The Ugi Five-Component Condensation Using CO_2, CS_2, and COS as Oxidized Carbon Sources

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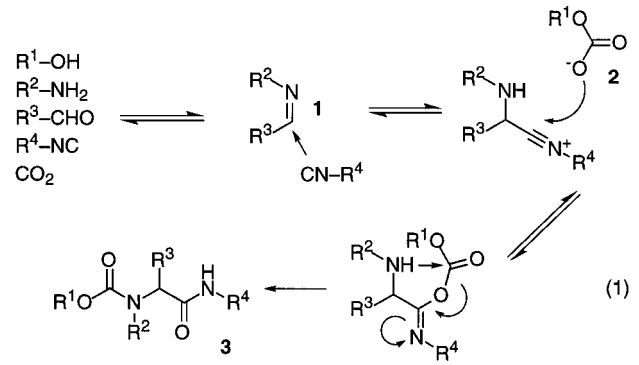
Multiple-component reactions hold great promise for combinatorial chemistry[1,2] because they can greatly reduce the time and effort needed to synthesize a library of compounds. We have focused on broadening the scope of known multiple-component reactions to facilitate the synthesis of a diverse range of core structures.[3−5] For example, by using a convertible isocyanide in the Ugi four-component condensation (4CC), we have transformed a library of initially formed α-acylaminoamides into amino acids and esters, pyrroles, sugar derivatives, and 1,4-benzodiazepine-2,5-diones.[6,7] Herein, we describe our investigations into the Ugi five-component condensation (5CC), which enables the synthesis of carbamate-protected aminoamide, aminothioamide, and thiourea-thioamide core structures in a single reaction.

The 5CC was originally reported by Ugi in 1961.[8] It involves the condensation of an alcohol, an amine, a carbonyl compound, an isocyanide, and carbon dioxide to yield an α-(alkoxylcarbonylamino)amide **3** (eq 1).



Presumably, the reaction proceeds through addition of the isocyanide to the imine **1** followed by acylation by the alkyl carbonate **2** which is formed from the alcohol and CO_2. An intramolecular acyl transfer is functionally irreversible and provides some driving force for the reaction. Looked at another way, the Ugi 5CC is the alkyl carbonic acid equivalent of the Ugi 4CC, which employs a carboxylic acid instead.

Only two literature examples of this reaction exist,[8] both of which employ methanol as the alcohol component. We decided to reinvestigate this reaction with a variety of inputs to test its generality as a combinatorial tool.

For low molecular weight/volatile alcohols such as methanol, ethanol, trifluoroethanol, etc., the alcohol was used as solvent for the reaction (the Ugi reaction has been shown to run well in a variety of solvents, including alcohols, methylene chloride, chloroform, and THF[9]). The solvent was presaturated at 0 °C with CO_2 by bubbling the gas through the cooled solvent. The remaining components were then added (amine, carbonyl compound, and isocyanide in 1.25:1:1 ratio), and the mixture was stirred overnight to 3 days at room temperature under a CO_2 atmosphere. An aqueous wash and chromatography yielded the product.

For higher a boiling or solid alcohols such as benzyl or 9-fluorenylmethyl, the alcohol was used in 10-fold excess with chloroform as solvent.[10]

The results are shown in Figure 1. Yields of product range from very good to poor and show that methanol is clearly the superior alcohol substrate. In all low-yielding examples the bulk of the starting material could be recovered; the only isolable byproducts were α-aminoamide and formamide, probably arising from water participation as the acid component in the Ugi 4CC and isocyanide hydrolysis, respectively. In the synthesis of compounds **6**, **8**, and **13**, in which the amine input is ammonia, the ammonia was either bubbled through the solvent (**6**) or supplied along with CO_2 as ammonium carbamate ($[H_2NCOO]^-[NH_4]^+$) (**8** and **13**).

From the results of the initial trials, a few improvements suggested themselves. The presence of aminoamide side products (from water participation) could be effectively eliminated by adding 3 Å molecular sieves to sequester the water produced from imine formation. Additionally, we expected that pressurizing the reaction with CO_2 would result in higher concentrations of dissolved gas and carbonic acid, and thus higher product yields. Using a Parr hydrogenation apparatus with CO_2 to run the Ugi 5CC at 23 psi over atmospheric pressure, we achieved modest yield improvements (e.g., **14**: 8−15%, **18**: <5−11%, **19**: <5−18%). We are investigating the effects of even higher pressures of CO_2 on the reaction.

The modest success of the CO_2 five-component condensation inspired us to consider CO_2 analogues. We thus investigated the use of CS_2 in place of CO_2 in the Ugi 5CC, to our knowledge an unprecedented reaction. The expected product would be **21** if the analogous

(1) For a recent, comprehensive review, see: Balkenhohl, F.; Bussche-Hünnefeld, C. v. d.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288−2337.

(2) For a recent, comprehensive review, see: Thompson, L. A.; Ellman, J. A. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 555−600.

(3) Armstrong, R. W.; Brown, S. D.; Keating, T. A.; Tempest, P. A. In *Combinatorial Chemistry: Synthesis and Application*; Wilson, S. R., Czarnik, A. W., Eds.; Wiley: New York, 1997; pp 153−190.

(4) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res* **1996**, *29*, 123−131.

(5) Tempest, P. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7607−7608.

(6) (a) Keating, T. A.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 8935−8939. (b) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574−2583. (c) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 7842−7843.

