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Ring Expansion of Lactones and Lactams via Propiolate 1-Carbon Intercalation

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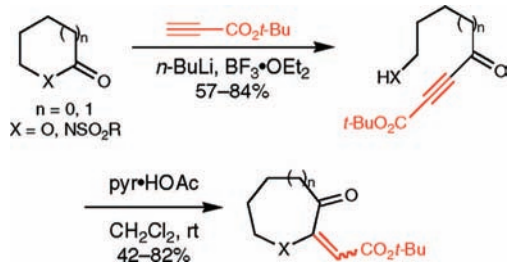
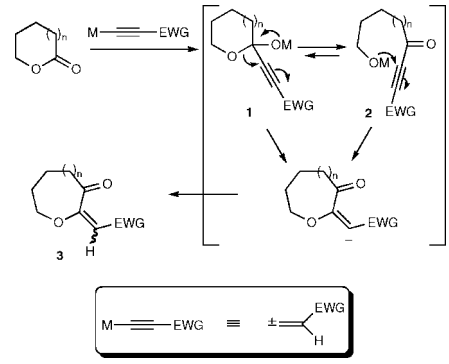
ABSTRACT



Readily available five- and six-membered lactones and *N*-sulfonyllactams undergo efficient addition of *t*-butyl propiolate, and the resulting adducts undergo cycloisomerization to six- and seven-membered cyclic ethers or amines in the presence of pyridinium acetate. The ring expansion process occurs in generally good yields and is proposed to involve a nucleophilic catalysis mechanism.

Saturated oxygen and nitrogen heterocycles are found in many natural products and other medicinally important compounds. Construction of these rings by direct ring closure of acyclic precursors is the most straightforward approach[1] but is not uniformly effective with seven-membered and larger rings. We have been interested in the development of new and general methods for heterocycle synthesis, especially as applied to the assembly of polycyclic systems such as those found in the polyether marine ladder toxins.[2] An approach entailing the ring enlargement of simple lactones or lactams was especially appealing, given their general availability. In particular, we envisioned a process in which an acetylide ion substituted with a suitable electron-withdrawing group could undergo addition to a lactone carbonyl, with the intermediate tetrahedral adduct **1** then undergoing a one-atom expansion to furnish a cyclic ether **3** bearing an exocyclic alkene moiety (Scheme 1). Should the tetrahedral intermediate open to ynone alkoxide **2**,

Scheme 1



(1) Recent reviews: (a) Banwell, M. G. *Pure Appl. Chem.* **2008**, *80*, 669–679. (b) Larosa, I.; Romea, P.; Urpi, F. *Tetrahedron* **2008**, *64*, 2683–2723. (c) Snyder, N. L.; Haines, H. M.; Peczuh, M. W. *Tetrahedron* **2006**, *62*, 9301–9320. (d) Inoue, M. *Chem. Rev.* **2005**, *105*, 4379–4405. (e) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238. (f) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2309.

(2) (a) Marmsäter, F. P.; Vanecko, J. A.; West, F. G. *Tetrahedron* **2002**, *58*, 2027–2040. (b) Marmsäter, F. P.; West, F. G. *Chem.−Eur. J.* **2002**, *8*, 4346–4353. (c) Liu, X.; West, F. G. *Chem. Commun.* **2006**, 5036–5038.

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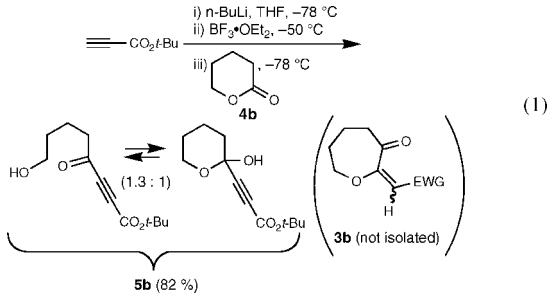
product **3** might still be attained through an exocyclic Michael addition directed by the terminal electron-withdrawing group. In effect, the acetylenic nucleophile would function as a 1,1-dipole, intercalating between the carbonyl carbon and the oxygen of the lactone ring.[3] Described here are the preliminary results of this study, entailing a convenient method for accessing six- and seven-membered heterocycles from lactones and lactams via sequential propiolate addition and pyridine-mediated rearrangement.

