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Smart Cleavage Reactions: the Synthesis of an Array of Ureas from Polymer-Bound Carbamates

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The solid-phase synthesis of a library of di-, tri-, and tetrasubstituted ureas is described. In this approach, an array of polymer-bound carbamates was synthesized. These polymer-bound primary and secondary amine carbamates were then treated under "smart" diversity-building cleavage conditions using a series of aluminum amide complexes to form the corresponding urea cleavage products. The crude cleavage products from this study were isolated in excellent yield and purity. To show the applicability of this strategy, a series of biaryl ureas were synthesized using sequential solid-phase Suzuki coupling and urea formation reactions.

Introduction

The solid-phase synthesis of small-molecule libraries is now an accepted methodology to provide large numbers of candidates for drug discovery programs.[1] Solid-phase chemistry has a considerable advantage over solution-phase synthetic methodology, since the polymer-bound intermediates are easily handled and can be purified from the excess reagents used to drive reactions to completion by employing simple filtration and washing protocols.[2] However, solid-phase synthesis can have some drawbacks. For example, the development of new solid-phase methodology and the adaptation of existing methods onto the solid phase can sometimes be difficult. In addition, solid-phase syntheses require two additional steps within a given reaction sequence, namely, attachment to the resin at the start and then cleavage from the resin at the end of the library synthesis. This can be viewed as two unwanted and potentially problematic steps, similar to protecting group manipulations found in traditional synthesis. In light of this, research from our own laboratory has focused upon overcoming both of these drawbacks. We have developed a considerable amount of methodology that harnesses the potential of polymer-bound α-diazo-*β*-ketoesters[3] as key building blocks for the synthesis of diverse nitrogen-containing heterocycle libraries such as oxazoles,[4] indoles,[5] and imidazolones.[6] In all of these applications, we have utilized an amidation, or as we have dubbed, a "smart" cleavage reaction, to introduce yet further diversity onto the core scaffold during release from the resin.[7] We have extended this chemistry through the finding that when polymer-bound esters are treated with 1,2-phenylenediamines or 2-aminothiophenols in the presence of a Lewis acid, the corresponding benzimidazole and benzothiazole "scaffolds upon scaffolds" cleavage products are furnished.[8] More recently, we have discovered that when carbamates are treated with aluminum amide reagents, the corresponding ureas are formed.[9] This methodology has a significant advantage over many existing urea syntheses, since it enables the direct conversion of a carbamate-protected primary or secondary amine into the corresponding di-, tri- and tetrasubstituted ureas in one step.

Ureas are important targets in combinatorial chemistry since this motif is prevalent in many biologically relevant molecules.[10] In addition to its application as a core for displaying molecular diversity, the urea functionality has been utilized in many other aspects of combinatorial library production, such as the replacement of the amide linkage in peptides, to provide peptidomimetics that are resistant to proteolytic degradation[11] and as building blocks for the synthesis of heterocycle libraries.[12] Thus, it is not surprising that a number of solid-phase strategies have been published that provide arrays of urea containing compounds,[13−15] and these strategies can be categorized within three general themes. In the first case, a polymer-bound scaffold with an amine functional group is treated with an isocyanate to provide the corresponding urea, which is then cleaved from the resin using a standard cleavage protocol.[11,13] The second strategy involves attachment of the urea to the solid support directly through one of its nitrogen atoms and employing acid-labile amide releasing,[11,14a−c] triazene,[14d] or hydroxylamine[14e] linkers, which are cleaved to provide the desired urea products. However, these methods also have the shortcoming in that only a maximum of trisubstituted urea products are produced. The last strategy holds greater merit for the solid-phase synthesis of ureas because it employs a diversity-building cleavage reaction. Here, the carbamoyl or urea synthon is attached to the resin via an activated leaving group,[15] which is then treated with an amine cleavage component to yield the desired urea products. Although all

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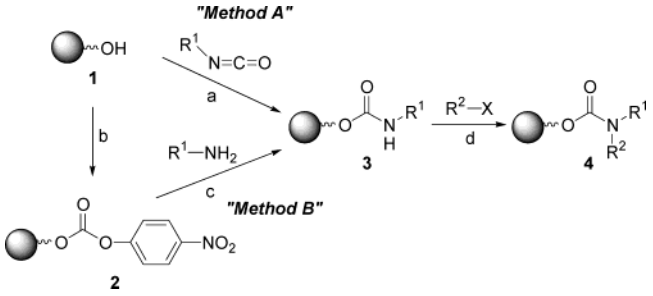
Scheme 1[a]



