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Catalytic Oxidative Carbonylation of Primary and Secondary α,ω-Diamines to Cyclic Ureas

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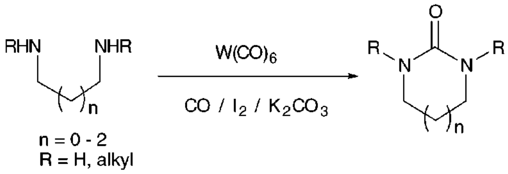
ABSTRACT



Primary and secondary diamines can be catalytically carbonylated to cyclic ureas using $W(CO)_6$ as the catalyst, I_2 as the oxidant, and CO as the carbonyl source. Preparation of five-, six-, and seven-membered cyclic ureas from the diamines $RNHCH_2(CH_2)_nCH_2NHR$ ($n = 0$–2; R = H, Me) and $RNHCH_2CH_2NHR$ (R = Et, *i*-Pr, Bz) was achieved in moderate to good yields.

Cyclic ureas have interesting pharmacological properties which have led to their use as inhibitors of a broad set of retroviral proteases, including HIV protease.[1] In addition, they have also found use as chiral auxiliaries for asymmetric synthesis.[2]

Several synthetic routes from diamines to the corresponding cyclic ureas have been described.[3] Most of these rely on nucleophilic reactions of the amines with phosgene and related compounds. Methods that convert primary diamines to the corresponding cyclic ureas have utilized carbonyl sources including phosgene,[4] phosgene derivatives,[5] dialkyl carbonates,[6] carbonyl sulfide,[7] carbonyl selenide,[8] and urea.[2] Due to the facile closure of five-membered rings, the conversion of ethylenediamine to 2-imidazolidinone has served as a test case for many of these methods. Phosgene itself is ineffective for this substrate, producing the five-membered cyclic urea in only 13% yield.[9] However, when the related aromatic phenylenediamine is reacted with phosgene, the cyclic urea is produced in a 50% yield.[4b] Phosgene derivatives, such as *S*,*S*-dimethyl dithiocarbonate, can be used to carbonylate ethylenediamine to the five-membered cyclic urea in 80% yield.[5] Furthermore, disuccinimido carbonate (DSC) serves to carbonylate ethylenediamine to 2-imidazolidinone in a 90% yield.[6] Urea itself can be transaminated in the presence of water at 200 °C to produce five-membered cyclic ureas from the corresponding diamines in about 85% yield.[2]

While there are several synthetic routes to prepare the parent cyclic ureas directly from primary diamines, the general difficulties associated with synthesis of tetrasubstituted ureas[10] render direct synthesis of *N*,*N*′-disubstituted cyclic ureas from secondary diamines more challenging. As

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(1) Hodge, C. N.; Lam P. Y. S.; Eyermann, C. J.; Jadhav, P. K.; Ru, Y.; Fernandez, C. H.; De Lucca, G. V.; Chang, C.; Kaltenbach, R. F.; Holler, E. R.; Woerner, F.; Daneker, W. F.; Emmett, G.; Calabrese, J. C.; Aldrich, P. E. *J. Am. Chem. Soc.* **1998**, *120*, 4570−4581 and references therein.

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10.1021/ol990690f CCC: $18.00

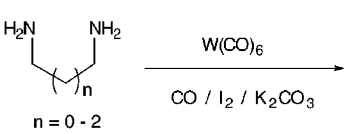
a result, *N,N′*-disubstituted cyclic ureas are often prepared by deprotonation and alkylation of their unsubstituted analogues.[11]

Catalytic oxidative carbonylation of diamine substrates would provide an alternative route to cyclic ureas in which CO could be used as the carbonyl source. Oxidative carbonylation of primary amines to acyclic ureas has been reported to be catalyzed by complexes of Ni,[12] Co,[13] W,[14] Mn,[15] Ru,[16] and Pd.[17] However, the transition metal-catalyzed reactions generally require high temperatures and pressures, and yields tend to be much lower for aliphatic amines than for aromatic ones. Main group elements such as sulfur[18] and selenium[19] can also serve as catalysts.

