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Synthesis of Amides and Lactams in Supercritical Carbon Dioxide

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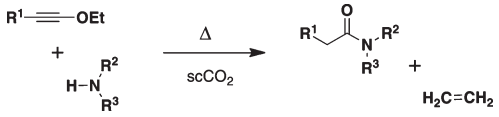

Supercritical carbon dioxide can be employed as an environmentally friendly alternative to conventional organic solvents for the synthesis of a variety of carboxylic amides. The addition of amines to ketenes generated in situ via the retro-ene reaction of alkynyl ethers provides amides in good yield, in many cases with ethylene or isobutylene as the only byproducts of the reaction. Reactions with ethoxy alkynes are performed at 120−130 °C, whereas *tert*-butoxy derivatives undergo the retro-ene reaction at 90 °C. With the exception of primary, unbranched amines, potential side reactions involving addition of the amines to carbon dioxide are not competitive with the desired C−N bond-forming reaction. The amide synthesis is applicable to the preparation of β-hydroxy and β-amino amide derivatives, as well as amides bearing isolated carbon−carbon double bonds. Preliminary experiments aimed at developing an intramolecular variant of this process to afford macrolactams suggest that the application of CO_2/co-solvent mixtures may offer advantages for the synthesis of large-ring compounds.

Introduction

A major goal of research in "green chemistry" involves the replacement of conventional organic solvents with more "environmentally friendly" alternatives.[1] Supercritical carbon dioxide ($scCO_2$) has attracted considerable attention in recent years as an alternative to conventional solvents for organic synthesis.[2] This interest derives from the fact that carbon dioxide is relatively nontoxic and nonflammable, inexpensive, and widely available and poses minimal problems with regard to waste disposal. The tunable solvent properties of $scCO_2$ have also attracted interest, as relatively small changes in temperature and pressure often allow for significant changes in viscosity, density, and self-diffusivity.[2] The successful application of $scCO_2$ as a reaction solvent for a variety of synthetic transformations is now well documented. To date, however, only a few examples have been reported of carbon−nitrogen bond formation in $scCO_2$,[3] principally due to the facility of the reaction of amines with this electrophilic solvent (vide infra). One goal of our program is the development of general strategies for the utilization of amines (and amine derivatives) in $scCO_2$, and the application of these strategies in C−N bond-forming reactions and the synthesis of nitrogen heterocycles.

The carboxamide functional group occurs in the structure of 25% of known pharmaceuticals according to a 1999 analysis of the Comprehensive Medicinal Chemistry database.[4] A recent study of the syntheses of drug candidates at

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(3) For examples, see: (a) Jessop, P. G.; Hsiao, Y.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 344. (b) Wittmann, K.; Wisniewski, W.; Mynott, R.; Leitner, W.; Kranemann, C. L.; Rische, T.; Eilbracht, P.; Kluwer, S.; Ernsting, J. M.; Elsevier, C. J. *Chem.—Eur. J.* **2001**, *7*, 4584. (c) Shi, M.; Cui, S.-C.; Li, Q.-J. *Tetrahedron* **2004**, *60*, 6163. (d) Smith, C. J.; Early, T. R.; Holmes, A. B.; Shute, R. E. *Chem. Commun.* **2004**, 1976. (e) Smith, C. J.; Tsang, M. W. S.; Holmes, A. B.; Danheiser, R. L.; Tester, J. W. *Org. Biomol. Chem.* **2005**, *3*, 3767. (f) Dunetz, J. R.; Ciccolini, R. P.; Fröling, M.; Paap, S. M.; Allen, A. J.; Holmes, A. B.; Tester, J. W.; Danheiser, R. L. *Chem. Commun.* **2005**, 4465. (g) Fuchter, M. J.; Smith, C. J.; Tsang, M. W. S.; Boyer, A.; Saubern, S.; Ryan, J. H.; Holmes, A. B. *Chem. Commun.* **2008**, 65.

(4) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*, 55.

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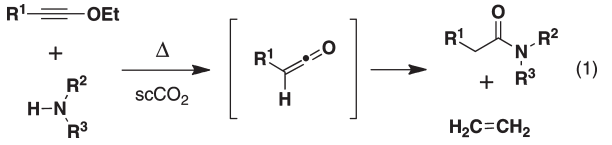
Pfizer, GSK, and AstraZeneca revealed that acylations of amines (to produce amides) comprise fully 8% of all of the reactions involved in the 128 syntheses surveyed![5] Amide bond formation generally requires initial conversion of the carboxylic acid component to an "activated" acyl derivative, which is then reacted in situ or in a second step with an amine.[6] In the recent survey of drug candidate syntheses cited above,[5] acid chlorides were found to be the most common acylating agents employed in amide bond formation. Mixed anhydrides were the next most frequently used derivatives, followed by various activated carboxyl species generated by the reaction of acids with "coupling agents" such as carbonyldiimidazole and carbodiimides. Although the use of acid chlorides and mixed anhydrides may be economically attractive, none of these standard methods are atom-economical, some involve toxic reagents (many diimides are sensitizers), and all are carried out in volatile organic solvents and result in the production of considerable quantities of chemical waste.[7]

The aim of this investigation was the development of a method for amide bond formation compatible with the use of $scCO_2$ as the reaction medium. In this initial study we focused our attention on the reaction of amines with ketenes generated in situ by the retro-ene reaction of alkynyl ethers (eq 1). In this process, $scCO_2$ would function as an environmentally friendly "replacement solvent" and might also provide important advantages in intramolecular applications leading to medium- and large-ring lactams (vide infra). A particularly noteworthy feature of this atom-economical approach would be the formation of ethylene as the only byproduct of the reaction. Provided that side reactions were minimal and starting materials were completely consumed, simple depressurization could potentially provide the amide products free from contamination by solvent residues in what would constitute an exceptionally green process.



