ORGANIC LETTERS

2004
Vol. 6, No. 17
2885−2888

Carboxylation and Mitsunobu Reaction of Amines to Give Carbamates: Retention vs Inversion of Configuration Is Substituent-Dependent

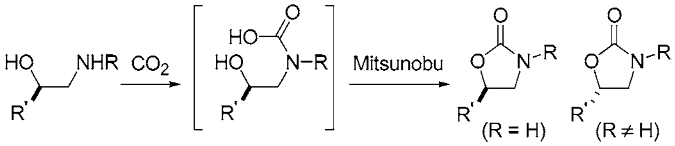
Christopher J. Dinsmore* and Swati P. Mercer

Department of Medicinal Chemistry, Merck Research Laboratories,
West Point, Pennsylvania 19486

christopher_dinsmore@merck.com

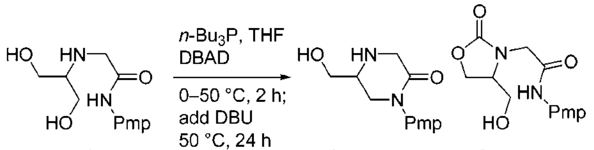
Received May 14, 2004

ABSTRACT



A mild method for the synthesis of carbamates from amino alcohols involves sequential carboxylation with carbon dioxide, followed by a Mitsunobu reaction. Unexpectedly, the stereochemical course of the Mitsunobu reaction is dependent on whether the carbamic acid intermediate is *N*-substituted with hydrogen (retention) or carbon (inversion).

Cyclic carbamates are frequently employed as fragments in biologically active materials for pharmaceutical and agricultural use[1] and as auxiliaries in useful synthetic transformations.[2] These materials are most commonly prepared from amino alcohols by carbonylation using phosgene or its functional equivalent or by oxidative carbonylation using CO and a catalyst. Using these methods, stereochemistry at the oxygen-bearing center is retained in the product. Alternatively, methods involving the cyclization of *N*-(hydroxyalkyl)carbamates, following activation of the hydroxyl group for displacement, affect inversion of configuration at the oxygen-bearing center. In a synthesis of 2-oxazolidinones from ethanolamines by in situ *N*-carboxylation and Mitsunobu cyclodehydration reported by Kodaka et al.,[3a] retention of configuration was observed. Here, we have optimized and expanded the scope of this reaction[3b] and have discovered that either inversion or retention of stereochemistry unexpectedly occurs in a manner dictated by the amino alcohol substituents. Mechanistic studies support an *N*-substituent-dependent dual reaction manifold.



(1)

1 2 *not observed* 3 *only product*

Pmp = *p*-methoxyphenyl

In the course of a recent drug discovery program, an unintended result provided the stimulus for this study (eq 1). In an attempt to cyclize the hydroxy amide **1** under Mitsunobu conditions[4] to produce piperazinone **2** in accordance with close literature precedent,[5] we were surprised

---

[1] (a) Dyen, M. E.; Swern, D. *Chem. Rev.* **1967**, *67*, 197. (b) Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673.

[2] (a) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23. (b) Alger, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.

[3] (a) Kodaka, M.; Tomohiro, T.; Okuno, H. *J. Chem. Soc., Chem. Commun.* **1993**, 81. (b) Although the utility of this reaction was established, the substrate scope in this study was limited to a small set of 2-amino alcohols and the reported yields were based on HPLC analysis rather than product isolation.

[4] (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127.

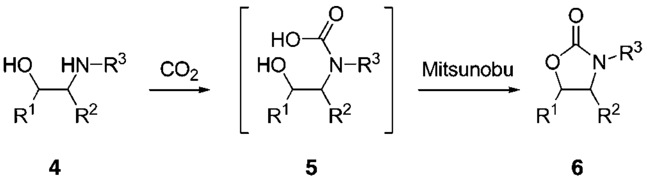
[5] Weissman, S. A.; Lewis, S.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 7459.

10.1021/ol0491080 CCC: $27.50

to find that no reaction had taken place. However, adding the base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to the reaction mixture triggered the accumulation of oxazolidinone **3** as the only observed product. We assumed that the source of carbon in this reaction was CO_2, likely present in the nondegassed commercial anhydrous THF used as solvent. The fixation of CO_2 in a zwitterionic DBU−CO_2 complex is a known process, as is the subsequent transcarboxylation of this complex and amines.[6] Thus, in the errant reaction it appeared that DBU promoted the carboxylation of amine **1** to produce a carbamic acid intermediate that underwent Mitsunobu cyclization to provide **3**.

