

One-pot synthesis of cyclic enecarbamates from lactam carbamates

Jurong Yu,^{a,*} Vu Truc,^a Peter Riebel,^b Elizabeth Hierl^a and Boguslaw Mudryk^a

^aDepartment of Process Research and Development, Bristol-Myers Squibb, New Brunswick, NJ 08903-0191, USA

^bResCom, DSM Pharma Chemicals Regensburg GmbH, D-93055 Regensburg, Germany

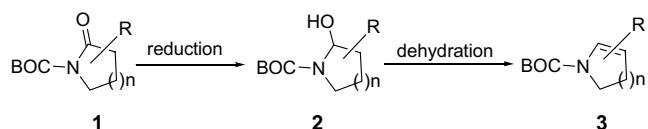
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Abstract—A general, practical and efficient one-pot synthesis of cyclic enecarbamates is described. The protocol proceeds via reduction of lactam carbamate with Super-Hydride®, followed by in situ dehydration with trifluoroacetic anhydride (TFAA) and diisopropylethylamine (DIPEA).

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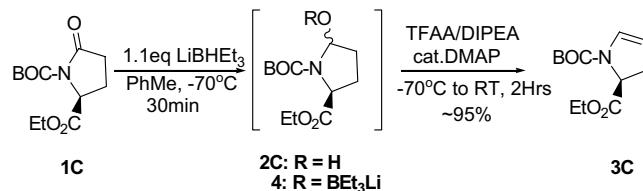
Cyclic enecarbamates **3**, a class of deactivated enamines, are versatile intermediates for the synthesis of alkaloids and nitrogen-containing heterocycles.^{1,2} Among the available methodologies for their preparation, the reduction of lactam carbamates **1**, followed by dehydration of the ensuing lactamol **2** is the most straightforward approach (Scheme 1).^{3–6} Recently, Correia and co-workers⁷ developed a mild dehydration protocol, where **2** was dehydrated with TFAA and a hindered nitrogen base, such as 2,6-lutidine or DIPEA. That protocol is compatible with a number of protecting groups and with epimerizable stereogenic centers.

To support the preparation of a drug development candidate, we needed to develop a process for the synthesis of enecarbamate **3C** (Scheme 2). We first took the stepwise approach, where **1C** was reduced by Super-Hydride® to lactamol **2C**, which was isolated as a diastereomeric mixture. Following Correia's procedure, **2C** was dehydrated with TFAA and 2,6-lutidine in toluene at reflux to enecarbamate **3C**. Although the dehydration worked quite well, we found that the isolation and purification of **2C** were somewhat difficult due to ring open-



Scheme 1.

* Corresponding author. Tel.: +1 732 227 7485; fax: +1 732 227 3938; e-mail: jurong.yu@bms.com



Scheme 2.

ing to the tautomeric aldehyde.⁸ Therefore, we focused our efforts on telescoping the reduction and dehydration steps so that the isolation of **2C** could be eliminated. We now report such a one-pot conversion.

Lactam carbamate **1C** was first reduced by Super-Hydride® at -70°C to lactamol **2C** which, without quench and isolation, was treated directly with TFAA, 2,6-lutidine or DIPEA, and a catalytic amount of DMAP. The dehydration proceeded smoothly at room temperature and gave enecarbamate **3C** in excellent yield. It is worth mentioning that the one-pot dehydration proceeds readily at room temperature, while the stepwise protocol typically requires reflux conditions. We believe that the observed difference in reaction rate is consistent with the higher reactivity of intermediate **4** compared to that of lactamol **2C**.

