ORGANIC LETTERS

2009
Vol. 11, No. 16
3774−3776

Olefinic-Amide and Olefinic-Lactam Cyclizations

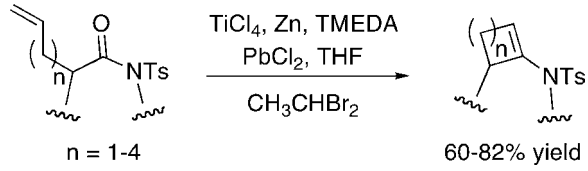
Jie Zhou and Jon D. Rainier*

Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, Utah 84112

rainier@chem.utah.edu

Received June 25, 2009

ABSTRACT



Olefinic-amide and olefinic-lactam cyclization reactions that result in the generation of cyclic enamides are described.

Small molecules that contain electron-rich olefins (enol ethers and enamides) are both valuable in their own right and are interesting precursors to more elaborate substrates.[1,2] Over the past few years we have been interested in the generation and use of cyclic enol ethers and have recently described their synthesis from olefinic-ester and olefinic-lactone cyclizations using an in situ generated Ti reagent that is presumed to be a Ti ethylidene.[3] Although the corresponding olefinic-amide cyclizations would be synthetically useful,[4] to the best of our knowledge there are only two reports of related reactions that employ amides. Takeda has described Ti(II)-promoted cyclizations of dithianes having pendant amides,[5] and in work more closely related to that proposed here, Bennasar and co-workers have successfully carried out two-step olefinic-amide cyclizations to enamides.[6] The Bennasar chemistry involves the initial conversion of amides into mixtures of cyclic and acyclic enamides using dimethyltitanocene followed by the conversion of the acyclic enamides into the corresponding cyclic enamides using the second generation Grubbs catalyst.[7] With a limited number of substrates they observed a mixture of cyclic and acyclic products from the dimethyltitanocene reaction. Representative of their results was the generation of indole **2** in 40% overall yield from olefinic-amide **1**. In addition to synthesizing indoles, they also generated dihydroquinolines and dihydroisoquinolines using this chemistry. More problematic was the use of the two-step protocol to generate seven-membered ring substrates as olefin isomerization competed

(1) For representative examples of the use of enol ethers in synthesis, see: (a) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939–3002. (b) Johnson, H. W. B.; Majumder, U. *J. Am. Chem. Soc.* **2005**, *127*, 848–849.

(2) For representative examples of the use of enamides in synthesis, see: (a) Carbery, D. R. *Org. Biomol. Chem.* **2008**, *6*, 3455–3460. (b) Song, Z.; Lu, T.; Hsung, R. P.; Al-Rashid, Z. F.; Ko, C.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4069–4072. (c) Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2000**, *122*, 7843–7844. (d) Harrison, T. J.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2007**, *9*, 367–370.

(3) (a) Iyer, K.; Rainier, J. D. *J. Am. Chem. Soc.* **2007**, *129*, 12604–12605. (b) Rohanna, J.; Rainier, J. D. *Org. Lett.* **2009**, *11*, 493–495. (c) Zhang, Y.; Rainier, J. D. *Org. Lett.* **2009**, *11*, 237–239.

(4) For reviews on the generation of heterocycles using a combination of metathesis and alkylidenation, see: (a) Hartley, R. C.; Li, J.; Main, C. A.; McKiernan, G. J. *Tetrahedron* **2007**, *63*, 4825–4864. (b) Hartley, R. C.; Mckiernan, G. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2763–2793.

(5) (a) Takeda, T.; Saito, J.; Tsubouchi, A. *Tetrahedron Lett.* **2003**, *44*, 5571–5574. (b) Takeda, T.; Yatsumonji, Y.; Tsubouchi, A. *Tetrahedron Lett.* **2005**, *46*, 3157–3160.

(6) (a) Bennasar, M. L.; Roca, T.; Monerris, M.; García-Diaz, D. *J. Org. Chem.* **2006**, *71*, 7028–7034. (b) Bennasar, M.-L.; Roca, T.; Monerris, M.; Garcia-Diaz, D. *Tetrahedron Lett.* **2005**, *46*, 4035–4038.

(7) For examples of RCM cyclizations of enamides generated using non-carbonyl olefination strategies, see: (a) Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, P. J. T. *Org. Lett.* **2001**, *3*, 2045–2048. (b) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4732–4734. (c) Van Otterlo, W. A. L.; Pathak, R.; de Koning, C. B. *Synlett* **2003**, 1859–1861. (d) Rosillo, M.; Dominguez, G.; Casarrubios, L.; Amador, U.; Pérez,-Castells, J. *J. Org. Chem.* **2004**, *69*, 2084–2093. (e) Katz, J. D.; Overman, L. E. *Tetrahedron* **2004**, *60*, 9559–9568. (f) Manzoni, L.; Colombo, M.; Scolastico, C. *Tetrahedron Lett.* **2004**, *45*, 2623–2625. (g) Van Ortterlo, W. A. L.; Morgans, G. L.; Khanye, S. D.; Aderibigbe, B. A. A.; Michael, J. P.; Billing, D. G. *Tetrahedron Lett.* **2004**, *45*, 9171–9175. Liu, G.; Tai, W.-Y.; Li, Y.-L.; Nap, F.-J. *Tetrahedron Lett.* **2006**, *47*, 3295–3298. (h) Toumi, M.; Couty, F.; Evano, G. *J. Org. Chem.* **2008**, *73*, 1270–1281.

