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The direct conversion of carbamates to ureas using aluminum amides

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Abstract—The conversion of carbamates into ureas using aluminum amide complexes is reported. This reaction is a convenient method to prepare bi-, tri- and tetra-substituted ureas from carbamate-protected primary or secondary amines by reaction with primary or secondary amines in the presence of stoichometric quantities of trimethylaluminum. A reactivity trend of the various carbamates was observed and methyl and benzyl carbamates were reacted selectively in the presence of *t*-butyl carbamates.

1. Introduction

The urea functional group plays an important role in organic and medicinal chemistry; many biologically active compounds either contain the urea functionality[1] or are synthesized from urea-containing starting materials.[2] In addition, ureas have been utilized for the synthesis of peptidomimetic compounds whereby the amide bond of the peptide is replaced by a urea bond so that the peptide mimic possesses many of the key structural features of the parent peptide, but has increased bioavailability since the urea bond is not susceptible to proteolytic cleavage.[3] Accordingly, simple and efficient methods for the synthesis of ureas are of interest. Since ureas are derived from amine constituents, a common method for their preparation involves conversion of the first amine component to an isocyanate or an activated carbamate[4] (e.g., *p*-nitrophenyl) followed by reaction with the second amine component. However, the shortcomings of this methodology become apparent when the first amine component bears more than one substituent. Specifically, secondary amines cannot be converted to the corresponding isocyanates and secondary *p*-nitrophenyl carbamates suffer from low reactivity toward a second amine nucleophile; in the latter case, more drastic conditions such as the preparation of the corresponding carbamoyl chloride[5] are required. Furthermore, quite often in any given synthetic sequence, the first amino component may have been previously protected by a common carbamate protecting group such as Boc, Cbz, Fmoc, Alloc or methyl carbamate, and thus, prior removal of such a protecting group adds yet another step to the aforementioned two step reaction sequence. Although the direct conversion of carbamate-protected primary amines into ureas has been reported,[6] in both cases, carbamate-protected secondary amines could not be used since these reactions proceed via the in situ conversion of the carbamate to the isocyanate by reaction with a halosilane. Accordingly, a simple and efficient method that enables the conversion of both carbamate-protected primary and secondary amines into the corresponding di-, tri- and tetra- substituted ureas is of great interest and importance to synthetic chemists.

Our own interest in the synthesis of ureas stems from our recent studies in the solid-phase synthesis of heterocycle libraries.[7] Here, we have utilized an ester moiety to link the target library scaffold to the polymer-support; a Lewis acid-mediated amidation reaction[8] was employed to afford an array of amide cleavage products.[9] Lewis acid-mediated amide bond forming reactions have been used extensively in synthetic chemistry and a plethora of reagents including $AlMe_3$ and $AlCl_3$ have been used. In addition, the use of aluminum amides has also been applied toward the synthesis of guanidines[10] and the ring opening of oxazolidinones to form hydroxyl ureas.[11] More recently, we have also expanded the scope of amide forming reactions using 1,2-phenylenediamines or 1,2-aminothiophenols as substrates to produce the corresponding benzimidazole or benzothiazole cleavage products from polymer-bound ester substrates.[12] Unexpectedly, during our investigations of Lewis acid mediated C–N bond forming reactions, we also discovered that under mild conditions, carbamates are converted into the corresponding ureas by reaction with aluminum amides. Reported herein are these findings.

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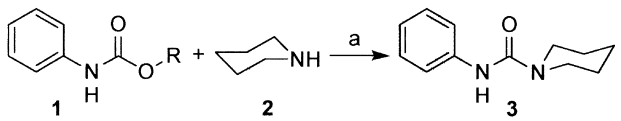
2. Results and discussion

To begin with, we investigated the conversion of a series of carbamate protected anilines **1**, into the corresponding ureas **3**, Scheme 1, Table 1. In this study, we tested the most widely used carbamate protecting groups, such as methyl carbamate, Boc, Cbz, Alloc, Troc, Fmoc and Teoc.[13] In most instances, when the carbamates **1a–g** were treated with an excess of piperidine **2** and $AlMe_3$ (amine/metal/carbamate ratio 3:2.5:1) the corresponding urea **3** was formed in good to excellent yields after only 2–5 h. at room temperature. When the *t*-butyl carbamate **1b** was used (Boc), the rate of conversion proved to be very slow as estimated by TLC; however, when heated to 50 °C this reaction was complete within 1.5 h. The only example that gave a poor yield in these experiments was the Fmoc-protected aniline **1f** where the desired product **3** was only isolated in 34% yield. This low yield was attributed to the high lability of the Fmoc group to piperidine **2**.