The formation of cyclic ureas by catalytic carbonylation has been much less well explored than the acyclic cases. Catalytic carbonylation of diamines with carbon monoxide to form cyclic ureas in high yields has been reported to proceed in the presence of elemental selenium; however, the reaction generates hydrogen selenide as a byproduct and certain substrates such as 2-(2-aminoethylaniline) only form the cyclic urea in the presence of stoichiometric or excess selenium.[19] Prior reports of transition metal-catalyzed carbonylation of diamines cite cyclic ureas only as very minor or side products. As an example, $Mn_2(CO)_{10}$-catalyzed carbonylation of the diamines $H_2N(CH_2)_nNH_2$ ($n = 2-4$ and 6) yielded no cyclic products when $n = 2$, 4, or 6 and only 6% of the six-membered urea when $n = 3$.[15b] Carbonylation of ethylenediamine catalyzed by $Ni(CO)_4$ yielded 2-imidazolidinone as a minor product in 10% yield.[20] In addition to the catalytic cases involving CO, there is also a report of carbonylation of both primary and secondary diamines to cyclic ureas in moderate to good yields using CO_2 as the carbonyl source and Ph_3SbO/P_4S_{10} as catalyst.[21]

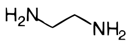
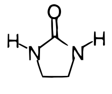
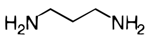
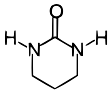
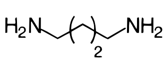
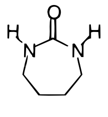
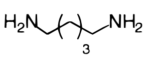
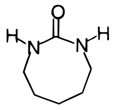
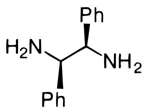
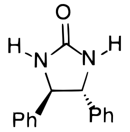
We recently reported the catalytic oxidative carbonylation of primary amines to ureas using either $[(CO)_2W(NPh)I_2]_2$ or $W(CO)_6$ as the catalyst and I_2 as the oxidant.[14b] We now report the catalytic oxidative carbonylation of α,*ω*-diamines to cyclic ureas. Both primary and secondary diamines are substrates for the reaction, with secondary diamines being converted directly to the corresponding *N,N′*-disubstituted cyclic ureas. To our knowledge, this simple procedure is the first example of a transition metal-catalyzed method to convert both primary and secondary diamines to cyclic ureas using carbon monoxide as the carbonyl source.

When the primary diamines $H_2NCH_2(CH_2)_nCH_2NH_2$ ($n = 0-2$) were reacted with CO (100 atm) in the presence of catalytic amounts of $W(CO)_6$ and nearly stoichiometric I_2, the diamines were converted to the corresponding cyclic ureas (eq 1).[22] Note that the reactions were run at room temperature, in contrast to the 100−200 °C ranges that are typical for catalytic oxidative carbonylation. The yields are significantly improved by addition of excess K_2CO_3 to scavenge the byproduct HI. Because the competitive formation of oligomers[17c] is favored by high concentrations of diamine, it was necessary to employ high dilution conditions. The results for a series of primary diamines are shown in Table 1. Preparation of the five-, six-, and seven-membered cyclic ureas was achieved in moderate to good yields. The highest isolated yield was obtained for the six-membered cyclic urea, while only trace amounts of the eight-membered



(1)

Table 1. Catalytic Carbonylation of Primary α,*ω*-Diamines to Cyclic Ureas

Diamine	Urea	% Yield[a]
		40
		51
		38
		trace
		46

[a] Isolated yield per equivalent of starting diamine.

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(11) See, for example: Nugiel, D. A.; Jacobs, K.; Worley, T.; Patel, M.; Kaltenbach, R. F.; Meyer, D. T.; Jadhav, P. K.; DeLucca, G. V.; Smyser, T. E.; Klabe, R. M.; Bacheler, L. T.; Rayner, M. M.; Seitz, S. P. *J. Med. Chem.* **1996**, *39*, 2156−2169.

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(14) (a) McCusker, J. E.; Abboud, K. A.; McElwee-White, L. *Organometallics* **1997**, *16*, 3863−3866. (b) McCusker, J. E.; Logan, J.; McElwee-White, L. *Organometallics* **1998**, *17*, 4037−4041.

(15) (a) Calderazzo, F. *Inorg. Chem.* **1965**, *4*, 293−296. (b) Dombek, B. D.; Angelici, R. J. *J. Organomet. Chem.* **1977**, *134*, 203−217.

(16) Mulla, S. A. R.; Rode, C. V.; Kelkar, A. A.; Gupte, S. P. *J. Mol. Catal. A.* **1997**, *122*, 103−109.