At the outset of this study, we recognized that a potential obstacle toward the successful implementation of the proposed method would be the reactivity of carbon dioxide toward basic amino groups. It is well documented that nucleophilic amines react reversibly with carbon dioxide to form carbamic acids of type **1** and ammonium carbamate salts of type **2** (eq 2).[8] This can pose a significant challenge to the transfer of C−N bond-forming reactions from conventional solvents to $scCO_2$, as the formation of carbamic acids (and salts) can inhibit the reaction of the amine in the desired fashion and can lead to the formation of undesired byproducts and polymers. A key to the success of the proposed amide synthesis was therefore to identify conditions under which the reaction of the amine with carbon dioxide would not be competitive with the desired C−N bond-forming reactions.

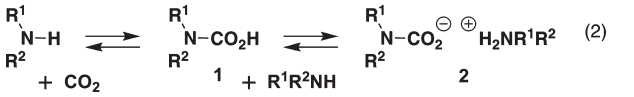
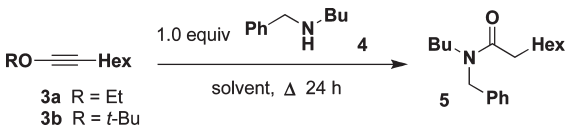


TABLE 1. Optimization of Conditions for Amide Synthesis



entry	alkynyl ether	solvent	temp (°C)	pressure (bar)	yield (%)[a]
1	**3a**	toluene	120	1.3[b]	88
2	**3a**	CO_2	120	215	85
3	**3a**	CO_2	120	394	86
4	**3a**	CO_2	130	228	88
5	**3b**	CO_2	90	218	82

[a]Isolated yield of products purified by column chromatography on silica gel. [b]Calculated value based on the vapor pressure of toluene at 120 °C.

Results and Discussion

Optimization of Conditions for Amide Synthesis in $scCO_2$. Initial feasibility experiments were carried out using 1-ethoxy-1-octyne (**3a**) and the corresponding *tert*-butoxy alkyne, **3b**. Ethoxyoctyne **3a** was conveniently prepared in high yield via the alkylation of the lithium derivative of commercially available ethoxyacetylene with 1-iodohexane as previously reported by Kocienski.[9] The *tert*-butoxy derivative was prepared in a similar fashion by alkylation of lithium *tert*-butoxyacetylide. Greene has developed an efficient one-pot method for the generation of lithium alkoxyacetylides that involves the addition of a potassium alkoxide to dichloroacetylene (generated in situ from trichloroethylene) followed by treatment with *n*-BuLi.[10] Our attempts to employ this one-pot procedure in the preparation of **3b** gave the desired alkyne in poor yield; however, improved results were obtained by isolating the product of the first stage of the reaction (*tert*-butyl 1,2-dichlorovinyl ether) and then subjecting it to reaction with 2.4 equiv of *n*-BuLi followed by iodohexane.[11] Although not especially attractive from the standpoint of "green chemistry", these approaches to the synthesis of **3a** and **3b** provided us with rapid access to abundant quantities of the alkynes as required for our initial feasibility and optimization studies.

Table 1 summarizes the results of initial experiments to establish the feasibility of carrying out the desired amide

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(7) For recent examples of environmentally friendly methods for amide synthesis, see: (a) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, *317*, 790. (b) Nordstrøm, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672. (c) Al-Zoubi, R. M.; Marion, O.; Hall, D. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 2876. (d) Comerford, J. W.; Clark, J. H.; Macquarrie, D. J.; Breeden, S. W. *Chem. Commun.* **2009**, 2562.
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(9) Pons, J.-M.; Kocienski, P. *Tetrahedron Lett.* **1989**, *30*, 1833.
(10) Denis, J.-N.; Moyano, A.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 3461.
(11) For details, see Supporting Information.

synthesis in supercritical carbon dioxide. Thermolysis of ethoxyoctyne in the presence of *N*-benzylbutylamine was examined first. A temperature of 120 °C was initially selected for this reaction on the basis of a review of conditions previously reported for related transformations involving alkynyl ethers. The retro-ene reaction of alkynyl ethers to form ketenes[12] was first observed in the laboratories of Ficini[13] and Arens,[14] and Ficini appears to have been the first to employ this process for the synthesis of amides. Subsequent researchers have applied this process to generate ketenes for cyclizations leading to lactones,[15] lactams,[16a] and cyclic imides.[16b] Solvents typically employed in these reactions include xylene, toluene, chloroform, and acetonitrile. The retro-ene reaction of ethoxy alkynes typically takes place at 100−120 °C, but more highly substituted ethers undergo the reaction at lower temperatures, as low as 50 °C in the case of *tert*-butyl derivatives.[15a,b,17,18]

We were pleased to find that addition of *N*-benzylbutylamine to the ketene generated in situ from ethoxyoctyne proceeds as cleanly and efficiently in $scCO_2$[19] as the reaction carried out via the conventional procedure using toluene in a sealed tube (Table 1, entries 1−3). Particularly significant is the fact that no interference from the reversible reaction of the amine with CO_2 (see eq 2) was observed in this case. The optimal temperature for the reaction in $scCO_2$ was 130 °C (entry 4); at 110 °C unreacted alkynyl ether (ca. 25%) was recovered even after 39 h. The use of the *tert*-butoxy octyne **3b** permits the reaction to be carried out at 90 °C and also affords the desired amide **5** in excellent yield (entry 5).