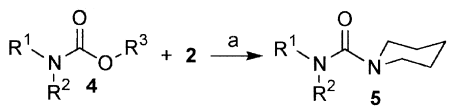
Scheme 1. Reagents and conditions: (a) **2** (3 equiv.), $AlMe_3$ (2.5 equiv.), toluene.

Table 1.

Entry	Substrate (R=)		Temperature (°C)	Time (h)	Yield (%)
1	**1a**	CH_3	Room temperature	2.5	78
2	**1b**	*t*-Butyl	50	1.5	92
3	**1c**	Bn	Room temperature	3.5	93
4	**1d**	Allyl	Room temperature	2	89
5	**1e**	Cl_3CCH_2	Room temperature	2	96
6	**1f**	Fluorenylmethyl	80	2	34[a]
7	**1g**	$Me_3Si(CH_2)_2$	Room temperature	5	90

[a] 5 equiv. of $AlMe_3$ used.

With these results in hand, the next variable to be investigated was the effect of the type, and number of substituents on the nitrogen atom of the carbamate. Thus, this study would enable us to assess the scope of the Lewis acid mediated reaction with regards to establishing the reactivity of mono- and di-substituted carbamates **4** and the ease of preparation of the corresponding tri- and tetra-substituted ureas **5**, Scheme 2, Table 2.



Scheme 2. Reagents and conditions: (a) **2** (3 equiv.), $AlMe_3$ (2.5 equiv.), toluene.

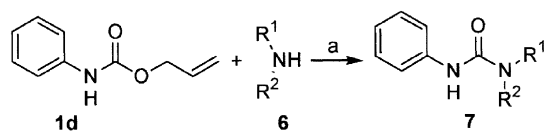
Table 2.

Entry	Sub.	R^1	R^2	R^3	Temperature (°C)	Time (h)	Prod.	Yield (%)
1	**4a**	Bn	H	Bn	50	4.5	**5a**	95
2	**4b**	Ph	Me	Et	110	3	**5b**	96
3	**4c**	$Ph(CH_2)_2$	H	Et	50	4	**5c**	98
4	**4d**	$-(CH_2)_4-$		Bn	110	3	**5d**	91[a]
5	**4e**	Ph	Ph	Et	110	5	**5e**	99

[a] Phenylethylamine used in place of piperidine.

Once again, the reaction showed broad scope and excellent reliability. There was a discernable difference between the rate of conversion of primary and secondary carbamates **4** into the respective ureas **5**. For example, when ethyl carbamate **4b** was reacted with the piperidine/$AlMe_3$ adduct (amine/metal/substrate ratio 3:2.5:1), the reaction had to be heated to 110 °C to give the desired product **5b** in 96% yield after 3 h. However, our previous experiments had shown that the primary amine **1a** (aniline methyl carbamate) was readily converted into the desired urea **3** at room temperature over a similar reaction time (Table 1, entry 1 vs Table 2, entry 2). A similar trend was observed when carbamates derived from secondary amines, *N*-Cbz piperidine and diphenylamine *N*-ethyl carbamate were converted into the corresponding urea products **5d** and **5e** (Table 2, entries 4 and 5); in both cases, the reactions had to be heated to 110 °C to enable good conversion to the desired product in an acceptable period of time.

We also investigated what effect the nature of the amine component **6** of the reaction would have on the rate of formation of the urea product **7**, Scheme 3, Table 3. It appears that both the nucleophilicity of the amine coupling partner and the steric bulk of the amine substituents have a dramatic effect on the rate of conversion into the desired ureas. For example, when butylamine **6** (R^1=Bu, R^2=H) was reacted with *N*-Alloc aniline **1d**, the corresponding urea **7a** was formed in 99% yield after heating at 50 °C for 30 min; however, when the bulky diisopropylamine **6** (R^1=R^2=*i*-Pr) was used, the corresponding urea **7c** was formed in 94% yield after heating to 50 °C for 1 h (Table 3, entries 1 and 3). In addition, when benzylamine **6** was used in the reaction, the desired urea **7b** was formed within 30 min. but when the similar sized but when less nucleophilic aniline **6** (R^1=Ph, R^2=H) was used, the reaction time had to be extended to 4 h to give the corresponding urea **7d** in 83% yield (Table 3, entries 2 vs 4). Finally, when diphenylamine **6** (R^1=R^2=Ph) was used, the reaction required heating to 110 °C to achieve and acceptable rate of conversion to product **7f**.



