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Catalytic Carbonylation of Functionalized Diamines: Application to the Core Structure of DMP 323 and DMP 450

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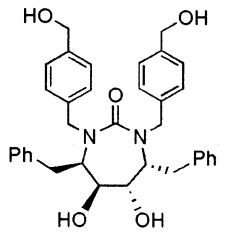
Abstract: $W(CO)_6$-catalyzed carbonylation provides an alternative to phosgene or phosgene derivatives such as 1,1-carbonyldiimidazole (CDI) for the conversion of amines to ureas. As an illustration, the core structure of the HIV protease inhibitors DMP 323 and DMP 450 has been prepared by catalytic carbonylation of diamine intermediates from the original syntheses.

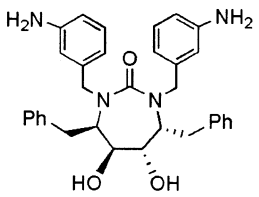
Methods for conversion of amines to ureas are generally based on the nucleophilic attack of amines on phosgene or a phosgene derivative.[1] A variant of this strategy involves reaction of amines with isocyanates, which also ultimately derive from phosgene. For a variety of reasons including concerns about phosgene[2] and the benefits of having alternative procedures available for synthetic transformations, we have been developing metal-catalyzed methods for the formation of ureas from amines and CO.

There are several reasons why prior work on metal-catalyzed oxidative carbonylation of amines has not been extended to applications in organic synthesis. Although transition-metal catalysts involving Ni,[3] Co,[4] Mn,[5,6] Ru,[7] Au,[8] and Pd[9−11] have been demonstrated to yield at least some urea from amines and CO, it is often a minor product. These transition-metal-catalyzed processes generally require high temperatures and pressures and frequently produce complex mixtures of ureas, formamides, and oxamides. In addition, yields of ureas from aliphatic amines are generally lower than those obtained from aromatic substrates, limiting their potential utility in organic synthesis. Main group elements such as selenium[12−14] can also serve as catalysts; however, certain aspects of these reactions (e.g., generation of hydrogen selenide and the need for stoichiometric or excess selenium for certain substrates[13,14]) are problematic.

We recently reported the catalytic carbonylation of aliphatic amines to ureas using $W(CO)_6$ as the catalyst and I_2 as the oxidant.[15−18] Diamine substrates with simple hydrocarbon linkers were converted to cyclic ureas with five- to eight-membered rings.[19,20] Because the reaction conditions are relatively mild and the functional group tolerance is surprisingly broad, this procedure was a reasonable candidate for use in synthesis of complex targets. As an illustration of its utility, we now report installation of the urea moiety into the core structure of the HIV protease inhibitors DMP 323 and DMP 450[21−23] by catalytic carbonylation of the corresponding diamine. The availability of a substantial body of literature on the synthesis of DMP 323 and DMP 450 derivatives allows direct comparison of the catalytic carbonylation reaction with stoichiometric reaction of the same substrates with phosgene derivatives.



DMP 323



DMP 450

In previously reported routes to DMP 323, DMP 450, and related compounds, the urea moiety was installed by reaction of phosgene or a phosgene equivalent with an O-protected diaminediol. In the initial small-scale preparations, a primary diamine was reacted with the phosgene derivative 1,1′-carbonyldiimidazole (CDI),[22,24−26] followed by N-alkylation as appropriate. The practical route to DMP 450 utilizes phosgene to form the cyclic

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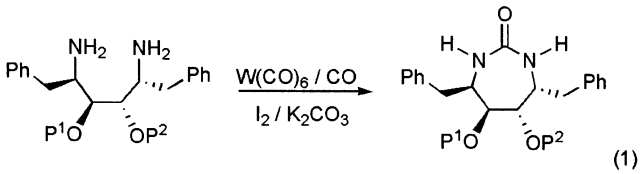
TABLE 1. Carbonylation of Diamines 1−3 to Ureas 4−6[a]

diame	reagent	solvent	*T* (°C)	urea yield (%)	ref
1	CDI	CH_3CN	NR[b]	15	25
1	CDI	TCE	147	67	25
1	$W(CO)_6$/CO	CH_2Cl_2/H_2O	80	38	*c*
1	$W(CO)_6$/CO	CH_2Cl_2	80	23	*c*
2	CDI	CH_2Cl_2	rt	62, 76[d]	22, 26, 29
2	$W(CO)_6$/CO	CH_2Cl_2/H_2O	80	49	*c*
3	CDI	CH_2Cl_2	rt	52, 93[d]	22, 26
3	$W(CO)_6$/CO	CH_2Cl_2/H_2O	80	75	*c*