(7) For solid-supported applications of the Ugi 4CC for pyrrole synthesis, see: (a) Strocker, A. M.; Keating, T. A.; Tempest, P. A.; Armstrong, R. W. *Tetrahedron Lett.* **1996**, *37*, 1149−1152. (b) Mjalli, A. M. M.; Sarshar, S.; Baiga, T. J. *Tetrahedron Lett.* **1996**, *37*, 2943−2946 and references contained therein.

(8) Ugi, I.; Steinbrückner, C. *Chem. Ber.* **1961**, *94*, 2802−2814.

(9) Ugi, I.; Lohberger, S.; Karl, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 2; pp 1083−1109.

(10) Chloroform is one of the better organic solvents for CO_2, 0.012 mole fraction at 1 atm and 0 °C, as compared to mole fractions of 0.007 for methanol and 0.0007 for water. Hildebrand, J. H.; Scott, R. L. *The Solubility of Nonelectrolytes*, 3rd ed.; Reinhold Publishing Corp.: New York, 1950; pp 248−249.

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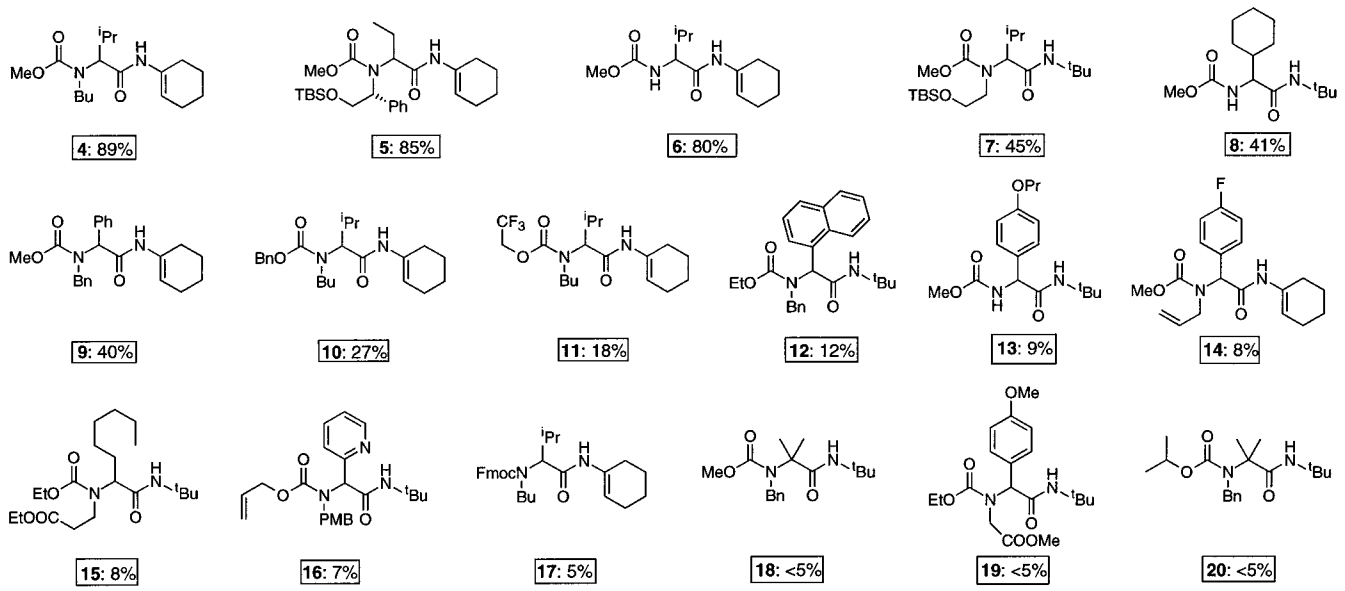

Figure 1. Products and isolated yields from the Ugi 5CC (Bn = benzyl, TBS = *tert*-butyldimethylsilyl, PMB = *p*-methoxybenzyl, Fmoc = 9-fluorenylmethoxycarbonyl).

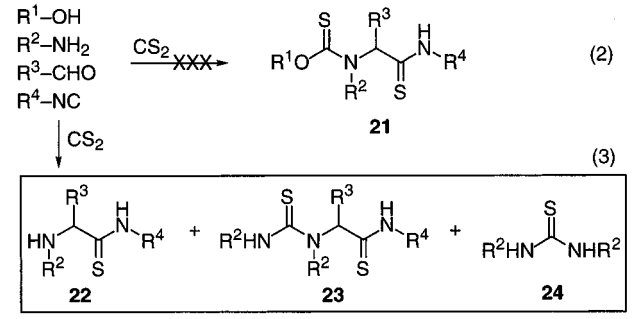

Figure 2. Expected (eq 2) and actual (eq 3) products from CS_2 5CC reaction.

reaction were to occur (Figure 2). However, we observed no **21** in the actual reaction, and instead only **22**−**24**, with the ratios of these three products dependent on the amine equivalency. No alcohol incorporation was seen.

Several observations suggest a plausible mechanism. First, product **24** was always observed in varying amounts. This is a known product of reaction between primary amines and CS_2, resulting from the loss of H_2S[11] (Figure 3). Apparently the amine is a much better nucleophile toward CS_2 even when the alcohol is present in much higher molarity. Second, when an excess of amine over aldehyde/isocyanide (>3 equiv) was employed, only products **22** and **24** were observed. Third, with 2 equiv or fewer of amine, all three products were seen, but product **23** was never present in > 50%.