It was also reported⁷ in Correia's stepwise protocol that DIPEA typically generates more side products⁹ than 2,6-lutidine. In the one-pot conversion of **1C** to **3C**, we observed no difference between DIPEA and 2,6-lutidine. Therefore, DIPEA was chosen due to its ease of

Table 1. One-pot conversion of carbamate to enecarbamate

| Entry | Carbamate 1 ¹⁰ | Enecarbamate 3 | Isolated yield (%) |
|-------|----------------------------------|-----------------------|--------------------|
| A | | | 81 |
| B | | | 78 |
| C | | | 95 |
| D | | | 83 |
| E | | | 89 |
| F | | | 90 |

Typical laboratory procedure: To a solution of lactam carbamate **1** (5.0 mmol) in toluene (10 mL) at -70°C Super-Hydride (1.0 M in THF, 5.3 mL) was added dropwise. After stirring at -70°C for 30 min, DIPEA (5.0 mL, 28.5 mmol), DMAP (\sim 12 mg, 0.1 mmol) and TFAA (0.85 mL, 6.0 mmol) were added. The mixture was warmed to room temperature and stirred for 2 h. H_2O (10 mL) was added. Organic layer was separated and washed with H_2O (2×10 mL). Evaporation and silica gel pad filtration gave cyclic enecarbamate **3** in 78–95% yield.

removal. This one-pot protocol was applied successfully to other ring systems (six and seven membered). Due to the mild reaction conditions, this protocol is compatible with a number of protecting groups (BOC, CBZ, Bn) and with epimerizable compounds, for example, 3C. Results are summarized in Table 1.

In summary, a general, practical and efficient one-pot conversion of lactam carbamates to cyclic enecarbamates was developed by reduction with Super-Hydride, followed by in situ dehydration with TFAA and DIPEA at room temperature. Simple operation, higher overall yields, and fewer side products are the main advantages of this procedure, which has successfully been used to convert L-pyroglutamate **1C** to enecarbamate **3C** on greater than 100 kg scale.

References and notes

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|--|----------------------------------|-----------------------|--------------------|
| Entry | Carbamate 1 ¹⁰ | Enecarbamate 3 | Isolated yield (%) |
| A | | | 81 |
| B | | | 78 |
| C | | | 95 (>99.5% ee) |
| D | | | 83 |
| E | | | 89 |
| F | | | 90 |

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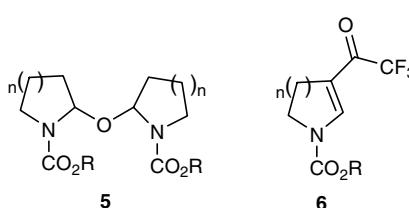
5. (a) Reduction with DIBAL-H, see Langlois, N.; Rojas, A. *Tetrahedron* **1993**, *49*, 77, see also Ref. 3e; (b) Reduction with Super-Hydride, see Choi, J. K.; Ha, D. C.; Hart, D. L.; Lee, C. S.; Ramesh, S.; Wu, S. *J. Org. Chem.* **1989**, *54*, 27, See also Ref. 3e; (c) Reduction with NaBH₄, see Altman, K. W. *Tetrahedron Lett.* **1993**, *34*, 7721; Chamberlin, A. R.; Nguyen, H. D.; Chung, J. Y. L. *J. Org. Chem.* **1984**, *49*, 1682; Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

6. (a) Most frequently used dehydration methods are: dehydration involving methanol elimination: see Ref. 3g, h; (b) Dehydration with HMPA: see Ref. 3e; (c) Dehydration with weakly acidic quinolinium camphor-sulfonate: see Ref. 3b.

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9. In Ref. 7, side products (**5** and **6**) were observed at elevated levels when DIPEA was used instead of 2,6-lutidine. In our case, however, these side products were only present in trace amount.



10. (a) Carbamates **1A,C**, and **1D** are commercially available; (b) Compound **1B** was prepared by esterification of Z-PRY-OH; (c) For **1E**, see Reddy, P.; Kondo, S.; Toru, T.; Ueno, Y. *J. Org. Chem.* **1997**, *62*, 2652; (d) For **1F**, see Lepifre, F.; Clavier, S.; Bouyssou, P.; Coudert, G. *Tetrahedron* **2001**, *57*, 6969–6975.