At 120 °C, the minimum pressure required to completely solubilize the reactants was found to be ca. 215 bar (entry 2). At this temperature and pressure, the reaction mixture is initially monophasic and then becomes biphasic after ca. 5 h, at which point a new liquid phase is observed to form. As shown in Figure 1a, eventually the reaction mixture consists of a (top) lower-density, CO_2-rich, supercritical-like phase and a (bottom) higher-density, product amide-rich,[20] liquid phase. Initially, the appearance of a liquid phase led to some concern with regard to the potential detrimental effects of phase partitioning of the reactants. However, no difference in yield was observed when the reaction was performed at 394 bar (entry 3), a pressure at which a single phase was observed throughout the entire duration of the reaction (Figure 1b).

FIGURE 1. Phase behavior observed for reactions in Table 1 entry 2 (a) and entry 3 (b). The solid object is a stir bar.

Notably, no ketene dimer or products of [2 + 2] cycloaddition of the ketene and alkynyl ether starting material were detected in the crude products of these reactions. Depressurization of the reaction mixture after 24 h provided the amide **5** as an oil, which was determined to be 95−98% pure by ^{1}H NMR analysis. In these experiments the product was generally found to be contaminated with some solid debris originating from abrasion of the o-rings and reactor wall. Consequently, the amide **5** was transferred out of the reactor and subjected to column chromatography to remove this material, resulting in the loss of ca. 5% of product as estimated on the basis of control experiments.

Scope of the Reaction with Respect to Amine. As shown in Table 2, a variety of amines participate in the desired amide bond-forming reaction in supercritical carbon dioxide. In these reactions the amine was heated with 1 equiv of ethoxyoctyne (**3a**) at 120 or 130 °C for 24 h; the higher temperature was required in some cases as ca. 5% of **3a** remained after 24 h at 120 °C. The reaction pressure (230−284 bar) was selected on the basis of the minimum pressure sufficient to solubilize both the amine and alkynyl ether and at least initially afford a homogeneous solution at the elevated reaction temperature. In each case, however, the product amides were observed to eventually separate from the reaction mixture as a second, liquid phase.

As demonstrated by the examples in Table 1 and Table 2 (entries 1 and 2), secondary amines such as **4**, **6**, and **8** readily undergo reaction in $scCO_2$ to afford the desired amides in good yield. The α-branched *primary* amines **10** and **14** also gave the expected amides in good yield (entries 3 and 5); however, in these cases insoluble solids that we suspect to be carbamate salts were observed to form upon initial addition of CO_2 to the reactor at room temperature (Figure 2). As the reactor temperature warmed to ca. 100 °C, these solids disappeared, forming a liquid phase that dissolved in CO_2 upon further heating to the final reaction temperature.[8f]

In the case of the less nucleophilic primary amine aniline, amide formation also proceeded in fairly good yield (entry 4). The limit with regard to the scope of this reaction of primary amines in $scCO_2$ was revealed by the reaction of benzylamine (entry 6). As in the case of entries 3 and 5, immediate precipitation of a carbamate salt was observed upon introduction of CO_2 to a mixture of this amine and alkynyl ether at room temperature. However, in this case the desired amide **17** was obtained in only 37−43% yield. We suspect that with this less sterically hindered amine the equilibrium described in eq 2 is shifted more in favor of the carbamic acid, thereby inhibiting addition of the amine to the transient ketene intermediate. In support of this

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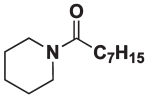
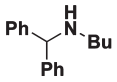
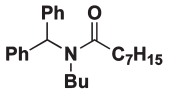
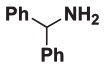
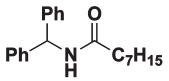
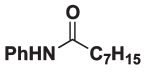
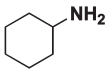
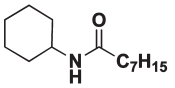
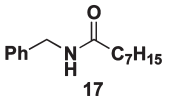
(17) (a) Valenti, E.; Pericàs, M. A.; Serratosa, F.; Mañà, D. *J. Chem. Res., Synop.* **1990**, 118. (b) Valentí, E.; Pericàs, M. A.; Serratosa, F. *J. Org. Chem.* **1990**, *55*, 395.

(18) van Daalen, J. J.; Kraak, A.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 810.

(19) All reactions in $scCO_2$ were performed in a 25-mL Thar stainless steel view cell reactor fitted with two coaxial sapphire windows to allow visual monitoring of the reaction. A detailed description of the reactor setup is included in Supporting Information.

(20) Amide **5** was found to be insoluble at 211 bar in $scCO_2$ at 120 °C.

TABLE 2. Synthesis of Amides by Reaction of Amines and 1-Ethoxy-1-octyne in Supercritical Carbon Dioxide

entry	amine	amide[a]	yield (%)[b]
1	 **6**	 **7**	87
2	 **8**	 **9**	87
3	 **10**	 **11**	79[c]
4	$PhNH_2$ **12**	 **13**	61
5	 **14**	 **15**	74
6	 **16**	 **17**	37-43[c]

[a]Reaction conditions: 1:1 ratio of amine and **3a**, $scCO_2$ (230−284 bar, see text), 130 °C (120 °C in the case of entry 2), 24 h. [b]Isolated yield of products purified by column chromatography on silica gel unless otherwise indicated. [c]Isolated yield of product purified by trituration with dichloromethane/hexanes.