We interpret these results as follows (Figure 3). Ugi has previously shown that $H_2S_2O_3$ (hydrogen thiosulfate) can serve as an acid in the 4CC[9,12] to yield aminothioamide products **22**. H_2S produced from the formation of **24**[11] is most likely operating analogously, as shown in Figure 3. The route to product **23** is similar to the CO_2 Ugi 5CC route except the acylating agent is not an alkyl carbonate nor a xanthate but rather the dithiocarbamate[11] species **25**. An excess of amine seems to serve only to increase the amounts of **24** and H_2S and therefore increases production of **22** at the expense of **23**.

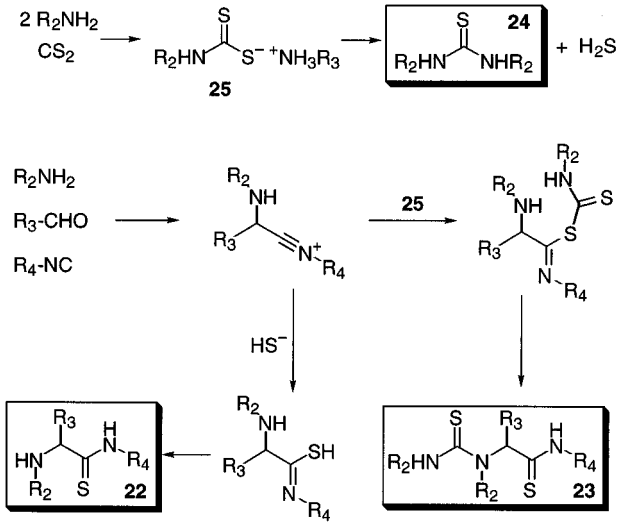

Figure 3. Proposed mechanism for CS_2 analogue of the Ugi 5CC.

We conclude that the Ugi reaction with CS_2 is most useful in its 4CC incarnation to yield α-aminothioamides **22**, because this product can be isolated as the major product, with the only byproduct being the (unavoidable) thiourea **24**. The thiourea−thioamide **23**, while an interesting 5CC product, cannot be produced cleanly. At the heart of this mechanism is the instability of dithiocarbamate **25**. Reaction to form thiourea **24** occurs to liberate hydrogen sulfide even at −78 °C. Attempts to sequester H_2S with 4 Å molecular sieves were unsuccessful, as were attempts to synthesize thiocarbamate−thioamide **21** by adding a separately formed xanthate species. Figure 4 shows several α-aminothioamides that have been synthesized in fair to high yield, in all cases with a 4:1:1:1 amine:aldehyde:isocyanide:CS_2 ratio in methylene chloride. It must be noted again, however, that it would be easier to synthesize the compounds in

(11) Dunn, A. D.; Rudorf, W.-D. *Carbon Disulphide in Organic Chemistry*; Ellis Horwood Ltd.: Chichester, England, 1989; pp 226−367.

(12) Ugi, I.; Steinbrückner, C. *Angew. Chem.* **1960**, *72*, 267.

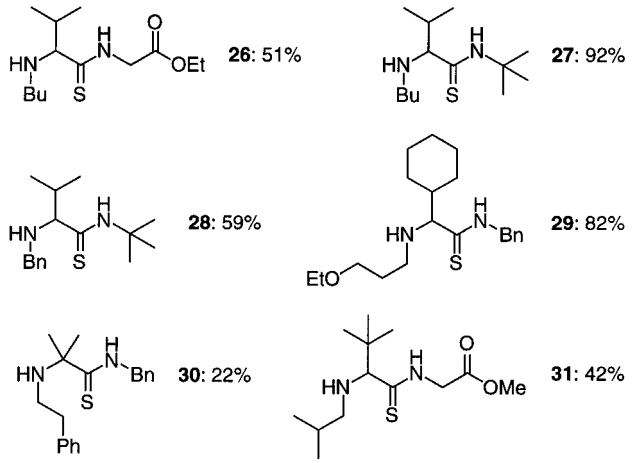

Figure 4. α-Amino thioamides and isolated yields from the CS_2 4CC.

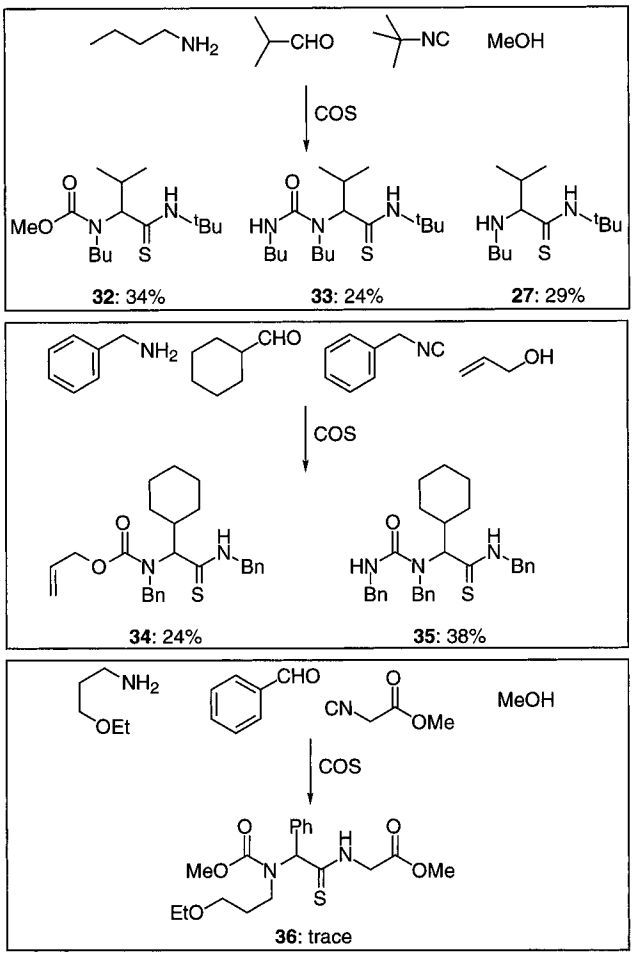

Figure 5. The Ugi 5CC with carbonyl sulfide.