[a] Typical reaction conditions: diamine **2** (0.200 mmol), $W(CO)_6$ (0.0219 mmol), K_2CO_3 (0.635 mmol), and I_2 (0.213 mmol), solvent (32 mL of CH_2Cl_2/8 mL of water), 80 atm of CO, 80 °C, 18 h. [b] Not reported. [c] This work. [d] Yields are from a two-step sequence involving deprotection of the Cbz-protected diamine. Deprotection is assumed to be quantitative for the purpose of the table.

urea from a secondary diamine.[25] Since all of these routes require protection of the diol, extensive protecting group studies have been carried out.[25,27] We have chosen three of the previously described O-protected diamine diols, acetonide **1**,[28] MEM ether **2**,[22,29] and SEM ether **3**,[22] as representative examples bearing cyclic and acyclic protecting groups, respectively. Carbonylation of **1**−**3** (eq 1) allows comparison of the $W(CO)_6$-catalyzed process to the stoichiometric reactions of the phosgene derivative CDI.



(1)

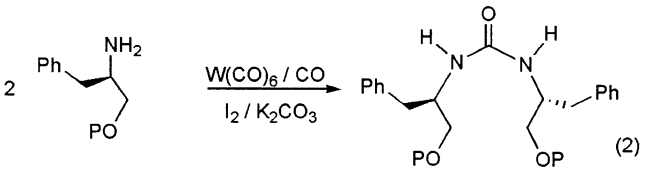
1 $P^1, P^2 =$ $C(CH_3)_2$
2 P^1, P^2 = MEM, MEM
3 P^1, P^2 = SEM, SEM

4 $P^1, P^2 =$ $C(CH_3)_2$
5 P^1, P^2 = MEM, MEM
6 P^1, P^2 = SEM, SEM

The difficulties associated with converting acetonide **1** to urea **4** have been discussed in the literature. Reaction of **1** with CDI in acetonitrile under standard conditions results in a 15% yield of **4** (Table 1) with the low conversion attributed to strain in the bicyclic product.[25] Although higher yields of **4** could be obtained by monoacylation of **1** with CDI followed by reflux at high dilution in tetrachloroethane (TCE), there were practical difficulties with this two-step procedure.[25] In comparison, catalytic oxidative carbonylation of **1** in the biphasic CH_2Cl_2/H_2O solvent system afforded **4** in 38% yield. As we had observed for the carbonylation of functionalized benzylamines,[15] yields obtained by using the biphasic solvent system were higher than those in CH_2Cl_2. Efforts to optimize the reaction conditions by varying CO pressure, temperature, concentration, and solvent did not result in higher yields of **4**. Although the yields of **4** from **1** are modest, results from the catalytic carbonylation compare favorably to those obtained with CDI under typical conditions.

Acyclic protecting groups such as MEM and SEM had been previously explored as alternatives that would lessen the strain problems that had plagued preparation of bicyclic acetonide **4** from diamine **1**.[22,29] Accordingly, MEM ether **2** and SEM ether **3** were chosen as additional test substrates for conversion to the corresponding cyclic ureas via catalytic carbonylation. Carbonylation of **2** and **3** was carried out under the conditions used for **1**, with the exception of substrate concentration, which was optimized for **2** and the same used for **3**. In comparison to the literature yields of 62 and 76% for formation of urea **5** from Cbz-protected MEM ether **2** and CDI under slightly different conditions, the catalytic carbonylation reaction provided **5** in 49% yield from **2**. Promising results were also obtained for SEM ether **3**, for which catalytic carbonylation afforded urea **6** in 75% yield, a value intermediate between the reported yields for reaction of **3** with CDI. Although the yields from both the stoichiometric CDI and catalytic carbonylation methods for urea formation varied with the nature of the protecting group on the diol, the overall results from the two methods were roughly comparable. These experiments establish that the catalytic reaction is compatible with acid-sensitive substrates and fluoride-sensitive protecting groups.

Intermolecular urea formation in related acyclic systems was probed by catalytic carbonylation of the O-protected amines **7**[30] and **8**. Both substrates afforded the corresponding ureas in moderate to good yields (eq 2), demonstrating that this catalytic methodology can also be used for formation of symmetrical ureas from the corresponding amines. The reaction conditions were identical to those used for diamines **1**−**3**, with the exception of concentration. As expected for intermolecular reactions, the maximum yields of urea were obtained at higher substrate concentrations than those used with the diamines, for which oligomerization competes with ring closure.



