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A facile synthesis of cyclic enecarbamates using Dess–Martin periodinane

Chengzhi Yu and Longqin Hu*

Department of Pharmaceutical Chemistry, College of Pharmacy, Rutgers, The State University of New Jersey, 160 Frelinghuysen Road, Piscataway, NJ 08854-8020, USA

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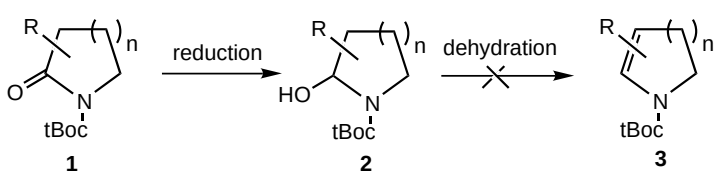
Abstract—A simple and efficient synthesis of cyclic enecarbamates from ω-hydroxycarbamates via tandem oxidative cyclization–dehydration was achieved in 84% to quantitative yield using Dess–Martin periodinane in methylene chloride.

There is a growing interest in enecarbamates and enamides in recent years.[1] Enecarbamates are used strategically as intermediates in the assembly of polycyclic structure motifs in natural products[2] and in the development of synthetically useful reactions such as hydroborations and Friedel–Crafts reactions.[1] Cyclic enecarbamates are also versatile building blocks for the synthesis of bicyclic ring compounds[3] and nitrogen-containing heterocycles such as alkaloids.[4] Cyclic enecarbamates can be prepared by oxidation of carbamates or *N*-formyl derivatives to *N*,*O*-mixed acetals followed by the elimination of methyl alcohol[5a] or its derivative such as phenylsulfonate.[5b] Recently, a simple alternative was developed by reduction of a readily available lactam followed by dehydration (Scheme 1).[5c] Although this method is straightforward and the reduction of cyclic imides **1** to lactamols **2** is well documented,[6] Nagasaka and co-workers found that sometimes the enecarbamates **3** could not be obtained through the dehydration of intermediate **2**.[7] Under the reduction conditions, compound **2** readily underwent ring-opening with the resulting aldehyde being further reduced to ω-hydroxycarbamate.

In our efforts to synthesize potential protein kinase inhibitors, we needed to oxidize the primary hydroxy group in **4** to the corresponding aldehyde **5** (Scheme 2). However, several oxidizing conditions we tried failed to give the desired product **5**, but the major product isolated was cyclic enecarbamate **6**. The conditions we tried and the yields of **6** were as follows: (a) Dess–Martin periodinane, pyridine, CH_2Cl_2, rt, 100%; (b) TPAP, NMO, 4 Å mole sieves, CH_3CN, rt, 72%; (c) DMSO, $(COCl)_2$, −78°C, THF, then Et_3N, −78°C to rt, 65%; (d) PDC, 4 Å molecular sieves, CH_2Cl_2, rt, 59%; and (e) TEMPO, NaClO (aq.), KBr, CH_2Cl_2, 0–15°C, 62%. Dess–Martin periodinane[8] was the most efficient condition giving the cyclic enecarbamate in quantitative yield. Similar results were reported by Ganem and co-workers for the oxidation of Cbz-protected ω-hydroxycarbamate using PCC, where no aldehyde but cyclic enecarbamate was obtained in 46%.[9] Rapoport and co-workers have also found such unexpected cyclization of δ-aldocarbamate to enecarbamate when they tried to purify the δ-aldocarbamate.[10]

We believe that cyclic enecarbamate product **6** was formed preferentially through a tandem oxidative cyclization–dehydration mechanism and that the cyclization was entropically favored. The oxidation of ω-hydroxycarbamate **4** by Dess–Martin periodinane



Scheme 1.