Figure 4 via the known Ugi 4CC route using H_2S or $H_2S_2O_3$ as the acid, as there are no thiourea byproducts.

Finally, we discovered that carbonyl sulfide, COS, can also be used in an analogous Ugi 5CC (Figure 5). Given the different reaction paths for CO_2 and CS_2 detailed above, the results of this experiment are particularly interesting. The procedure consists of combining the amine and aldehyde components in the alcohol as solvent and then bubbling the COS (bp = −50 °C) through the solution at −78 °C. The isocyanide is then added, and the reaction is allowed to slowly warm to room temperature, venting to permit COS escape.

In the three examples shown in Figure 5, the carbamate−thioamides **32**, **34**, and **36** were formed consistently, although in varying yields (we do not know why the yield of **36** was so poor). These three products arise from a mechanism analogous to the original CO_2 5CC route: alcohol addition to COS produces **37**, which acylates the isocyanide carbon (eq 1) with the more nucleophilic sulfur end of the thiocarbonate, resulting in the products shown, instead of the sulfur/oxygen switched thiocarbamate−amides.

Likewise, urea−thioamides **33** and **35** were formed from acylation of the same isocyanide carbon with **38** (the amine−COS addition product), again with the sulfur acting as nucleophile. As with the carbamate−thioamides, none of the products with sulfur and oxygen reversed was observed. Product **27** can be possibly accounted for by addition of HS^- to the isocyanide carbon, as in the CS_2 series of reactions. The thiolate anion could have been produced from decomposition of the ammonium salts of **37** and **38**; however, the analogue of **27**

was not observed in two of the three COS reactions. The 5CC with COS thus constitutes a valuable "labeling" experiment in two respects. Not only do the products shed light on the course of the reaction but the specific placement of the sulfur and oxygen atoms by the reaction results in complex products with minimal synthetic effort.

In conclusion, the Ugi five-component condensation has proved to be a useful tool for the synthesis of *N*-(alkoxylcarbonyl)aminoamides. In addition, the use of CS_2 and COS in this reaction has led to unexpected products and to a useful, alternative one-step synthesis of aminothioamides in the case of CS_2 and novel carbamate−thioamides and urea−thioamides in the case of COS. The mechanism and products of these reactions are intriguing and will be explored further in expanded scope.

Experimental Section

General Procedures. All reactions unless otherwise indicated were performed in oven- or flame-dried glassware under an inert atmosphere. Solvents were distilled immediately prior to use. Anhydrous chloroform was purchased from Aldrich and used directly. NMR spectra were obtained with a Bruker ARX-500, ARX-400, or AM-360 spectrometer in a $CDCl_3$ solvent and referenced to residual $CHCl_3$. Coupling constants are listed in hertz.

General Procedure for Ugi 5CC Using Unpressurized Carbon Dioxide. The amine (1.25 equiv) and the aldehyde/ketone (1.0 equiv) were combined neat. Solvent (the neat alcohol for methanol, ethanol, allyl alcohol, 2-propanol; chloroform for benzyl alcohol and 9-fluorenylmethanol) that had been saturated with carbon dioxide at 0 °C with a gas bubbler was added to achieve a final concentration of approximately 0.1 M. The isocyanide (1.0 equiv) was added (and for benzyl alcohol and 9-fluorenylmethanol, 10 equiv of the alcohol), and a slight positive pressure of carbon dioxide was maintained over the reaction while stirring for 18−24 h. The solvent was then evaporated, and the residue taken up in ethyl acetate, washed with saturated sodium bicarbonate, and dried with sodium sulfate. The residue after solvent evaporation was chromatographed on silica gel, eluting with a 100% hexanes to 1:1 hexanes:ethyl acetate gradient.

General Procedure for Ugi 5CC Using Pressurized Carbon Dioxide. The procedure was identical with that described above except the reagents were combined in a Parr pressure bottle with 3 Å molecular sieves and the reaction was placed under 23 psi carbon dioxide using a Parr hydrogenation apparatus.

General Procedure for Ugi 5CC Using Carbon Disulfide. The amine (4.0 equiv) and the aldehyde/ketone (1.0 equiv) were combined in CH_2Cl_2 to a concentration of approximately 1 M. The isocyanide (1.0 equiv) and carbon disulfide (Aldrich, 1.0 equiv) were added, and the reaction was stirred for 12−18 h. After the solvent was evaporated, the residue was chromatographed on silica gel, eluting with a 100% hexanes to 1:1 hexanes:ethyl acetate gradient. In addition to the compounds described below, varying amounts of the symmetrical thiourea resulting from amine and CS_2 condensation were isolated. If 2.0 equiv of amine were used, the thiourea-thioamide described in the text was also isolated.

General procedure for Ugi 5CC using carbonyl sulfide. The amine (2 equivalents) and the aldehyde (1 equivalent) were combined neat. The flask was cooled to −78 °C and 5 mL alcohol was added. COS was bubbled into this cooled solution, thus adding COS as a cosolvent (COS bp = −50 °C). The isocyanide was added, and the flask was capped and allowed to warm to room-temperature overnight, venting to allow COS to escape. Reaction workup and purification was performed as described in the General Procedures.