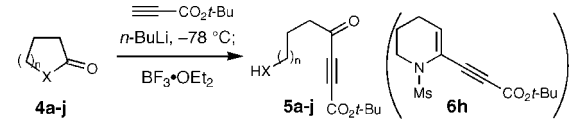
Initial experiments were designed to determine the optimal conditions for acetylide addition using δ-valerolactone **4b** as the lactone partner. There is ample precedent for generation of acetylides derived from propiolate esters and their addition to various electrophiles,[4] and with this in mind, *t*-butyl propiolate was chosen as the acetylide precursor. Deprotonation with *n*-BuLi or LDA could be effected at low temperature, and the resulting lithium acetylides or their transmetallated cerium acetylides underwent addition to the lactone. However, yields for this process were capricious, prompting the examination of addition of the lithium acetylide in the presence of $BF_3 \cdot OEt_2$. These conditions have been applied with success to acetylide additions to esters and lactones[5] and are presumed to operate via an intermediate lithium alkynyltrifluoroborate salt formed in situ. However, in contrast to the corresponding potassium organotrifluoroborates,[6] the lithium salts are not air-stable and have not been fully characterized, so the exact nature of the reactive nucleophile remains uncertain. In the event, addition to valerolactone furnished the adduct **5b** as a mixture of open-chain ynone and the corresponding hemiketal (eq 1). Under no circumstances was the desired ring-expansion product **3b** observed.



(1)

With no evidence for spontaneous formation of **3**, it became apparent that a separate step would be required to effect this conversion. However, the generality of the propiolate addition process was first evaluated, using a range of lactones and lactams **4** (Table 1). In all cases, moderate

Table 1. *t*-Butyl Propiolate Additions to Lactones and Lactams[a]



entry	lactone/lactam	X	*n*	product[b]	yield (%)[c]
1	**4a**	O	1	**5a**	63[d]
2	**4b**	O	2	**5b**	82[d]
3	**4c**	O	3	**5c**	83
4	**4d**	NBoc	2	**5d**	77
5	**4e**	NTs	1	**5e**	60
6	**4f**	NTs	2	**5f**	84
7	**4g**	NMs	1	**5g**	63
8	**4h**	NMs	2	**5h**	57[e]
9	**4i**	NNs	1	**5i**	37 (39)[f]
10	**4j**	NNs	2	**5j**	37 (40)[f]

[a] General procedure: *n*-BuLi (1.6 M in hexanes; 1.1 equiv) was added dropwise to a −78 °C solution of *t*-Bu propiolate in THF (0.2 M). After stirring for 0.5 h, the reaction temperature was allowed to rise to −50 °C, and BF_3•OEt_2 (1.1 equiv) was added dropwise. After 10 min, the reaction mixture was cooled to −78 °C, and **4** was added neat (entries 1−3, 9−10) or as a THF solution (entries 4−8). After stirring for 1.5 h, the reaction was allowed to warm to rt and was quenched with sat. NH_4Cl. [b] Unless otherwise indicated, product **5** was isolated exclusively as the open-chain ynone. [c] All reported yields are for isolated homogeneous product after chromatographic purification. [d] Adducts **5a** (4:1) and **5b** (1.3:1) were isolated as inseparable mixtures of open-chain and hemiketal forms. [e] Adduct **5h** was accompanied by 25% of enyne **6h**. [f] Recovered starting material (%).

to good yields of adducts **5** were obtained. With the exception of five- and six-membered lactones **4a**,**b**, the products were isolated as the open-chain ynones. The six-membered *N*-methanesulfonyllactam **4h** furnished a significant quantity of elimination product **6h** along with the desired ynone **5h**. Addition to *N*-nosyllactams **4i**,**j** did not proceed to completion even with extended stirring in the presence of several equivalents of propiolate salt, suggesting competing enolization of the starting lactams.