(17) (a) Pri-Bar, I.; Alper, H. *Can. J. Chem.* **1990**, *68*, 1544−1547. (b) Gupte, S. P.; Chaudhari, R. V. *J. Catalysis* **1988**, *114*, 246−258. (c) Dahlen, G. M.; Sen, A. *Macromolecules* **1993**, *26*, 1784−1786.

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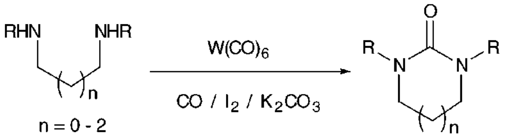
ring compound could be detected in the reaction mixtures. Failure to close the eight-membered ring was not surprising as there are no reports in the literature of preparation of this compound from 1,5-pentanediamine. In addition, (+)-(1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine was carbonylated to the chiral 2-imidazolidinone in a 46% yield. All of the product cyclic ureas are known compounds, and they were characterized by comparison to authentic samples purchased from Aldrich or by comparison of their spectral data to literature values.

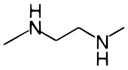
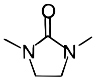
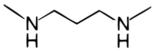
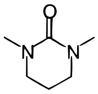
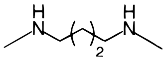
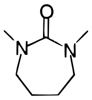
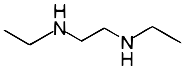
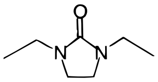
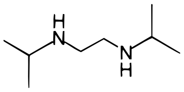
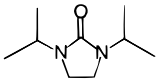
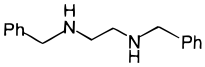
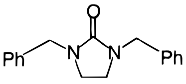
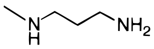
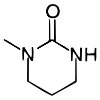
Reaction of secondary diamines under similar catalytic oxidative carbonylation conditions resulted in conversion of the diamines to the corresponding *N*,*N*′-disubstituted cyclic ureas (eq 2).[23] Once again it was necessary to employ high dilution conditions to minimize formation of oligomers. The results for a series of secondary diamines are shown in Table 2.



(2)

Closure of the diamines $CH_3NHCH_2(CH_2)_nCH_2NHCH_3$ (*n* = 0−2) to the corresponding five-, six-, and seven-membered cyclic ureas was achieved. The highest isolated yield (52%) was obtained for the six-membered ring. Note that yields for closure of the *N*,*N*′-dimethyldiamines are comparable to those of their primary counterparts. In addition, pure material of the *N*,*N*′-dialkyl compounds in Table 2 can be obtained by chromatography in contrast to the parent cyclic ureas of Table 1 which were purified by sublimation due to their insolubility.

Table 2. Catalytic Carbonylation of Secondary α,*ω*-Diamines to Cyclic Ureas

Diamine	Urea	% Yield[a]
		48
		52
		36
		46
		10
		31
		31

[a] Isolated yield per equivalent of starting diamine.

To probe steric limitations on the ring closure reaction, *N*,*N*′-diethyl, diisopropyl, and dibenzyl diamines were reacted under the standard conditions.[23] The *N*,*N*′-disubstituted cyclic ureas were formed in varying yields, as shown in Table 2. As expected, 1,3-diethyl-2-imidazolidinone was produced in 46% yield, similar to the yield of 1,3-dimethyl-2-imidazolidinone. Changing the substituents to benzyl groups dropped the yield only slightly. However, the steric hindrance of the bulky isopropyl groups dramatically reduced the yield of 1,3-diisopropyl-2-imidazolidinone to only 10%. Attempts to increase yields of the diisopropyl cyclic urea by raising the reaction temperature to 90 °C did not result in meaningful improvement (13% vs 10% at room temperature). In a test case with one primary and one secondary amine terminus, *N*-methylpropanediamine reacted under the oxidative carbonylation conditions to produce the corresponding *N*-methyl cyclic urea in 31% yield, indicating that cyclization can compete with acyclic urea formation through the more reactive primary amines. Once again, all of the products listed in Table 2 are known compounds and were characterized by comparison to authentic samples purchased from Aldrich or by comparison to literature data.