FIGURE 2. Phase behavior initially observed for reactions in Table 2, entries 3, 5, and 6.

hypothesis, we found that in toluene the reaction of benzylamine with alkynyl ether **3a** takes place efficiently at 130 °C to afford amide **17** in 98% yield.[8e]

Alternative explanations to account for the lower yields in the case of reactions of primary amines were ruled out by control experiments. For example, initially we considered the possibility that the lower yields observed for certain amines could also be a consequence of phase partitioning effects. More polar amines such as the unbranched primary amine **16** might be expected to partition more than less polar amines into the amide-rich liquid phase that appears during the course of the reaction. This could result in a shift of the equilibrium of eq 2 more in favor of carbamic acid due to the greater polarity of this phase as compared to the upper CO_2-rich phase.[8] Amide formation would also be less favorable in this scenario since partitioning of the amine to a greater extent into the amide-rich liquid phase would reduce the efficiency of its reaction with the ketene intermediate in the upper CO_2-rich phase. That effects such as these may not be operating is suggested by the results of carrying out the reaction of benzhydrylamine **10** at a pressure (208 bar) at which the amine was observed to be insoluble in the CO_2-rich phase that alkynyl ether **3a** (and the derived ketene) were shown to be present in. In this experiment, the yield of amide **11** was unchanged from that observed under the monophasic conditions of entry 3.

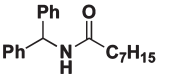
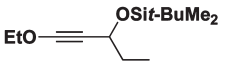
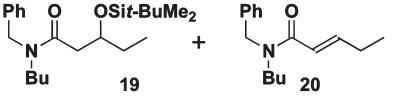
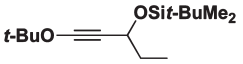
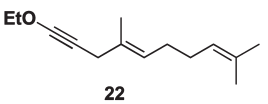
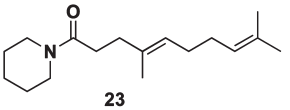
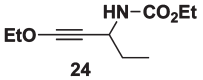
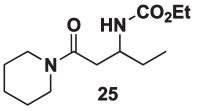
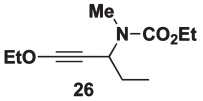
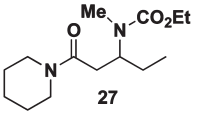
Scope of the Reaction with Respect to Alkynyl Ether. Further studies focused on the application of this chemistry to the preparation of amides starting from a variety of alkynyl ether derivatives.[21] Table 3 summarizes our results. Reactions involving ethoxy alkynes were carried out at 130 °C, while the use of *tert*-butoxy alkynyl ethers allows the reaction to be achieved at lower temperature (entries 1 and 3). For example, primary amine **10** reacts with *tert*-butoxy alkyne **3b** at 90 °C (entry 1) to afford amide **11** in essentially the same yield as that obtained via reaction at 130 °C using ethoxyoctyne **3a** (Table 2, entry 3). Interestingly, in the reaction at 90 °C the initially formed precipitate (that we suspect to be carbamate salt) was observed to be present for nearly the entire duration of the reaction, in contrast to reaction at the higher temperature where the solid eventually disappeared. The fact that the yield of amide product was nearly identical in these two cases suggests that in the lower temperature reaction sufficient free amine is present via the equilibrium described in eq 2 to allow amide formation to compete with undesired ketene dimerization and cycloaddition pathways.

Entries 2 and 3 describe our attempts to apply this chemistry to the preparation of β-hydroxy amide derivatives. Reaction of the ethyl alkynyl ether **18** with *N*-benzylbutylamine (**4**) afforded the desired amide **19** in 56% yield, accompanied by 31% of the β-elimination product **20** (entry 2). Interestingly, when this reaction was carried out in toluene (also at 130 °C), the desired amide was obtained in only 10% yield together with 80% of the elimination product. Improved results were obtained by carrying out the reaction at lower temperature in $scCO_2$ (entry 3). Thus, reaction at 90 °C employing the *tert*-butoxy alkynyl ether **21** led to the desired amide **19** in 80% yield with only trace amounts of the α,β-unsaturated byproduct observed under these conditions.

Reaction of alkynyl ether **22** to form amide **23** proceeded in good yield (entry 4). As expected, [2 + 2] cycloaddition of the ketene intermediate to the isolated carbon−carbon double bonds was found not to be competitive with the desired nucleophilic addition of the amine. Our focus turned next to the synthesis of β-amino amides. For this purpose, alkynyl ethers **24** and **26** were prepared via the addition of a lithium ethoxyacetylide to the α-amido sulfone **28**, which serves in this reaction as an *N*-acyl imine equivalent (Scheme 1).[22] Reaction of these alkynyl ethers with piperidine furnished the expected amides in good

(21) The alkynyl ethers were prepared via alkylation or addition reactions of alkoxyacetylides. For details, see Supporting Information.
(22) Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970.

