chloride, 99-33-2; ethyl lavandulate, 133872-90-9; ethyl 3,3-dimethyl acrylate, 638-10-8; prenyl bromide, 870-63-3; (1*R*,3*R*)-chrysanthemic acid, 4638-92-0; (1*R*,3*R*)-ethyl chrysanthemate, 41641-25-2.

Supplementary Material Available: Chemical and spectral characterization data for compounds **9a,b**, **10a,b**, **11**, **16a**, ethyl lavandulate, and ethyl chrysanthemate (3 pages). Ordering information is given on any current masthead page.

Ruthenium-Catalyzed Synthesis of Symmetrical *N*,*N*′-Dialkylureas Directly from Carbon Dioxide and Amines

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Aliphatic and araliphatic primary amines react with carbon dioxide at 120–140 °C in the presence of ruthenium complexes and terminal alkynes, especially propargyl alcohols, to directly afford N,N′-disubstituted symmetrical ureas. The alkyne ruthenium intermediate acts as a dehydrating reagent. This new and mild method avoids the classical use of carbonyl precursors like phosgene or isocyanates.

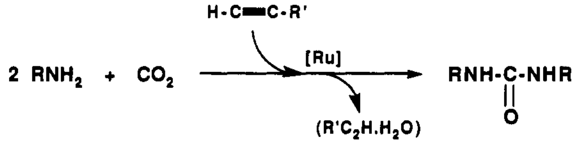
Introduction

Because they often display biological activity, ureas are an important class of organic compounds. The urea functional group is commonly found in natural products. Urea derivatives are widely used as agricultural pesticides, e.g., uron herbicides, or as pharmaceuticals.[1,2] Most syntheses of ureas involve the reaction of an amine either with compounds that incorporate an NCO linkage, like isocyanates,[1,3] formamides,[4] carbamates[1,5] and reactive imidazole ureas,[1,6] or with carbonyl compounds like phosgene,[1] chloroformates,[7] carbonates,[8] or CO itself in the presence of sulfur.[9] The synthesis of ureas by the catalyzed carbonylation of amines with carbon monoxide in the presence of various transition-metal catalysts, e.g., Pd,[10] Mn,[11] Pt,[12] and Cu,[13] has been described. Urea itself and some *N*,*N*′-dialkylureas can be produced by the reaction of carbon dioxide and ammonia[14] or primary amines[15] at 150–250 °C and pressures of 5–25 MPa. Under milder conditions, ureas can be prepared on a laboratory scale by the reaction of CO_2 and amines in the presence of *N*,*N*′-dicyclohexylcarbodiimide[16] or *N*-phosphonium salt derivatives.[17] In this case, activated carbamates are intermediates. In the presence of molecular sieve as a dehydrating agent, triphenylstibine oxide (Ph_3SbO) catalyzes the direct conversion of diamines and CO_2 under pressure to cyclic ureas.[18] *N*,*N*,*N*′,*N*′-Tetraethylurea has also been obtained from the reaction of carbon dioxide and diethylamine in the presence of Pd(II) complexes, but in poor yield.[19] Apart from these, few reports of the catalyzed synthesis of ureas from CO_2 have appeared.

A more direct synthesis of ureas, and urea itself, from amines and CO_2, would also involve the elimination of water, but under milder conditions. We previously showed that CO_2 and secondary amines can add to terminal alkynes in the presence of ruthenium catalysts to afford carbamates.[20,21]

We now report that, under very similar conditions (e.g., in the presence of a terminal alkyne and a ruthenium complex), CO_2 reacts with primary amines to give ureas in good yield. The reaction is a catalyzed one-step synthesis of symmetrical ureas and represents a new use of carbon dioxide. Preliminary results were reported in a patent.[22]

Scheme I



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(1) Petersen U. In *Methoden der Organischen Chemie*, Houben-Weyl, E4, G. Thieme Verlag: New York, 1983; p 334.

(2) *Inf. Chim.* **1989**, *306*, 146–149.

(3) Ozaki, S. *Chem. Rev.* **1972**, *72*, 457, 469.

(4) Kotachi, S.; Tsuji, Y.; Kondo, T.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 549.

(5) Basha, A. *Tetrahedron Lett.* **1988**, *29*, 2525.

(6) Staab, H. A.; Wendel, H. K. *Chem. Ber.* **1960**, *93*, 2902.

(7) Abrahart, E. N. *J. Chem. Soc.* **1936**, 1273.

