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# Synthesis of Carbamates and Ureas Using Zr(IV)-Catalyzed Exchange Processes

**Chong Han and John A. Porco, Jr***

*Department of Chemistry and Center for Chemical Methodology and Library Development, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215*

*porco@bu.edu*

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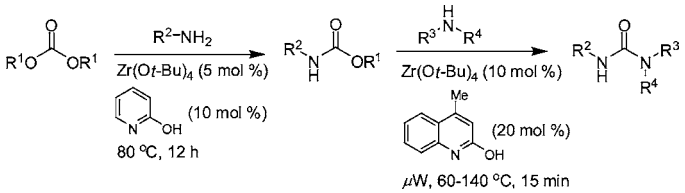
## ABSTRACT




**Zirconium(IV)-catalyzed exchange processes have been developed to prepare both carbamates and ureas from dialkyl carbonates and carbamates employing 2-hydroxypyridine (HYP) and 4-methyl-2-hydroxyquinoline (MeHYQ) as catalytic additives, respectively. A microwave acceleration effect was observed in Zr(IV)-catalyzed carbamate–urea exchange.**

Carbamate and urea functional groups play important roles in organic, medicinal, supramolecular, and material chemistry.[1] For example, recent reports have cited examples of ureas as potent HIV-1 protease inhibitors,[2] p38 MAP kinase inhibitors for the treatment of inflammatory diseases,[3] and peptidomimetics with increased metabolic stability. Although a number of methodologies, including oxidative carbonylation of amines,[4] have been developed, the standard preparation of carbamates and ureas generally involves use of toxic and highly reactive phosgene,[5] phosgene derivatives,[6] or isocyanates.[7]

Recently, dialkyl carbonates[8] have emerged as environmentally friendly and nontoxic substitutes for phosgene and phosgene derivatives in alkoxycarbonylation reactions. For instance, metal-catalyzed carbamate syntheses using dimethylcarbonate and amines have been reported.[9] Related syntheses of ureas from *O*-alkyl carbamates and amines have also been accomplished in the presence of stoichiometric amounts of mediators.[10] Direct conversion of carbamates to ureas obviates the need for intermediate deprotection and activation steps. On the basis of our previous work concern-

(1) (a) Vishnyakova, T. P.; Golubeva, I. A.; Glebova, E. V. *Russ. Chem. Rev. (Engl. Transl.)* **1985**, *54*, 249. (b) Gabriele, B.; Salerno, G.; Mancuso, R.; Costa, M. *J. Org. Chem.* **2004**, *69*, 4741 and references therein.

(2) (a) Han, Q.; Chang, C.-H.; Li, R.; Ru, Y.; Jadhav, P. K.; Lam, P. Y. S. *J. Med. Chem.* **1998**, *41*, 2019 and references therein. (b) Guichou, J.-F.; Viaud, J.; Mettling, C.; Subra, G.; Lin, Y.-L.; Chavanieu, A. *J. Med. Chem.* **2006**, *49*, 900.

(3) Regan, J.; Breitfelder, S.; Cirillo, P.; Gilmore, T.; Graham, A. G.; Hickey, E.; Klaus, B.; Madwed, J.; Moriak, M.; Moss, N.; Pargellis, C.; Pav, S.; Proto, A.; Swinamer, A.; Tong, L.; Torcellini, C. *J. Med. Chem.* **2002**, *45*, 2994 and references therein.

(4) McCusker, J. E.; Main, A. D.; Johnson, K. S.; Grasso, C. A.; McElwee-White L. *J. Org. Chem.* **2000**, *65*, 5216 and references therein.

(5) Babad, H.; Zeiler, A. G. *Chem. Rev.* **1973**, *73*, 75.

(6) For a review on the use of phosgene substitutes, see: Biggi, F.; Maggi, R.; Sartori, G. *Green Chem.* **2000**, *2*, 140.

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

(8) For recent reviews on the chemistry of dialkyl carbonates, see: (a) Shaikh, A.-A. G.; Sivaram, S. *Chem. Rev.* **1996**, *96*, 951. (b) Parrish, J. P.; Salvatore, R. N.; Jung, K. W. *Tetrahedron* **2000**, *56*, 8207. For a review on the chemistry of dimethylcarbonate, see: (c) Tundo, P.; Selva, M. *Acc. Chem. Res.* **2002**, *35*, 706.

