ORGANIC LETTERS

2007
Vol. 9, No. 4
659−662

Titanium- and Lewis Acid-Mediated Cyclopropanation of Imides

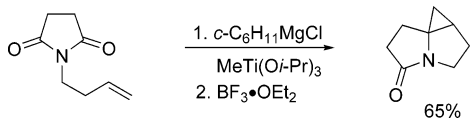
Philippe Bertus* and Jan Szymoniak

UMR 6519, Réactions Sélectives et Applications, CNRS, Université de Reims Champagne−Ardenne, BP 1039, 51687 REIMS Cedex 2, France

philippe.bertus@univ-reims.fr

Received December 4, 2006

ABSTRACT

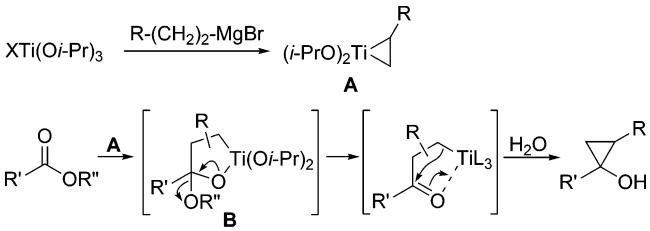


We report a straightforward synthesis of 1-azaspirocyclopropane lactams from imides. Following the described procedure, polycyclic nitrogen heterocycles containing a cyclopropane unit could be obtained from unsaturated imides.

The Kulinkovich reaction, i.e., titanium-mediated formation of cyclopropanols from carboxylic esters and Grignard reagents, has extensively been studied since its discovery in 1989.[1,2]

This reaction involves the formation of titanacyclopropane intermediates **A** and insertion of esters to afford **B**, which spontaneously rearrange to afford cyclopropanol derivatives after hydrolysis (Scheme 1).

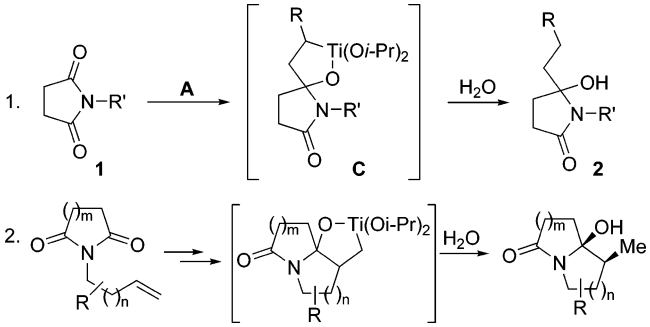
Scheme 1. Kulinkovich Reaction



X = O*i*-Pr, Cl, Me. L = –OR",–O*i*-Pr or –$(CH_2)_2$–R.

The scope of substrates has gradually been extended, leading to the preparation of a wide range of substituted cyclopropanes. In addition to carboxylic esters used in the original Kulinkovich reaction, tertiary amides[3] and dialkyl carbonates[4] have been employed, leading, respectively, to tertiary cyclopropylamines and cyclopropanone hemiacetals after hydrolysis. In contrast, Cha and co-workers reported that cyclic imides did not afford cyclopropane compounds under the Kulinkovich conditions.[5] *N*-Acyl hemiaminals were solely obtained, resulting from the hydrolysis of the five-membered ring intermediate **C**, stable in this case (Scheme 2, eq 1).[6] The reaction was applied to the synthesis of

Scheme 2. Reaction of Titanacyclopropanes with Imides



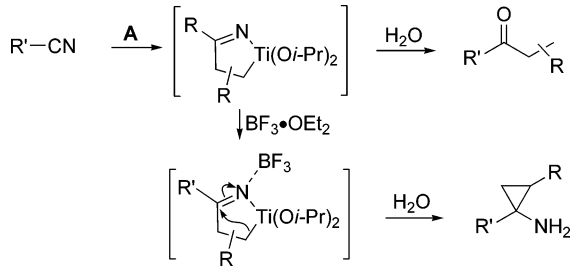
pyrrolizidine, indolizidine, and related alkaloids by a titanium-mediated cyclization of ω-vinyl imides (Scheme 2, eq 2).[5,7]

More recently, we have developed a synthesis of primary cyclopropylamines, based on the reaction of titanacyclopropanes (**A**) with nitriles (Scheme 3).[8] Whereas under the

(1) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevsky, D. A.; Prityts kaja, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244−2245; *J. Org. Chem. USSR* **1989**, *25*, 2027−2028.