With the propiolate adducts in hand, conditions for cyclization to cyclic ethers or amides **3** could be explored. Inital experiments utilized adduct **5b**. Anionic conditions analogous to those occurring in situ during Schreiber's two-carbon ring expansion[3] failed to furnish the desired product. In contrast, treatment with excess pyridine or DMAP at rt could effect clean conversion of **5b** to **3b** (Scheme 2), although the reaction was capricious. Optimally reproducible conditions employed 1.5 equiv of pyridinium acetate, providing oxepane **3b** in 78% yield. Other pyridinium salts (e.g., pyr•HCl or pyr•TsOH) were also more effective than pyridine alone, presumably due to enhanced rates of proton transfer.[7] This transformation is believed to occur via nucleophilic activation of the ynone to give allenol **7b**, which can then undergo intramolecular Michael addition and expulsion of

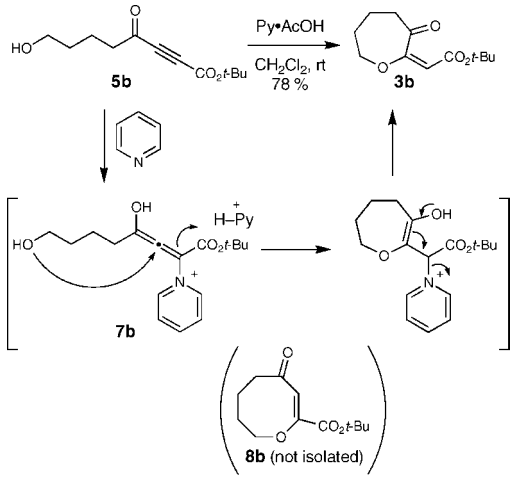
(3) For an alternative *two-carbon* intercalation process involving the addition of simple acetylides to lactones or lactams followed by endocyclization, see: (a) Schreiber, S. L.; Kelly, S. E. *Tetrahedron Lett.* **1984**, *25*, 1757–1760. (b) Schreiber, S. L.; Kelly, S. E.; Porco, J. A., Jr.; Sammakia, T.; Suh, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 6210–6218. (c) Suzuki, K.; Ohkuma, T.; Tsuchihashi, G. *J. Org. Chem.* **1987**, *52*, 2929–2930.

(4) (a) Vedejs, E.; Dax, S. L. *Tetrahedron Lett.* **1989**, *30*, 2627–2630. (b) Comins, D. L.; Huang, S.; McArdle, C. L.; Ingalls, C. L. *Org. Lett.* **2001**, *3*, 469–471. (c) Trost, B. M.; Crawley, M. L. *Chem.−Eur. J.* **2004**, *10*, 2237–2252.

(5) (a) Yamaguchi, M.; Shibato, K.; Fujiwara, S.; Hirao, L. *Synthesis* **1986**, 421–422. (b) Krafft, M. E.; Boñaga, L. V. R.; Felts, A. S.; Hirosawa, C.; Kerrigan, S. *J. Org. Chem.* **2003**, *68*, 6039–6042. (c) Doubsky, J.; Streinz, L.; Leseticky, L.; Koutek, B. *Synlett* **2003**, *7*, 937–942. (d) Doubsky, J.; Streinz, L.; Saman, D.; Zednik, J.; Koutek, B. *Org. Lett.* **2004**, *6*, 4909–4911.

(6) Reviews: (a) Molander, G. A.; Rigueroa, R. *Aldrichimica Acta* **2005**, *38*, 49–56. (b) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623–3658.

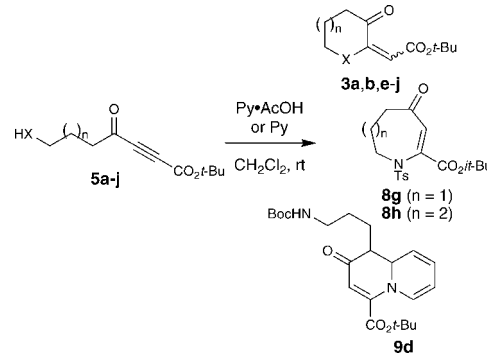
Scheme 2



pyridine. An analogous mechanism has been proposed in the Bu_3P-mediated reaction of arylpropiolate esters with bifunctional sulfur nucleophiles.[8] Notably, the alternative eight-membered product **8b** was not isolated,[9] consistent with initial attack by pyridine β to the more electrophilic keto group rather than the ester. Although this mechanism implies a catalytic role for pyridine, stoichiometric quantities were employed to ensure complete reaction within 2.5 h.