(8) (a) Takeda, K.; Ogura, H. *Synth. Commun.* **1982**, *12*, 213. (b) Adamiak, R. W.; Stawinski, J. *Tetrahedron Lett.* **1977**, 1935.

(9) (a) Franz, R. A.; Applegath, F. *J. Org. Chem.* **1961**, *26*, 3304. (b) Franz, R. A.; Applegath, F.; Morriss, F. V.; Baiocchi, F. *Ibid.* **1961**, *26*, 3306. (c) Franz, R. A.; Applegath, F.; Morriss, F. V.; Baiocchi, F.; Bolze, C. *Ibid.* **1961**, *26*, 3309.

(10) Giannoccaro, P. *J. Organomet. Chem.* **1987**, *336*, 271.

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

(12) Tsuji, Y.; Takeuchi, R.; Watanabe, Y. *J. Organomet. Chem.* **1985**, *290*, 249.

(13) Brackman, W. British Patent 868460, 1961; *Chem. Abstr.* **1962**, *56*, P1434c.

(14) For example, see: Forlani, P.; Paris, I.; Zardi, V. Ger. Patent 1962862, 1968; *Chem. Abstr.* **1968**, *73*, P77840p.

(15) Charlu, T. V.; Rao, M. R. A. *Ind. J. Technol.* **1969**, *7*, 111.

(16) Ogura, H.; Takeda, K.; Tokue, R.; Kobayashi, T. *Synthesis* **1978**, 394.

(17) (a) Yamazaki, N.; Higashi, F.; Iguchi, T. *Tetrahedron lett.* **1974**, 1191. (b) Yamazaki, N.; Iguchi, T.; Higashi, F. *Tetrahedron* **1975**, *31*, 3031.

(18) Nomura, R.; Yamamoto, M.; Matsuda, H. *Ind. Eng. Chem. Res.* **1987**, *26*, 1056.

(19) Morimoto, Y.; Fujiwara, Y.; Taniguchi, H.; Hori, Y.; Nagano, Y. *Tetrahedron Lett.* **1986**, *27*, 1809.

(20) (a) Mahé, R.; Sasaki, Y.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1989**, *54*, 1518. (b) Sasaki, Y.; Dixneuf, P. H. *J. Chem. Soc., Chem. Commun.* **1986**, 790. (c) Mahé, R.; Dixneuf, P. H.; Lécolier, S. *Tetrahedron Lett.* **1986**, *27*, 6333.

(21) (a) Bruneau, C.; Dixneuf, P. H. *Tetrahedron Lett.* **1987**, *28*, 2005. (b) Sasaki, Y.; Dixneuf, P. H. *J. Org. Chem.* **1987**, *52*, 4389.

(22) Dixneuf, P. H.; Bruneau, C.; Fournier, J.; Lécolier, S. French Patent 8901939, 1989.

0022-3263/91/1956-4456$02.50/0 © 1991 American Chemical Society

Table I. Formation of *N,N'*-Dicyclohexylurea. Effect of the Catalyst[a]

run	catalyst	yield of urea (%)
1	$RuCl_3 \cdot 3H_2O$	39
2	$RuCl_3 \cdot 3H_2O/2$ *n*-Bu_3P	61
3	(hexamethylbenzene)$RuCl_2(PMe_3)$	61
4	(*p*-cymene)$RuCl_2(PPh_3)$	56
5	(*p*-cymene)$RuCl_2(P(OMe)_3)$	50
6	$Ru_3(CO)_{12}$	31
7	$OsCl_3 \cdot xH_2O$	17

[a] Reaction conditions: catalyst (0.2 mmol), cyclohexylamine (20 mmol), 2-methylbut-3-yn-2-ol (B; 50 mmol), CO_2 (5 MPa), 20 h, 140 °C; yield of urea based on the amine.

Results

The activation of terminal alkynes toward the nucleophilic addition of carbamates can be effected by ruthenium complexes, which serve as catalyst precursors. Ammonium carbamates, formed in situ by the reaction of secondary amines with CO_2, react with activated terminal alkynes to regioselectively produce vinyl carbamates[20] (eq 1).

$$R_2NH + CO_2 + HC{\equiv}CR' \xrightarrow{[Ru]} R_2NCO_2CH{=}CHR' \quad (1)$$

Similarly, CO_2 and secondary amines react with propargyl alcohols to give β-oxopropyl carbamates[21] (eq 2).

$$R_2NH + CO_2 + HC{\equiv}CCR'_2OH \xrightarrow{[Ru]} R_2NCO_2CR'_2C(O)CH_3 \quad (2)$$

An attempt to extend these catalyzed reactions to include primary amines led not to the formation of the analogous carbamates but, unexpectedly, to the formation of symmetric ureas. The reaction requires the presence of both a terminal alkyne and a ruthenium catalyst precursor (Scheme I).