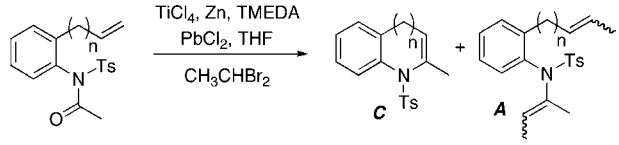
10.1021/ol901448n CCC: $40.75
Published on Web 07/23/2009

with cyclization. With some substrates they were able to overcome this problem by adding dihydroquinone to the reaction mixture.[8]

When combined with our experience with olefinic-ester and olefinic-lactone cyclizations, the Bennasar chemistry outlined above peaked our interest in studying olefinic-amide and olefinic-lactam cyclization reactions. Described here is the successful use of in situ generated titanium ethylidenes in this context.

To compare the titanium ethylidene reagent with Bennasar's two-step protocol, we decided to initially examine the cyclization of aromatic substrates **4**−**6**. Concerned about the potential reaction of carbonyl protecting groups with the titanium reagent, i.e., Boc, CBz, etc., we opted to initially avoid this potential problem by employing a Ts group in this capacity. As illustrated in Table 1, the cyclization of

Table 1. Olefinic-Amide Cyclizations to Benzyl Fused Enamides

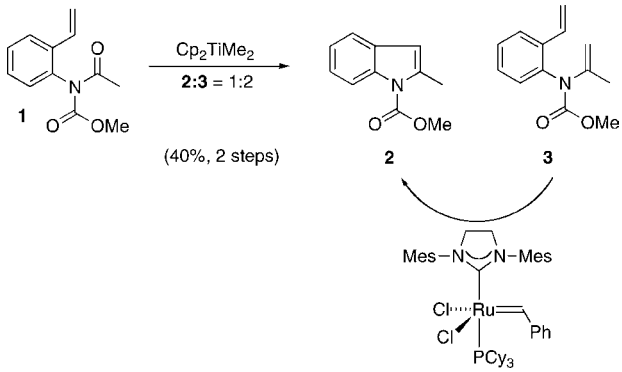


entry	amide	*n*	enamide	yield (%)[a]	C:A[b]
1	**4**	0	**7**	70	>95:5
2	**5**	1	**8**	78	>95:5
3	**6**	2	**9**	76	76:24

[a] Combined yield of cyclic and acyclic enamides. [b] From isolated cyclic and acyclic enamide.

ene-amide **5** gave a 78% yield of dihydroquinoline **8C** (entry 2). Bennasar's two-step protocol on a related substrate resulted in a 41% overall yield. The cyclization to indole **7C** was also successful, giving it in 70% yield versus 40% overall using the two-step procedure (entry 1 and Scheme 1). Finally, the use of

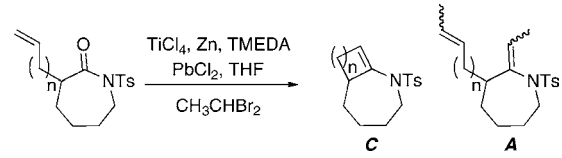
Scheme 1. Bennasar Synthesis of Indole **2** via RCM



ene-amide **6** resulted in a 58% yield of seven-membered ring substrate **9C** along with 18% of the corresponding acyclic enamide **9A**. Bennasar's procedure was more competitive here; they were able to isolate a 50% overall yield of the seven-membered ring substrate along with 7% of the corresponding dihydroquinoline from olefin isomerization and cyclization. Olefin isomerization does not appear to be a problem with the titanium reagent.

Having established the viability of the olefinic-amide cyclizations to aromatic substrates, we next explored the cyclization of nonaromatic olefinic-lactams. When ε-caprolactam substrates **10**, **11**, and **12** were subjected to the titanium ethylidene reagent, we isolated cyclic enamides **14C**, **15C**, and **16C** as the exclusive products (Table 2, entries

Table 2. Olefinic-Lactam Cyclizations

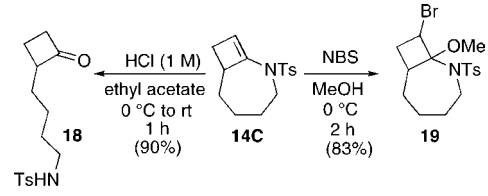


entry	amide	*n*	enamide	yield (%)[a]	C:A[b]
1	**10**	1	**14**	70	>95:5[c]
2	**11**	2	**15**	80	>95:5
3	**12**	3	**16**	82	>95:5
4	**13**	4	**17**	70	86:14[d]

[a] Combined yield of cyclic and acyclic enamide. [b] From isolated cyclic and acyclic enamides. [c] Characterized as the corresponding aminal and/or ketone (see Scheme 2). [d] Minor product was the corresponding lactam in which the alkene had undergone metathesis (see Supporting Information).