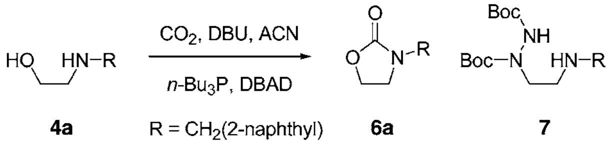
Following from this and Kodaka's earlier observations,[3] we became interested in further expanding the scope of a tandem amino alcohol carboxylation and Mitsunobu reaction strategy for preparing carbamates. Given the mildness with which an amino alcohol could be carboxylated to give a carbamic acid intermediate (e.g., **4** → **5**, Scheme 1), the stereoselectivity of the Mitsunobu transformation (e.g., **5** → **6**), and the potential for adapting the reaction to other substrate types, this method was anticipated to compliment existing carbamate synthesis strategies.

Scheme 1



The conversion of aminoethanol **4a** to oxazolidinone **6a** was chosen to optimize reaction conditions (Table 1). Consistent with literature examples of amine carboxylation, we selected acetonitrile as solvent and DBU−CO_2 as the carboxylation promoter.[6,7] Subjecting **4a** to 1 equiv each of DBU, tributylphosphine, and di-*tert*-butyl azodicarboxylate under a balloon of CO_2 gas resulted in 55% conversion to an equal mixture of the desired oxazolidinone **6a** and the hydrazine adduct **7** (entry 1). Using substoichiometric DBU gave the same result (entry 2). These results implied the incomplete formation of carbamic acid intermediate (e.g., **4** → **5**), allowing Mitsunobu alkylation of di-*tert*-butyl hydrazine-1,2-dicarboxylate to compete (**4a** → **7**). Gratifyingly, pretreating **4a** with DBU−CO_2 for 45 min prior to adding the *n*-Bu_3P and DBAD completely suppressed the formation of byproduct **7** (entry 3).[8] Finally, increasing the number of equivalents of Mitsunobu reagents (entries 4 and 5) led to complete and clean conversion of **4a** to **6a**, isolated in 92% yield after purification.

Table 1. Optimization of Reaction Conditions



entry	load time[a] CO_2	equiv of DBU/*n*-Bu_3P/DBAD	conversion[b] (%)	ratio[b] **6a**:**7**
1	0 min	1.1/1.1/1.1	55	52:48
2	0 min	0.1/1.1/1.1	57	50:50
3	45 min	0.1/1.1/1.1	74	100:0
4	45 min	0.1/1.5/1.5	95	100:0
5	45 min	0.1/2.1/2.1	100	100:0

[a] Time for which solution of **4a** and DBU are pretreated with CO_2 via balloon, before *n*-Bu_3P/DBAD were added. [b] Determined by LC−MS (UV, $\lambda = 215$ nm).

These reaction conditions were applied to a variety of substrates (Table 2). After the successful cyclization of the simple *N*-substituted ethanolamine **4a** (entry 1), we were gratified to find that a variety of substitution patterns are accommodated in high-yielding reactions. The aniline **4b** gave *N*-phenyloxazolidinone **6b** in almost quantitative yield (entry 2). Primary amines gave *N*-unsubstituted oxazolidinones with substituents at either the 4-position (**6c**, **6d**), the 5-position (**6e**), or both (**6e**, **6f**) in good yields. Consistent with earlier work,[3] primary amine substrates **4e**−**g** produced **6e**−**g** with *retention of configuration* at the oxygen-bearing center (entries 5−7). However, this was not the case for analogous substrates containing secondary amines, which unexpectedly gave oxazolidinones with *inversion of configuration* at the oxygen-bearing center.[9] This stereochemical divergence was most evident in comparisons of **4g** with **4h** (entry 7 vs 8) and **4i** with **4j** (entry 9 vs 10). Further exploring the scope of the reaction, we found that **4k** produced the bicyclic oxazolidinone **6k** efficiently and that the 1,3-amino alcohol **8** cyclized readily to provide the six-membered oxazinone **9** in high yield.

Intrigued by the *N*-substitution-dependent stereochemical divergence observed in these reactions, we undertook isotope labeling experiments designed to differentiate pathways involving either retention or inversion of configuration in the Mitsunobu cyclization.[10] In the reaction of a carbamic acid **5** to produce **6** (Scheme 1), the use of ^{18}O-labeled carbon

---

[6] (a) Mizuno, T.; Okamoto, N.; Ito, T.; Miyata, T. *Tetrahedron Lett.* **2000**, *41*, 1051. (b) Perez, E. R.; da Silva, M. O.; Costa, V. C.; Rodrigues-Filho, U. P.; Franco, D. W. *Tetrahedron Lett.* **2002**, *43*, 4091.