Thus, when a mixture of cyclohexylamine (20 mmol), $RuCl_3 \cdot 3H_2O$ (0.2 mmol), *n*-Bu_3P (0.4 mmol), and a terminal alkyne (20 mmol) was pressurized to 5 MPa with CO_2 and then was heated at 140 °C for 20 h, *N,N'*-dicyclohexylurea was produced, in 34% yield when the alkyne was acetylene and in 55% yield when it was octa-1,7-diyne. Under similar conditions, the urea was also produced when the alkyne was a propargylic alcohol. Thus, a 31% yield of *N,N'*-dicyclohexylurea was obtained with propargyl alcohol (**A**) itself and a 28% yield with 2-methylbut-3-yn-2-ol (**B**). On the other hand, disubstituted alkynes, e.g., diphenylacetylene, hex-3-yne, or but-2-yne, or sterically hindered terminal alkynes, e.g., *tert*-butylacetylene, failed to induce formation of the urea.

Several ruthenium complexes successfully catalyzed the formation of *N,N'*-dicyclohexylurea (Table I). (η^6-arene)$(PR_3)RuCl_2$ complexes were good catalyst precursors: the urea was formed in more than 50% yield (runs 3–5). Commercial ruthenium trichloride trihydrate was also an efficient catalyst (39% yield of urea), but the yield of urea could be greatly increased by adding tri-*n*-butylphosphine. An optimum yield of the urea (61%) was obtained with an *n*-Bu_3P/Ru ratio of 2 (run 2).

Osmium trichloride also served as a catalyst precursor, but it was less effective than the ruthenium compounds (17% yield, run 7).

Table II. Ru-Catalyzed Synthesis of *N,N'*-Dicyclohexylurea. Effects of Solvent, Initial CO_2 Pressure, and Temperature[a]

run	solvent	CO_2 pressure (MPa)	temp (°C)	alkyne	time (h)	urea (%)
8	toluene	5	120	A	20	36
9	water	5	120	A	20	6
10	pyridine	5	140	B	20	36
11	decaline	5	160	B	20	41
12	none	5	140	B	20	61
13	none	4	140	B	20	62
14	toluene	5	120	B	20	15
15	toluene	5	160	B	20	40
16	toluene	5	120	A	20	30[b]
17	toluene	5	140	A	20	29[b]

[a] Reaction conditions: cyclohexylamine (20 mmol), alkyne (20 mmol or 50 mmol in the absence of solvent), solvent (10 mL or none), $RuCl_3 \cdot 3H_2O/2$ *n*-Bu_3P (0.2/0.4 mmol), 20 h; A, propargyl alcohol; B, 2-methylbut-3-yn-2-ol. Yield of urea based on the amine. [b] Catalyst: $[(norbornadiene)RuCl_2]_n$ (0.4 mmol).

Different solvents could be used without significantly affecting the yield of urea (Table II). Thus, toluene (36%, run 8), acetonitrile (33%), ethanol (32%), pyridine (36%), and decalin (41%) (runs 10, 11) were all used. Even when water was the solvent, a 6% yield of the urea was isolated after reaction under standard conditions (run 9). It was noteworthy that the yield of urea increased when the reaction was performed with excess alkyne as the solvent. Thus, reaction at 140 °C for 20 h in the presence of $RuCl_3 \cdot 3H_2O$, 2 *n*-Bu_3P, and a large excess of phenylacetylene or 2-methylbut-3-yn-2-ol (**B**) gave a 27 and 61% (run 12) yield of *N,N'*-dicyclohexylurea, respectively. In contrast, when the reaction was performed in toluene (10 mL) in the presence of the alkyne (20 mmol), the yield of the urea was 6% when phenylacetylene was used and 28% when **B** was used.

