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A Kulinkovich Entry into Tertiary *N*-Acyliminium Ion Chemistry

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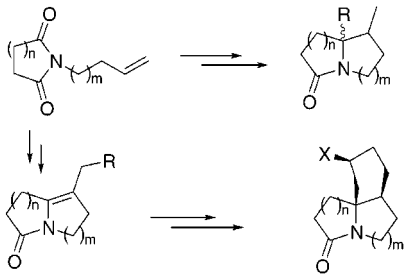
ABSTRACT



Subjection of *N*-alkenylimides to Kulinkovich cyclopropanation conditions led to different types of *N,O*-acetals, which were used as precursors for tertiary *N*-acyliminium ion chemistry. In this way, a variety of bi- and tricyclic lactams were efficiently synthesized.

N-Acyliminium ions are highly versatile carbon electrophiles for use in CC-bond-forming reactions, both in inter-[1] and intramolecular cases.[2] They have been extensively used as intermediates to form a large variety of structurally diverse nitrogen heterocycles and have continued to be used, as shown by the numerous publications that have appeared on their application.[3] The most commonly used precursors are N-acylated *N,O*-acetals, stable compounds that undergo conversion to *N*-acyliminium ions under the influence of Lewis or protic acids, which then can be trapped by weak carbon nucleophiles. These systems are usually prepared by reduction of the corresponding carbonyl group of imides or N-acylated lactams[4a] or α-oxidation of primary or secondary amides,[4b−d] thus resulting in primary or secondary carbocations. Tertiary *N*-acyliminium ions, in contrast, have received little attention, probably due to the difficulty of generation and the instability of the corresponding precursors. Over the years only a limited number of examples have appeared in the literature.[5]

(1) (a) Zaugg, H. E. *Synthesis* **1984**, *85*, 181. (b) Cushman, M.; Wong, W. C. *J. Org. Chem.* **1984**, *49*, 1278.

(2) (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (b) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 2, pp 1047−1082. (c) Hiemstra, H.; Speckamp, W. N. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1988; Vol. 32, p 271. (d) De Koning, H.; Moolenaar, M. J.; Hiemstra, H.; Speckamp, W. N. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1993; Vol. 13, pp 473−518. (e) De Koning, H.; Speckamp. W. N. In *Methods of Organic Chemistry (Houben-Weyl)*; Thieme: Stuttgart, Germany, 1995; Vol. E 21b, pp 1953−2009. (f) Flann, C.; Malone, T. C.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6097.

(3) For some recent examples see: (a) Newcombe, N. J.; Ya, F.; Vijn, R. J.; Hiemstra, H.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1994**, 767. (b) Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 2657. (c) Lögers, M.; Overman, L. E.; Welmaker, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 9139. (d) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202. (e) Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3592. (f) Padwa, A. *J. Chem. Soc., Chem. Commun.* **1998**, 1417. (g) Remuson, R.; Chalard, P.; Gelas-Mialhe, Y.; Gramain, J. C.; Canet, I. *Tetrahedron Lett.* **1999**, *40*, 1661. (h) Beyersbergen van Henegouwen, W. G.; Fieseler, R. M.; Rutjes, F. P. J. T.; Hiemstra, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2214.

(4) See e.g.: (a) Wijnberg, J. B. P. A.; Schoemaker, H. E.; Speckamp. W. N. *Tetrahedron* **1978**, *34*, 179. (b) For electrochemical oxidation, see e.g.: Shono, T. *Tetrahedron* **1984**, *40*, 811. (c) Shono, T.; Matsumura, Y.; Tsubata, K. *Org. Synth.* **1985**, *63*, 206. (d) For other types of oxidation, see, for example, ref 2b, pp 1051−1053.

(5) (a) Brodney, M. A.; Padwa, A. *J. Org. Chem.* **1999**, *64*, 556. (b) Langlois, N. Choudhury, P. K. *Tetrahedron Lett.* **1999**, *40*, 2525. (c) Martin, S. F.; Bur, S. K. *Tetrahedron Lett.* **1997**, *38*, 7641. (d) Heaney, H., Shuhaibar, K. F. *Tetrahedron Lett.* **1994**, *35*, 2751. (e) Moeller, K. D.; Rutledge, L. D. *J. Org. Chem.* **1992**, *57*, 6360. (f) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858.