Scheme 3. Reagents and conditions: (a) **6** (3 equiv.), $AlMe_3$ (2.5 equiv.), toluene.

Table 3.

Entry	R^1	R^2	Temperature (°C)	Time	Product	Yield (%)
1	Bu	H	50	0.5	**7a**	99
2	Bn	H	50	0.5	**7b**	94
3	*i*-Pr	*i*-Pr	50	1	**7c**	94
4	Ph	H	50	4	**7d**	83
5	Me	Ph	50	5	**7e**	95
6	Ph	Ph	110	2	**7f**	97

We note that when inexpensive and readily available amine starting materials were used, a slight excess of the amine over the carbamate was employed to drive the reaction to completion in shorter period of time, although further experiments have shown that with more valuable amines or for chemoselective reactions, the stoichiometry can be reduced (amine/metal/substrate ratio 1.1:1:1). The use of a slight excess of amine is also not critical to the work up and purification of the desired urea products. After completion of the reaction, (estimated by TLC), the reaction was quenched using water and then passed through a strong-acid ion exchange resin to remove unreacted starting materials and aluminum salt byproducts to furnish an essentially pure product.

The final part of our study was to investigate if we could selectively react one carbamate over another and also, selectively react a carbamate over an ester or vice versa. The first of these experiments involved the preparation of the bis-carbamate **8** that was synthesized from 4-nitro aniline by protecting the aniline with a Boc group, followed by reduction of the nitro group to the amine, which was then converted to the benzyl carbamate (Cbz). When **8** was reacted with 1 equiv. of the piperidine trimethylaluminum adduct at room temperature for 24 h, the expected reaction occurred exclusively at the Cbz group, and the Boc protected product **9** was isolated in 95% yield. A Boc and Cbz-protected alkyl diamine **10** was also prepared and subjected to similar urea formation conditions. Once again, the Cbz group was selectively reacted in the presence of a Boc group to give the desired product **11** in 92% isolated yield.

We also discovered that esters are significantly more reactive than the corresponding carbamate under Lewis acid promoted C–N bond forming conditions. When Cbz protected glycine methyl ester **12a** was reacted with 1 equiv. of the piperidine trimethylaluminum adduct at room temperature for 24 h the corresponding amides **13** was formed exclusively in 92% yield. Moreover, we also investigated the reaction of Cbz glycine benzyl ester **12b** to unequivocally prove that the ester can be selectively reacted in the presence of a similarly functionalized carbamate, the corresponding amide **13** was similarly formed in 92% yield. Our observations consolidate previous findings by Martin and co-workers for the synthesis of carbamate protected peptide fragments via aluminum amide intermediates.[14]

Our final investigation of these competition experiments was to see if we could tune the reactivity of both the carbamate and ester groups to achieve selective reaction of the urea in the presence of an ester. Accordingly, methoxy carbamate glycine *t*-butyl ester **14** was prepared and reacted with 1 equiv. of the piperidine trimethylaluminum adduct. Unfortunately, this experiment failed since both groups reacted at similar rates; this reaction afforded a mixture of the piperidine amide urea **15** in 46% yield and the remainder was unreacted starting material **14** (Scheme 4).