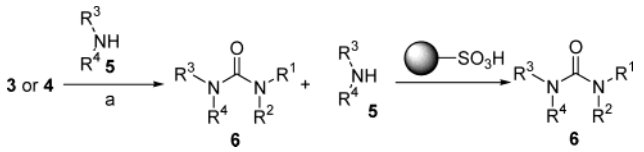
[a] Reagents and conditions: (a) isocyanate (5 equiv), Et_3N (5 equiv), CH_2Cl_2, 24 h. (b) *p*-Nitrophenyl chloroformate (3 equiv), *N*-methylmorpholine (3.3 equiv), CH_2Cl_2, 0 °C to room temperature, 24 h. (c) For benzyl and alkylamines: R^1NH_2 (5 equiv), $^iPrEt_2N$ (5 equiv), CH_2Cl_2, 24 h.; For arylamines: R^1NH_2 (5 equiv), NaHMDS (2.5 equiv), THF, −78 to 0 °C, 3 h. (d) LiO^tBu (5 equiv), R^2X (10 equiv), TBAI (2.5 equiv), DMF/THF (2:1), 24 h.

of these methods hold promise, they often only provide, at maximum, trisubstituted ureas. Finally, these methods also possess an inherent drawback because the use of an activated leaving group linker often precludes the use of many additional chemical reactions that could have provided a greater diversity upon the scaffold. Clearly, a solid-phase method that would enable the synthesis of tetrasubstituted ureas using a diversity-building cleavage reaction that can be selectively accomplished with a linker that is robust enough for a wide range of chemical reactions would be of great utility. Reported herein are our recent results in this area.

Results and Discussion

The starting point for our urea library was the preparation of polymer-bound carbamates **3** and **4** (Scheme 1). In the first approach, hydroxymethyl *J*anda*J*el[16] resin **1** was treated with an array of isocyanates (R^1NCO) in the presence of triethylamine to provide the polymer-bound primary amine carbamates **3**. However, this method proved unreliable for isocyanates other than aryl, and given the small number of diverse isocyanates that are commercially available, an alternative procedure was developed. In the second approach, polymer-bound *p*-nitrophenyl carbonate **2** was synthesized from the hydroxymethyl resin **1** by reaction with *p*-nitrophenyl chloroformate according to literature precedent.[17] *p*-Nitrophenyl carbonate resin **2** was then treated with a series of primary amines (R^1NH_2) to provide the desired primary amine polymer-bound carbamates **3**. When this reaction was performed with alkyl- and benzylamines, the reaction proceeded readily at room temperature using Hunigs base; however, the lesser reactive anilines required more forcing conditions, namely sodium bis(trimethylsilyl)amide. Next, the conversion of these polymer-bound primary amine carbamates **3** into the corresponding secondary amine carbamates **4** was investigated. For this transformation, IR spectroscopy was used to monitor the progress of the reaction by disappearance of the carbamate N−H stretch at ∼3300 to 3400 cm^{-1}. When alkyl iodides, benzyl bromides, and allyl bromides were employed as the alkylating reagent, the reaction proved to be straightforward, and complete conversion to the desired carbamates, **4**, could be achieved using lithium *tert*-butoxide base at room temperature. When the less reactive alkyl bromides were employed, the addition of tetrabutylammonium iodide was required to ensure complete formation of carbamate **4**.

Scheme 2[a]



[a] Reagents and conditions: (a) (i) R^3R^4NH (5 equiv), $AlMe_3$ (2.5 equiv), toluene, 0 °C to room temperature, 1 h, then **3** or **4**, 50−110 °C, 2−24 h. (ii) THF/H_2O (7:3), 20 min.

With an array of polymer-bound carbamates **3** and **4** in hand, we set out to investigate the diversity-building cleavage/urea formation reaction (Scheme 2, Table 1). Fortunately, our solution-phase reaction conditions could be transferred directly onto the solid-phase format. First, the aluminum amide reagent was prepared by addition of $AlMe_3$ (2.5 equiv) to the amine (R^3R^4NH) **5** (5 equiv). After allowing sufficient time for the formation of the aluminum amide complex, this mixture was then added to the polymer-bound carbamates **3** and **4**, and the reaction was heated between 50 and 110 °C for the appropriate period of time before quenching the reaction with water in THF. After quenching, the reaction mixture was passed through a strong-acid ion-exchange resin that removes both the excessively used amine starting materials **5** and the aluminum salts, providing essentially pure urea products **6**, which were isolated as either solids or oils after concentration under reduced pressure. We note that when weakly basic amines **5**, such as diphenylamine or indole, were used (Table 1, entries 3, 9, and 10), the ion-exchange resin did not remove these amines from the crude products, and preparative TLC was employed to isolate the corresponding urea products.