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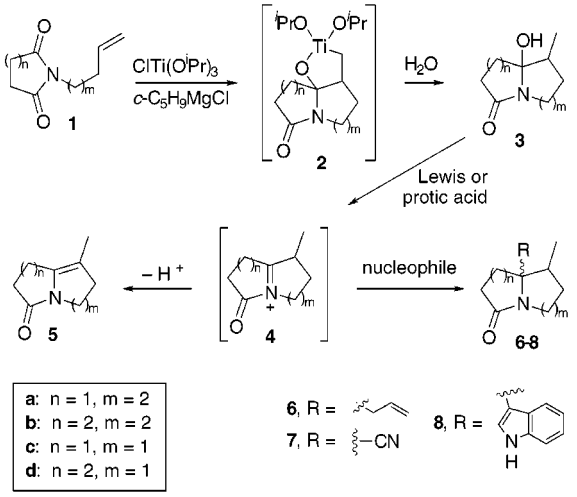
Recently, Cha and co-workers published a method that might circumvent these difficulties. They extended the Kulinkovich cyclopropanation reaction[6] to imides in such a way that *N*,*O*-acetals were generated that might serve as precursors of tertiary *N*-acyliminium ions.[7] In this paper, we describe the application of this methodology to explore the synthetic utility of such cationic intermediates in inter- and intramolecular reactions and extend it to the synthesis of the skeleton of the natural product lepadiformine.

The *N*,*O*-acetals **3a**−**d** were obtained as reported by Cha.[7a] Treatment of imides **1a**−**d**[8] with an excess of cyclopentylmagnesium chloride in the presence of 1.5 equiv of ClTi(O^{i}Pr)$_3$ to generate the titanacycle **2**, followed by an aqueous workup, led to the *N*,*O*-acetals **3** (Scheme 1). First, the

Scheme 1



feasibility of intermolecular CC-bond formation was investigated. The precursors were subjected to different Lewis and protic acids in order to generate the corresponding tertiary *N*-acyliminium ions in the presence of a nucleophile. Lewis acids such as BF_3·OEt_2, Me_3SiOTf, and $TiCl_4$, all of them in combination with allyltrimethylsilane, afforded exclusively the corresponding elimination compounds **5** (Table 1). $SnCl_4$, on the other hand, appeared to be a more suitable Lewis acid for this system, leading to the introduction of a cyanide group at the tertiary position in moderate yields. Remarkably, only in one case could an allyl substituent be introduced (Table 1, entry 5). Alternatively, subjection of the enamides **5** to a protic acid to generate the *N*-acyliminium ions proved to be only useful in combination with a very stable nucleophile such as indole (Table 1, entry 9).

(6) (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Prityts kaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244. (b) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A. *Synthesis* **1991**, 234. (c) Kulinkovich, O. G.; Savchenko, A. I.; Sviridov, S. V.; Vasilevskii, D. A. *Mendeleev Commun.* **1993**, 192 and references therein.

(7) (a) Lee, J.; Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1997**, *119*, 8127. (b) Sung, M. J.; Lee, C.-W.; Cha, J. K. *Synlett* **1999**, 561.

(8) Imides **1a**−**d** were obtained by alkylation of succinimide or glutarimide with 4-bromo-1-butene or 5-bromo-1-pentene using NaH in DMF/THF (3:1).

Table 1. Intermolecular Reactions with Tertiary *N*-Acyliminium Ions

entry	*N*,O-acetal	nucleophile[a]	product	*cis*/*trans* ratio[c]	yield (%)[d]
1	**3a**	allylSiMe$_3$	**5a**		55
2	**3a**	Me$_3$SiCN	**7a**	1:0	54
3	**3b**	allylSiMe$_3$	**5b**		39
4	**3b**	Me$_3$SiCN	**7b**	5:1	44
5	**3c**	allylSiMe$_3$	**6c**	1:1	58
6	**3c**	Me$_3$SiCN	**7c**	8:1	49
7	**3d**	allylSiMe$_3$	**5d**		78
8	**3d**	Me$_3$SiCN	**7d**	11:1	64
9	**3a**	indole[b]	**8a**	1:1	51

[a] Reaction conditions: $SnCl_4$ (1.5 equiv), nucleophile (10 equiv), CH_2Cl_2, 17 h. [b] Reaction conditions: CF_3CO_2H (1.1 equiv), nucleophile (10 equiv), CH_2Cl_2, 60 h. [c] This stereochemistry was tentatively assigned after reduction of cyanide **7a** to the corresponding aminomethylene compound and analysis of ^{1}H NMR NOE data of this product. [d] Isolated yields after chromatography.