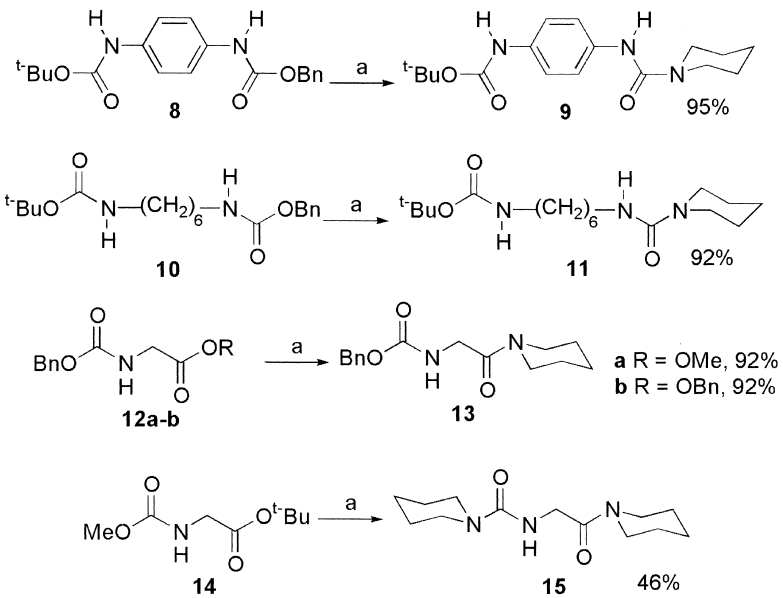
3. Conclusion

In summary, we have developed a highly efficient method for the direct conversion of carbamates into the corresponding ureas. Our method enabled the synthesis of di-, tri- and tetra- substituted ureas and we have also been able to show complete chemoselectivity in the reaction of one carbamate over another. Further investigations into the reaction of carbonyls with aluminum amides are ongoing in our laboratory and will be reported in due course.

4. Experimental

4.1. Representative procedure

Trimethylaluminum (2.0 M in toluene, 1.25 mL,



Scheme 4. Reagents and conditions: (a) **2** (1.1 equiv.), $AlMe_3$ (1.0 equiv.), toluene.

2.50 mmol) was slowly added to a solution of piperidine **2** (0.30 mL, 3.00 mmol) in toluene (5 mL) at 0 °C under argon. After being stirred for 10 min at 0 °C, the resulting solution was allowed to warm up to room temperature and then stirred for 1 h. The mixture was added dropwise to a stirred solution of the *N*-Boc-aniline **1b** (152.6 mg, 1.00 mmol) and toluene (3 mL) in a 40 mL vial at 0 °C under argon and the resulting solution was heated to 50 °C for 1.5 h. The reaction was quenched by the addition of a mixture of THF (10 mL) and H_2O (3 mL) and stirring was continued for a further 20 min before the solution was passed through a work-up cartridge that contained a strong acid ion exchange resin (DOWEX 500WX2-200) that was further eluted with THF. The combined filtrates were concentrated under reduced pressure to yield the crude product was then purified by column chromatography over silica (3% CH_3CN in $CHCl_3$) to give *N*-phenyl-*N*′,*N*′-pentamethylene urea as a colorless solid (159.5 mg, 0.78 mmol, 78%).

4.2. Spectroscopic data

4.2.1. Compound 3. Colorless solid; mp 169.5–171 °C; IR 3284, 2925, 2855, 1629, 1591, 1533, 1434 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.56–1.65 (6H, m), 3.42–3.44 (4H, m), 6.49 (1H, br s), 6.99–7.02 (1H, m), 7.24–7.27 (2H, m), 7.34–7.36 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.3 (t), 25.6 (t), 45.2 (t), 119.8 (d), 122.7 (d), 128.7 (d), 139.3 (s), 155.0 (s); HRMS *m*/*z*=205.1334 [M+H], calcd for $C_{12}H_{17}N_2O$=205.1335.

4.2.2. Compound 5a. Colorless solid; mp 102 °C; IR 3339, 2927, 2850, 1622, 1533 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.52–1.62 (6H, m), 3.32–3.34 (4H, m), 4.42 (2H, d, *J*=5.5 Hz), 4.75 (1H, br s), 7.24–7.34 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4 (t), 25.6 (t), 44.9 (t), 45.0 (t), 127.2 (d), 127.7 (d), 128.5 (d), 139.6 (s), 157.5 (s); HRMS *m*/*z*=219.1491 [M+H], calcd for $C_{13}H_{19}N_2O$=219.1492.

4.2.3. Compound 5b. Colorless oil; IR 2934, 1635, 1594, 1495, 1429, 1399 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.24–1.29 (4H, m), 1.36–1.41 (2H, m), 3.07–3.10 (4H, m), 3.13 (3H, s), 6.99–7.01 (3H, m), 7.22–7.25 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.2 (t), 25.1 (t), 39.1 (q), 46.4 (t), 123.2 (d), 123.8 (d), 129.0 (d), 146.9 (s), 160.9 (s); HRMS *m*/*z*=219.1490 [M+H], calcd for $C_{13}H_{19}N_2O$=219.1492.