Cyclization was then attempted using the other propiolate adducts (Table 2). Butyrolactone adduct **5a** underwent clean conversion to pyranone **3a**; however, caprolactone adduct **5c** failed to produce the desired oxocane under a wide variety of conditions. Thus, it appears that this methodology may not be applicable to eight-membered rings. All of the *N*-sulfonyllactam adducts underwent cyclization to provide the corresponding piperidones or azepinones in 42−77%, although the three seven-membered examples required the use of pyridine in place of pyridinium acetate due to rapid decomposition of **5f**,**h**,**j** under the standard conditions. While the cyclic ether products **3a** and **3b** were formed as single geometrical isomers,[10] the azacycles **3e**−**j** were obtained as *E*/*Z* mixtures, typically inseparable. Fortunately, the seven-membered *N*-Ts derivative **3f** was subject to chromatographic separation, and the geometry of the *E*-isomer was confirmed by X-ray crystallography. Moreover, catalytic hydrogenation of a mixture of the *Z*- and *E*-isomers of **3f** furnished a single reduction product **10f** (Scheme 3), indicating that they only differ in alkene geometry. Geometrical isomers in the

Table 2. Cyclization of Propiolate Adducts **5**[a]

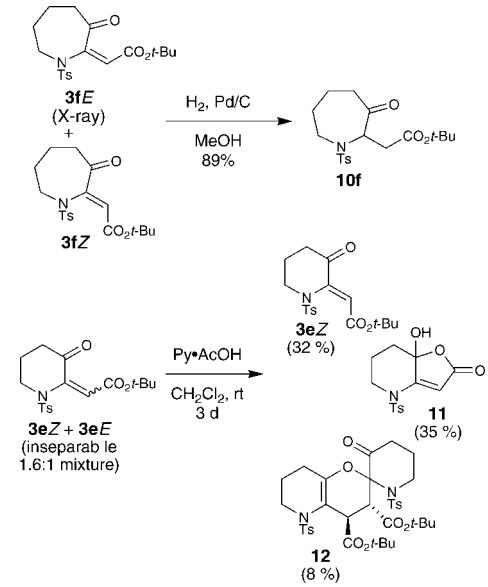


substrate	X	n	conditions	products	ratio	yield (%)[b]
5a	O	1	Py · AcOH	**3a** (*E* only)	−	82
5b	O	2	Py · AcOH	**3b** (*E* only)	−	78
5c	O	3	Py · AcOH	−	−	−
5d	NBoc	2	Py · AcOH	**9d**	−	28
5e	NTs	1	Py · AcOH	**3e** (*Z* + *E*)	1.6:1	58
5f	NTs	2	Py	**3f** (*Z* + *E*)	1:1.6	74
5g	NMs	1	Py · AcOH	**3g** (*Z* + *E*)/**8g**	23:6:1	60
5h	NMs	2	Py	**3h** (*Z* + *E*)/**8h**	2:5:1	77
5i	NNs	1	Py · AcOH	**3i** (*Z* + *E*)	1:1.3	42
5j	NNs	2	Py	**3j** (*Z* + *E*)	1:1.8	55

[a] General procedure: Pyridinium acetate (1.5 equiv) *or* pyridine (1.5 equiv) was added in one portion to a solution of the substrate in CH_2Cl_2 (0.1 M). The reaction mixture was allowed to stir at room temperature and monitored for the disappearance of starting material by TLC analysis (1−2.5 h). The reaction was then quenched with 1 N HCl. [b] Yields given are for isolated homogeneous product after chromatographic purification.

inseparable mixtures isolated in the other cases were assigned as *E* or *Z* based on ^{1}H NMR spectral analogy, with the alkene proton of the *Z*-isomers appearing consistently at lower field

Scheme 3



(7) A similar explanation was given for the superiority of the Keck lactonization conditions (DMAP/DMAP•HCl): (a) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394–2395. (b) See also: Spivey, A. C.; Arseniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436–5441.

(8) Gabillet, S.; Lecerclé, D.; Loreau, O.; Carboni, M.; Dézard, S.; Gomis, J.-M.; Taran, F. *Org. Lett.* **2007**, *9*, 3925–3927.