Compound 4. Yield = 89%. ^{1}H NMR (360 MHz): δ 7.62 (s, 1), 6.03 (s, 1), 3.68 (s, 4), 3.22−3.18 (m, 1), 3.13−3.05 (m, 1), 2.37 (m, 1), 2.05−2.03 (m, 4), 1.64−1.40 (m, 6), 1.19 (td, 2, J = 7.3, 7.3), 0.92 (d, 3, J = 6.5), 0.84 (t, 3, J = 7.3), 0.81 (d, 3, J = 6.4). HRMS (EI): m/z (M^+) calcd 310.2256, found 310.2259.

Compound 5. Yield = 85% of a 1:1 mixture of inseparable diastereomers. ^{1}H NMR (both diastereomers) (500 MHz): δ 8.65 (s, 1), 8.29 (s, 1), 7.32 (m, 5), 6.08 (s, 1), 5.71 (s, 1), 5.50 (s, 1), 5.00 (s, 1), 4.33−3.99 (m, 4), 3.77 (m, 1), 3.70 (s, 3), 3.49 (m, 1), 2.30−2.00 (m, 5), 1.90−1.60 (m, 5), 0.93−0.86 (m, 11), 0.41 (m, 3), 0.12 (m, 2), 0.06 (s, 6). HRMS (EI): m/z (M^+) calcd 474.2914, found 474.2919.

Compound 6. Yield = 80%. ^{1}H NMR (major rotamer) (400 MHz): δ 7.62 (s, 1), 6.04 (s, 1), 5.72 (d, 1, J = 6.0), 4.01 (t, 1, J = 7.8), 3.67 (s, 3), 2.14−2.04 (m, 5), 1.64−1.51 (m, 4), 0.94−0.90 (m, 9). ^{13}C NMR (major rotamer) (101 MHz): δ 170.0, 157.3, 132.5, 113.6, 60.9, 58.8, 31.4, 27.8, 24.0, 22.5, 21.4, 19.2, 18.1. HRMS (EI): m/z (M^+) calcd 254.1630, found 254.1636.

Compound 7. Yield = 45%. ^{1}H NMR (360 MHz): δ 6.13 (s, 1), 3.71 (d, 1, J = 11.3), 3.67 (s, 3), 3.57 (t, 2, J = 7.2), 3.36 (m, 1), 3.24 (m, 1), 2.27 (m, 1), 1.26 (s, 9), 0.89 (d, 3, J = 6.7), 0.83 (s, 9), 0.78 (d, 3, J = 6.7), 0.03 (s, 3), 0.00 (s, 3). ^{13}C NMR (91 MHz): δ 169.9, 157.5, 67.4, 60.5, 52.8, 50.9, 46.5, 28.5, 26.6, 25.8, 25.6, 19.6, 18.7, 18.2, −5.4, −5.5. HRMS (EI): m/z [(M + H)$^+$] calcd 389.2836, found 389.2835.

Compound 8. Yield = 41%. ^{1}H NMR (360 MHz): δ 5.97 (s, 1), 5.50 (d, 1, J = 8.7), 3.83 (t, 1, J = 7.7), 3.64 (s, 3), 1.72−1.63 (m, 6), 1.32 (s, 9), 1.25−0.93 (m, 5). HRMS (EI): m/z [(M + H)$^+$] calcd 271.2022, found 271.2017.

Compound 9. Yield = 40%. ^{1}H NMR (360 MHz): δ 7.37−7.09 (m, 10), 7.02 (s, 1), 6.04 (s, 1), 5.52 (s, 1), 4.66 (d, 1, J = 15.9), 3.35 (d, 1, J = 16.0), 2.10−1.90 (m, 4), 1.70−1.50 (m, 4). HRMS (EI): m/z (M^+) calcd 378.1943, found 378.1950.

Compound 10. Yield = 27%. ^{1}H NMR (360 MHz): δ 7.62 (s, 1), 7.34 (m, 5), 6.06 (s, 1), 5.16 (s, 2), 3.69 (d, 1, J = 9.7), 3.35−3.27 (m, 1), 3.22−3.14 (m, 1), 2.45 (m, 1), 2.10−1.95 (m, 4), 1.70−1.45 (m, 6), 1.22 (td, 2, J = 7.3, 7.3), 0.97 (d, 3, J = 6.5). HRMS (EI): m/z (M^+) calcd 386.2569, found 386.2573.

Compound 11. Yield = 18% of an approximately 2:1 mixture of rotational isomers. NMR data are listed for each isomer, when resonances from each can be identified. ^{1}H NMR (360 MHz): (major) δ 7.30 (s, 1), 6.08 (s, 1), 4.59−4.39 (m, 2), 3.72 (d, 1, J = 11.1), 3.33 (td, 1, J = 7.1, 7.1), 3.19 (td, 1, J = 7.1, 7.1), 2.42 (m, 1), 2.19 (m, 2), 2.10−2.08 (m, 4), 1.69−1.49 (m, 4), 1.36 (dq, 1, J = 7.6, 7.6), 1.25 (dq, 1, J = 7.4, 7.4), 0.97 (t, 3, J = 6.7), 0.88 (d, 3, J = 9.8), 0.88 (d, 3, J = 4.3); (minor) δ 7.30 (s, 1), 5.29 (s, 1), 4.59−4.39 (m, 2), 4.10 (d, 1, J = 2.7), 3.60 (m, 1), 3.05 (m, 1), 2.42 (m, 1), 2.19 (m, 2), 2.10−2.08 (m, 4), 1.69−1.49 (m, 4), 1.36 (dq, 1, J = 7.6, 7.6), 1.25 (dq, 1, J = 7.4, 7.4), 1.15 (d, 3, J = 7.0), 1.01 (d, 3, J = 6.7), 0.93 (t, 3, J = 6.9). HRMS (EI): m/z (M^+) calcd 378.2130, found 378.2135.