The effects of the initial CO_2 pressure, the reaction time, and the reaction temperature on the yield of *N,N'*-dicyclohexylurea were also studied. As the initial CO_2 pressure was increased from 1.1 to 3 to 4 to 5 MPa, the yield of the urea changed from 40 to 54 to 62 (run 13) to 61% (run 12). The yield of the urea increased as the reaction time was increased. Thus, reaction for 2.5, 10, and 15 h gave the urea in yields of 18, 52, and 56%, respectively. However, a reaction time greater than ca. 20 h did not significantly improve the yield. For example, after 60 h, a 64% yield of the urea was produced.

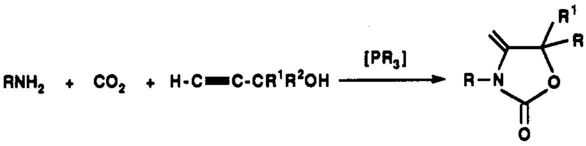
Temperatures above 120 °C were necessary to obtain satisfactory yields of the urea (Table II). However, polymerization and degradation of the alkyne were observed as the reaction temperature was raised to 160 °C, and the yield of the urea decreased drastically. 2-Methylbut-3-yn-2-ol (**B**) was less easily thermally degraded than was propargyl alcohol (**A**), so the reaction was performed at 140 °C in the presence of alcohol **B**.

The synthesis of other symmetrical ureas was attempted using the experimental conditions that gave the best results with cyclohexylamine (run 12). Thus, a mixture of the primary amine (20 mmol), $RuCl_3 \cdot 3H_2O$ (0.2 mmol), *n*-Bu_3P (0.4 mmol), and excess **B** (50 mmol) was pressurized to 5 MPa with CO_2 and was heated at 140 °C for 20 h. So obtained were *N,N'*-di-*n*-propylurea (45%), *N,N'*-diallylurea (27%), *N,N'*-di-*n*-pentylurea (41%), *N,N'*-dicyclopentylurea (41%), *N,N'*-di-*n*-hexylurea (57%), *N,N'*-dicyclohexylurea (61%), *N,N'*-di-*n*-decylurea (68%), *N,N'*-dibenzylurea (27%), *N,N'*-di-β-phenethylurea (50%), *N,N'*-bis(β-*p*-chlorophenethyl)urea (52%). Aromatic amines did not react, and no *N,N'*-diarylureas were obtained by this method.

Discussion

In run 12, besides *N,N'*-dicyclohexylurea, *N*-cyclohexyl-5,5-dimethyl-4-methyleneoxazolidin-2-one (**C**) was isolated in 24% yield. This represented an 85% overall incorporation of the initial amount of cyclohexylamine.

The yield of byproduct **C** increased as the reaction time was increased from 2.5 to 20 h. Moreover, when the amount of tri-*n*-butylphosphine was increased to 3.2 mmol ($Bu_3P/Ru = 16$, $Bu_3P/amine = 0.16$), the formation of the oxazolidinone **C** became the predominant product and no urea was detected. Thus, Bu_3P catalyzed the formation of oxazolidinones directly from primary amines, CO_2, and propargylic alcohols[23] (eq 3).

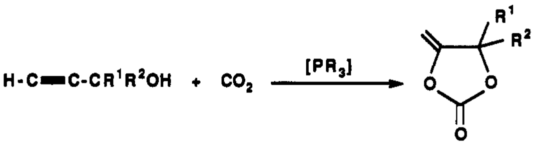


(3)

(C) : R= cyclohexyl, $R^1 = R^2 =$ Me

Treatment of oxazolidinone **C** with cyclohexylamine and CO_2 under conditions similar to those used to prepare *N,N'*-dicyclohexylurea gave none of the urea. Thus, the trialkylphosphine-catalyzed formation of oxazolidinone **C** competed with the ruthenium/trialkylphosphine complex catalyzed formation of the urea. The optimum yield of the area was obtained when 2 equiv of phosphine to 1 equiv of ruthenium were used.

It is known that cyclic methylene carbonates can be formed from propargyl alcohol derivatives in the presence of CO_2 and ruthenium catalysts[24] (eq 4). The easy synthesis of such compounds from tertiary propargylic alcohol derivatives and CO_2 in the presence of a phosphine has also been demonstrated.[25] However, in the reactions described here the presence of compound **D** was not detected.