After these preliminary studies, a small pilot library was prepared from a series of different polymer-bound carbamates **3** or **4** and amine components **5** in order to assess the optimal cleavage conditions. This was easily accomplished since the progress of cleavage was monitored by disappearance of the carbonyl peak within the IR of a small sample of resin and also by the appearance of urea product **6**, as estimated by TLC. As a general rule, when the cleavage reaction was performed using primary amines **5**, the cleavage reaction occurred within a few hours at 50 °C. Bulky secondary amines **5** often required more elevated temperatures and extended reaction times to achieve complete cleavage from the resin, but despite these more forcing conditions, the desired ureas **6** were isolated in excellent yields (based upon the original hydroxyl loading of resin **1**) and purity as estimated using HPLC and ^1H NMR. A similar pattern of reactivity was also observed for the polymer-bound carbamates, since the secondary amine carbamates **4** required more forcing conditions than the primary amine carbamates **3**.

With reliable urea cleavage conditions developed, we set out to further expand the application of this methodology. Since the polymer-bound carbamate substrates **3** and **4** are essentially analogous to a CBZ protecting group, this can be considered as a very robust linkage that can be exposed to a range of reaction conditions without being cleaved, yet

Table 1. Solid-Phase Synthesis of Di-, Tri-, and Tetrasubstituted Ureas

entry	method	R^1	R^2	R^3	R^4	temp, °C	time, h	yield[a]	purity[b]
1	A	Ph	H	Ph	H	50	2	80	99
2	A	Ph	H	2-Ph-ethyl	H	50	2	63	87
3	A	Ph	H	Ph	Ph	110	4	69[c]	nd[d]
4	A	Ph	H	Et	Et	80	4	86	97
5	A	Ph	H	$-(CH_2)_5-$		rt	20	62	98
6	A	4-BrPh	H	Ph	H	50	4	93	98
7	A	4-MeOPh	H	2-Ph-ethyl	H	50	4	76	95
8	B	Bn	H	Ph	H	50	24	98	97
9	B	Bn	H	Ph	Ph	110	22	48[c]	nd[d]
10	B	Bn	H	indole		110	4	66[c]	nd[d]
11	A	2-MePh	H	Et	Et	110	22	100	96
12	B	Et	H	Ph	H	50	24	100	77
13	A	Ph	Me	$-(CH_2)_5-$		110	14	86	97
14	A	Ph	Bn	$-(CH_2)_5-$		110	14	76	96
15	A	Ph	allyl	$-(CH_2)_5-$		110	14	84	91
16	A	Ph	3-Ph-propyl	$-(CH_2)_5-$		110	14	79	95
17	A	Ph	cyclopropylmethyl	$-(CH_2)_5-$		110	14	78	94
18	A	Ph	Me	Et	Et	110	21	77	94
19	A	4-BrPh	Bn	Ph	H	110	24	74	88
20	A	4-BrPh	3-Ph-propyl	Ph	H	110	24	100	86
21	A	4-MeOPh	3-MeOBn	2-Ph-ethyl	H	110	24	70	67
22	A	4-MeOPh	cyclopropylmethyl	2-Ph-ethyl	H	110	24	58	87
23	B	Bn	4-BrBn	$-(CH_2)_5-$		110	72	72	68
24	A	Ph	Me	*n*-Bu	H	110	21	100	69
25	B	Et	Et	Ph	H	110	25	75	65

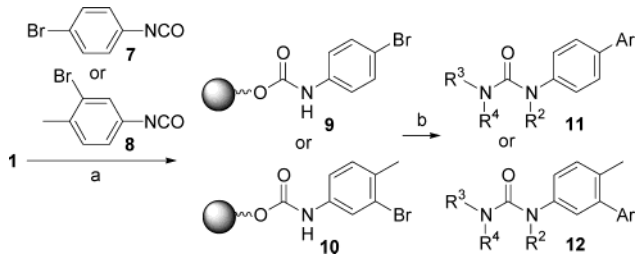
[a] Yield of crude product **6** based upon original loading of resin **1**. [b] Purity estimated by HPLC, gradient elution from 10 to 100% acetonitrile in water, detection by UV at 254 nm. [c] Isolated yield of product after purification using preparative TLC. [d] Not determined.

