiv) were dissolved in DMF (0.2 mL) and acetonitrile (1.0 mL). The solution was stirred at room temperature for 2 h and concentrated under an air stream. Flash chromatography with 5% MeOH/CH_2Cl_2 gave **12** as a colorless oil (80.9 mg, 94% yield). R_f = 0.52 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (t, J = 1.0 Hz, 1H), 7.33−7.25 (m, 4H), 7.16 (dd, J = 8.0, 1.5 Hz, 2H), 7.09 (dd, J = 1.5, 1.0 Hz, 1H), 6.20 (br d, J = 7.0 Hz, 1H), 4.79 (ddd, J = 7.0, 5.5, 5.5 Hz, 1H), 3.25 (dd, J = 14.0, 5.5 Hz, 1H), 3.21 (dd, J = 14.0, 5.5 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 148.0, 135.9, 135.2, 130.9, 129.4, 128.6, 127.4, 115.6, 83.5, 54.7, 37.8, 28.0; IR (thin film in CH_2Cl_2) ν_{max} 3214, 3030, 2978, 2934, 1724, 1545, 1481, 1370, 1229, 1153, 1101, 1071, 845, 741 cm^{-1}; MS (DART) m/z (rel intensity) 317 (18), 316 (100); HRMS (DART) m/z calcd for $C_{17}H_{22}N_3O_3$ (MH^+) 316.1661, found 316.1656.

(*S*)-*tert*-Butyl 2-(3-Phenethylureido)-3-phenylpropanoate (13). To a solution of **12** (32.5 mg, 0.103 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) were added phenethylamine (13.0 mL, 0.103 mmol, 1.0 equiv) and Et_3N (15.0 μL, 0.108 mmol, 1.0 equiv). The solution was stirred for 18 h and concentrated under reduced pressure. Flash chromatography with 5% MeOH/CH_2Cl_2 gave **13** as a colorless oil (35.6 mg, 94% yield). R_f = 0.55 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.19 (m, 6H), 7.17−7.14 (m, 4H), 4.91 (br d, J = 8.0 Hz, 1H), 4.65 (ddd, J = 8.0, 6.0, 6.0 Hz, 1H), 4.54 (br t, J = 6.0 Hz, 1H), 3.47−3.32 (m, 2H), 3.04 (dd, J = 15.0, 6.0 Hz, 1H), 3.01 (dd, J = 15.0, 6.0 Hz, 1H), 2.77 (dd, J = 14.0, 7.0 Hz, 1H), 2.76 (dd, J = 14.0, 7.0 Hz, 1H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 157.0, 139.1, 136.6, 129.6, 128.8, 128.5, 128.3, 126.7, 126.4, 82.1, 54.3, 41.7, 38.7, 36.3, 28.0; IR (thin film in CH_2Cl_2) ν_{max} 3337, 3028, 2978, 2930, 1732, 1634, 1568, 1497, 1368, 1254, 1223, 1153, 700 cm^{-1}; MS (DART) m/z (rel intensity) 370 (24), 369 (100), 314 (11), 313 (58); HRMS (DART) m/z calcd for $C_{22}H_{29}N_2O_3$ (MH^+) 369.2178, found 369.2179.

***N*-(4-Methoxybenzyl)-1*H*-imidazole-1-carboxamide (14).** To a solution of 4-methoxybenzylamine (65.0 μL, 0.501 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was added 4.0 M HCl in 1,4-dioxane (130 μL, 0.520 mmol, 1.0 equiv), giving a thick white precipitate that was stirred for 5 min before the addition of CDI (98.0 mg, 0.544 mmol, 1.1 equiv) and DMF (0.80 mL). The solution was stirred for 2 h and concentrated under an air stream. Flash chromatography with 5% MeOH/CH_2Cl_2 gave **14** as a white solid (113 mg, 98% yield). R_f = 0.23 (5% MeOH/CH_2Cl_2); mp = 113−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (br s, 1H), 7.33 (br s, 1H), 7.28 (d, J = 9.0 Hz, 2H), 7.05 (br s, 1H), 6.90 (d, J = 9.0 Hz, 2H), 6.23 (br s, 1H), 4.53 (d, J = 5.5 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 148.9, 135.9, 130.0, 129.4, 129.1, 116.3, 114.2, 55.3, 44.4; IR (thin film in CH_2Cl_2) ν_{max} 3221, 3036, 3011, 2957, 2934, 1717, 1514, 1288, 1248, 1177, 1032 cm^{-1}; MS (ESI) m/z (rel intensity) 254 (19), 232 (12), 121 (100); HRMS (ESI) m/z calcd for $C_{12}H_{14}N_3O_2$ (MH^+) 232.1080, found 232.1074.

AR-A014418[26] (15). To a solution of **14** (23.4 mg, 0.101 mmol, 1.0 equiv) and 2-amino-5-nitrothiazole (15.0 mg, 0.103 mmol, 1.0 equiv) in DMF (1.0 mL) was added 60% NaH in mineral oil (5.7 mg, 0.14 mmol, 1.4 equiv). The red solution was stirred at room temperature for 20 h and concentrated under an air stream. Flash chromatography with 5% MeOH/CH_2Cl_2 gave **15** as a pale yellow solid (30.2 mg, 97% yield). R_f = 0.41 (5% MeOH/CH_2Cl_2); mp = 208−211 °C decomp (lit.[26b] >190 °C decomp); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.62 (br s, 1H), 8.50 (s, 1H), 7.25−7.22 (m, 3H), 6.90 (d, J = 9.0 Hz, 2H), 4.29 (d, J = 6.0 Hz, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.3, 158.4, 153.3, 143.4, 140.8, 130.8, 128.7, 113.8, 55.1, 42.6.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray crystallographic data and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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