10.1021/ol062938o CCC: $37.00
Published on Web 01/20/2007

Scheme 3. Ti-Mediated Cyclopropanation of Nitriles

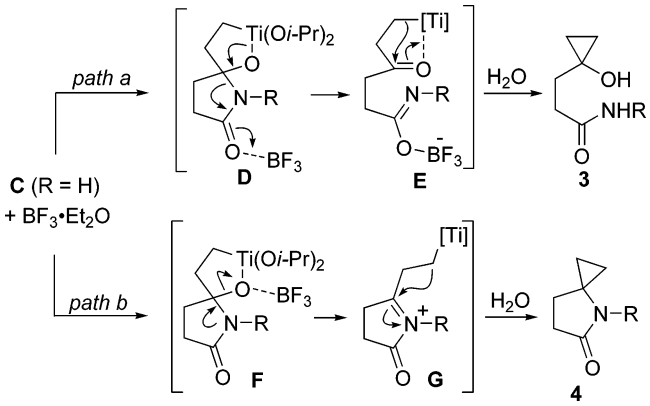


Kulinkovich conditions the ketone was the major product of hydrolysis, the addition of BF_3•OEt_2 to the metallacycle modified dramatically the outcome of the reaction, affording cyclopropylamines in good yields. The Lewis acid was assumed to induce the ring contraction of the five-membered metallacycle in this case.

The formation of cyclopropane derivatives would similarly be expected through a Lewis acid activation of **C** (Scheme 4). In this case, two products can be anticipated, depending on the selectivity of the Lewis acid addition. Following path a, the coordination of a Lewis acid on the carbonyl moiety would induce the formation of the homoenolate equivalent **E**, in the way analogous to that encountered in the Kulinkovich cyclopropanation of esters, to produce the amide-substituted cyclopropanol **3**.[9] In path b, coordination of the Lewis acid on the oxygen linked to titanium would produce the azaspirocyclic compound **4** through the iminium intermediate **G**.[10]

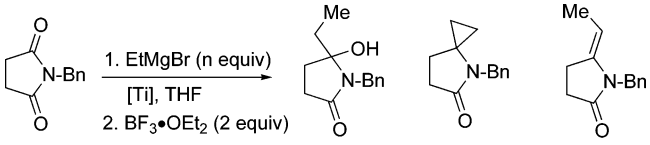
Initial experiments were carried out with *N*-benzylsuccinimide (**1a**). As expected, the addition of EtMgBr to a solution

Scheme 4. Proposed Paths for the Lewis Acid Activation of **C**



of Ti(O*i*-Pr)$_4$ and **1a** in THF led to the *N*-acyl hemiaminal **2a** in 89% yield (Table 1, entry 1).

Table 1. Ti-Mediated Addition of EtMgBr to Imide **1a**



			yield (%)[a]			
entry	[Ti] (equiv)	*n*	**1a**	**2a**	**4a**	**5a**
1[b]	Ti(O*i*-Pr)$_4$ (1.2)	2.4	–	89 (75)	–	–
2	Ti(O*i*-Pr)$_4$ (1.2)	2.4	–	–	49	34
3[c]	Ti(O*i*-Pr)$_4$ (1.2)	2.4	–	–	50	39
4	ClTi(O*i*-Pr)$_3$ (1.2)	2.4	–	–	62	21
5	MeTi(O*i*-Pr)$_3$ (1.2)	1.2	49	–	38	2
6	MeTi(O*i*-Pr)$_3$ (1.5)	1.5	–	–	79 (75)	2
7[d]	MeTi(O*i*-Pr)$_3$ (1.5)	1.5	–	–	78 (74)	3

[a] NMR yields; isolated yields in parentheses. [b] Reaction performed without the addition of BF_3•OEt_2. [c] Reaction carried out in Et_2O. [d] Me_3SiOTf used instead of BF_3•OEt_2.