TABLE 3. Synthesis of Amides in Supercritical Carbon Dioxide: Scope with Regard to Alkynyl Ether

entry	alkynyl ether	amine	amide(s)[a]	yield (%)[b]
1	**3b**	**10**	 **11**	79[c, d]
2	 **18**	**4**	 **19** + **20**	**19** 56 **20** 31
3	 **21**	**4**	**19** + **20**	**19** 80[c, d] **20** 3
4	 **22**	**6**	 **23**	68
5	 **24**	**6**	 **25**	66
6	 **26**	**6**	 **27**	85

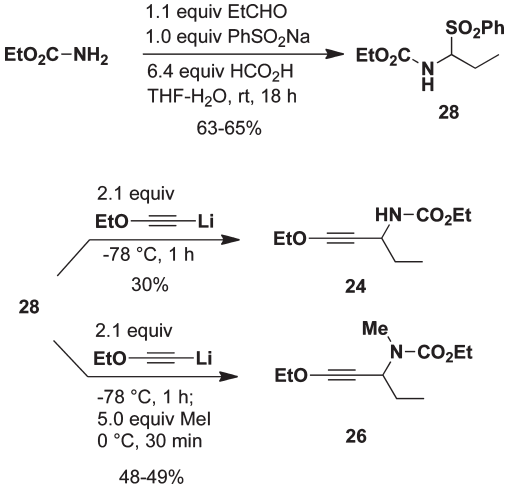
[a]Reaction conditions for entries 2−6: 1:1 ratio of amine and alkynyl ether, $scCO_2$ (241−277 bar, see text), 130 °C, 24 h unless othewise indicated. [b]Isolated yield of products purified by column chromatography on silica gel unless otherwise indicated. [c]Isolated yield of product purified by trituration with dichloromethane/hexanes. [d]Reaction conditions: 1:1 ratio of amine and alkynyl ether, $scCO_2$ (218 bar), 90 °C, 24 h.

yield (entries 5 and 6) with no evidence for formation of β-elimination side products in either case.

Lactam Synthesis in Supercritical Carbon Dioxide. Having completed our study of the scope of the intermolecular reaction of amines with alkynyl ethers in $scCO_2$, we next turned our attention to extending this strategy to the synthesis of macrocyclic lactams.[23] The efficient synthesis of medium- and large-ring compounds typically requires the application of high dilution conditions in order to minimize competitive intermolecular oligomerization processes.[24] The use of $scCO_2$ as a replacement solvent is obviously quite attractive for reactions such as these in which large volumes of solvent are a necessity.

Unfortunately, preliminary screening experiments indicated that lactam **30** is formed in lower yield when $scCO_2$ is employed as the reaction medium as compared to the same reaction performed in toluene in a sealed tube (Scheme 2). For the reaction in $scCO_2$, the reaction mixture was monophasic for the first 5 h, after which time a film-like liquid phase developed, believed to contain the dilactam **31**[25]

SCHEME 1. Synthesis of Alkynyl Ethers 24 and 26



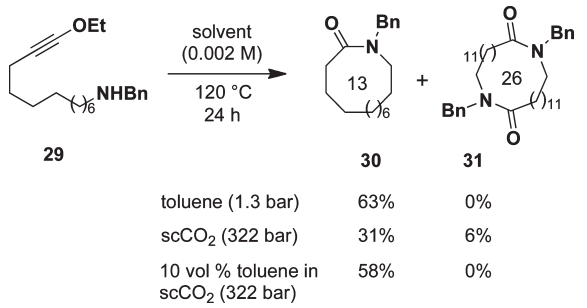
and higher molecular weight oligomeric products. Some improvement in lactam yield was observed when toluene (10% by volume) was added as a co-solvent; under these conditions a liquid phase did not appear until near the very end of the reaction. This observation suggests that the lower yield obtained in the absence of co-solvent may be due to the preferential partitioning of the amine starting material **29** into the more polar and smaller volume liquid phase that develops as the reaction proceeds. Migration of the starting

(23) For elegant examples of the synthesis of macrocyclic lactams (and lactones) via intramolecular trapping of ketenes generated in situ by thermolysis of dioxolenones, see: Boeckman, R. K.; Weidner, C. H.; Perni, R. B.; Napier, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 8036 and references cited therein.

(24) Reviewed in: (a) Knops, P.; Vögtle *Top. Curr. Chem.* **1991**, *161*, 1. (b) Meng, O.; Hesse, M. *Top. Curr. Chem.* **1991**, *161*, 107. (c) Nubbemeyer, U. *Top. Curr. Chem.* **2001**, *216*, 125.

(25) Dilactam **31** was found to be insoluble at 322 bar and 120 °C in $scCO_2$.

SCHEME 2



material **29** into the liquid phase would promote oligomerization pathways as these intermolecular reactions would be favored with the increase in molar concentration relative to the initial concentration (0.002 M) of **29** in the bulk CO_2-rich phase.

Conclusions

From the standpoint of green chemistry, synthetic reactions should ideally be carried out in the absence of any solvent. Unfortunately, most synthetic transformations require the use of a solvent in order to ensure adequate mixing and contact between reactants (particularly solid compounds), to facilitate transfer of materials, and to control reaction temperature. Consequently, much effort has been devoted in recent years to the development of "alternative solvents" that are superior to conventional volatile organic solvents in terms of environmental impact and toxicity. Supercritical carbon dioxide ranks as one of the most attractive alternative solvents with regard to these considerations.[26]

In this paper, we have demonstrated that carbon dioxide in its supercritical state is an environmentally attractive alternative to conventional liquid organic solvents for the synthesis of a variety of carboxylic amides. The addition of amines to ketenes generated in situ via the retro-ene reaction of alkynyl ethers provides amides in good yield, in many cases with ethylene or isobutylene as the only byproducts of the reaction. With the exception of primary, unbranched amines, the competitive side reaction of the amines with carbon dioxide does not interfere with the desired C−N bond-forming reaction. Preliminary experiments aimed at developing an intramolecular variant of this process to afford macrolactams suggest that the application of CO_2/co-solvent mixtures may offer advantages for the synthesis of large-ring compounds.