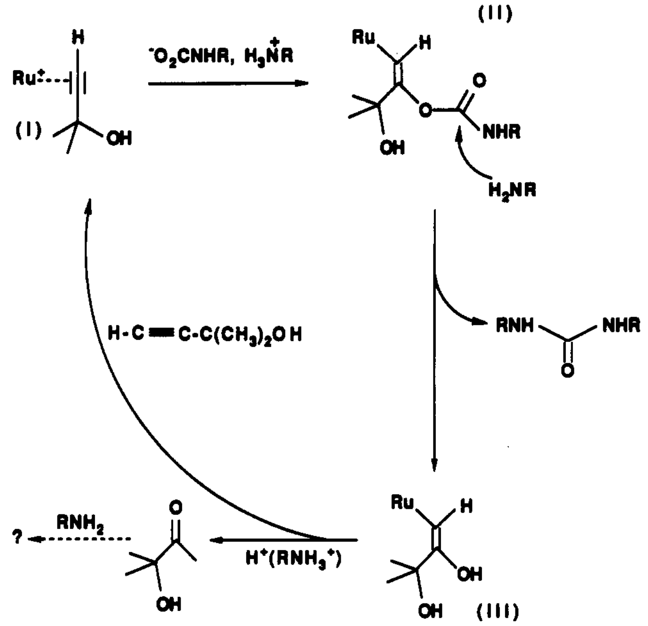
(4)

(D) : $R^1 = R^2 =$ Me

That the cyclic carbonate **D** formed from alcohol **B** did not provide a urea in the presence of the amine under the reaction conditions described here has been demonstrated. Thus, neither oxazolidinone **C** nor cyclic carbonate **D** is an intermediate in the formation of the urea. However, when 20 mmol of cyclohexylamine and 1.5 mmol of 2-methylbut-3-yn-2-ol (**B**) were allowed to react with CO_2 in toluene at 140 °C for 20 h, almost 1.5 mmol of the urea was formed. Thus, the presence of a stoichiometric amount of an alkyne is necessary for the formation of *N,N'*-dicyclohexylurea.

It should be noted that the catalytic formation of the urea is not possible in the absence of a terminal acetylenic compound. Ruthenium complexes are known to activate terminal alkynes to form either a (η^2-alkyne)–metal or a (η^1-vinylidene)–metal complex. Although the mechanism of the reaction cannot be proven, the catalytic cycle shown in Scheme II does account for the observed facts. The initial step is probably coordination of the alkyne with the metal to generate an activated alkyne (**I**). The nucleophilic ammonium carbamate formed in situ from the primary amine and CO_2 should then add to the carbon–carbon triple bond of **I** to give a ruthenium-coordinated vinyl carbamate species (**II**). Nucleophilic addition of the amine to **II** should lead to the urea and a ruthenium-coordinated enol (**III**). Subsequent protonation of **III** and elimination of a ruthenium species could regenerate the active catalytic species and provide an organic molecule, which would in fact be the product that would result from the formal addition of a water molecule to the alkyne. From simple alkynes, ketones or aldehydes would be expected to be formed and, from propargylic alcohols, keto alcohols or keto aldehydes. In the presence of an amine, these carbonyl compounds would be expected to react further. However, the presence of an organic compounds that would support this hypothesis has not been detected.

Scheme II



Experimental Section

In a typical run, solvent (10 mL), primary amine (20 mmol), alkyne (20 mmol), and ruthenium complex (0.2 mmol) were placed in a 125-mL stainless steel autoclave. When the solvent was excess alkyne, especially in the case of propargyl alcohol derivatives, 50 mmol of alkyne were used. The reactor was flushed with CO_2, and then it was pressurized with the gas to 5 MPa. The reaction mixture was then magnetically stirred at 140 °C for 20 h. After it cooled, the autoclave was rinsed twice with CH_2Cl_2. The combined rinses were concentrated, and the solid urea was collected. It was then recrystallized from hexane or Et_2O.

The products were characterized by IR, ^1H NMR, and elemental analysis.[20a] These data were compared with those in the literature. Melting points are uncorrected.

The primary amines, acetylenic compounds, tri-*n*-butylphosphine, solvents, and CO_2 were commercially available and were used without further purification. The transition-metal complexes were prepared from commercially available salts by reported methods.[26]

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Supplementary Material Available: Elemental analyses and IR and ^1H NMR data for various ureas (2 pages). Ordering information is given on any current masthead page.

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(23) Fournier, J.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron Lett.* **1990**, *31*, 1721.

(24) Sasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 1573.

(25) Fournier, J.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron Lett.* **1989**, *30*, 3981.

(26) Bennett, M. A.; Smith, A. K. *J. Chem. Soc., Dalton Trans.* **1974**, 233.