A successive addition of BF_3•OEt_2 to the reaction mixture led to the formation of two new products, the enamide **5a**, resulting probably from the dehydration of **2a**, and the azaspirocyclic compound **4a** as the sole cyclopropane-containing derivative (entry 2). Whereas the use of ClTi(O*i*-Pr)$_3$ instead of Ti(O*i*-Pr)$_4$ had a moderate effect on the **4a**/**5a** ratio (entry 4), the use of MeTi(O*i*-Pr$_3$)[11] was found to significantly increase the ratio of the cyclopropane **4a** to the detriment of **5a** (entries 5−7). In fact, MeTi(O*i*-Pr$_3$) requires only one equivalent of EtMgBr to form the titanacyclopropane, thus limiting side reactions resulting from the

(2) Reviews: (a) Kulinkovich, O. G. *Eur. J. Org. Chem.* **2004**, 4517−4529. (b) de Meijere, A.; Kozhushkov, S. I.; Savchenko, A. I. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 390−434. (c) de Meijere, A.; Kulinkovich, O. G. *Chem. Rev.* **2000**, *100*, 2789−2834.

(3) Review: de Meijere, A.; Kozhushkov, S. I.; Savchenko, A. I. *J. Organomet. Chem.* **2004**, *689*, 2033−2055.

(4) Lee, J.; Kim, Y. G.; Bae, J. G.; Cha, J. K. *J. Org. Chem.* **1996**, *61*, 4878−4879.

(5) (a) Lee, J.; Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1997**, *119*, 8127−8128. (b) Lee, K.; Kim, S.-E.; Cha, J. K. *J. Org. Chem.* **1998**, *63*, 9135−9138. (c) Sung, M. J.; Lee, C.-W.; Cha, J. K. *Synlett* **1999**, 561−562. (d) Kim, S.-H.; Park, Y.; Choo, H.; Cha, J. K. *Tetrahedron Lett.* **2002**, *43*, 6657−6660. (e) Santra, S.; Masalov, N.; Epstein, O.; Cha, J. K. *Org. Lett.* **2005**, *7*, 5901−5904.

(6) Similarly to imides, *N*-acylpyrroles did not afford cyclopropane derivatives under Kulinkovich conditions; see: Epstein, O. L.; Seo, J. M.; Masalov, N.; Cha, J. K. *Org. Lett.* **2005**, *7*, 2105−2108.

(7) (a) Kim, S.-H.; Kim, S.-I.; Lai, S.; Cha, J. K. *J. Org. Chem.* **1999**, *64*, 6771−6775. (b) Kim, S.-H.; Cha, J. K. *Synthesis* **2000**, 2113−2116. (c) Ollero, L.; Mentink, G.; Rutjes, F. P. J. T.; Speckamp, W. N.; Hiemstra, H. *Org. Lett.* **1999**, *1*, 1331−1334.

(8) (a) Bertus, P.; Szymoniak, J. *Chem. Commun.* **2001**, 1792−1793. (b) Bertus, P.; Szymoniak, J. *J. Org. Chem.* **2002**, *67*, 3965−3968. (c) Bertus, P.; Szymoniak, J. *Synlett* **2003**, 265−267. (d) Laroche, C.; Bertus, P.; Szymoniak, J. *Tetrahedron Lett.* **2003**, *44*, 2485−2487. (e) Bertus, P.; Szymoniak, J. *J. Org. Chem.* **2003**, *68*, 7133−7136. (f) Laroche, C.; Harakat, D.; Bertus, P.; Szymoniak, J. *Org. Biomol. Chem.* **2005**, *3*, 3482−3487. (g) Laroche, C.; Behr, J.-B.; Szymoniak, J.; Bertus, P.; Plantier-Royon, R. *Eur. J. Org. Chem.* **2005**, 5084−5088. See also: (h) Gensini, M.; Kozhushkov, S. I.; Yufit, D. S.; Howard, J. A. K.; Es-Sayed, M.; de Meijere, A. *Eur. J. Org. Chem.* **2002**, 2499−2507.

(9) Closely related to imides, acyloxazolidinones afforded cyclopropanols under Kulinkovich conditions; see: Mizojiri, R.; Urabe, H.; Sato, F. *J. Org. Chem.* **2000**, *65*, 6217−6222.