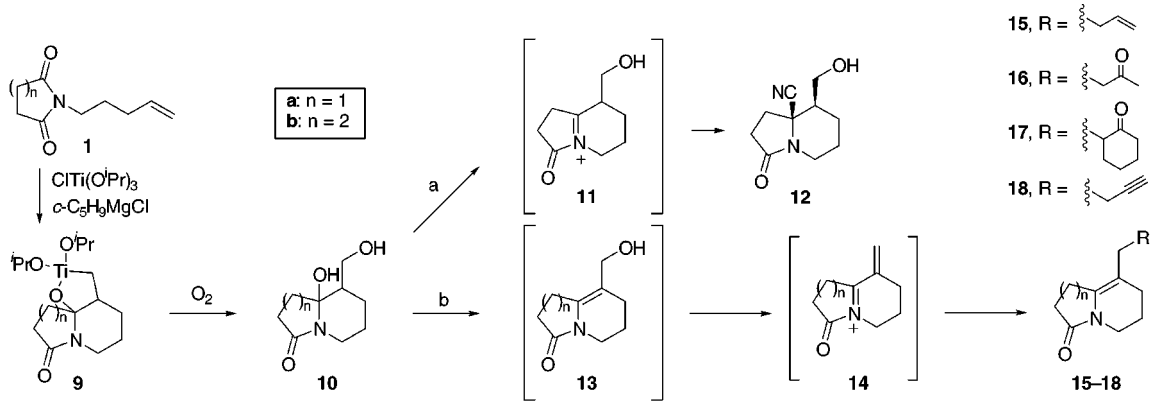
Although these reactions show that intermolecular CC-bond formation at tertiary *N*-acyliminium ion centers is feasible, the scope so far has been somewhat limited. Inspired by the tendency of these systems to form enamides and the results of Cha in oxidizing the intermediate Ti species by using oxygen,[7a] we reasoned that formation of the vinylogous *N*-acyliminium ion precursors **13** should be possible. Thus, treatment of the titanacycle intermediate **9** with molecular oxygen previous to workup led to diols **10a**,**b** (Scheme 2). Subsequent treatment of diol **10a** with a Lewis acid and trimethylsilyl cyanide led to incorporation of the cyanide nucleophile at the bridgehead position in a diastereoselective manner (Scheme 2, pathway a). In analogy with the assigned stereochemistry in bicyclic lactam **7a**, both substituents are most likely *cis* with respect to each other. In all other cases, the anticipated elimination reaction occurred, giving rise to the vinylogous *N*,*O*-acetal **13**, which under the reaction conditions led to the conjugated *N*-acyliminiun ion **14** (Scheme 2, pathway b).

This process was followed by selective reaction of the nucleophile at the least hindered γ-position. Using this pathway, a variety of functional groups were introduced in reasonable to good yields (viz. lactams **15**−**18**) via reaction with different nucleophiles such as allyltrimethylsilane, two silyl enol ethers, and allenyltributyltin (Table 2).

Having obtained the alkylated bicyclic enamides **15**−**18**, we envisioned that these compounds could also serve as *N*-acyliminium ion precursors and react intramolecularly with the internal nucleophile to give tricyclic structures. Indeed, stirring the enamides **15a** and **15b** in formic acid at room temperature yielded—after treatment with NH_3/MeOH—compounds **19a** and **19b** in 92 and 62% yields, respectively, as single diastereomers (Scheme 3). The relative stereochemistry was proven via determination of the X-ray structure of **19b** and comparison of the ^{1}H NMR data.

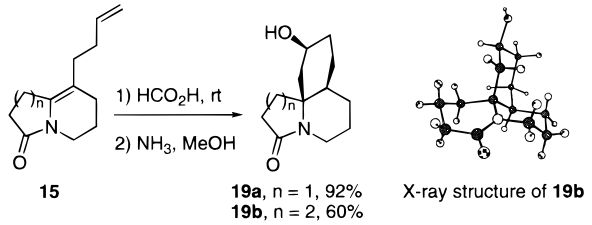
Interestingly, this type of tricyclic core is present in several natural products such as lepadiformine (**25**) and the cylindricines, recently isolated marine alkaloids which display