1−3). Noteworthy because it is unlikely that this substrate could be formed from an acyclic olefinic-enamide cyclization was the fact that this chemistry was successful in the generation of four-membered ring substrate **14C**.[9,10] As with the aromatic substrate **6**, lactam **13** gave a mixture of the cyclized seven-membered enamide **17C** and an uncyclized product (entry 4).

Scheme 2. Enamide Derivatization



Not surprisingly enamide **14C** was not stable to SiO_2 chromatography. For characterization purposes, we converted

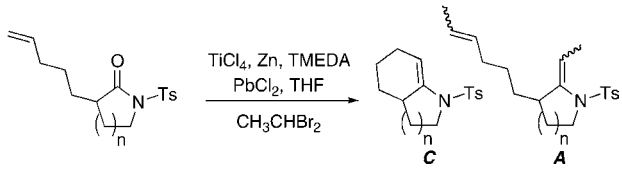
(8) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161.

(9) In their synthesis of capnellene, the Grubbs group generated a cyclobutene from a related ring-opening metathesis, carbonyl olefination reaction. See: (a) Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 855–856. (b) Stille, J. R.; Santarsiero, B. D.; Grubbs, R. H. *J. Org. Chem.* **1990**, *55*, 843–862.

14C into cyclobutanone **18** by subjecting it to aqueous acid (Scheme 2).[11] Additionally, bromoaminal **19** was generated from the treatment of **14C** with NBS in MeOH.[12]

The lactam cyclizations are not limited to ε-caprolactam substrates. Cyclic enamides **22C** and **23C** were the major products from the cyclization of 2-pyrrolidinone **20** and δ-valerolactam **21**, respectively (entries 2 and 3, Table 3).

Table 3. Olefinic-Lactam Cyclizations



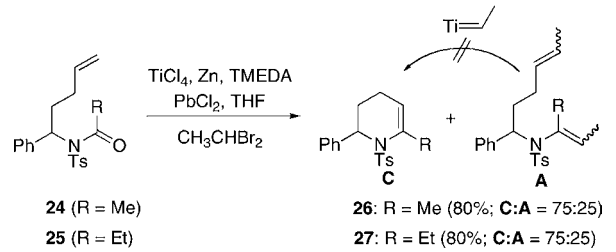
entry	amide	n	enamide	yield (%)[a]	C:A[b]
1	**12**	3	**16**	82	>95:5
2	**20**	1	**22**	75	87:13
3	**21**	2	**23**	78	90:10

[a] combined yield of cyclic and acyclic enamine. [b] ratio determined by ^{1}H NMR of the crude reaction mixture.

In contrast to the cyclization of ε-caprolactam substrate **12** to give **16C**, however, these reactions did result in the formation of small amounts of acyclic enamide.

As a final test of the methodology, we examined the cyclization of methyl- and ethyl-substituted amides **24** and **25** (Scheme 3) When these substrates were subjected to the titanium ethylidene reagent, cyclic enamide was isolated in

Scheme 3. Olefinic-Amide Cyclizations



synthetically useful quantities but as a mixture with the corresponding acyclic enamides. As a mechanistic test, we did not observe the formation of **26C** when we resubjected acyclic enamide **26A** to the reaction conditions. This is consistent with the notion that cyclic enamide results from an olefin-metathesis, carbonyl-olefination pathway.[13]

In summary, we have demonstrated that titanium ethylidenes can be utilized in olefinic-amide and olefinic-lactam cyclization reactions and that the efficiency of the reaction depends somewhat on the nature of the substrate. We plan to continue examining the scope of olefinic-carbonyl cyclizations and their use in total synthesis efforts.

Acknowledgment. We are grateful to the National Institutes of Health, General Medical Sciences (GM56677) for support of this work. We would like to thank the support staff at the University of Utah and especially Dr. Peter Flynn (NMR) and Dr. Jim Muller (mass spectrometry) for help in obtaining data.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901448N

(10) For selected examples of the use of four-membered rings in ring-opening metathesis, see: (a) Maughon, B. R.; Grubbs, R. H. *Macromolecules* **1997**, *30*, 3459–3469. (b) White, B. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2003**, *125*, 14901–145904. (c) Mori, M.; Wakamatsu, H.; Tonogaki, K.; Fujita, R.; Kitamura, T.; Sato, Y. *J. Org. Chem.* **2005**, *70*, 1066–1069.

(11) (a) Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509–1511. (b) Baktharaman, S.; Selvakumar, S.; Singh, V. K. *Org. Lett.* **2006**, *8*, 4335–4338.

(12) For related reactions of enamines see Hurley, P. B.; Dake, G. R. *J. Org. Chem.* **2008**, *73*, 4131–4138.

(13) Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997–2009.