Compound 12. Yield = 12%. ^{1}H NMR (400 MHz): δ 8.10−7.25 (m, 7), 7.0−6.5 (m, 5), 5.50 (s, 1), 4.81 (s, 1), 4.50−4.20 (m, 2), 3.89 (d, 1, J = 13.1), 3.85 (d, 1, J = 13.1), 1.39 (s, 9), 1.28−1.23 (m, 3). HRMS (FAB): m/z [(M + H)$^+$] calcd 419.2335, found 419.2336.

Compound 13. Yield = 9%. ^{1}H NMR (500 MHz): δ 7.29 (d, 2, J = 9.3), 6.91 (d, 2, J = 10.6), 6.09 (s, 1), 5.55 (s, 1), 5.08 (d, 1, J = 3.6), 3.94 (t, 2, J = 6.6), 3.67 (s, 3), 1.83 (td, 2, J = 7.1, 7.1), 1.32 (s, 9), 1.06 (t, 3, J = 7.4). ^{13}C NMR (126 MHz): δ 169.2, 159.0, 156.3, 130.6, 128.4, 114.8, 69.5, 58.3, 52.2, 51.6, 28.5, 22.5, 10.5. HRMS (EI): m/z (M^+) calcd 323.1971, found 323.1967.

Compound 14. Yield = 8%, 15% when repeated using pressurized CO_2. ^{1}H NMR (360 MHz): δ 7.35 (dd, 2, J = 8.5, 5.4), 7.02 (t, 2, J = 8.6), 6.76 (s, 1), 6.08 (s, 1), 5.61 (s, 1), 5.60−5.50 (m, 1), 4.96−4.88 (m, 2), 3.93 (dd, 1, J = 16.2, 6.0), 3.75 (dd, 1, J = 16.2, 6.1), 3.69 (s, 3), 2.07 (m, 4), 1.67−1.63 (m, 2), 1.55−1.52 (m, 2). HRMS (FAB): m/z [(M + H)$^+$] calcd 347.1771, found 347.1767.

Compound 15. Yield = 8%. ^{1}H NMR (400 MHz): δ 6.05 (s, 1), 4.12 (q, 2, J = 6.8), 4.07 (q, 2, J = 7.1), 3.46 (m, 1), 2.58−2.40 (m, 2), 1.85 (m, 1), 1.58 (m, 1), 1.27 (s, 9), 1.25−1.18 (m, 12), 0.82 (m, 3). HRMS (EI): m/z [(M + H)$^+$] calcd 387.2859, found, 387.2863.

Compound 16. Yield = 7%. ^{1}H NMR (400 MHz): δ 8.48 (dd, 1, J = 4.1, 0.8), 7.58 (td, 1, J = 7.8, 1.8), 7.32 (d, 1, J = 7.9), 7.15 (dd, 3, J = 7.1, 5.0), 6.75 (d, 2, J = 8.4), 5.82 (m, 1), 5.12 (m, 3), 4.61 (m, 4), 3.74 (s, 3), 1.27 (s, 9). ^{13}C NMR (101 MHz): δ 167.1, 158.8, 156.7, 156.5, 148.2, 136.6, 132.4, 129.9, 129.6, 123.5, 122.4, 117.4, 113.7, 66.4, 65.3, 55.2, 51.1, 50.9, 28.5. HRMS (EI): m/z [(M + H)$^+$] calcd 412.2236, found 412.2229.

Compound 17. The alkyl carbonate formed from 9-fluorenylmethanol precipitated from chloroform, limiting its concentration and therefore perhaps yields. Yield = 5%. ^{1}H NMR (400 MHz): δ 7.76 (d, 2, J = 7.5), 7.57 (d, 2, J = 7.4), 7.40 (t, 2, J = 7.4), 7.31 (t, 2, J = 7.4), 6.05 (s, 1), 4.58 (t, 2, J = 6.3), 4.23 (t, 1, J = 5.5), 3.63 (d, 1, J = 10.1), 3.10−2.94 (m, 2), 2.38 (m, 1), 2.07 (m, 4), 1.67−1.54 (m, 4), 1.26 (m, 2), 1.04 (td, 2, J = 7.3, 7.3), 0.94 (d, 3, J = 6.2), 0.81 (d, 3, J = 6.2), 0.79 (t, 3, J = 7.6). HRMS (EI): m/z (M^+) calcd 474.2882, found 474.2874.

Compound 18. Yield = 4%, 11% when repeated using pressurized CO_2. ^{1}H NMR (360 MHz): δ 7.31−7.23 (m, 5), 5.50 (s, 1), 4.61 (s, 2), 3.72 (s, 3), 1.35 (s, 6), 1.22 (s, 9). HRMS (EI): m/z [(M + H)$^+$] calcd 307.2022, found 307.2021.