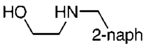
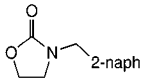
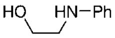
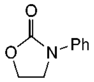
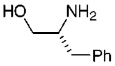
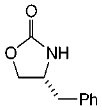
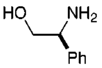
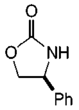
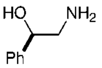
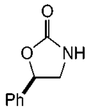
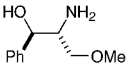
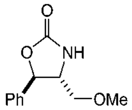
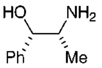
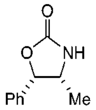
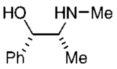
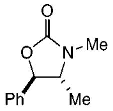
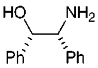
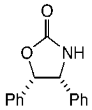
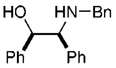
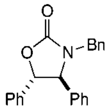
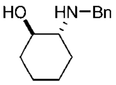
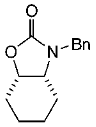
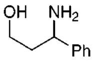
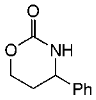
[7] Alternatively, the use of Cs_2CO_3, either in the presence or absence of added CO_2, met with limited success, affording only partial conversion of **4a** to **6a**. For reports of amine carboxylation using carbonate salts, see: (a) Butcher, J. K. *Synlett* **1994**, 825. (b) Inesi, A.; Mucciante, V.; Rossi, L. *J. Org. Chem.* **1998**, *63*, 1337. (c) Salvatore, R. N.; Chu, F.; Nagle, A. S.; Kapxhiu, E. A.; Cross, R. M.; Jung, K. W. *Tetrahedron* **2002**, *58*, 3329.

[8] In this and related reactions a precipitate often appears during the CO_2 pretreatment period, implying that an alkylammonium *N*-alkylcarbamate salt ($RNH_3^{+}\cdot{}^{-}O_2CNHR$) is formed. The extent to which complete conversion to carbamic acid **5** occurs before *n*-Bu_3P and DBAD are added is unknown. See: Hampe, E. M.; Rudkevich, D. M. *Tetrahedron* **2003**, *59*, 9619.

[9] Kodaka et al.[3a] had found that although **4c** and **4i** were converted to **6c** and **6i** with retention of configuration, using Ph_3P instead of *n*-Bu_3P promoted inversion in the case of **4c** → **6c**. No secondary amine substrates were evaluated for stereochemical outcome.

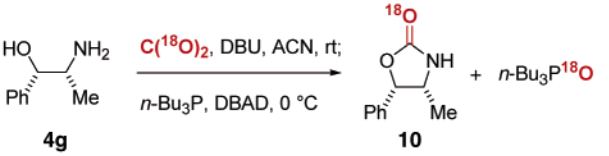
[10] Retention of configuration in the Mitsunobu reaction: (a) Ahn, C.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1754. (b) Smith, A. B.; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102. (c) Liao, X.; Wu, Y.; De Brabander, J. K. *Angew. Chem., Int. Ed.* **2003**, *42*, 1648.

Table 2. Examples of Carboxylation/Mitsunobu Cyclization Reaction[a]

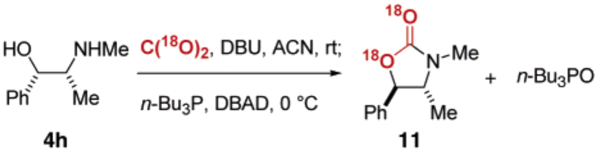
entry	aminoalcohol		product		% yield[b]
1		(**4a**)		(**6a**)	92
2		(**4b**)		(**6b**)	99
3		(**4c**)		(**6c**)	78
4		(**4d**)		(**6d**)	95
5		(**4e**)		(**6e**)	85
6		(**4f**)		(**6f**)[c]	92
7		(**4g**)		(**6g**)	84
8		(**4h**)		(**6h**)	73
9		(**4i**)		(**6i**)	96
10		(**4j**)		(**6j**)[d]	84
11		(**4k**)		(**6k**)[d]	69
12		(**8**)		(**9**)	95

[a] Reactions were run on a 0.5−2 mmol scale according to the conditions described in Supporting Information. [b] Yield of isolated carbamate product after purification. ^{1}H NMR and mass spectra are in accordance with assigned structures. Diastereomeric purities of relevant products were >95:5 by ^{1}H NMR spectroscopy. Unless otherwise indicated, relative and absolute stereochemistry were confirmed by comparison to commercially available materials or based on literature data. [c] Hydrolysis of **6f** (20% KOH, EtOH, 60 °C) gave amino alcohol **4f**, confirming structure. [d] Hydrolysis of **6j** and **6k** (20% KOH, EtOH, 60 °C) gave diastereomers of **4j** and **4k**, respectively.