(9) The seven-membered product **3b** could not easily be distinguished from the alternative isomeric structure **8b** by standard 1D NMR techniques. However, HMBC experiments clearly indicated a correlation between H-4 and C-2, which would not be observable in **8b** (see Scheme 2).

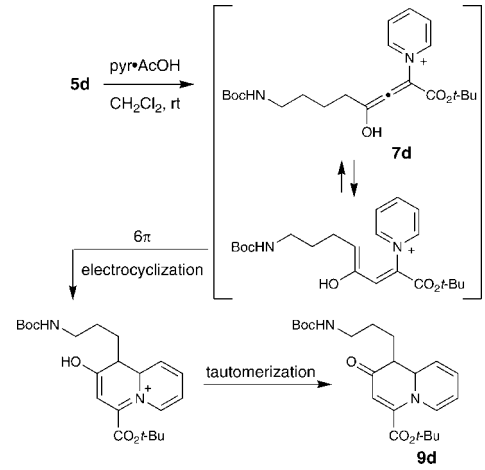
(10) **3a**,**b** were tentatively assigned as the *E*-isomers based on comparison of the ^{1}H NMR chemical shifts of the alkene proton to those of **3f*Z*** and **3f*E*** as well as related literature compounds. See Supporting Information for a discussion of these assignments.

due to anisotropic deshielding from the adjacent ketone carbonyl. No evidence was seen for interconversion of **3f***Z* and **3f***E* under the standard cyclization conditions. Notably, divergent reactivity was observed when the inseparable mixture of **3e***Z* and **3e***E* was subjected to prolonged reaction under the same conditions. After stirring for 3 days, pure **3e***Z* was isolated, along with comparable amounts of lactone hemiacetal **11** and minor quantities of spirocyclic dimer **12**. Since the geometric isomers are presumed not to equilibrate under reactions conditions, **11** could arise only from the *E*-isomer. Dimer **12**, an apparent Diels−Alder adduct, was obtained as a single diastereomer. While the *trans* relationship at the two ester-substituted centers was assigned with some confidence,[11] it was not possible to determine the relative configuration of the spiro center.

N-Mesyl substrates **5g**,**h** were notable for being the only examples in which the corresponding endocyclization products (**8g**,**h**) were isolated,[12] albeit in very minor amounts. It is unclear why this alternative regiochemistry was seen only in these two cases. The divergent behavior of *N*-Boc derivative **5d** is also notable. In this case, none of the expected azepinone was isolated, perhaps due to diminished acidity of the carbamate nitrogen. The only isolable product was pyridine adduct **9d**, which is presumed to form via tautomerization of the intermediate allenol **7d**, followed by electrocyclization and proton transfer (Scheme 4).[13] Isolation of **9d** offers compelling support for the involvement of pyridine as a nucleophilic catalyst in these reactions.

In summary, a two-step process resulting in a net one-carbon ring expansion of lactones and lactams has been developed, providing convenient access to six- and seven-membered cyclic ethers and amines. This method uses *t*-butyl propiolate as a 1,1-dipole equivalent, resulting in the intercalation of the β-carbon of the propiolate between the carbonyl and the adjacent heteroatom, with installation of an ester-substituted alkylidene unit. The second step appears to involve nucleophilic catalysis, as shown by the unexpected incorporation of pyridine in one case. Further applications of this interesting chemistry will be described in due course.

Scheme 4



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Supporting Information Available: Experimental procedures, physical data, and NMR spectra for all compounds and synthetic intermediates as well as CIF data for **3f***E*. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) A vicinal coupling of 9.5 Hz between the adjacent ester-substituted methines was observed, consistent with a *trans* relationship. See Supporting Information for additional discussion of structural assignments.

(12) The connectivity of endocyclization products **8g**,**h** was established via HMBC correlations between the alkene proton (H-3) and C-5.

(13) For earlier examples of similar pyridine-ynone adducts, see: (a) Crabtree, A.; Jackman, L. M.; Johnson, A. W. *J. Chem. Soc.* **1962**, 4417–4420. (b) Acheson, R. M.; Gagan, J. M. F.; Harrison, D. R. *J. Chem. Soc.* **1968**, 362–378. (c) Acheson, R. M.; Wallis, J. D.; Woollard, J. *J. Chem. Soc., Perkin Trans. I* **1979**, 584–590.