(2)

7 P = MEM
8 P = SEM

9 P = MEM 82% yield
10 P = SEM 53% yield

In summary, we have established that catalytic carbonylation of amines can be used in the preparation of functionalized ureas. Use of this chemistry in preparation

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of the core structure of DMP 323 and DMP 450 provides the first demonstration of catalytic amine carbonylation as synthetic methodology. Due to the extensive literature on these compounds, the results can be compared with those previously reported for the stoichiometric reactions of the phosgene derivative CDI. Yields of the ureas from the catalytic reaction vary with the protecting group on the diol, as do those reported for ring closure with stoichiometric CDI. Studies of the carbonylation reaction and its application in approaches to complex targets are continuing.

Experimental Section

General Methods. All experimental procedures were carried out under nitrogen and in oven dried glassware unless otherwise indicated. Solvents and reagents were obtained from commercial vendors in the appropriate grade and used without purification except for solvents used in carbonylation reactions that were dried, degassed, and distilled. Syntheses of diamines **1**,[28] **2**,[22,29] and **3**[22] and amine **7**[22] were carried out according to literature procedures. $W(CO)_6$ was purified by chromatography on alumina using hexanes as eluent.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-*O*-isopropylidene-4,7-bis-(phenylmethyl)-2*H*-1,3-diazapin-2-one (4). To a glass-lined 300 mL Parr high-pressure vessel containing 18 mL of CH_2Cl_2 and 3 mL of water were added diamine **1** (126.7 mg, 0.37 mmol), $W(CO)_6$ (8.8 mg, 0.025 mmol), K_2CO_3 (164.9 mg, 1.19 mmol), and I_2 (100.5 mg, 0.39 mmol). The vessel was then charged with 85 atm of CO and heated at 81 °C 48 h. *(CAUTION: CO is a toxic gas.)* The pressure was released, and 15 mL of water was added. The organics were then separated and washed with a saturated solution of Na_2SO_3 followed by brine. The resulting solution was dried over magnesium sulfate and filtered. The solvent was removed by evaporation, and the resulting residue was purified via column chromatography on silica using ether as eluent. Removal of the solvent afforded **4** as a white solid in 38% yield. The product was identified by comparison with literature data.[27] IR (neat) ν_{CO} 1671 cm^{-1}; HRMS $(M + H)^+$ calcd 367.2021, found 367.2012.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-bis(2-methoxyethoxymethoxy)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (5). To a glass-lined 300 mL Parr high-pressure vessel containing 32 mL of CH_2Cl_2 and 8 mL of water were added diamine **2** (101.1 mg, 0.200 mmol), $W(CO)_6$ (7.7 mg, 0.0219 mmol), K_2CO_3 (87.8 mg, 0.635 mmol), and I_2 (54.2 mg, 0.213 mmol). The vessel was then charged with 80 atm of CO and heated at 82 °C overnight. The pressure was released, and 15 mL of water was added. The organics were then separated and washed with a saturated solution of Na_2SO_3 followed by brine. The resulting solution was dried over magnesium sulfate and filtered. The solvent was removed by evaporation, and the resulting residue was purified to obtain **5** as a white solid in 49% yield after purification using literature procedures.[29] The product was identified by comparison with literature data.[29] IR (neat) ν_{CO} 1674 cm^{-1}; HRMS $(M + H)^+$ calcd 503.2752, found 503.2797.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-bis[2-(trimethylsilyl)-ethoxymethoxy]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (6). To a glass-lined 300 mL Parr high-pressure vessel containing 32 mL of CH_2Cl_2 and 8 mL of water were added diamine **3** (92.9 mg, 0.164 mmol), $W(CO)_6$ (2.4 mg, 0.0068 mmol), K_2CO_3 (68.8 mg, 0.497 mmol), and I_2 (42.2 mg, 0.166 mmol). The vessel was then charged with 77 atm of CO and heated at 82 °C overnight. The pressure was released, and 15 mL of water was added. The organics were then separated and washed with a saturated solution of Na_2SO_3 followed by brine. The resulting solution was dried over magnesium sulfate and filtered. The solvent was removed by evaporation, and the resulting residue was purified via column chromatography on silica using 2:1 hexanes/ethyl acetate as eluent. Removal of the solvent afforded **6** as a white solid in 75% yield. The product was identified by comparison with literature data.[22] IR (neat) ν_{CO} 1679 cm^{-1}; HRMS $(M + H)^+$ calcd 587.3336, found 587.3355.