Experimental Section

General Procedure for the Synthesis of Amides in $scCO_2$. *N*-Benzyl-*N*-butyloctanamide (5). A 25-mL, stainless steel view cell reactor (see Supporting Information for details on the reactor setup) was charged with *N*-benzylbutylamine (**4**) (0.556 g, 3.40 mmol) and 1-ethoxy-1-octyne **3a** (0.525 g, 3.40 mmol). The reactor was pressurized to 50 bar with CO_2, heated to 130 °C, and then pressurized with additional CO_2 to 228 bar. The reaction mixture was stirred at 130 °C (228 bar) for 24 h and then allowed to cool to rt. The reactor outlet valve was opened, and the CO_2 phase was vented through a bubbler containing 15 mL of CH_2Cl_2. The residual oil in the reactor was purified by column chromatography on 12 g of silica gel (elution with 15% EtOAc/hexanes) to provide 0.871 g (88%) of amide **5** as a yellow oil: IR (neat) 2926, 1651, and 1453 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): major rotamer δ 7.16−7.38 (m, 5H), 4.61 (s, 2H), 3.18 (t, J = 7.7 Hz, 2H), 2.38 (t, J = 7.6 Hz, 2H), 1.48−1.75 (m, 4H), 1.26−1.35 (m, 10H), and 0.85−0.94 (m, 6H); minor rotamer δ 4.54 (s), 3.36 (t, J = 7.6 Hz), and 2.31 (t, J = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): major rotamer δ 173.3, 138.3, 128.6, 128.1, 127.3, 48.2, 47.0, 33.3, 31.9, 29.7, 29.3, 25.8, 22.8, 20.2, 14.3, and 14.0; minor rotamer 173.6, 137.5, 129.0, 127.6, 126.3, 51.2, 46.1, 33.5, 30.8, 29.9, 29.5, 29.3, 25.6, 22.8, 20.4, 14.3, and 14.0. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{19}H_{31}NO$ 312.2298; found 312.2292.

Reaction of *N*-benzylbutylamine (0.506 g, 3.10 mmol) with 1-*tert*-butoxy-1-octyne **3b** (0.565 g, 3.10 mmol) at 90 °C (218 bar) for 24 h according to the General Procedure provided ca. 1.0 g of a yellow-orange oil. Purification by column chromatography on 15 g of silica gel (elution with 10% EtOAc/hexanes) afforded 0.738 g (82%) of amide **5** as a pale yellow oil.

1-Piperidinyloctanamide (7). Reaction of piperidine (0.34 mL, 3.40 mmol) with 1-ethoxy-1-octyne **3a** (0.525 g, 3.40 mmol) at 130 °C (230 bar) for 24 h according to the General Procedure provided 0.703 g of brown oil. Purification by column chromatography on 15 g of silica gel (gradient elution with 10−20% EtOAc/hexanes) afforded 0.623 g (87%) of amide **7** as a pale yellow oil with spectral data consistent with that previously reported.[27]

***N*-Butyl-*N*-(diphenylmethyl)octanamide (9).** Reaction of *N*-butylbenzhydrylamine **8** (0.551 g, 2.30 mmol) with 1-ethoxy-1-octyne **3a** (0.350 g, 2.27 mmol) at 120 °C (280 bar) for 24 h according to the General Procedure provided 0.860 g of brown oil. Purification by column chromatography on 25 of silica gel (elution with 15% EtOAc/hexanes) afforded 0.720 g (87%) of **9** as a pale yellow oil: IR (neat) 2920, 1644, and 1454 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.28−7.37 (m, 6H), 7.15−7.19 (m, 4H), 6.29 (s, 1H), 3.24−3.31 (m, 2H), 2.44 (t, J = 7.5 Hz, 2H), 2.39 (t, minor rotamer), 1.73−1.77 (m, 2H), 1.65−1.68 (m, minor rotamer), 1.25−1.36 (m, 9H), 0.81−0.99 (m, 6H), and 0.59−0.66 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): major rotamer δ 173.6, 140.1, 129.1, 128.4, 127.4, 60.8, 45.9, 33.7, 31.9, 31.8, 29.7, 29.5, 25.9, 22.8, 20.3, 14.2, and 13.5; minor rotamer δ 139.7, 128.9, 128.6, 127.9, 64.9, 45.0, 33.9, 32.0, 31.7, 30.2, 29.6, 25.5, 20.4, and 13.6). HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{25}H_{35}NO$ 366.2791; found 366.2796.