Compound 19. Yield = 3% of a 1.7:1 mixture of rotational isomers, 18% when repeated using pressurized CO_2. NMR data are listed for each isomer, when resonances from each can be identified. ^{1}H NMR (400 MHz): (major) δ 8.07 (s, 1), 7.16 (d, 2, J = 8.3), 6.88 (d, 2, J = 8.1), 5.37 (s, 1), 4.25−4.17 (m, 2), 3.93−3.70 (m, 2), 3.80 (s, 3), 3.70 (s, 3), 1.43 (s, 9), 1.32 (t, 3, J = 7.0); (minor) δ 8.07 (s, 1), 7.23 (d, 2, J = 7.8), 6.88 (d, 2, J = 8.1), 5.67 (s, 1), 4.25−4.17 (m, 2), 3.91 (d, 1, J = 17.7), 3.80 (s, 3), 3.62 (s, 3), 3.35 (d, 1, J = 17.7), 1.39 (s, 9), 1.22 (t, 3, J = 6.7). ^{13}C NMR (101 MHz): (both rotamers) δ 172.6, 171.4, 169.4, 168.9, 159.8, 159.6, 156.2, 130.8, 127.2, 126.7, 98.7, 68.4, 65.5, 63.6, 62.6, 62.2, 55.3, 52.4, 52.1, 51.5, 51.4, 51.1, 46.4, 46.1, 28.6, 14.6. HRMS (EI): m/z [(M + H)$^+$] calcd 381.2026, found 381.2021.

Compound 20. Yield = 2%. ^{1}H NMR (400 MHz): δ 7.35−7.27 (m, 5), 5.55 (s, 1), 5.00 (qq, 1, J = 6.3, 6.3), 4.63 (s, 2), 1.39 (s, 6), 1.28 (d, 6, J = 6.3), 1.24 (s, 9). ^{13}C NMR (101 MHz): δ 174.1, 156.3, 140.4, 128.9, 127.2, 127.1, 69.8, 63.3, 50.6, 47.5, 28.5, 25.1, 22.1. HRMS (EI): m/z [(M + H)$^+$] calcd 335.2335, found 335.2330.

Compound 26. Yield = 51%. ^{1}H NMR (400 MHz): δ 9.91 (s, 1), 4.38 (dd, 1, J = 18.8, 3.5), 4.28 (dd, 1, J = 18.9, 2.5), 4.12 (q, 2, J = 7.1), 3.29 (d, 1, J = 3.3), 2.45−2.36 (m, 3), 1.35 (tt, 2, J = 7.3, 7.3), 1.24 (m, 2), 1.18 (t, 3, J = 7.2), 0.94 (d, 3, J = 7.1), 0.78 (t, 3, J = 7.3), 0.63 (d, 3, J = 7.0). ^{13}C NMR (101 MHz): δ 205.1, 168.2, 75.0, 61.2, 48.8, 45.9, 32.8, 31.9, 20.0, 19.9, 15.3, 13.8, 13.6. HRMS (EI): m/z (M^+) calcd 275.1793, found 275.1798.

Compound 27. Yield = 92%. ^{1}H NMR (400 MHz): δ 9.45 (s, 1), 3.02 (dd, 1, J = 3.1, 2.6), 2.41−2.33 (m, 2), 2.24−2.17 (m, 1), 1.39 (s, 9), 1.38−1.16 (m, 5), 0.87 (dd, 3, J = 7.1, 2.0), 0.74 (td, 3, J = 7.1, 2.1), 0.52 (dd, 3, J = 7.0, 1.8). ^{13}C NMR (101

MHz): δ 201.0, 76.5, 53.8, 48.5, 32.2, 31.9, 27.1, 20.1, 19.9, 14.9, 13.5. HRMS (EI): *m*/*z* (M^+) calcd 244.1973, found 244.1970.

Compound 28. Yield = 59%. ^{1}H NMR (400 MHz): δ 9.46 (s, 1), 7.34−7.21 (m, 5), 3.61 (d, 1, J = 13.2), 3.58 (d, 1, J = 13.3), 2.54 (m, 1), 1.69 (s, 1), 1.51 (s, 9), 0.98 (d, 3, J = 7.1), 0.70 (d, 3, J = 7.0). ^{13}C NMR (101 MHz): δ 200.7, 139.0, 128.4, 128.0, 127.2, 76.3, 54.2, 53.0, 32.5, 27.3, 20.2, 15.3. HRMS (EI): *m*/*z* [$(M + H)^+$] calcd 279.1895, found 279.1894.

Compound 29. Yield = 82%. ^{1}H NMR (500 MHz): δ 9.88 (s, 1), 7.37−7.29 (m, 5), 4.91 (dd, 1, J = 15.1, 4.1), 4.80 (dd, 1 J = 15.1, 3.3) 3.45−3.42 (m, 3), 3.40 (q, 2, J = 7.0), 2.58 (m, 2), 2.25 (m, 1), 1.77−1.64 (m, 7), 1.45−1.30 (m, 2), 1.35−1.18 (m, 2), 1.17 (t, 3, J = 7.0), 1.10−1.00 (m, 1), 0.87 (qd, 1, J = 12.5, 3.5). ^{13}C NMR (126 MHz): δ 203.3, 136.1, 128.2, 127.4, 127.2, 75.1, 69.1, 65.7, 48.3, 47.3, 42.6, 30.5, 29.2, 25.9, 25.8, 25.7 (2), 14.7. HRMS (EI): *m*/*z* (M^+) calcd 348.2235, found 348.2230.

Compound 30. Yield = 22%. ^{1}H NMR (400 MHz): δ 9.86 (br, 1), 7.35−7.09 (m, 10), 4.66 (s, 2), 2.74−2.70 (m, 2), 2.66−2.63 (m, 2), 1.49 (s, 6). ^{13}C NMR (101 MHz): δ 208.3, 139.5, 136.8, 128.6, 128.4, 127.7, 127.6, 126.3, 63.8, 49.0, 44.7, 36.9, 28.7. HRMS (EI): *m*/*z* (M^+) calcd 313.1738, found 313.1732.