dioxide should afford an ^{18}O-labeled carbonyl group oxygen, but the origin of the ring oxygen would depend on whether cyclodehydration of **5** occurs with loss of an OH group from the hydroxyl group (configurational inversion) or the carbamic acid group (configurational retention). As expected, we found that the reaction of primary amine **4g** in the presence of $C(^{18}O)_2$ gave mono-^{18}O-labeled oxazolidinone **10**, along with ^{18}O-tributylphosphine oxide (eq 2).[11a] In contrast, the analogous secondary amine **4h** produced doubly labeled **11** with no isotope label in the tributylphosphine oxide (eq 3).[11b]



(2)



(3)

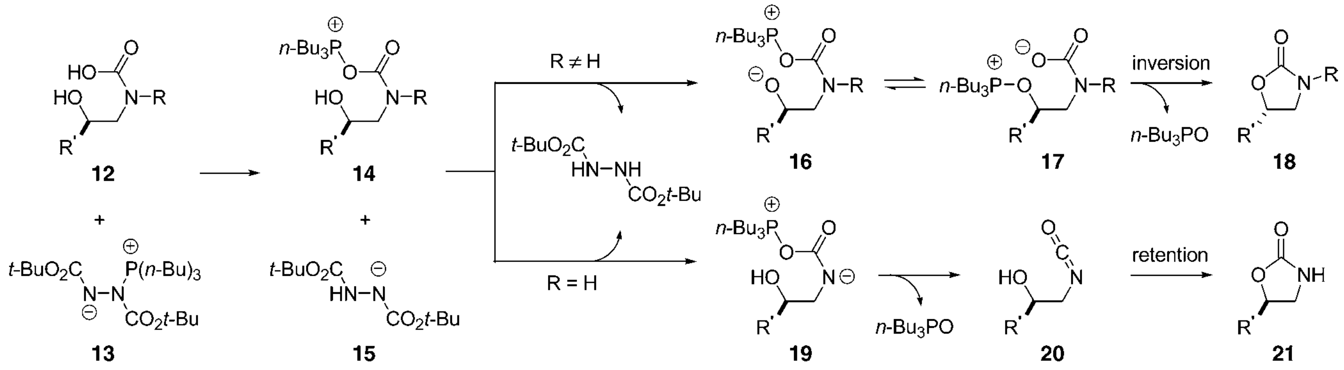
A proposed reaction mechanism (Scheme 2) accounts for the *N*-substitution-dependent stereochemical divergence characteristic of this carboxylation−Mitsunobu cyclization method. After carboxylation of an amino alcohol with CO_2 to produce carbamic acid **12** the addition of n-Bu_3P and DBAD to the reaction mixture provides the ylide **13**.[12a,b,d] Consistent with literature evidence for the formation of acyloxyphosphoniun ion intermediates during the traditional Mitsunobu reaction,[12c,f,g] the carbamoyloxyphosphonium ion **14** is produced along with hydrazide anion **15**. If the nitrogen atom of **14** bears a carbon substituent (R ≠ H), then hydroxyl group deprotonation gives the carbamoyloxyphosphonium alkoxide **16**, which isomerizes to the oxyphosphonium carbamate intermediate **17**.[10a,12f] Cyclization of **17** with loss of n-Bu_3PO gives the final product **18** with inversion of configuration. The defining characteristic responsible for retention vs inversion of stereochemistry in this reaction is the availability of a carbamoyl N−H group. If the nitrogen atom of **14** bears a proton (R = H), then N−H deprotonation gives the zwitterion **19**, which collapses with loss of n-Bu_3PO to give the isocyanate **20**. The cyclization of a 2-(hydroxyethyl)isocyanate (e.g., **20**) to give an oxazolidinone (**21**) with retention of configuration is a known transformation,[13] and would account for

---

(11) Reactions were conducted as per the standard conditions reported in Supporting Information, substituting CO_2 for $C(^{18}O)_2$. (a) The ^{1}H NMR (500 MHz) spectrum of the crude reaction mixture containing **10** was identical to that for crude **6g**. The position of the ^{18}O atom in **10** is not proven. HRMS (APCI): exact mass calcd for **10**, $C_{10}H_{12}NO^{18}O$ $(M + H^+)$ 180.0905; found 180.0906. Calcd for n-$Bu_3P^{18}O$, $C_{12}H_{28}P^{18}O$ $(M + H^+)$ 221.1915; found 221.1915. (b) The ^{1}H NMR (500 MHz) spectrum of the crude reaction mixture containing **11** was identical to that for crude **6h**. HRMS (APCI): exact mass calcd for **11**, $C_{11}H_{14}N^{18}O_2$ $(M + H^+)$ 196.1104; found 196.1106. Calcd for n-Bu_3PO, $C_{12}H_{28}PO$ $(M + H^+)$ 219.1872; found 219.1875.