* Corresponding author. Tel.: +1 732 445 5291; fax: +1 732 445 6312; e-mail: longhu@rci.rutgers.edu

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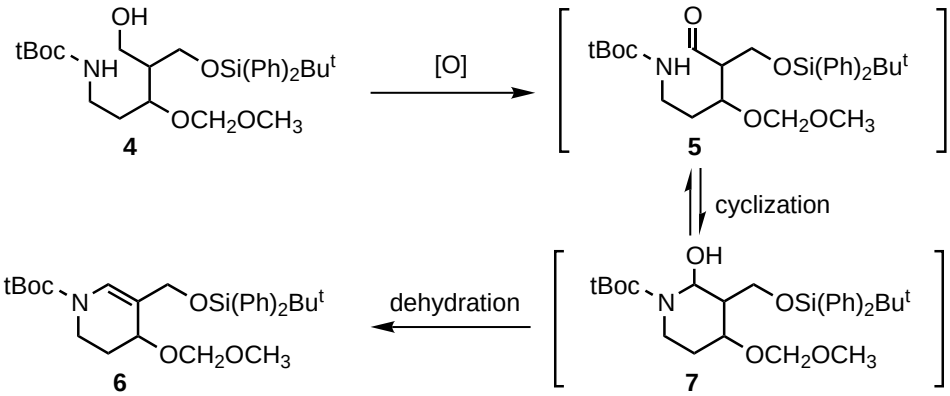


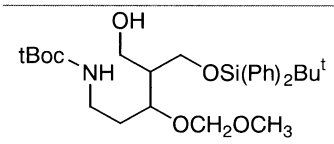
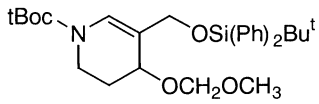
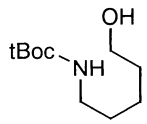
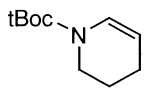
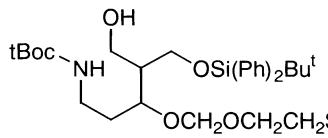
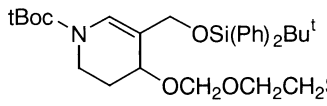
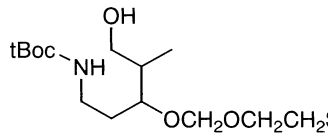
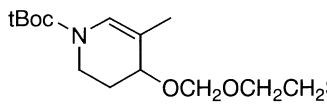
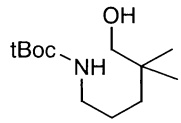
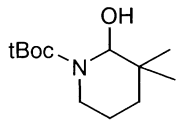
Scheme 2.

and the subsequent cyclization–dehydration were very mild and efficient. Thus, we optimized the conditions and developed a general procedure for the preparation of the synthetically useful cyclic enecarbamates.[11]

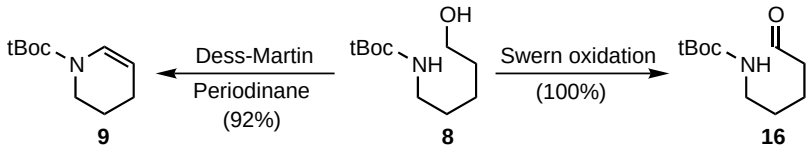
As shown in Table 1, various cyclic enecarbamates with functionalized substitutions could be prepared from their corresponding ω-hydroxycarbamates (**4**, **8**, **10**, and **12**) in very high yields (84–100%) using this condition. All products listed were identified by ^{1}H NMR, ^{13}C NMR, LC–MS, and HRMS.[12] In a separate experiment, we found that Swern oxidation[13] of ω-hydroxycarbamate **8** could produce the corresponding aldehyde **16**[14] in quantitative yield. The fact that Dess–Martin periodinane-mediated oxidation of **8** gave the cyclic enecarbamate **9** as the major product (Scheme 3) suggests that the oxidative cyclization–dehydration was favored under Dess–Martin periodinane conditions. Dehydration requires a hydrogen C_α to the aldehyde group. As expected, compound **14** without the C_α hydrogen atom could only give the lactamol intermediate **15** as the major stable product in 88% yield. This result is consistent with our proposed mechanism shown in Scheme 2.

To explore what was causing the cyclization and the subsequent dehydration under the Dess–Martin periodinane condition, we did two control experiments. In our first control experiment, a suspension of ω-hydroxycarbamate **8** and Dess–Martin periodinane in methylene chloride was stirred at room temperature in the absence of pyridine. After 24 h, only a small amount of **8**

Table 1. The oxidative cyclization–dehydration of ω-hydroxycarbamate using Dess–Martin periodinane[a]

Alcohol[b]	Product	Yield %[c]
 **4**	 **6**	100
 **8**	 **9**	92
 **10**	 **11**	98
 **12**	 **13**	84
 **14**	 **15**	88

[a] General conditions: alcohol (1 mmol), Dess-Martin periodinane (1 equiv), pyridine (2 equiv), CH_2Cl_2 (10 mL), rt, 30 min;[b] Substrates **4**, **10**, and **12** were racemic; [c] Isolated yields.