(9) $Pb(NO_3)_2$: (a) Baba, T.; Fujiwara, M.; Oosaku, A.; Kobayashi, A.; Deleon, R. G.; Ono, Y. *Appl. Catal., A* **2002**, *227*, 1. $Yb(OTf)_3$: (b) Curini, M.; Epifano, F.; Maltese, F.; Rosati, O. *Tetrahedron Lett.* **2002**, *43*, 4895. $Sc(OTf)_3$ and $La(OTf)_3$: (c) Distaso, M.; Quaranta, E. *Tetrahedron* **2004**, *60*, 1531.

(10) $SiR_nCl_{4-n}$: (a) Chong, P. Y.; Janicki, S. Z.; Petillo, P. A. *J. Org. Chem.* **1998**, *63*, 8515. $\gamma$-$Al_2O_3$: (b) Vauthey, I.; Valot, F.; Gozzi, C.; Fache, F.; Lemaire, M. *Tetrahedron Lett.* **2000**, *41*, 6347. $SiI_2H_2$: (c) Gastaldi, S.; Weinreb, S. M.; Stien D. *J. Org. Chem.* **2000**, *65*, 3239. $AlMe_3$: (d) Lee, S.-H.; Matsushita, H.; Clapham, B.; Janda, K. D. *Tetrahedron* **2004**, *60*, 3439.

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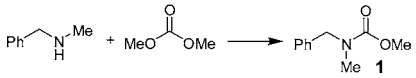
ing Zr(IV)-catalyzed ester−amide exchange,[11] we wished to extend our methodology to the synthesis of carbamates and ureas by reaction of amines with both dialkyl carbonates and carbamates.

In line with our previous studies concerning the additive acceleration effects in Zr(IV)-catalyzed ester−amide exchange,[11a] initial experiments focused on evaluation of catalytic amounts of Zr(O*t*-Bu)$_4$ and a series of nucleophilic additives in the reaction of *N*-Me benzylamine and dimethylcarbonate in the absence of solvent (Table 1). Among

**Table 1.** Optimization of Carbonate−Carbamate Exchange[a,b]



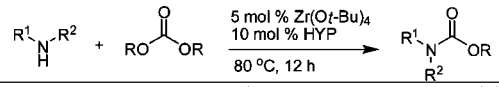
| entry | conditions | conversion (%)[c] |
|---|---|---|
| 1 | none | 7 |
| 2 | Zr(O*t*-Bu)$_4$ (5 mol %) | 69 |
| 3 | Zr(O*t*-Bu)$_4$ (5 mol %), HOAt (5 mol %) | 75 |
| 4 | Zr(O*t*-Bu)$_4$ (5 mol %), HOBt (5 mol %) | 47 |
| 5 | Zr(O*t*-Bu)$_4$ (5 mol %), MeHYQ (5 mol %) | 58 |
| 6 | Zr(O*t*-Bu)$_4$ (5 mol %), HYP (5 mol %) | 79 |
| 7 | Zr(O*t*-Bu)$_4$ (5 mol %), HYP (10 mol %) | 87 (85)[d] |
| 8 | Zr(O*t*-Bu)$_4$ (5 mol %), HYP (20 mol %) | 88 |
| 9 | HYP (10 mol %) | 17 |

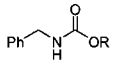
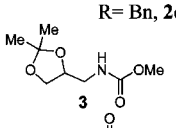
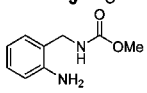
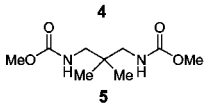
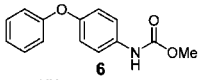
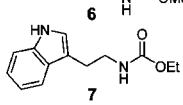
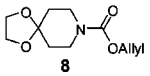
[a] Reaction conditions: amine (1.0 equiv), dimethylcarbonate (1.1 equiv), neat, 80 °C, 16 h. [b] HOAt = 1-hydroxy-7-azabenzotriazole, HOBt = 1-hydroxybenzotriazole, MeHYQ = 4-methyl-2-hydroxyquinoline, HYP = 2-hydroxypyridine. [c] Conversions based on $^1$H NMR analysis of the crude reaction mixture. [d] Isolated yield indicated in parenthesis.

additives evaluated,[12] 2-hydroxypyridine (HYP)[13] was found to be optimal. Control experiments without catalyst or with 10 mol % HYP showed low conversions (Table 1, entries 1 and 9). The effect of the ratio of metal to additive on catalyst efficiency was also examined (Table 1, entries 6−8). Increasing the ratio beyond 1:2 did not show noticeable improvement on product conversions. Further optimization to shorten the reaction time using microwave irradiation was unsuccessful.