Table 2. Solid-Phase Synthesis of Biaryl Ureas

entry	product	R^2	R^3	R^4	Ar	yield[a]	purity[b]
1	**11**	Me	Ph	H	Ph	100	96
2	**11**	Me	morpholine		Ph	99	96
3	**11**	cyclopropylmethyl	2-Ph-ethyl	H	4-MeOPh	100	85
4	**11**	cyclopropylmethyl	morpholine		4-MeOPh	100	83
5	**12**	Bn	Ph	H	Ph	100	93
6	**12**	Bn	2-Ph-ethyl	H	Ph	100	87
7	**12**	Pr	Ph	H	4-Ph-Ph	100	95
8	**12**	Pr	morpholine		4-Ph-Ph	96	85

[a] Yield of crude product based upon original loading of resin **1**. [b] Purity estimated by HPLC, gradient elution from 10 to 100% acetonitrile in water, detection by UV at 254 nm.

Scheme 3[a]



[a] Reagents and conditions: (a) isocyanate (5 equiv), Et_3N (5 equiv), CH_2Cl_2, 24 h. (b) (i) LiO^tBu (5 equiv), R^2X (10 equiv), TBAI (2.5 equiv), DMF/THF (2:1), 24 h. (ii) $ArB(OH)_2$ (7 equiv), K_3PO_4 (7 equiv), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (2 mol %), dioxane, 90 °C, 20 h. (iii) **5** (R^3R^4NH) (5 equiv), $AlMe_3$ (2.5 equiv), toluene, 110 °C, 24 h.

still be selectively cleaved during the final urea formation reaction. Thus, urea formation should be applicable to the cleavage of many different substrates that are attached to the resin via a carbamate linkage. To demonstrate this, we synthesized a series of polymer-bound carbamate-linked biaryls using a solid-phase Suzuki coupling reaction[18] followed by cleavage to provide the corresponding urea products, Scheme 3. The starting hydroxymethyl *J*anda*J*el resin **1** was treated with 4-bromophenyl isocyanate **7**, and 3-bromo-4-methylphenyl isocyanate **8**, to provide the corresponding polymer-bound carbamates **9** and **10**. Each of these substrates was then subjected to N-alkylation and Suzuki coupling reaction conditions to provide the polymer-bound secondary amine carbamates that were cleaved from the resin using the diversity-building urea formation reaction. We note that the order of N-alkylation and Suzuki coupling reactions is not important, since we performed this reaction sequence in both orders with similar results (data not shown). The biaryl ureas **11** and **12** were all isolated in excellent yield and purities, and these results are outlined in Table 2.

Conclusion

In summary, we have developed a highly robust, simple, and cost-effective method for the "smart" cleavage of polymer-bound carbamates into their corresponding urea products. The reaction furnishes good to excellent yields of high-purity cleavage products, and the methodology has been extended to the preparation of di-, tri-, and tetrasubstituted ureas. We have further utilized this methodology for the preparation of an array of biraryl ureas, and we anticipate broad applicability in the synthesis and cleavage of additional carbamate-linked libraries.

Experimental Section

General methods and procedures for the purification of the DOWEX ion-exchange resin have been disclosed elsewhere.[5,6,16c] All reactions were performed under an atmosphere of argon. Product purity was estimated using RP-HPLC using a gradient elution from 10 to 100% acetonitrile in water mixtures with detection at 254 nm and also using ^{1}HNMR analysis of the crude materials.

Representative Procedures. Polymer-Bound Carbamates (3); Method A. To a suspension of hydroxymethyl *J*anda*J*el **1** (2.00 g, 2.5 mmol) in CH_2Cl_2, under argon was added Et_3N (1.39 mL, 10 mmol). The mixture was cooled to 0 °C, and phenyl isocyanate (1.10 mL, 10.0 mmol) was added slowly. The reaction was allowed to warm to room temperature and stirred for 24 h. The resin was collected by filtration and washed with DMF, THF, ether, $CHCl_3$, and hexanes and dried in vacuo to give carbamate resin **3** (R^1 = Ph) as a white powder (2.30 g, 100%); IR: 1716 cm^{-1}.

Polymer-Bound Carbamates (3); Method B. To a suspension of hydroxymethyl *J*anda*J*el **1** (5.00 g, 6.25 mmol) in CH_2Cl_2 (80 mL) under argon was added *N*-methylmorpholine (1.82 mL, 16.5 mmol). The mixture was cooled to 0 °C, and *p*-nitrophenyl chloroformate (3.00 g, 15.0 mmol) was added slowly. The reaction was allowed to warm to room temperature and stirred for 24 h. The resin was collected by filtration and washed with DMF, THF, ether, $CHCl_3$, and hexanes and dried in vacuo to give nitrophenyl carbonate resin **2** as a white powder (6.08 g, 100%); IR: ~3300, 1764 cm^{-1}.