Scheme 3.

(<20%) was consumed to produce a complex mixture, among which we could observe the corresponding aldehyde **16** as well as the cyclic enecarbamate **9**. This is consistent with the fact that pyridine is an important promoting factor in the oxidation using Dess–Martin periodinane. In our second control experiment, we added separately acetic acid (2 equiv.), pyridine (2 equiv.), and an equimolar mixture of pyridine (2 equiv.) and acetic acid (2 equiv.) to a stock solution of aldehyde **16** (0.1 M) in methylene chloride. The mixtures were then stirred under argon at room temperature and monitored by TLC. Interestingly, we found that the cyclization–dehydration of aldehyde **16** could be effected in the presence of either acetic acid (pH 1.3) or the equimolar mixture of acetic acid and pyridine (pH 4.4). In the presence of acetic acid, the cyclization–dehydration of **16** to give the cyclic enecarbamate **9** was faster than that in the presence of equimolar mixture of acetic acid and pyridine (completion times of 45 min and 5.5 h, respectively).[15] In contrast, there was no cyclization–dehydration of **16** occurring in the presence of two equiv of pyridine (pH 8.0) after 24 h. Furthermore, we found that the reaction mixture in the oxidation of **8** quickly turned acidic, with pH dropping down to about 3.4 after only five minutes of stirring. These results strongly suggest that the cyclization–dehydration of **16** was promoted by the acid produced or the pyridinium ion, the conjugate acid form of pyridine added. It should be pointed out that the cyclization–dehydration of aldehyde **16** in the presence of equimolar mixture of acetic acid and pyridine was much slower than the oxidative cyclization–dehydration of ω-hydroxycarbamate **8** in the presence of Dess–Martin periodinane and pyridine, suggesting that there might be other mechanisms involved in the production of cyclic enecarbamate **9** in addition to the one proposed in Scheme 3. It should also be noted that the Dess–Martin periodinane condition did not work for the formation of five- and seven-membered enecarbamates from their corresponding hydroxy carbamates. In both cases, the corresponding aldehydes were found to be the major product as determined by ^{1}H NMR.

In summary, we explored the application of Dess–Martin periodinane in the conversion of ω-hydroxycarbamates into cyclic enecarbamates via a tandem oxidative cyclization–dehydration mechanism, avoiding the multistep preparation of enecarbamates through lactams and lactamols. The procedure can accommodate additional functionality and provides opportunity for the introduction of substituents onto the cyclic enecarbamate ring systems, thereby making the cyclic enecarbamates more synthetically accessible.

Acknowledgements

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11. Experimental procedure: To a solution of substrate ω-hydroxycarbamate (1 mmol) in freshly distilled methylene chloride (10 mL) was added anhydrous pyridine (2 equiv.) and Dess–Martin periodinane (1 equiv.) under argon at room temperature. The reaction mixture was stirred for 30 min, quenched with ethyl alcohol (5 mL), and then diluted with ethyl ether (50 mL). The precipitate was separated by filtration and washed with ethyl ether (2×50 mL). The combined filtrate was washed with satu-

rated $Na_2S_2O_3$–$NaHCO_3$ (1:1, 2×80 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with hexane and ethyl ether.