With effective conditions in hand, we next examined the scope of Zr(IV)-catalyzed carbonate−carbamate exchange (Table 2). In general, reactions were performed neat with 1.0 equiv of amine and 1.5 equiv of dialkyl carbonate in the presence of 5 mol % Zr(O*t*-Bu)$_4$ and 10 mol % HYP at 80 °C

**Table 2.** Scope of Carbonate−Carbamate Exchange[a]

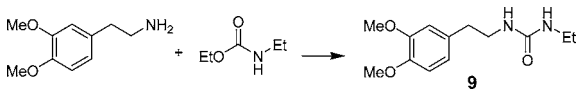


| entry | product | yield (%)[b] |
|---|---|---|
| 1 |  R= Me, **2b** | 88 |
| | R= Et, **2c** | 90 |
| | R= Allyl, **2d** | 95[c] |
| | R= Bn, **2e** | 95 |
| 2 |  **3** | 96 |
| 3 |  **4** | 97[d] |
| 4 |  **5** | 91[d,e] |
| 5 |  **6** | 85[d,e] |
| 6 |  **7** | 98[e,f] |
| 7 |  **8** | 95[c] |

[a] Reaction conditions: amine (1.0 equiv), carbonate (1.5 equiv), Zr(O*t*-Bu)$_4$ (5 mol %), HYP (10 mol %), neat, 80 °C, 12 h. [b] Isolated yield after purification by silica gel chromatography. [c] 1.1 equiv of carbonate employed. [d] Zr(O*t*-Bu)$_4$ (10 mol %), HYP (20 mol %) employed. [e] 3 equiv of carbonate employed. [f] Reaction conducted at 100 °C.

(12 h). Four different carbonates (Me, Et, Bn, allyl) examined showed similar reactivities in reactions with benzylamine. In terms of the amine scope, both aliphatic and aromatic amines performed well. The reaction of 2-aminobenzylamine with dimethylcarbonate was found to be chemoselective for aliphatic versus aromatic amines (Table 2, entry 3). In contrast, 2-aminobenzylamine has been shown to react with methyl chloroformate to afford the corresponding biscarbamate without selectivity.[14] Functional groups

**Table 3.** Optimization of Carbamate−Urea Exchange[a,b]



| entry | conditions | conversion (%)[c] |
|---|---|---|
| 1 | none | 3 |
| 2 | Zr(O*t*-Bu)$_4$ (10 mol %) | 74 |
| 3 | Zr(O*t*-Bu)$_4$ (10 mol %), HYP (20 mol %) | 62 |
| 4 | Zr(O*t*-Bu)$_4$ (10 mol %), HYQ (20 mol %) | 86 |
| 5 | Zr(O*t*-Bu)$_4$ (10 mol %), MeHYQ (20 mol %) | 95 |
| 6 | MeHYQ (20 mol %) | 13 |
| 7[d] | Zr(O*t*-Bu)$_4$ (10 mol %), MeHYQ (20 mol %) | 99 (94)[e] |

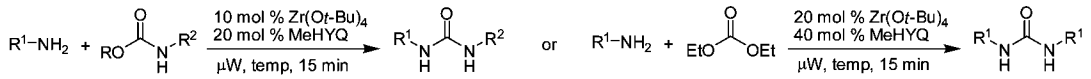
[a] Reaction conditions: amine (1.1 equiv), urethane (1.0 equiv), neat, 100 °C, 12 h. [b] HYQ = 2-hydroxyquinoline. [c] Conversions based on $^1$H NMR analysis of the crude reaction mixture. [d] $\mu$W, 120 °C, 15 min. [e] Isolated yield indicated in parenthesis.