Compound 31. Yield = 42%. ^{1}H NMR (400 MHz): δ 9.29 (br, 1), 4.45 (dd, 1, J = 18.8, 5.0), 4.36 (dd, 1, J = 18.8, 4.7), 3.72 (s, 3), 3.32 (s, 1), 2.26 (dd, 1, J = 11.5, 6.0), 2.16 (dd, 1, J = 11.5, 7.4), 1.65 (dqq, 1, J = 6.7, 6.7, 6.7), 1.60 (br, 1), 0.98 (s, 9), 0.86 (d, 3, J = 6.7), 0.83 (d, 3, J = 6.7). ^{13}C NMR (101 MHz): δ 204.1, 168.9, 79.7, 56.3, 52.2, 46.0, 34.0, 28.3, 27.4, 20.4, 20.3. HRMS (EI): *m*/*z* (M^+) calcd 274.1715, found 274.1722.

Compound 32. Yield = 34%. ^{1}H NMR (400 MHz): δ 3.69 (s, 3), 3.61 (d, 1, J = 9.1), 3.34 (m, 1), 3.21 (m, 1), 2.69 (m, 1), 1.59−1.50 (m, 2), 1.48 (s, 9), 1.22 (tq, 2, J = 7.6, 7.6), 0.98 (d, 3, J = 6.6), 0.87 (t, 3, J = 7.3), 0.85 (d, 3, J = 6.5). ^{13}C NMR (101 MHz): δ 200.6, 158.1, 55.0, 52.7, 50.7, 30.8, 28.3, 27.2, 20.1, 19.9, 19.8, 13.7. HRMS (EI): *m*/*z* (M^+) calcd 302.2028, found 302.2019.

Compound 33. Yield = 24%. ^{1}H NMR (500 MHz): δ 4.43 (s, 1), 3.36−3.26 (m, 3), 3.19−3.13 (m, 1), 2.79 (s, 1), 1.70−1.51 (m, 4), 1.54 (s, 9), 1.40 (tq, 2, J = 7.6, 7.6), 1.32 (tq, 2, J = 7.4, 7.4), 1.03 (d, 3, J = 6.6), 0.97 (t, 3, J = 7.3), 0.96 (t, 3, J = 7.3), 0.88 (d, 3, J = 6.5). ^{13}C NMR (126 MHz): δ 201.1, 158.9, 83.0, 54.8, 40.4, 32.4, 30.8, 28.6, 27.2, 20.5, 20.2, 20.0, 13.8 (2). HRMS (EI): *m*/*z* (M^+) calcd 343.2657, found 343.2656.

Compound 34. Yield = 24%. ^{1}H NMR (400 MHz): δ 9.78 (br, 1), 7.37−7.26 (m, 10), 5.87−5.79 (m, 1), 5.25−5.17 (m, 2), 4.87 (dd, 1, J = 15.2, 5.0), 4.79 (d, 1, J = 14.4), 4.77 (dd, 1, J = 14.9, 5.1), 4.62−4.53 (m, 2), 4.45 (d, 1, J = 15.2), 4.10 (m, 1), 2.45 (m, 1), 1.79 (d, 1, J = 11.8), 1.68 (d, 1, J = 13.1), 1.56 (t, 2, J = 14.3), 1.44 (d, 1, J = 12.8), 1.23−1.11 (m, 2), 1.03 (t, 1, J = 12.3), 0.91 (m, 1), 0.40 (br, 1). ^{13}C NMR (101 MHz): δ 201.5, 157.3, 137.3, 136.3, 132.2, 128.7, 128.6, 128.3, 127.8, 127.6, 127.5, 117.9, 66.6, 49.9, 37.1, 30.6, 29.8, 26.0, 25.36, 25.5. HRMS (EI): *m*/*z* (M^+) calcd 436.2185, found 436.2193.

Compound 35. Yield = 38%. ^{1}H NMR (400 MHz): δ 7.30−7.20 (m, 15), 6.91 (br, 2), 4.90 (d, 1, J = 15.1), 4.89 (d, 1, J = 15.1), 4.80 (d, 1, 15.1), 4.79 (d, 1, J = 15.1), 4.44 (d, 1, 17.1), 4.26−4.22 (m, 2), 2.55 (br, 1), 1.88 (m, 1), 1.76−1.66 (m, 4), 1.31−1.17 (m, 3), 1.00−0.97 (m, 2). ^{13}C NMR (101 MHz): δ 202.3, 159.2, 138.6, 137.0, 136.4, 129.0, 128.7, 128.5, 127.9, 127.7, 127.6, 127.1, 126.9, 126.7, 49.5, 44.7, 38.1, 30.9, 26.3, 25.7. HRMS (EI): *m*/*z* (M^+) calcd 485.2501, found 485.2505.

Compound 36. Yield = trace (not completely purified). ^{1}H NMR (360 MHz): δ 9.20 (br, 1), 7.37−7.35 (m, 5), 5.93 (s, 1), 4.60 (dd, 1, J = 19.0, 4.8), 4.36 (dd, 1, J = 19.0, 4.8), 3.78 (s, 3), 3.73 (s, 3), 3.50−3.40 (m, 2), 3.37 (q, 2, J = 7.0), 1.72−1.55 (m, 4), 1.13 (t, 3, J = 7.0). HRMS (EI): *m*/*z* (M^+) calcd 382.1562, found 382.1565.

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Supporting Information Available: ^{1}H NMR spectra (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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