A flask was charged with nitrophenyl carbonate resin **2** (2.00 g, 2.10 mmol) and 3-bromo-4-methylaniline (1.86 g, 10.0 mmol), and THF (50 mL) was added. The mixture was cooled to −78 °C, and a solution of NaHMDS in THF (5.0 mL, 5.00 mmol) was slowly added. The resultant mixture was stirred and allowed to warm to room temperature over 3 h before acetic acid (5.7 mL, 100 mmol) was added. Stirring was continued for an additional 20 min, and then the resin was collected by filtration and washed with DMF, DMF/water (1:1), THF, methanol, ether, $CHCl_3$, and hexanes and dried in vacuo to give polymer-bound carbamate **4** as a white powder (1.93 g, 89%); IR 1734 cm^{-1}.

Alkylation of Primary Amine Carbamate (3) To Provide Secondary Amine Carbamate (4). A suspension of polymer-bound carbamate **3** (R^1 = 3-Br-4-MePh), (800 mg, ~0.80 mmol) in DMF (8 mL) and THF (4 mL) was cooled to 0 °C under argon, and a solution of LiO^tBu (1 M in THF, 4.0 mL, 4.0 mmol) was added. This mixture was stirred for 1 h, and then benzylbromide (950 μL, 8.0 mmol) was added. The reaction mixture was warmed to room temperature, and stirring was continued for 24 h, after which time acetic acid (2.0 mL) was added to quench the reaction. The resin was collected by filtration and washed with DMF, DMF/water (1:1), THF, methanol, ether, $CHCl_3$, and hexanes and dried in vacuo to give polymer-bound carbamate **4** (R^1 = 3-Br-4-Ph, R^2=Bn) as a white powder. (801 mg, 92%), IR: 1704 cm^{-1}. (When alkyl bromides were used in this reaction, tetrabutylammonium iodide (2.5 equiv) was added to the mixture after the addition of the alkyl bromide).

Suzuki Coupling Reaction of Polymer-Bound Aryl Bromides 9 and 10. A 10-mL vial was charged with carbamate resin **9** (R^1 = 4-BrPh, R^2 = Me), (500 mg, 0.50 mmol), phenylboronic acid (426 mg, 3.50 mmol), Pd(dppf)-Cl_2·CH_2Cl_2 (8 mg, 0.010 mmol), and K_3PO_4 (743 mg, 3.50 mmol). The vial was sealed with a Teflon-lined septa lid, purged with argon, and dioxane (6.0 mL) was added. The resulting mixture was heated to 90 °C with shaking for 20 h. After cooling, the resin was collected by filtration and washed with DMF, DMF/water (1:1), THF, methanol, ether, $CHCl_3$, and hexanes and dried in vacuo to give polymer-bound carbamate (R^5 = Ph) as a black powder (483 mg, 96%).

Cleavage Reaction to Form Ureas 6, 11, and 12. A solution of trimethylaluminum (2 M in toluene, 250 μL, 0.50 mmol) was added to a solution of aniline (R^3 = Ph, R^4 = H), (91 μL, 1.0 mmol) in toluene (1.0 mL) at 0 °C under an atmosphere of argon. After stirring at 0 °C for 10 min., the mixture was warmed to room temperature, and stirring was continued for an additional 1 h. This solution was then added to a suspension of carbamate resin **3** (R^1 = Ph, R^2 = H) (200 mg, 0.22 mmol) in toluene (2.0 mL). The mixture was then warmed to 50 °C for 2 h. After cooling, the reaction was quenched by the addition of a mixture of THF/water (7:3, 1.0 mL), and the reaction was stirred for an additional 20 min before filtration through a strong-acid ion-exchange resin. The ion-exchange resin was further eluted with $CHCl_3$/THF (1:1), and the combined eluent and filtrate were concentrated under reduced pressure to provide urea **6** (R^1 = Ph, R^2 = H, R^3 = Ph, R^4 = H) (37.1 mg, 80%) as a pale yellow solid.

Spectrocopic Data for Ureas 6, 11 and 12, Table 1. Entry 1. Pale yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.95−6.98 (2H, m), 7.26−7.29 (4H, m), 7.44−7.46 (4H, m), 8.65 (2H, s); HRMS *m*/*z* = 213.1022 [M + H], calcd for $C_{13}H_{13}N_2O$ = 213.1022.

Entry 2. Pale yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.75 (2H, t, *J* = 7.1 Hz), 3.31−3.35 (2H, m), 6.14 (1H, t, *J* = 5.6 Hz), 6.87 (1H, dd, *J* = 7.3, 7.3 Hz), 7.19−7.25 (5H, m), 7.30−7.33 (2H, m), 7.38 (2H, d, *J* = 7.7 Hz), 8.51 (1H, s); HRMS *m*/*z* = 241.1335 [M + H], calcd for $C_{15}H_{17}N_2O$ = 241.1335.

