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Facile Ring-Opening of Azabicyclic [3.1.0]- and [4.1.0]Aminocyclopropanes to Afford 3-Piperidinone and 3-Azepinone

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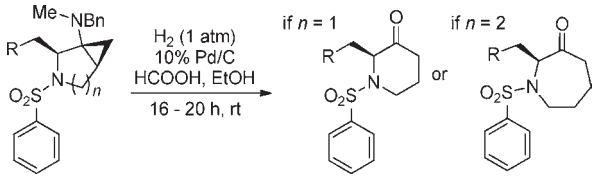
ABSTRACT



Azabicyclic [3.1.0] and [4.1.0] Kulinkovich products underwent a facile reduction/fragmentation to afford a variety of 3-piperidinones and 3-azepinones, respectively, in the presence of catalytic palladium on carbon and formic acid in an atmosphere of hydrogen.

The Kulinkovich reaction[1] has been generally utilized to access a number of biologically and structurally interesting cyclopropanols and aminocyclopropanes from simple starting materials.[2,3] We recently reported the synthesis of a range of azabicyclic [3.1.0]cyclopropylamines derived from amino acids,[3] and we now wish to report the ring-opening of these systems to afford piperidinone and azepinone derivatives. Piperidinones are often used as intermediates in organic synthesis,[4] and azepinone moieties are found in pharmaceuticals and biologically important compounds.[5] Azepinones also pose synthetic challenges due to their nitrogen-containing seven-membered ring.[6]

Ring-opening of cyclopropanols is a relatively facile process compared to ring-opening of tertiary aminocyclopropanes,[7] which require high temperatures,[8] photooxidative, or aerobic oxidative conditions.[9] To the best of our knowledge, no ring-opening reactions of azabicyclic aminocyclopropanes have been reported under the conditions presented.

We began our studies by testing traditional (i.e., SiO_2 and $FeCl_3$, pyridine, DMF) oxidative ring-opening of the strained aminocyclopropanes, which resulted in decomposition of starting material.[10] Hence, a different approach

(1) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, D. A. *Synthesis* **1991**, 234.

(2) (a) Ollero, L.; Mentink, G.; Rutjes, F.; Speckamp, W. N.; Hiemstra, H. *Org. Lett.* **1999**, *1*, 1331. (b) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789. (c) Quan, L. G.; Kim, S. H.; Lee, J. C.; Cha, J. K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2160. (d) Tebben, G. D.; Rauch, K.; Stratmann, C.; Williams, C. M.; de Meijere, A. *Org. Lett.* **2003**, *5*, 483. (e) de Meijere, A.; Kozhushkov, S. I.; Savchenko, A. I. *J. Organomet. Chem.* **2004**, *689*, 2033. (f) Gensini, M.; de Meijere, A. *Chem.—Eur. J.* **2004**, *10*, 785. (g) Lack, O.; Martin, R. E. *Tetrahedron Lett.* **2005**, *46*, 8207. (h) Faler, C. A.; Joullié, M. M. *Tetrahedron Lett.* **2008**, *49*, 6512. (i) Madelaine, C.; Buzas, A. K.; Lowalska-Six, J. A.; Six, Y.; Crousse, B. *Tetrahedron Lett.* **2009**, *50*, 5367.

(3) (a) Cao, B.; Xiao, D.; Joullié, M. M. *Org. Lett.* **1999**, *1*, 1799. (b) Faler, C. A.; Cao, B.; Joullié, M. M. *Heterocycles* **2006**, *67*, 519.

(4) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953.

(5) Most recent article on cathepsin K inhibitors: Wang, H.; Matsuhashi, H.; Doan, B. D.; Goodman, S. N.; Ouyang, X.; Clark, W. M., Jr. *Tetrahedron* **2009**, *65*, 6291.

(6) Dubinina, G. G.; Yoshida, W. Y.; Chain, W. J. *Tetrahedron Lett.* **2010**, *51*, 5325.

(7) Most recent review on Kulinkovich reaction and its applications: Wolan, A.; Six, Y. *Tetrahedron* **2010**, *66*, 15.

(8) Kuehne, M. E.; King, J. *J. Org. Chem.* **1973**, *38*, 304.

(9) (a) Lee, J. W.; U, J. S.; Blackstock, S. C.; Cha, J. K. *J. Am. Chem. Soc.* **1997**, *119*, 10241. (b) Lee, H. B.; Sung, M. J.; Blackstock, S. C.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 11322.