1-Benzyl-2-[2-(trimethylsilyl)ethoxymethoxy]ethylamine (8). A solution of (R)-*N*-Cbz-phenylalaninol (999.5 mg, 3.54 mmol), [2-(trimethylsilyl)]ethoxymethoxy chloride (SEMCl) (2.40 mL, 13.5 mmol), and 2.5 mL of diisopropylethylamine in 10 mL of dry methylene chloride was stirred at room temperature overnight until TLC indicated that no starting material was present. The reaction mixture was washed once with water. The water layer in turn was washed with 4 × 10 mL of methylene chloride, and the combined organics were washed with water (2 × 10 mL). The combined water layers were washed once with 10 mL of methylene chloride. The combined organics were dried over magnesium sulfate, and the solvent was removed by evaporation to yield 1.456 g of the crude SEM ether as a brown oil.

To a solution of 496.0 mg (1.19 mmol) of the crude SEM ether in 10 mL of EtOH was added 44.2 mg of 5% Pd/C. The reaction mixture was degassed and subsequently filled with hydrogen at 1 atm. The reaction mixture was then stirred for 2.5 h until TLC showed no starting material. The mixture was then filtered and evaporated to dryness to yield 320.5 mg of crude **8**. The crude amine was purified by column chromatography eluting with 2/1 hexanes/ethyl acetate with 1% triethylamine followed by 1:1 hexanes/ethyl acetate with 1% triethylamine to afford **8** as an oil in 68% yield: ^1H NMR ($CDCl_3$) δ 0.05 (s, 9H), 0.97 (t, 2H, J = 8.1 Hz), 2.56−2.63 (m, 1H), 2.81−2.87 (m, 1H), 3.27−3.28 (m, 1H), 3.39−3.44 (m, 1H), 3.57−3.69 (m, 3H), 4.73 (s, 2H), 7.22−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −1.2, 18.3, 41.0, 52.7, 65.4, 72.8, 95.4, 126.5, 128.7, 129.4, 139.0; HRMS $(M + H)^+$ calcd 282.1889, found 282.1886.

1,3-Bis[1-(2-methoxyethoxymethoxymethyl)-2-phenylethyl]urea (9). To a glass-lined 300 mL Parr high-pressure vessel containing 34 mL of CH_2Cl_2 and 9 mL of water were added amine **7** (106.8 mg, 0.379 mmol), $W(CO)_6$ (6.8 mg, 0.019 mmol), K_2CO_3 (78.8 mg, 0.570 mmol), and I_2 (48.2 mg, 0.189 mmol). The vessel was then charged with 80 atm of CO and heated at 82 °C overnight. The pressure was released, 15 mL water was added, and the organics were separated and washed with a saturated solution of Na_2SO_3, water, and brine. The resulting solution was dried over magnesium sulfate and filtered. The solvent was removed by evaporation, and the resulting residue was purified by washing with 2:1 hexanes/ethyl acetate and hexanes to afford **9** as a white solid in 82% yield. The product was identified by comparison with literature data.[24] IR (neat) ν_{CO} 1673 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.75−2.94 (m, 4H), 3.36 (s, 6H), 3.45−3.54 (m, 8H), 3.67−3.68 (m, 4H), 4.09−4.11 (m, 2H), 4.63−4.71 (q, 4H (J = 6.3 Hz), 5.03−5.06 (d, 2H, J = 8.1 Hz), 7.21−7.29 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 38.4, 51.2, 59.1, 67.1, 69.8, 72.0, 96.1, 126.4, 128.5, 129.6, 138.6, 157.5; HRMS $(M + H)^+$ calcd 505.2914, found 505.2902.

1,3-Bis[2-phenyl-1-[2-(trimethylsilyl)ethoxymethoxymethyl]ethyl]urea (10). Following the same procedure used to prepare **9**, urea **10** was obtained as an oil in 53% yield after chromatography on silica using 2/1 hexanes/ethyl acetate as eluent. Urea **10** was comprised of isomers in a 3:1 ratio. The spectral data of the major isomer follow: IR (neat) ν_{CO} 1673 cm-1; ^1H NMR ($CDCl_3$) δ 0.02 (s, 18H), 0.93 (t, 4H, J = 8.1 Hz), 2.84 (m, 4H), 3.46 (m, 4H), 3.62 (m, 4H), 4.08 (m, 2H), 4.65 (s, 4H), 7.22−7.29 (m, 10H); ^{13}C NMR ($CDCl_3$) δ −1.4, 18.0, 38.1, 51.3, 64.4, 68.8, 95.3, 126.3, 128.4, 129.3, 138.2, 157.2; HRMS $(M + H)^+$ calcd 589.3493, found 589.3475.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **8** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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