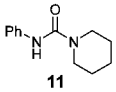
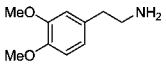
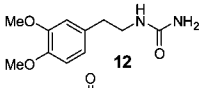
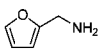
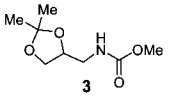
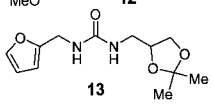
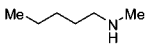
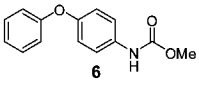
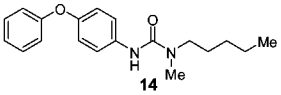
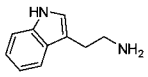
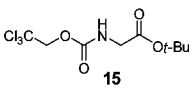
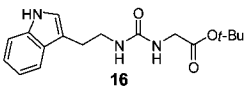
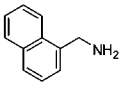
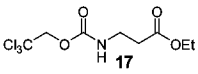
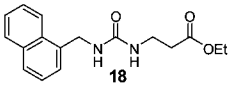
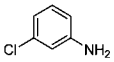
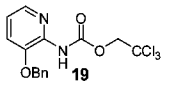
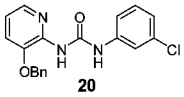
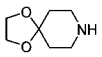
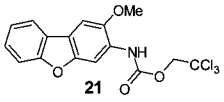
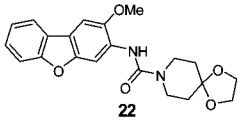
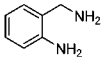
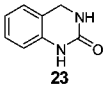
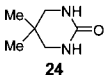
(11) (a) Han, C.; Lee, J. P.; Lobkovsky, E.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 10039 and references therein. For recent reports on Ti(IV)-catalyzed transamidation, see: (b) Eldred, S. E.; Stone, D. A.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 3422. (c) Kissounko, D. A.; Hoerter, J. M.; Guzei, I. A.; Cui, Q.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 1776.

(12) See Supporting Information for complete experimental details.

(13) For representative examples of metal complexes containing HYP or HYP derivatives, see: Cu, Ni, and Co: (a) Parsons, S.; Winpenny, R. E. P. *Acc. Chem. Res.* **1997**, *30*, 89. Pd: (b) Maity, S.; Roy, R.; Sinha, C.; Sheen, W.-J.; Panneerselvam, K.; Lu, T.-H. *J. Organomet. Chem.* **2002**, *650*, 202. Au: (c) Thwaite, S. E.; Schier, A.; Schmidbaur, H. *Inorg. Chim. Acta* **2004**, *357*, 1549. Ti and Zr: (d) Takashima, Y.; Nakayama, Y.; Hashiguchi, M.; Hosoda, T.; Yasuda, H.; Hirao, T.; Harada, A. *Polymer* **2006**, *47*, 5762.

**Table 4.** Urea Synthesis by Reaction of Amines and Carbamates or Carbonates[a]




| entry | amine | carbamate | product | temp | yield (%)[b] |
|---|---|---|---|---|---|
| 1 |  |  R=Me, **10a**<br>R=Et, **10b**<br>R=Allyl, **10c**<br>R=Bn, **10d**<br>R=$CH_2CCl_3$, **10e**<br>R=*t*-Bu, **10f** |  **11** | 120 °C<br>120 °C<br>100 °C<br>120 °C<br>60 °C<br>160 °C | 96<br>96<br>98<br>94<br>98<br>73 |
| 2 |  |  |  **12** | 100 °C | 91 |
| 3 |  |  **3** |  **13** | 140 °C | 80[c] |
| 4 |  |  **6** |  **14** | 120 °C<br>120 °C | 99[d]<br>95[d,e] |
| 5 |  |  **15** |  **16** | 100 °C | 85[d] |
| 6 |  |  **17** |  **18** | 100 °C | 81[d] |
| 7 |  |  **19** |  **20** | 100 °C | 98[d] |
| 8 |  |  **21** |  **22** | 80 °C | 97[d] |
| 9 |  |  |  **23** | 140 °C | 70 |
| 10 |  |  |  **24** | 140 °C | 85 |

[a] Reaction conditions: amine (1.0 equiv), carbamate (1.1 equiv), Zr(O*t*-Bu)$_4$ (10 mol %), MeHYQ (20 mol %), neat, $\mu$W, temp, 15 min. For entries 9−10: amine (2.2 equiv), carbonate (1.0 equiv), Zr(O*t*-Bu)$_4$ (20 mol %), MeHYQ (40 mol %), chlorobenzene (1.0 M), $\mu$W, temp, 15 min. [b] Isolated yield after purification by silica gel chromotagraphy. [c] Carbamate (1.5 equiv) employed. [d] Reaction performed in chlorobenzene (2.0 M). [e] Carbamate **6** was prepared in situ without purification.

including acetonide (Table 2, entry 2), indole (entry 6), and cyclic ketal (entry 7) were found to be tolerated under the reaction conditions. For diamine substrates, cyclic urea products were not observed (Table 2, entries 3 and 4).