***N*-(Diphenylmethyl)octanamide (11).** Reaction of benzhydrylamine (0.585 g, 3.20 mmol) with 1-ethoxy-1-octyne **3a** (0.493 g, 3.20 mmol) at 130 °C (284 bar) for 24 h according to the General Procedure provided ca. 1.0 g of an orange solid. Purification by two trituration cycles with CH_2Cl_2/hexanes afforded 0.786 g (79%) of amide **11** as an off-white solid: mp 104−105 °C. IR (thin film): 2922, 1637, and 1544 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.22−7.36 (m, 10H), 6.27 (app d, J = 7.9 Hz, 1H), 5.98 (app d, J = 7.2 Hz, 1H), 2.27 (t, J = 7.6 Hz, 2H), 1.65−1.70 (m, 2H), 1.27−1.30 (m, 8H), and 0.87−0.89 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 141.8, 128.8, 127.6, 56.9, 37.0, 31.9, 29.4, 29.2, 25.9, 22.8, and 14.3. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{21}H_{27}NO$ 332.1985; found 332.1976.

Reaction of benzhydrylamine (0.623 g, 3.40 mmol, 1.0 equiv) with 1-*tert*-butoxy-1-octyne (**3b**) (0.620 g, 3.40 mmol, 1.0 equiv) at 90 °C (227 bar) for 24 h according to the General Procedure provided 1.08 g of a pale yellow solid. Purification by two trituration cycles with CH_2Cl_2/hexanes afforded 0.830 g (79%) of amide **11** as a white solid.

***N*-Phenyloctanamide (13).** Reaction of aniline (0.289 g, 3.10 mmol) with 1-ethoxy-1-octyne **3a** (0.478 g, 3.10 mmol) at 130 °C (235 bar) for 24 h according to the General Procedure

(26) Clark, J. H.; Tavener, S. J. *Org. Process Res. Dev.* **2007**, *11*, 149.

(27) Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79.

provided 0.833 g of a gray-yellow solid. Purification by column chromatography on 15 g of silica (elution with 10% EtOAc/hexanes) afforded 0.416 g (61%) of amide **13** as a pale yellow oil with spectral data consistent with that previously reported.[28]

***N*-Cyclohexyloctanamide (15).** Reaction of cyclohexylamine (0.39 mL, 0.34 g, 3.4 mmol) with ethoxy-1-octyne **3a** (0.235 g, 3.40 mmol) at 130 °C (230 bar) for 24 h according to the General Procedure provided 0.682 g of a tan solid, which was dissolved in CH_2Cl_2 and concentrated onto 1 g of silica gel. The free-flowing powder was placed at the top of a column of 10 g of silica gel and eluted with 10−20% EtOAc/hexanes to provide 0.564 g (74%) of amide **15** as a white solid with spectral data consistent with that previously reported.[29]

***N*-Benzyloctanamide (17).** Reaction of benzylamine (0.332 g, 3.10 mmol) with 1-ethoxy-1-octyne **3a** (0.478 g, 3.10 mmol) at 130 °C (284 bar) for 24 h according to the General Procedure provided 0.432 g of a yellow solid. Purification by two trituration cycles with CH_2Cl_2/hexanes afforded 0.270 g (37%) of amide **17** as a white solid with spectral data consistent with that previously reported.[30]

***N*-Benzyl-*N*-butyl-3-(*tert*-butyldimethylsiloxy)pentanamide (19).** Reaction of *N*-benzylbutylamine (0.556 g, 3.40 mmol) with alkynyl ether **18** (0.824 g, 3.40 mmol) at 130 °C (241 bar) for 24 h according to the General Procedure provided 1.32 g of a dark orange oil. Purification by column chromatography on 20 g of silica gel (gradient elution with 5−10% EtOAc/hexanes) afforded 0.717 g (56%) of the β-siloxy amide **19** as a pale yellow oil and 0.261 g (31%) of the α,β-unsaturated amide **20** as a yellow oil. Amide **19**: IR (thin film) 2959, 1646, and 1463 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.24−7.38 (m, 4H), 7.18 (d, J = 7.0 Hz, 1H), 4.37−4.81 (m, 2H), 4.20−4.32 (m, 1H), 3.33−3.40 (m, 1H), 3.16−3.31 (m, 1H), 2.32−2.63 (m, 2H), 1.41−1.66 (m, 4H), 1.24−1.34 (m, 2H), 0.83−0.98 (m, 6H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, minor rotamer), and 0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): major rotamer δ 172.0, 138.2, 128.3, 127.6, 126.4, 71.4, 48.8, 46.4, 40.7, 31.1, 30.7, 26.1, 20.3, 18.3, 14.0, 9.6, −4.4, and −4.5; minor rotamer δ 171.5, 137.5, 129.0, 128.6, 127.4, 51.5, 47.4, 40.4, 30.0, 20.5, 14.1, and 9.7. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{22}H_{39}NO_2Si$ 400.2642; found 400.2626. Amide **20**: IR (neat) 2962, 1660, 1615, and 1425 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.25−7.42 (m, 4H), 7.19 (d, J = 7.4 Hz, 1H), 7.03 (app ddd, J = 6.4, 13.3, 21.6 Hz, 1H), 6.27 (d, J = 15.0 Hz, 1H), 6.18 (d, minor rotamer), 4.66 (s, 2H), 4.60 (s, minor rotamer), 3.40 (t, minor rotamer), 3.24 (t, J = 7.3 Hz, 2H), 2.27 (app quint, J = 7.0 Hz, 2H), 2.19 (app quint, minor rotamer), 1.52−1.59 (m, 2H), 1.27−1.34 (m, 2H), 1.10 (t, J = 7.4 Hz, 3H), 1.01 (t, minor rotamer), and 0.85−0.94 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): major rotamer δ 167.0, 148.6, 138.2, 128.7, 128.2, 126.6, 119.4, 49.1, 47.1, 31.3, 25.8, 20.2, 14.0, and 12.8; minor rotamer δ 167.4, 137.6, 129.0, 127.6, 127.4, 119.7, 51.2, 46.5, 29.9, 26.1, 20.5, and 14.1. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{16}H_{23}NO$ 268.1672; found 268.1669.