The diamines in Tables 1 and 2 lack functionality because they are simple cases intended to illustrate the ring closure. In conjunction with studies of the oxidative carbonylation of primary amines to acyclic ureas with this $W(CO)_6/I_2$

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(22) The following procedure is typical for primary diamines. **Synthesis of 2-Imidazolidinone**. To a stirred solution of $W(CO)_6$ (30 mg, 0.085 mmol) in a 90 mL solution of CH_2Cl_2 in the glass liner of a Parr high-pressure vessel were added 100 equiv of ethylenediamine (0.57 mL, 8.54 mmol), 210 equiv of K_2CO_3 (2.47 g, 17.9 mmol), and 90 equiv of iodine (1.95 g, 7.68 mmol). The vessel was then charged with 100 atm of CO and left to stir under pressure at room temperature for 24 h. The pressure was released, and the maroon solution was filtered away from a red solid. The CH_2Cl_2 layer was concentrated and then taken up into methanol, while the red solid was rinsed with methanol. Both methanol fractions were combined and concentrated to obtain a yellow powder. The yellow powder was then sublimed to obtain a white solid (0.29 g, 40% yield, TON = 40). The solid was identified as 2-imidazolidinone by comparison with an authentic sample.

(23) The following procedure is typical for secondary diamines. **Synthesis of 1,3-Dimethyl-2-Imidazolidinone**. To a stirred solution of $W(CO)_6$ (30 mg, 0.085 mmol) in 90 mL of CH_2Cl_2 in the glass liner of a Parr high-pressure vessel were added 150 equiv of *N*,*N*′-dimethylethylenediamine (1.36 mL, 12.8 mmol), 310 equiv of K_2CO_3 (3.63 g, 26.4 mmol), and 140 equiv of iodine (3.02 g, 11.9 mmol). The vessel was then charged with 100 atm of CO and left to stir under pressure at room temperature for 24 h. The pressure was released, and the yellow solution was filtered away from a white solid and concentrated. The resulting pale yellow oil was dissolved in ethyl acetate and chromatographed on silica with ethyl acetate as eluent to obtain a colorless liquid (0.68 g, 47% yield, TON = 70). The liquid was identified as 1,3-dimethyl-2-imidazolidinone by comparison with an authentic sample.

(24) McCusker, J. E.; Main, A. D.; Johnson, K. S.; Grasso, C. A.; McElwee-White, L. Manuscript in preparation.

(25) These initial studies were carried out with substituted benzyl amines in which intramolecular reaction of the functional group with the amine was not possible. Studies of more complex substrates are in progress.

system, we are carrying out studies of functional group compatibility.[24,25] The results indicate that oxidative carbonylation of amines is tolerant of a wide variety of functionality, including halides, esters, alkenes, and nitriles. A distinguishing feature is the tolerance of unprotected alcohols, which would be problematic with phosgene derivatives.

The moderate yields of cyclic products can be attributed to competition of the ring closure reaction with the formation of acyclic oligomers. This problem has also been reported for the reactions of phosgene equivalents with diamines.[2c] The initial crude yields of material derived from oxidative carbonylation of the diamines are approximately 85−90%, similar to yields obtained for the oxidative carbonylation of primary amines.[24] However, purification results in loss of approximately 50% of the crude product. Depending on the method of purification, the remaining material is left behind as residue in the sublimator or adheres to the top of the column during chromatography. These properties are what would be expected for oligomeric ureas. Thus, the moderate yields do not appear to be the result of low amine conversion, but rather the competitive formation of oligomers. Attempts to minimize the amount of oligomerization by further diluting the reaction mixtures merely slowed the reaction, rather than increasing the yields of the cyclic ureas. As expected, increasing the concentration of the reaction mixtures led to decreased yields of the cyclic ureas while increasing the yields of the residue.

In conclusion, we have developed a simple method to catalytically convert α,ω-diamines and carbon monoxide to cyclic ureas at room temperature in moderate yields using the commercially available, inexpensive, and air-stable $W(CO)_6$ as catalyst. To our knowledge, this is the first example of a transition metal-catalyzed procedure in which both primary and secondary diamines can serve as substrates. In the cases of the primary diamines, the yields of this catalytic carbonylation reaction are moderate in comparison to those obtained by some of the methods that utilize phosgene derivatives. The yields from secondary diamines are similar in magnitude but in some ways more favorable because the direct conversion to the *N*,*N*′-disubstituted cyclic ureas by this method can be compared to multistep sequences in which conversion of the primary diamine to the corresponding cyclic urea is followed by deprotonation and alkylation. Such a sequence for preparation of protease inhibitors is described in ref 11. The simplicity of this method, the mild reaction conditions, the direct conversion of secondary diamines to *N*,*N*′-disubstituted cyclic ureas, and the functional group tolerance are positive features of this carbonylation reaction.

Further work on these oxidative carbonylation reactions is underway.

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