4.2.4. Compound 5c. Colorless solid; mp 78–78.5 °C; IR 3320, 2916, 2851, 1615, 1541 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.48–1.59 (6H, m), 2.81 (2H, t, *J*=7.0 Hz), 3.24–3.26 (4H, m), 3.47 (2H, dd, *J*=7.0, 12.8 Hz), 7.18–7.31 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.4 (t), 25.5 (t), 36.4 (t), 42.0 (t), 44.8 (t), 126.3 (d), 128.5 (d), 128.8 (d), 139.5 (s), 157.5 (s); HRMS *m*/*z*=233.1648 [M+H], calcd for $C_{14}H_{21}N_2O$=233.1648.

4.2.5. Compound 5d. Colorless oil; IR 2928, 2849, 1639, 1413 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.52–1.60 (12H, m), 3.15–3.17 (8H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.8 (t), 25.8 (t), 47.9 (t), 164.8 (s); HRMS *m*/*z*=197.1651 [M+H], calcd for $C_{11}H_{21}N_2O$=197.1648.

4.2.6. Compound 5e. Colorless solid; mp 117.5–118 °C; IR 2940, 1641, 1588, 1490, 1421 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.38–1.55 (6H, m), 3.32–3.34 (4H, m), 7.03–7.12 (6H, m), 7.28–7.31 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.4 (t), 25.4 (t), 46.5 (t), 124.4 (d), 124.8 (d), 129.1 (d), 145.1 (s), 159.8 (s); HRMS *m*/*z*=281.1650 [M+H], calcd for $C_{18}H_{20}N_2O$=281.1648.

4.2.7. Compound 7a. Colorless solid; mp 129 °C; IR 3378, 2960, 2932, 2870, 1652, 1597, 1552, 1498 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 0.94 (3H, t, *J*=7 Hz), 1.34–1.43 (2H, m), 1.47–1.53 (2H, m), 3.18 (2H, t, *J*=7.0 Hz), 6.93–6.96 (1H, m), 7.20–7.24 (2H, m), 7.31–7.33 (2H, m); ^{13}C NMR (125 MHz, CD_3OD) δ 14.1 (q), 21.0 (t), 33.4 (t), 40.5 (t), 120.1 (d), 123.3 (d), 129.8 (d), 141.0 (s), 158.4 (s); HRMS *m*/*z*=193.1336 [M+H], calcd for $C_{11}H_{16}N_2O$=193.1335.

4.2.8. Compound 7b. Colorless solid; colorless solid; mp 169.5–170 °C; IR 3301, 1599, 1545, 1498, 1469, 1441, 1310, 1222 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 4.34 (2H, d, *J*=5.9 Hz), 6.65 (1H, t, *J*=5.9 Hz), 6.92–6.95 (1H, m), 7.24–7.30 (3H, m), 7.34–7.39 (4H, m), 7.44–7.46 (2H, m), 8.59 (1H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 43.7 (t), 118.6 (d), 122.0 (d), 127.7 (d), 128.1 (d), 129.3 (d), 129.6 (d), 141.3 (s), 141.4 (s), 156.2 (s); HRMS *m*/*z*=227.1178 [M+H], calcd for $C_{14}H_{15}N_2O$=227.1179.

4.2.9. Compound 7c. Colorless solid; mp 113–115 °C; IR 3271, 2961, 2930, 1630, 1594, 1525, 1501, 1444 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.32 (12H, d, *J*=7.0 Hz), 3.98 (2H, quartet, *J*=7.0 Hz), 6.21 (1H, br s), 6.98–7.16 (1H, m), 7.25–7.28 (2H, m), 7.35–7.32 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5 (q), 45.4 (d), 119.6 (d), 122.6 (d), 128.8 (d), 139.3 (s), 154.6 (s); HRMS *m*/*z*=221.1650 [M+H], calcd for $C_{13}H_{21}N_2O$=221.1648.

4.2.10. Compound 7d. Colorless solid; mp 243 °C; IR 3271, 3034, 1645, 1592, 1545, 1496, 1439 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 6.99–7.02 (2H, m), 7.30–7.34 (4H, m), 7.49–7.51 (4H, m), 8.70 (2H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 119.1 (d), 122.8 (d), 129.7 (d), 140.7 (s), 153.5 (s); HRMS *m*/*z*=213.1023 [M+H], calcd for $C_{13}H_{13}N_2O$=213.1022.