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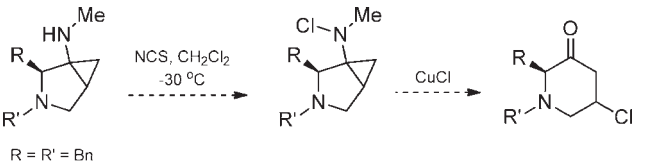
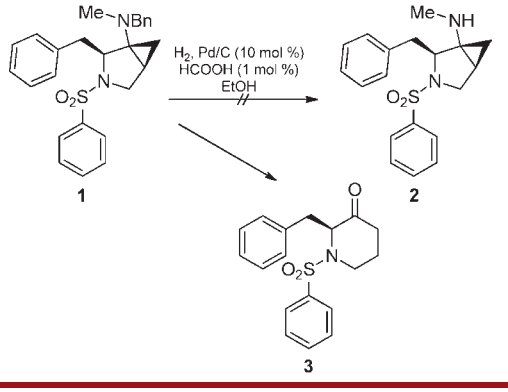
was considered on the basis of the work by Schulte-Wülwer et al.[11]

Scheme 1. CuCl Approach to Radical-Induced Cleavage of Cyclopropylamines



Formation of the highly reactive *N*-chloroaminocyclopropane derivative followed by reaction with CuCl could induce a nitrogen radical formation/cleavage event (Scheme 1). When previously synthesized phenylalanine aminocyclopropane[3] was employed in the proposed methodology, selective monodeprotection of the *N*-methylbenzylamine and subsequent chlorination were unsuccessful. Traditional palladium-catalyzed hydrogenolysis showed poor selectivity over the two secondary amines, and the subsequent chlorination product was highly unstable upon isolation. We therefore opted to protect the cyclic amine as its benzenesulfonamide to establish orthogonality within the route (Scheme 2).

Scheme 2. Pd/C-Catalyzed Hydrogenolysis/Fragmentation



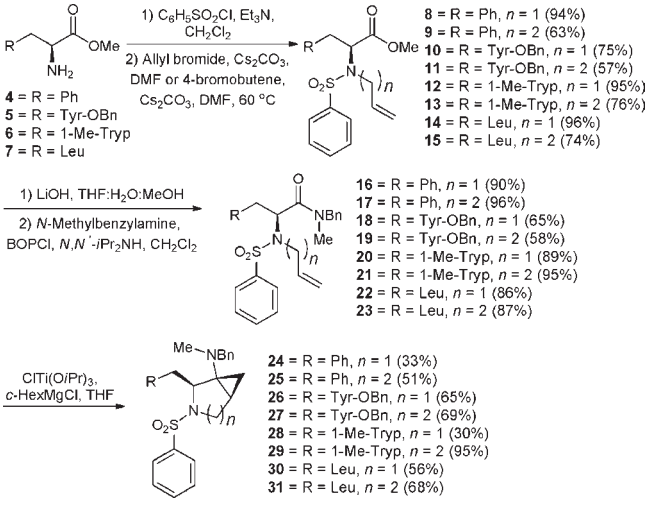
Upon synthesis of bicyclic [3.1.0]aminocyclopropane sulfonamide (**1**) using previously reported methods[3] with minor changes in amine protecting group, we turned our attention to hydrogenolysis of the benzylamine in order to proceed with *N*-chlorination. Palladium-on-carbon catalyzed hydrogenolysis of benzylamines is generally known to be slow compared to hydrogenolysis of benzyl ethers, but in the presence of a protic acid, this process can be expedited. Thus, treatment of **1** with 10% Pd/C in the presence of formic acid under a hydrogen atmosphere provided the debenzylated product, but to our surprise, the ring-opening of the aminocyclopropane also occurred predominantly to afford piperidinone derivative **3** in synthetically useful yield (Scheme 2).

(11) Schulte-Wülwer, I. A.; Helaja, J.; Gottlich, R. *Synthesis* **2003**, 1886.

The ring-opening presumably occurs via debenzylation followed by protonation of the cyclopropane ring and subsequent hydrolysis of the intermediate imine to the ketone.

Based on this fortuitous result, we synthesized a variety of azabicyclic [3.1.0]- and [4.1.0]aminocyclopropanes using a modified procedure to test the scope of the reaction (Scheme 3).