We next explored urea formation through carbamate−urea exchange. In contrast to the carbamate formation, additive screening identified 4-methyl-2-hydroxyquinoline (Me-HYQ)[15] as an optimal additive in model reactions between 3,4-dimethoxyphenethylamine and *N*-ethyl urethane (Table 3). Control experiments without catalyst or with 20 mol % MeHYQ showed low conversions (Table 3, entries 1 and 6). In contrast to carbamate formation, we found that urea formation was significantly accelerated using microwave irradiation.[16] For instance, 12 h was required for the model reaction to reach completion at 100 °C under conventional heating, whereas only 15 min was needed if the reaction was performed at 120 °C under microwave irradiation (Table 3,

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entry 7). Further experiments will be pursued to probe this apparent microwave effect.

The scope and limitations of urea formation using carbamate−urea exchange were evaluated under microwave irradiation using 10 mol % of $Zr(O\textit{t}\text{-}Bu)_4$ and 20 mol % of MeHYQ as catalyst (Table 4). In general, reactions to prepare mono-, di-, and trisubstituted ureas were completed in 15 min at temperatures varying from 60 to 140 °C depending on the specific substrate. During reaction optimization, we found that the reactions were best performed without solvent; however, a minimum amount of solvent (chlorobenzene, 1.0−2.0 M) was employed in some cases to aid in dissolving substrates. Based on observed reaction temperature differences, the reactivity of a number of synthetically useful carbamate protecting groups was found to decrease in the following order: Troc > Alloc > methyl carbamate, ethyl carbamate, Cbz > Boc (Table 4, entry 1).[17] The relatively high reactivity of the Troc carbamate[18] identifies it as a desirable precursor for the synthesis of complex ureas via exchange processes (Table 4, entries 5−8) including **20** (entry 7), a recently reported inhibitor of human cyclophilin A with potent anti-HIV activity.[2b] Of note is the chemoselective addition of amines to the Troc carbamate versus *tert*-butyl and ethyl esters, respectively (Table 4, entries 5 and 6). However, utilizing HYP as an additive or under conventional heating, a lower selectivity for urea formation was observed in the case of entry 6 (Table 4).

In comparison to the stepwise protocol, a one-pot urea synthesis sequence was also developed (Table 4, entry 4) in which carbamate **6** was prepared in situ from amine and carbonate and condensed with a second amine in the same reaction vessel without purification. A one-pot synthesis of cyclic ureas by condensation of diamines and diethyl carbonate was also found to be workable (Table 4, entries 9 and 10). It should be noted that carbamates derived from secondary amines were found to be inert under Zr(IV)-MeHYQ-catalyzed carbamate−urea exchange conditions in an attempt to prepare tetra-substituted ureas. This result indicates that an isocyanate intermediate[19,20] is likely generated in situ from the carbamate, which is consistent with literature precedents on carbamate decomposition.[10a,21] We believe that the greater reactivity of MeHYQ versus HYP for carbamate−urea exchange is likely due to the higher basicity of the conjugate base of MeHYQ, which facilitates isocyanate formation by deprotonation of the carbamate.[22]

In conclusion, zirconium(IV)-catalyzed exchange processes have been developed to prepare both carbamates and ureas from dialkyl carbonates and carbamates employing 2-hydroxypyridine (HYP) and 4-methyl-2-hydroxyquinoline (MeHYQ), respectively, as catalytic additives. Mechanistic studies and application of the exchange processes to the synthesis of complex carbamates and ureas are currently underway and will be reported in due course.

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**Supporting Information Available:** Experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Troc = 2,2,2-trichloroethyloxycarbonyl, Alloc = allyloxycarbonyl, Cbz = benzyloxycarbonyl, Boc = *tert*-butoxycarbonyl.

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