Scheme 2

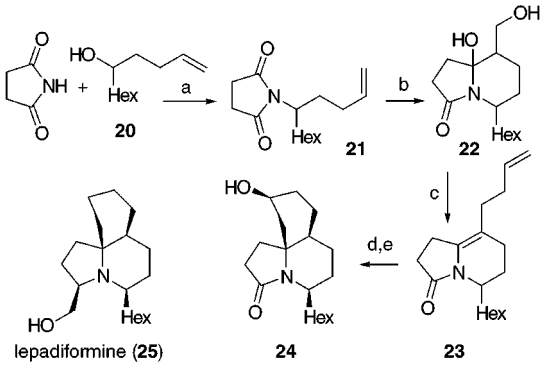


interesting pharmacological activities.[9] We anticipated that by using this route we might have an efficient entry into the lepadiformine skeleton (Scheme 4). The sequence commenced with imide **21**, obtained by Mitsunobu alkylation of succinimide with alcohol **20**. This substrate was subjected to the Kulinkovich conditions to afford the *N*,*O*-acetal **22**, which upon treatment with $SnCl_4$ and allyltrimethylsilane yielded enamide **23** in 36% overall yield from imide **21**.

Scheme 3



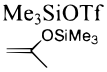
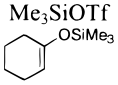
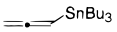
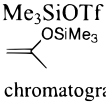
Scheme 4[a]



[a] Reagents and conditions: (a) PPh_3, DEAD, THF, 78%; (b) $ClTi(O^iPr)_3$, *c*-C_5H_9MgCl; then O_2, 41%; (c) $SnCl_4$, allylSiMe$_3$, CH_2Cl_2, −78 °C to room temperature, 17 h, 88% (d) HCO_2H, room temperature, 24 h; (e) NH_3, MeOH, room temperature, 70% over 2 steps.

Finally, cyclization to the tricyclic compound **24** was achieved through stirring in formic acid at room temperature followed by cleavage of the formate ester. In this process, all four new stereocenters were formed *with complete diastereoselectivity*, thus giving rise to the lepadiformine framework. Experiments to form the tricyclic structure in

Table 2. Intermolecular Reactions with Tertiary and Conjugated *N*-Acyliminium Ions

Entry	*N*,*O*-Acetal	Lewis acid, Nucleophile	Product	Yield (%)[a]
1	**10a**	$BF_3{\cdot}Et_2O$, AllylSiMe$_3$	**15a**	67
2	**10a**	Me$_3$SiOTf, 	**15a**	86
3	**10a**	Me$_3$SiOTf, 	**17a**	69
4	**10a**	$BF_3{\cdot}Et_2O$, 	**18a**	33
5	**10a**	Me$_3$SiOTf, Me$_3$SiCN	**12**	62
6	**10b**	$BF_3{\cdot}Et_2O$, AllylSiMe$_3$	**15b**	55
7	**10b**	$SnCl_4$, AllylSiMe$_3$	**15b**	70
8	**10b**	Me$_3$SiOTf, 	**16b**	80

[a] Isolated yields after column chromatography.

(9) (a) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691. (b) Werner, K. M.; de los Santos, J. M.; Weinreb, S. M. *J. Org. Chem.* **1999**, *64*, 686. (c) Pearson, W. H.; Ren, Y. *J. Org. Chem.* **1999**, *64*, 688. (d) Werner, K. M.; de los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 4865.

one step from **22** by using formic acid and allyltrimethylsilane were not very successful: although the cyclized product **24** was found in the reaction mixture, the yield was significantly lower than in the two-step sequence, probably due to the instability of the diol **22** in formic acid.

The stereochemistry of compound **24** was assigned by comparison with ^{1}H NMR spectra of **19a** and literature data[10] for similar lactams. The axial α-proton with respect to the nitrogen (**19a**, δ 2.52 ppm) was missing in the ^{1}H NMR spectrum of **24**, whereas the equatorial α-proton was clearly present (**19a**, δ 4.02 ppm, dd, J = 13.4, 4.8 Hz; **24**, δ 4.16, q, J = 7.1 Hz). Thus, the lepadiformine skeleton was formed in high overall yield in only five steps from succinimide. Further elaboration of this route to the synthesis of the natural product is currently under investigation.

In summary, we have demonstrated in a general sense the utilitity of tertiary *N*-acyliminium ions as intermediates in both inter- and intramolecular CC-bond-forming reactions. Furthermore, we have shown that this methodology holds a promising potential for natural product synthesis.

(10) *Org. Magn. Reson. Spectral Suppl. 5* **1973**, Spectrum No. 0586.

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Supporting Information Available: General procedures for the *N*-acyliminium ion reactions, full characterization data for compounds **5b**, **6c**, **7a**, **11**, **15a**,**b**, **16a**, **17a**, **19a**,**b**, **23** and **24**, and full crystallographic data of compound **19b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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