Entry 3. White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.36 (1H, s), 6.94 (1H, dd, *J* = 7.4, 7.4 Hz), 7.16−7.20 (4H, m), 7.25−7.26 (6H, m), 7.31−7.33 (4H, m); HRMS *m*/*z* =289.1336 [M + H], calcd for $C_{19}H_{17}N_2O$ = 289.1335.

Entry 4. Colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (6H, t, *J* = 7.2 Hz), 3.37 (4H, q, *J* = 7.2 Hz), 6.30 (1H, br s), 7.01 (1H, dd, *J* = 7.4 Hz), 7.25−7.29 (2H, m), 7.38−7.39 (2H, m); HRMS *m*/*z* = 193.1333 [M + H], calcd for $C_{11}H_{17}N_2O$ = 193.1335.

Entry 5. Colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58−1.66 (6H, m), 3.43−3.45 (4H, m), 6.49 (1H, br s), 7.00−7.03 (1H, m), 7.25−7.28 (2H, m), 7.34−7.36 (2H, m); HRMS *m*/*z* = 205.1332 [M + H], calcd for $C_{12}H_{17}N_2O$ = 205.1335.

Entry 6. Yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.96−6.99 (1H, m), 7.26−7.29 (2H, m), 7.44−7.45 (6H, m), 8.69 (1H, s), 8.80 (1H, s); HRMS *m*/*z* = 291.0127 [M + H], calcd for $C_{13}H_{12}BrN_2O$ = 291.0127.

Entry 7. Yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.73 (2H, t, *J* = 7.1 Hz), 3.29−3.33 (2H, m), 3.34 (3H,

s), 6.03 (1H, dd, J = 5.7 Hz), 6.78−6.82 (2H, m), 7.19−7.32 (7H, m), 8.30 (1H, s); HRMS m/z = 271.1443 [M + H], calcd for $C_{16}H_{19}N_2O_2$ = 271.1441.

Entry 8. Dark yellow solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.30 (2H, d, J = 5.9 Hz), 6.59−6.61 (1H, m), 6.88−6.90 (1H, m), 7.20−7.25 (3H, m), 7.29−7.35 (4H, m), 7.39−7.41 (2H, m), 8.54 (1H, s); HRMS m/z = 227.1179 [M + H], calcd for $C_{14}H_{15}N_2O$ = 227.1179.

Entry 9. Colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.44 (2H, d, J = 5.9 Hz), 4.88 (1H, br t, J = 5.4 Hz), 7.16−7.33 (15H, m); HRMS m/z = 303.1486 [M + H], calcd for $C_{20}H_{19}N_2O$ = 303.1492.

Entry 10. Brown solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.63 (2H, d, J = 5.6 Hz), 5.99 (1H, br s), 6.61 (1H, d, J = 3.7 Hz), 7.22−7.25 (1H, m), 7.31−7.34 (2H, m), 7.35−7.39 (4H, m), 7.45 (1H, d, J = 3.7 Hz), 7.60 (1H, d, J = 7.8 Hz), 8.11 (1H, d, J = 8.4 Hz); HRMS m/z = 251.1178 [M + H], calcd for $C_{16}H_{15}N_2O$ = 251.1179.

Entry 11. White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (6H, t, J = 7.2 Hz), 2.24 (3H, s), 3.38 (4H, q, J = 7.2 Hz), 6.13 (1H, br s), 6.96−6.99 (1H, m), 7.13−7.19 (2H, m), 7.76 (1H, d, J = 8.1 Hz); HRMS m/z = 207.1492 [M + H], calcd for $C_{12}H_{19}N_2O$ = 207.1492.

Entry 12. Yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 7.4 Hz), 1.42−1.50 (2H, m), 3.13 (2H, q, J = 6.9 Hz), 5.56 (1H, br s), 6.99−7.02 (1H, m), 7.22−7.28 (4H, m), 7.36 (1H, br s); HRMS m/z = 179.1181 [M + H], calcd for $C_{10}H_{15}N_2O$ = 179.1179.

Entry 13. Yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.32−1.36 (4H, m), 1.44−1.48 (2H, m), 3.14−3.16 (4H, m), 3.20 (3H, m), 7.07−7.09 (3H, m), 7.29−7.32 (2H, m); HRMS m/z = 219.1486 [M + H], calcd for $C_{13}H_{19}N_2O$ = 219.1492.