4.2.11. Compound 7e. Colorless solid; mp 97–99 °C; IR 3270, 3059, 2927, 1652, 1592, 1523, 1493, 1437 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.35 (3H, s), 6.23 (1H, br s), 6.97–7.01 (1H, m), 7.22–7.29 (4H, m), 7.33–7.39 (3H, m), 7.47–7.50 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.2 (q), 130.3 (d), 138.8 (s), 142.9 (s), 154.4 (s); HRMS *m*/*z*=227.1182 [M+H], calcd for $C_{14}H_{15}N_2O$=227.1179.

4.2.12. Compound 7f. Yellow solid; mp 106–107 °C; IR 3409, 1669, 1593, 1515, 1486, 1435 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.45 (1H, br s), 7.02–7.04 (1H, m), 7.25–7.42 (14H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 119.3 (d), 123.3 (d), 126.7 (d), 127.5 (d), 128.9 (d), 129.6 (d), 138.4 (s), 142.3 (s); HRMS *m*/*z*=289.1328 [M+H], calcd for $C_{19}H_{17}N_2O$=289.1335.

4.2.13. Compound 9. Colorless solid; mp >300 °C; IR 3305, 2934, 1693, 1641, 1543, 1514, 1416 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 1.46 (9H, s), 1.43–1.49 (4H, m),

1.54–1.58 (2H, m), 3.38 (4H, t, J=5.7 Hz), 7.27–7.30 (4H, m), 8.28 (1H, s), 9.13 (1H, br s); ^{13}C NMR (150 MHz, DMSO-d_6) δ 24.1 (t), 25.5 (t), 28.2 (q), 44.6 (t), 78.6 (s), 118.2 (d), 120.3 (d), 133.6 (s), 135.2 (s), 152.9 (s), 155.0 (s); HRMS m/z=320.1969 [M+H], calcd for $C_{17}H_{26}N_3O_3$=320.1969.

4.2.14. Compound 11. Colorless solid; mp 94–96 °C; IR cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19–1.23 (4H, m), 1.36 (9H, s), 1.32–1.40 (8H, m), 1.48–1.53 (2H, m), 2.88 (2H, q, J=6.6 Hz), 2.97 (2H, q, J=6.6 Hz), 3.22 (4H, t, J=5.3 Hz), 6.32 (1H, t, J=5.3 Hz), 6.76 (1H, t, J=5.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.2 (t), 25.4 (t), 26.1 (t), 26.1 (t), 28.3 (q), 29.5 (t), 29.9 (t), 44.3 (t), 77.3 (s), 155.6 (s), 157.3 (s); HRMS m/z=350.2412 [M+Na], calcd for $C_{17}H_{33}N_3O_3Na$=350.2414.

4.2.15. Compound 13. Colorless solid; mp 106–107 °C; IR 3309, 2940, 2923, 1713, 1631, 1442 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51–1.57 (4H, m), 1.61–1.66 (2H, m), 3.29 (2H, br dd, J=5.1, 5.1 Hz), 3.54 (2H, br dd, J=5.1, 5.1 Hz), 3.99 (2H, d, J=4.0 Hz), 5.11 (2H, s), 5.89 (1H, br s), 7.28–7.36 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.2 (t), 25.3 (t), 26.0 (t), 42.5 (t), 43.0 (t), 45.3 (t), 66.7 (t), 127.9 (d), 127.9 (d), 128.4 (d), 136.4 (s), 156.1 (s), 165.8 (s); HRMS m/z=277.1546 [M+H], calcd for $C_{15}H_{21}N_2O_3$=277.1547.

4.2.16. Compound 14. Colorless oil; IR 3348, 2980, 1707, 1523, 1367 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (3H, s), 1.41 (3H, s), 1.42 (3H, s), 3.63 (3H, s), 3.79–3.81 (2H, m), 5.31 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9 (q), 43.2 (t), 52.2 (q), 81.9 (s), 156.9 (s), 169.2 (s); HRMS m/z=212.0894 [M+Na], calcd for $C_8H_{15}NO_4Na$=212.0863.

4.2.17. Compound 15. Colorless oil; IR 3385, 2929, 2853, 1618, 1509, 1440, 1251, 1222 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47–1.64 (12H, m), 3.29–3.34 (6H, m), 3.50–3.54 (2H, m), 3.99 (2H, d, J=3.3 Hz), 5.62 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.3 (t), 24.3 (t), 25.3 (t), 25.5 (t), 26.0 (t), 42.5 (t), 43.0 (t), 44.7 (t), 45.2 (t), 157.1 (s), 167.2 (s); HRMS m/z=254.1859 [M+H], calcd for $C_{13}H_{24}N_3O_2$=254.1863.

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