12. For compound **6**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm 7.74–7.67 (m, 4H), 7.43–7.36 (m, 6H), 6.93 (s, 1H), 4.66 (ABq, $\Delta\gamma=16.7$ Hz, $J=7.1$ Hz, 2H), 4.27 (ABq, $\Delta\gamma=35.7$ Hz, $J=13.3$ Hz, 2H), 4.27–4.15 (m, 1H), 4.02–3.95 (m, 1H), 3.32 (s, 3H), 3.28–3.20 (m, 1H), 2.59 (dd, $J=14.5$, 3.5 Hz, 1H), 1.82–1.71 (m, 1H), 1.51 (s, 9H), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ/ppm 152.3, 135.8, 135.8, 133.8, 129.8, 127.8, 127.8, 125.1, 115.6, 95.8, 81.2, 67.3, 64.0, 55.6, 37.3, 28.5, 28.0, 27.1, 19.5; ESIMS m/z (relative intensity): 512.27 (M+H, 24), 450.25 (M–OMOM, 100). HRMS (ESI+) m/z calcd for $C_{29}H_{41}NO_5SiNa$ 534.2652 (M+Na), found 534.2630.
For compound **11**: δ/ppm 7.74–7.67 (m, 4H), 7.49–7.7.36 (m, 6H), 6.93 (s, 1H), 4.71 (ABq, $\Delta\gamma=15.0$ Hz, $J=7.4$ Hz, 2H), 4.28 (ABq, $\Delta\gamma=32.4$ Hz, $J=14.0$ Hz, 2H), 4.35–4.15 (m, 1H), 4.03–3.94 (m, 1H), 3.60 (t, $J=8.4$ Hz, 2H), 3.26 (t, $J=11.7$ Hz, 1H), 2.10 (d, $J=13.5$ Hz, 1H), 1.80–1.65 (m, 1H), 1.51 (s, 9H), 1.09 (s, 9H), 0.91 (s, $J=8.6$ Hz, 2H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ/ppm 152.3, 135.8, 135.8, 133.8, 129.8, 127.8, 127.8, 125.1, 115.6, 94.0, 87.9, 81.2, 67.4, 65.3, 64.0, 37.2, 28.5, 27.1, 19.5, 18.2, 1.25; ESIMS m/z (relative intensity): 598.34 (M+H, 47), 524.27 (M–tBuO, 100). HRMS (FAB+) m/z calcd for $C_{33}H_{51}LiNO_5Si_2$: 604.3466 (M+Li). Found: 604.3478.
For compound **13**: δ/ppm 6.63 (s, 1H), 4.74 (ABq, $\Delta\gamma=$ 24.5 Hz, $J=7.3$ Hz, 2H), 3.91–3.52 (m, 4H), 3.18–3.15 (m, 1H), 2.01–1.94 (m, 1H), 1.75 (s, 3H), 1.74–1.60 (m, 1H), 1.55 (s, 9H), 0.93 (t, $J=8.6$ Hz, 2H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ/ppm 152.2, 124.0, 112.5, 93.4, 87.9, 81.0, 70.4, 65.3, 37.8, 28.5, 18.7, 18.3, –1.23; ESIMS m/z (relative intensity): 366.35 (M+Na, 98), 198.18 (M–OSEM, 100). HRMS (ESI+) m/z calcd for $C_{17}H_{33}NO_4SiNa$ 366.2077 (M+Na), found 366.2056.
For compound **15**: δ/ppm 5.17 (d, $J=3.6$ Hz, 1H), 3.80 (d, $J=11.0$ Hz, 1H), 3.04 (dt, $J=12.8$, 3.8 Hz, 1H), 3.00 (d, $J=3.5$ Hz, 1H), 1.74–1.60 (m, 2H), 1.45 (s, 9H), 1.50–1.40 (m, 1H), 1.26–1.19 (m, 1H), 0.99 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ/ppm 155.6, 81.9, 80.0, 38.1, 34.4, 31.3, 28.6, 27.5, 24.1, 21.2; ESIMS m/z (relative intensity): 212.21 (M–OH, 96), 156.13 (M–tBuO, 100).
13. It has been reported that Swern oxidation of ω-hydroxycarbamate **8** gave a complicated mixture including a substantial amount of aldehyde **16**. See: Lee, B. H.; Miller, M. J.; Prody, C. A.; Neilands, J. B. *J. Med. Chem.* **1985**, *28*, 317–323. However, we found under careful control the same reaction was quite clean and gave high yield of the aldehyde product **16**.
14. For aldehyde **16**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm 9.78 (s, 1H), 4.62 (br s, 1H), 3.13 (dd, $J=13.0$, 6.6 Hz, 2H), 2.61–2.45 (m, 2H), 1.73–1.44 (m, 13H, singlet at 1.45 (3H)); ^{13}C NMR ($CDCl_3$, 50 MHz): δ/ppm 202.4, 156.2, 79.3, 43.6, 40.3, 29.7, 28.6, 19.3; IR (neat): ν 3354, 2964, 2923, 2862, 2810, 2718, 1708 cm^{-1}.
15. For similar Lewis acid-mediated cyclization and elimination of methanol from mixed acetals, see: (a) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110*, 649–651; (b) Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1985**, *50*, 3017–3019.