Entry 14. White solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.32−1.36 (4H, m), 1.45−1.49 (2H, m), 3.20−3.22 (4H, m), 4.86 (2H, s), 7.02−7.05 (3H, m), 7.19−7.30 (7H, m); HRMS m/z = 295.1800 [M + H], calcd for $C_{19}H_{23}N_2O$ = 295.1805.

Entry 15. Yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.32−1.36 (4H, m), 1.44−1.48 (2H, m), 3.16−3.18 (4H, m), 4.24−4.26 (2H, m), 5.06−5.13 (2H, m), 5.91−5.98 (1H, m), 7.05−7.08 (3H, m), 7.27−7.30 (2H, m); HRMS m/z = 245.1645 [M + H], calcd for $C_{15}H_{21}N_2O$ = 245.1648.

Entry 16. Yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.29−1.33 (4H, m), 1.43−1.46 (2H, m), 1.89−1.94 (2H, m), 2.62 (2H, t, J = 7.9 Hz), 3.13−3.14 (4H, m), 3.65 (2H, t, J = 7.9 Hz), 7.02−7.03 (2H, m), 7.05−7.08 (1H, m), 7.14−7.16 (3H, m), 7.23−7.29 (4H, m); HRMS m/z = 323.2112 [M + H], calcd for $C_{21}H_{27}N_2O$ = 323.2118.

Entry 17. Yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.08−0.11 (2H, m), 0.36−0.39 (2H, m), 1.07−1.14 (1H, m), 1.29−1.33 (4H, m), 1.43−1.47 (2H, m), 3.14−3.16 (4H, m), 3.49 (2H, d, J = 7.0 Hz), 7.06−7.09 (3H, m), 7.27−7.30 (2H, m); HRMS m/z = 259.1805 [M + H], calcd for $C_{16}H_{23}N_2O$ = 259.1805.

Entry 18. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (6H, t, J = 7.2 Hz), 3.11 (4H, q, J = 7.2 Hz), 3.15 (3H, s), 7.07−7.12 (3H, m), 7.30−7.33 (2H, m); HRMS m/z = 207.1499 [M + H], calcd for $C_{12}H_{19}N_2O$ = 207.1492.

Entry 19. Brown solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.91 (2H, s), 6.14 (1H, br s), 7.03−7.06 (2H, m), 7.24−7.32 (10H, m), 7.51−7.53 (2H, m); HRMS m/z = 381.0602 [M + H], calcd for $C_{20}H_{18}BrN_2O$ = 381.0597.

Entry 20. Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.93−1.99 (2H, m), 2.73 (2H, t, J = 8.0 Hz), 3.85−3.88 (2H, m), 6.12 (1H, s), 7.07−7.10 (1H, m), 7.22−7.38 (11H, m), 7.67−7.69 (2H, m); HRMS m/z = 409.0900 [M + H], calcd for $C_{22}H_{22}BrN_2O$ = 409.0910.

Entry 21. Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.75 (2H, t, J = 7.0 Hz), 3.43 (2H, dt, J = 7.0, 7.0 Hz), 3.76 (3H, s), 3.77 (3H, s), 4.23 (1H, br s), 4.78 (2H, s), 6.75−6.80 (4H, m), 6.85−6.87 (2H, m), 7.07−7.08 (2H, m), 7.16−7.23 (5H, m); HRMS m/z = 391.2034 [M + H], calcd for $C_{24}H_{27}N_2O_3$ = 391.2016.

Entry 22. Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07−0.10 (2H, m), 0.37−0.40 (2H, m), 0.80−0.96 (1H, m), 2.71 (2H, t, J = 6.9 Hz), 3.38 (2H, dt, J = 6.8, 6.8 Hz), 3.49 (2H, d, J = 6.8 Hz), 3.81 (3H, s), 4.11 (1H, br s), 6.84−6.87 (2H, m), 7.06 (4H, d, J = 8,8 Hz), 7.15−7.24 (3H, m); HRMS m/z = 325.1923 [M + H], calcd for $C_{20}H_{25}N_2O_2$ = 325.1910.

Entry 23. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42−1.48 (6H, m), 3.14−3.16 (4H, m), 4.08 (2H, s), 4.13 (2H, s), 6.92 (2H, d, J = 8.3 Hz), 7.02−7.03 (2H, m), 7.13−7.21 (3H, m), 7.30−7.31 (2H, m); HRMS m/z = 387.1068 [M + H], calcd for $C_{20}H_{24}BrN_2O$ = 387.1066.

Entry 24. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.3 Hz), 1.19−1.27 (2H, m), 1.34−1.40 (2H, m), 2.25 (3H, s), 3.12−3.19 (2H, m), 3.19 (3H, s), 4.04 (1H, br s), 7.18−7.19 (1H, m), 7.25−7.32 (3H, m); HRMS m/z = 221.1646 [M + H], calcd for $C_{13}H_{21}N_2O$ = 221.1648.