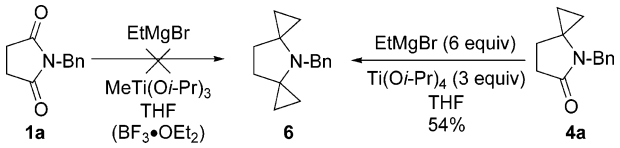
(10) (a) According to the referee's remark, **4** could also arise from the Lewis acid coordination on the alkoxy ligands. (b) Another site of coordination is the nitrogen atom. The expected final product would be the same as that in path a, i. e., the cyclopropanol **3**.

(11) MeTi(O*i*-Pr)$_3$ was prepared from ClTi(O*i*-Pr)$_3$ and MeLi; see: Reetz, M. T.; Westermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Ostarek, R.; Maus, S. *Chem. Ber.* **1985**, *118*, 1421−1440.

use of a larger amount of Grignard reagent.[12] A slightly higher excess of titanium and Grignard reagents was however required to obtain a total conversion of the starting imide (entry 6). The use of Me_3SiOTf gave similar results (entry 7). In all the experiments involving **1a**, the spirocyclic lactam **4a** was the only cyclopropane-containing product obtained. No trace of the cyclopropanol **3a** was detected, suggesting that the cyclopropanation reaction occurred via path b solely.

An overcyclopropanation of **1a**, possible with an excess of reagent, to afford the dispirocyclic amine **6** was not observed (Scheme 5). The amine **6** could be obtained from

Scheme 5. Preparation of the Dispirocyclic Amine **6**



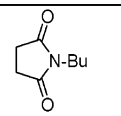
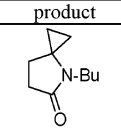
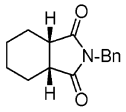
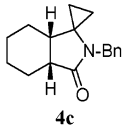
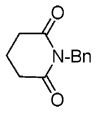
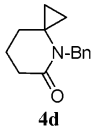
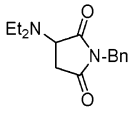
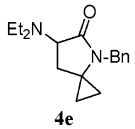
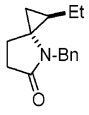
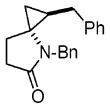
the isolated amide **4a**, without the subsequent use of a Lewis acid. In this case, a large excess of reagents was required to afford a total conversion of the starting amide.

The optimized conditions for efficiently preparing **4a** from **1a** were successfully applied to a series of imides and Grignard reagents, to afford the spirocyclopropane lactams **4b**−**g**, as shown in Table 2.

Good yields of **4b**−**e** were obtained from EtMgBr and the cyclic imides **1b**−**e** (entries 1−4). Particularly noteworthy is the regioselective cyclopropanation of the α-diethylaminosuccinimide **1e** at the less-hindered carbonyl moiety (entry 4). The use of higher Grignard reagents (*n*-BuMgBr and Ph-$(CH_2)_3$-MgBr) afforded the corresponding substituted cyclopropanes **4f** and **4g** with a low diastereocontrol (entries 5 and 6). In contrast, *N*,*N*-diacetylbenzylamine, the acyclic analogue of **1a**, was not a suitable substrate because only *N*-acetylbenzylamide was obtained in this case.[13]

We next turned to the cyclopropanation of *N*-alkenyl imides. Cha and co-workers extensively studied the regio- and stereocontrol of the titanium-mediated cyclization of unsaturated imides, providing an efficient access to substituted nitrogen heterocycles (Scheme 2, eq 2).[5] The scope of this method would be significantly extended if cyclopropane-containing polycyclic compounds are obtained by the addition of Lewis acids. Initial attempts to prepare the tricyclic amide **8a** from imide **7a** by activating the metallacycle **H** (generated following the reported procedures, *c*-C_5H_9MgCl/$ClTi(Oi\text{-}Pr)_3$[5a] or *n*-BuLi/$Ti(Oi\text{-}Pr)_4$[5e]) with BF_3•OEt_2 led to low yields of **8a**. The amide **8a** was obtained in 65% yield by the use of an excess of $MeTi(Oi\text{-}Pr)_3$ and cyclohexyl-