Reaction of *N*-benzylbutylamine (0.555 g, 3.40 mmol) and alkynyl ether **21** (0.920 g, 3.40 mmol) at 90 °C (218 bar) for 24 h according to the General Procedure provided 1.35 g of a yellow oil. Purification by column chromatography on 25 g of silica gel (gradient elution with 5−10% EtOAc/hexanes) afforded 1.03 g (80%) of the β-siloxy-amide **19** as a pale yellow oil and 0.027 g (3%) of the α,β-unsaturated amide **20** as a yellow oil.

(*E*)-4,9-Dimethyl-1-(piperidin-1-yl)deca-4,8-dien-1-one (23). Reaction of piperidine (0.264 g, 3.10 mmol) with alkynyl ether **22** (0.640 g, 3.10 mmol) at 130 °C (277 bar) for 24 h according to the General Procedure provided 0.757 g of a brown oil. Purification by column chromatography on 18 g of silica gel (elution with 20% EtOAc/hexanes) afforded 0.552 g (68%) of amide **23** as a yellow oil: IR (thin film) 2933, 1646, and 1436 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.14 (bs, 1H), 5.08 (t, J = 6.0 Hz, 1H), 3.55 (t, J = 5.5 Hz, 2H), 3.39 (t, J = 5.4 Hz, 2H), 2.33 (app s, 4H), 2.03−2.08 (m, 2H), 1.95−1.99 (m, 2H), 1.67 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H), and 1.49 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 136.3, 131.5, 124.4, 123.2, 46.8, 42.7, 39.9, 33.6, 26.8, 26.9, 25.9, 25.7, 24.7, 24.2, 17.8, and 16.2. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{17}H_{29}NO$ 286.2141; found 286.2152.

5-Oxo-5-(piperidin-1-yl)pentan-3-ylcarbamic Acid Ethyl Ester (25). Reaction of piperidine (0.34 mL, 0.29 g, 3.4 mmol) with alkynyl ether **24** (0.677 g, 3.40 mmol, 1.0 equiv) at 130 °C (242 bar) for 24 h according to the General Procedure provided 0.974 g of a viscous dark brown oil. Column chromatography on 40 g of acetone-deactivated silica gel (gradient elution with 20−75% EtOAc/hexanes) provided 0.576 g (66%) of amide **25** as a yellow-orange oil: IR (neat) 3314, 1718, 1628, 1533, and 1240 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.53 (d, J = 7.9 Hz, 1 H), 4.06 (q, J = 6.9 Hz, 2 H), 3.74−3.83 (m, 1 H), 3.46−3.57 (m, 2 H), 3.39 (t, J = 4.7 Hz, 2 H), 2.62 (dd, J = 15.3, 4.9 Hz, 1 H), 2.47 (dd, J = 15.3, 5.7 Hz, 1 H), 1.48−1.69 (m, 8 H), 1.21 (t, J = 7.1 Hz, 3 H), 0.92 (t, J = 7.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 156.5, 60.6, 50.1, 42.6, 37.0, 26.6, 25.7, 24.6, 14.7, 11.0. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{13}H_{25}N_2O_3$ 257.1860, found 257.1850.

5-Oxo-5-(piperidin-1-yl)pentan-3-yl-*N*-methylcarbamic Acid Ethyl Ester (27). Reaction of piperidine (0.34 mL, 0.29 g, 3.4 mmol) with alkynyl ether **26** (0.725 g, 3.40 mmol) at 130 °C (222 bar) for 24 h according to the General Procedure provided 1.007 g of a brown oil. Column chromatography on 40 g of acetone-deactivated silica gel (gradient elution with 25−60% EtOAc/hexanes) provided 0.778 g (85%) of amide **27** as a yellow oil: IR (neat) 1695, 1640, and 1254 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.21−4.32 (m, 1 H), 4.16−4.20 (m, minor rotamer), 4.15 (q, J = 7.0 Hz, minor rotamer), 4.09 (q, J = 7.2 Hz, 2 H), 3.35−3.62 (m, 4 H), 2.79 (s, 3 H), 2.66 (dd, J = 14.1, 7.9 Hz, 1 H), 2.57 (dd, J = 14.5, 6.5 Hz, minor rotamer), 2.46 (dd, J = 14.2, 7.0 Hz, 1 H), 2.41 (dd, J = 14.5, 7.7 Hz, minor rotamer), 1.42−1.71 (m, 8 H), 1.23 (t, J = 7.1 Hz, 3 H), 0.87 (t, J = 7.3 Hz, 3 H), 0.85 (t, J = 7.2 Hz, minor rotamer). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 156.6, 61.0, 56.0, 47.0, 42.6, 37.2, 26.6, 25.4, 24.5, 14.6, 10.9; minor rotamer δ 168.7, 156.7, 61.2, 55.1, 46.9, 42.7, 37.3, 26.5, 25.0, 14.7, 10.8. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{14}H_{26}N_2NaO_3$ 293.1841, found 293.1843.

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Supporting Information Available: Detailed description of the reactor setup, experimental procedures and characterization data for the preparation of all alkynyl ethers and amide products. This material is available free of charge via the Internet at http://pubs.acs.org.

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