Entry 25. Black solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (6H, t, J = 7.5 Hz), 1.62−1.69 (4H, m), 3.25−3.28 (4H, m), 6.27 (1H, br s), 7.00−7.02 (1H, m), 7.26−7.29 (2H, m), 7.37−7.38 (2H, m); HRMS m/z = 221.1647 [M + H], calcd for $C_{13}H_{21}N_2O$ = 221.1648.

Table 2. Entry 1. Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.39 (3H, s), 6.34 (1H, br s), 6.99−7.02 (1H, m), 7.23−7.27 (2H, m), 7.31−7.33 (2H, m), 7.39−7.42 (3H, m), 7.47−7.50 (2H, m), 7.61−7.63 (2H, m), 7.68−7.71 (2H, m); HRMS m/z = 303.1489 [M + H], calcd for $C_{20}H_{19}N_2O$ = 303.1492.

Entry 2. Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.24 (4H, t, J = 4.8 Hz), 3.27 (3H, s), 3.52 (4H, t, J = 4.8 Hz), 7.17−7.18 (2H, m), 7.33−7.36 (1H, m), 7.43−7.46 (2H, m), 7.57−7.58 (4H, m); HRMS m/z = 297.1598 [M + H], calcd for $C_{18}H_{21}N_2O_2$ = 297.1597.

Entry 3. Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.12−0.15 (2H, m), 0.40−0.44 (2H, m), 0.95−1.01 (1H, m), 2.75 (2H, t, J = 6.9 Hz), 3.42 (2H, dt, J = 6.9, 6.9 Hz), 3.56 (2H, d, J = 7.1 Hz), 3.87 (3H, s), 4.22 (1H, br s), 7.00−7.02 (2H, m), 7.07−7.09 (2H, m), 7.16−7.30 (5H, m), 7.51−7.53 (4H, m); HRMS m/z = 401.2214 [M + H], calcd for $C_{26}H_{29}N_2O_2$ = 401.2223.

Entry 4. Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.12−0.15 (2H, m), 0.39−0.43 (2H, m), 1.10−1.16 (1H, m), 3.23 (4H, t, J = 4.8 Hz), 3.49 (4H, t, J = 4.8 Hz), 3.54 (2H, d, J = 6.9 Hz), 3.85 (3H, s), 6.97−6.99 (2H, m), 7.15−7.16

(2H, m), 7.51−7.53 (4H, m); HRMS m/z = 367.2018 [M + H], calcd for $C_{22}H_{27}N_2O_3$ = 367.2016.

Entry 5. Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.30 (3H, s), 4.96 (2H, s), 6.34 (1H, br s), 6.69−6.70 (2H, m), 6.75−6.78 (1H, m), 6.99−7.07 (3H, m), 7.15−7.18 (2H, m), 7.22−7.43 (10H, m); HRMS m/z = 393.1954 [M + H], calcd for $C_{27}H_{25}N_2O$ = 393.1961.

Entry 6. Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23 (3H, s), 2.77 (2H, t, J = 6.7 Hz), 3.46 (2H, dt, J = 6.7, 6.7 Hz), 4.37 (1H, br s), 4.87 (2H, s), 6.82−6.85 (2H, m), 7.06−7.42 (16H, m); HRMS m/z = 421.2272 [M + H], calcd for $C_{29}H_{29}N_2O$ = 421.2274.

Entry 7. Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.4 Hz), 1.61−1.69 (2H, m), 2.42 (3H, s), 3.73−3.76 (2H, m), 6.29 (1H, s), 6,69−6.71 (1H, m), 6.99−7.02 (1H, m), 7.16−7.19 (1H, m), 7.22−7.51 (10H, m), 7.67−7.71 (4H, m); HRMS m/z = 421.2263 [M + H], calcd for $C_{29}H_{29}N_2O$ = 421.2274.

Entry 8. Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.4 Hz), 1.60−1.67 (2H, m), 2.30 (3H, s), 3.23 (4H, t, J = 4.8 Hz), 3.50 (4H, t, J = 4.8 Hz), 3.59−3.62 (2H, m), 7.00−7.03 (2H, m), 7.24 (1H, d, J = 8.0 Hz), 7.36−7.39 (3H, m), 7.46−7.49 (2H, m), 7.65−7.67 (4H, m); HRMS m/z = 415.2368 [M + H], calcd for $C_{27}H_{31}N_2O_2$ = 415.2380.

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Supporting Information Available. ^{1}H NMR spectra for all crude urea cleavage compounds **6**, **11**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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