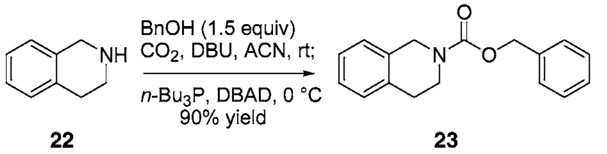
(12) Mechanistic studies of the Mitsunobu reaction: (a) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487. (b) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3045. (c) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3049. (d) Wilson, S. R.; Perez, J.; Pasternak, A. *J. Am. Chem. Soc.* **1993**, *115*, 1994. (e) Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967. (f) Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1751. (g) McNulty, J.; Capretta, A.; Laritchev, V.; Dyck, J.; Robertson, A. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4051.

Scheme 2



the observed results. Consistent with the proposed intermediacy of isocyanate **20**, benzylamine was subjected to the carboxylation−Mitsunobu reaction conditions in acetonitrile-d_3 and was found by ^{1}H NMR spectroscopy to produce benzyl isocyanate. An alternative mechanism for retention of configuration involving the direct cyclization of a carbamoyloxyphosphonium alkoxide **16** (with R = H) to give **21**, although mechanistically feasible, is less satisfactory since a role for the R-group in dictating the relative cyclization rates of **16** (retention) vs **17** (inversion) is not compelling.[14]

To further expand the scope of the tandem amine carboxylation and Mitsunobu reaction, we evaluated an intermolecular variant (eq 4). The conversion of the amine **22** to the benzyl carbamate **23** in good yield and under mild conditions indicates that the reaction is not restricted to intramolecular cyclizations.



(4)

In summary, we have expanded the scope of a mild and efficient carbamate synthesis method, involving in situ carboxylation with carbon dioxide followed by Mitsunobu cyclodehydration. Unexpectedly, the stereochemical course of the Mitsunobu cyclization is dependent on whether the carbamic acid intermediate is *N*-substituted with either a carbon (inversion) or hydrogen (retention), owing to a possible mechanistic divergence as evidenced by isotope labeling studies.

Acknowledgment. We thank Dr. David L. Hughes for helpful comments, Joan Murphy for mass spectral data, and Sandor Varga for NMR structure determinations.

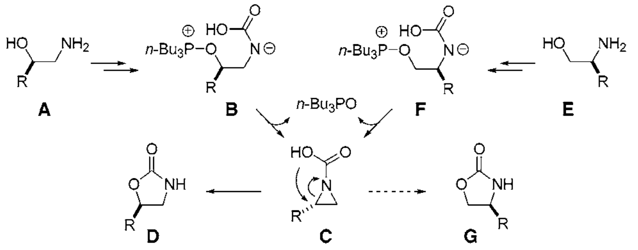
Supporting Information Available: Experimental procedures; characterization data for compounds; copies of ^{1}H NMR spectra for **6a**−**k**, **9**, and **23**; and LCMS and HRMS spectra for **10** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0491080

---

(13) (a) Matsushita, M.; Maeda, H.; Kodama, M. *Tetrahedron Lett.* **1998**, *39*, 3749. (b) Ariza, X.; Pineda, O.; Urpi, F.; Vilarassa, J. *Tetrahedron Lett.* **2001**, *42*, 4995.

(14) (a) Additionally, a mechanism for net retention of configuration involving aziridine formation (**A** → **B** → **C**) and regioselective rearrangement (**C** → **D**)[14b] is unsatisfactory, since the analogous pathway from **E** would afford the same aziridine intermediate (**E** → **F** → **C**) and therefore the same product distribution (**C** → **D** but not **G**). Since **4d** and **4e** provide different products (**6d** and **6e** respectively), an aziridine pathway is unlikely.



(b) Banks, M. R.; Cadogan, J. I. G.; Gosney, I.; Hodgson, P. K. G.; Thomson, D. E. *J. Chem. Soc., Perkin Trans. 1* **1991**, 961.