Scheme 3. Synthesis of 3-Piperidinone and 3-Azepinone Derivatives

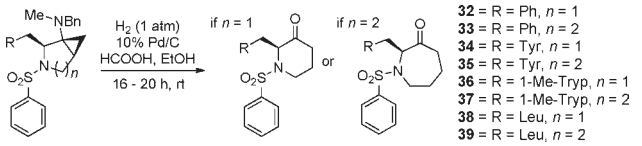


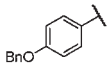
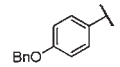
The syntheses of allylsulfonamides ($n = 1$) **8**, **10**, **12**, and **14** generally proceeded in good yield, whereas the homoallylsulfonamides ($n = 2$) were less reactive under the same reaction conditions because of the reduced nucleophilicity of the sulfonamide nitrogen[12] and afforded the product in lower yields but with recovery of starting materials. Other bases such as *n*-BuLi, LiHMDS, and NaH were screened, which resulted solely in the recovery of starting material. Reductive alkylation with allyltributylstannane only afforded starting material, even after prolonged reaction times. Saponification of the methyl ester followed by BOP mediated coupling of the acid and *N*-methylbenzylamine gave **16**−**23** in satisfactory yields considering this difficult coupling (a two-step EDCI mediated coupling and subsequent *N*-methylation procedure could also be utilized to give the desired product). Exposure of the allylsulfonamide or homoallylsulfonamide to stoichiometric ClTi(O-*i*-Pr)$_3$ afforded corresponding aminocyclopropanes in moderate to good yields. For certain homoallylsulfonamide substrates it was necessary to replace ClTi(O-*i*-Pr)$_3$ with MeTi(O-*i*-Pr)$_3$ to obtain the desired product, for the former resulted in no reaction.[13] The general decrease in yield for the synthesis of azabicyclic [3.1.0] ring system compared to that of [4.1.0] system is likely due to increase in ring-strain of five-membered compared to six-membered ring formations. Finally, exposure of the aminocyclopropanes to 10% Pd/C and catalytic amount of formic acid

(12) Bowman, W. R.; Coghlan, D. R. *Tetrahedron* **1997**, *53*, 15787.

(13) Gensini, M.; Kozhushkov, S. I.; Yufit, D. S.; Howard, J. A. K.; Es-Sayed, M.; de Meijere, A. *Eur. J. Org. Chem.* **2002**, *2002*, 2499.

Table 1. Scope of Ring-Opening Reactions of Azabicyclic [3.1.0] and [4.1.0] Kulinkovich Products



entry	R	n	10% Pd/C	HCOOH (equiv.)	yield (%)[a]
1		1	0.1	0.01	65
2		2	0.2	0.01	62
3[b]		1	0.1	0.01	75
4[b]		2	0.1	0.01	76
5		1	0.1	0.01	69
6		2	0.2	0.01	27
7		1	0.1	0.01	64
8		2	0.5	0.01	42
9		1	0.5	0	no product formation[c]
10		1	0	neat	no reaction[d]
11		1	0.1	neat	no reaction[d]

[a] Silica gel chromatography yields. [b] Benzyl ether moiety of tyrosine transformed to afford the corresponding alcohol under the reaction conditions. [c] Reaction time was extended to 48 h. [d] Recovered starting material.

(88% solution) afforded 3-piperidinone and 3-azepinone derivatives in satisfactory yields (Table 1).

When the scope of this interesting ring-expansion methodology was investigated, the presence of catalytic amounts of both palladium and formic acid proved to be essential for the reaction (Table 1). For instance, subjecting the cyclopropylamine to a solution of formic acid resulted in recovery of starting material, proving the need for palladium (entry 10, Table 1). When the cyclopropylamine was subjected under a hydrogen atmosphere with catalytic amount of palladium without the addition of formic acid, only insignificant amount of debenzylated amine was formed over prolonged reaction time (entry 9, Table 1). Furthermore, the importance of catalytic addition of formic acid was evident when the cyclopropylamine was exposed under a hydrogen atmosphere with catalytic amount of palladium in neat formic acid (entry 11, Table 1).

The ring-opening methodology on various azabicyclic [3.1.0] and [4.1.0] substrates proved to be generally acceptable, whereas in some cases the formation of 3-piperidinone is more favorable than 3-azepinone (Table 1). This observation may be due to the well-accepted fact that six-membered ring formations are more favorable than seven-membered ring formations. For instance, 3-azepinone formations of structurally more complex tryptophan and leucine derivatives (entries 6 and 8, Table 1) were relatively unsuccessful in comparison to the respective formations of 3-piperidinone (entries 5 and 7, Table 1).

In conclusion, we have provided a novel method to open bicyclic aminocyclopropanes in good yields under mild reaction conditions to provide a range of 3-piperidinone and 3-azepinone derivatives. The use of a sulfonamide as a protecting group may also provide interesting antimicrobial activities when coupled with the conformationally constrained Kulinkovich products, which we will investigate in due course.

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Supporting Information Available. General methods, experimental procedures, spectroscopic data, and HRMS of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.