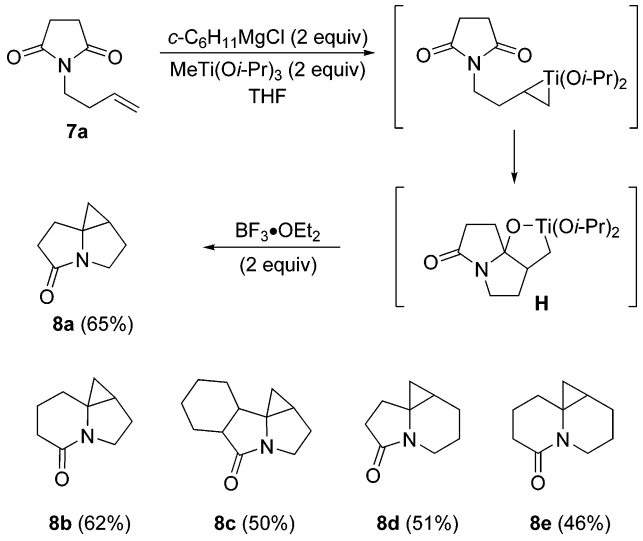
Table 2. Cyclopropanation of Imides **1a**−**e**

entry	imide	RMgX	product	yield (%)[a,b]
1	 **1b**	EtMgBr	 **4b**	74
2	 **1c**	EtMgBr	 **4c**	78
3	 **1d**	EtMgBr	 **4d**	67
4	 **1e**	EtMgBr	 **4e**	58
5	**1a**	*n*-BuMgBr	 **4f**[c]	51 (68:32)
6	**1a**	$Ph(CH_2)_3MgBr$	 **4g**[c]	48 (65:35)

[a] Isolated yields. [b] Ratio of diastereomers is in parentheses. [c] The configuration of the major stereoisomer was determined by NOE.

magnesium chloride, followed by the addition of BF_3•OEt_2 (Scheme 6). The cyclization was extended to the formation of polycyclic compounds with various cycle sizes leading

Scheme 6. Cyclopropanation of ω-Vinylimides



(12) $MeTi(Oi\text{-}Pr)_3$ was initially used by de Meijere and co-workers for the cyclopropanation of tertiary amides and was found to be generally more efficient than $Ti(Oi\text{-}Pr)_4$: Chaplinski, V.; Winsel, H.; Kordes, M.; de Meijere, A. *Synlett* **1997**, 111−114.

(13) Acyclic imides are known to be much more reactive toward nucleophiles than the cyclic ones. See, for example: (a) Murakami, Y.; Kondo, K.; Miki, K.; Akiyama, Y.; Watanabe, T.; Yokoyama, Y. *Tetrahedron Lett.* **1997**, *38*, 3751−3754. (b) Sykes, N. O.; Macdonald, S. J. F.; Page, M. I. *J. Med. Chem.* **2002**, *45*, 2850−2856.

to amides **8b**−**e** in 46−62% isolated yields. These compounds were obtained in a totally diastereoselective fashion.[14]

A short preparation of such polycyclic frameworks is very rare in the literature.[15] By a suitable use of substituted ω-vinyl tethered starting imides, this method should present a short access to new cyclopropane-containing pyrrolizidine and indolizidine derivatives.[16]

In summary, we have presented the unprecedented cyclopropanation of imides. The modification of the conditions applied by Cha and co-workers, mainly the use of MeTi(O*i*-Pr)$_3$ as a titanium reagent and the addition of $BF_3 \cdot OEt_2$, gave 1-azaspirocyclopropane lactams in 48−78% yield. The described method allows a direct access to polycyclic nitrogen heterocycles bearing a cyclopropane unit from readily available starting materials.

Acknowledgment. This work was supported by CNRS and the Reims-Champagne-Ardenne university.

Supporting Information Available: Experimental procedures, characterization data, and NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062938O

(14) The relative stereochemistry of compounds **8a**−**e** has not been established.

(15) Only two methods for preparing the tricyclic core of **8a** were reported in the literature, whereas the other polycyclic frameworks of **8b**−**e** are unknown to date: (a) Hanessian, S.; Buckle, R.; Bayrakdarian, M. *J. Org. Chem.* **2002**, *67*, 3387−3397. (b) Beak, P.; Wu, S.; Yum, E. K.; Jun, Y. M. *J. Org. Chem.* **1994**, *59*, 276−277.

(16) (a) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 603−626. (b) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773−781 and references therein.