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Addition of Tethered Nonaromatic Carbon Nucleophiles to Chemoselectively Activated Amides

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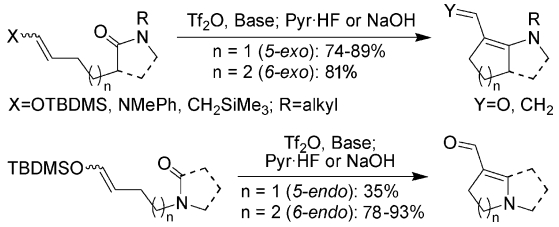
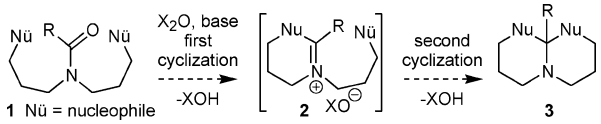
ABSTRACT



In an effort to develop new ways of synthesizing polycyclic alkaloids, we successfully added silyl enol ethers, allylsilanes, and enamines to iminium ions generated from amides. Because of their higher oxidation state, such iminiums show a yet unexploited advantage of potential double cyclizations over standard Mannich monocyclizations. We report herein the first example of tethered nonaromatic carbon nucleophiles adding to activated amides for the generation of enaminals of various ring sizes, with *endo*- or *exo*-cyclic nitrogen.

Numerous efficient approaches to construct biologically active polycyclic alkaloids use intramolecular Mannich addition to an iminium ion.[1] These iminium ions usually bear a carbon of oxidation state II (two *C*-heteroatom bonds), due to the ways they are usually generated,[1b,2] inherently limiting the approach to a monocyclization. Our goal is to exploit a higher level of oxidation state by generating iminium ions from amides.[3] With nucleophiles tethered to the amide (e.g., **1**, Scheme 1), we would have an access to polycyclic alkaloid skeletons in one synthetic step from linear precursors through novel sequential nucleophilic cyclizations on the same amide carbon,[4] thus creating a tertiary (**3**, R = H) or a quaternary (**3**, R = alkyl) center α to nitrogen, as found in the skeleton of a myriad of alkaloids. Since the ways to attach the nucleophiles to the amide are diverse (*C*- and/or *N*-bound), various complex alkaloid skeletons could be prepared, thus

Scheme 1. Representative Example of the Projected Biscyclization on Chemoselectively Activated Amides



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(1) (a) *Iminium Salts in Organic Chemistry*; Böhme, H., Viehe, H. G., Eds.; Wiley: New York, 1976 (part I); 1979 (part 2). (b) Overman, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Heathcock, C. H., Eds; Pergamon: Oxford, 1991; Vol. 2, p 1007.

(2) (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (b) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311.

(3) The next level of oxidation state would be carbamates or ureas. For a precise example using carbamates, see: Magnus, P.; Gazzard, L.; Hobson, L.; Payne, A. H.; Rainey, T. J.; Westlund, N.; Lynch, V. *Tetrahedron* **2002**, *58*, 3423. This work was published while we were already engaged in our studies with amides.

(4) For selected examples of sequential iminium cyclizations, although not performed on the same carbon, see: (a) Jackson, A. H.; Shannon, P. V. R.; Wilkins, D. J. *Tetrahedron Lett.* **1987**, *28*, 4901. (b) He, F.; Bo, Y.; Altom, D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771.

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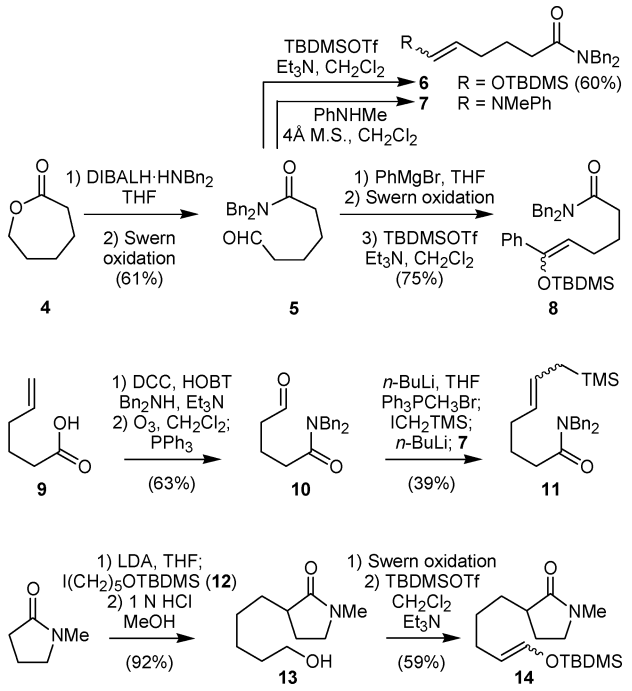
presenting a great versatility through rapid increase of complexity from easily assembled substrates.

The only reported examples of tethered carbon nucleophiles adding to iminium ions generated from amides[5] are either indoles[6] or activated benzene rings.[7] We wanted to find out if tethered nonaromatic carbon nucleophiles would participate in the cyclization. This however presents a serious difficulty: the usual amide activation conditions involve Lewis or Brønsted acids that react with most nucleophiles.[8] This paper summarizes the successful additions of different tethered nonaromatic carbon nucleophiles to activated amides (**1** → **2**). Additionally, this approach is very interesting because it offers an efficient way to generate various enaminals and enaminones known to be especially useful and versatile intermediates for natural product synthesis.[9]

Before attempting the entire bicyclization (**1** → **3**), we opted to set the monocyclization first. To this end, five- and six-membered rings were studied, as they are the most common in the vast majority of alkaloid skeletons. We elaborated a series of model substrates to tackle three different aspects of nucleophilic cyclizations on activated amides: (1) determining the nature of the nucleophiles that could trap the activated amides, (2) comparing five- and six-membered ring closures, and (3) investigating *endo* and *exo* types of cyclization. Both amides and lactams have been looked at, since they generate mono- or bicyclic adducts.

The syntheses of 5- and 6-*exo* cyclization[10] substrates started with the ring opening of ϵ-caprolactone (**4**) with a DIBALH−dibenzylamine complex,[11] followed by a Swern oxidation to furnish the aldehyde **5** (Scheme 2). The latter was treated either with TBDMSOTf to give the corresponding silyl enol ether **6** or with methyl aniline to lead to enamine **7**.[12]

Scheme 2. Syntheses of 5- and 6-*exo* Cyclization Substrates



Silyl enol ethers from ketones were also investigated. We prepared the phenyl ketone silyl enol ether **8**[13] by adding phenylmagnesium bromide to the aldehyde **5**, followed by a Swern oxidation and silylation. We also extended our study to other types of nucleophiles. The allylsilane **11** was thus synthesized in three steps from commercially available carboxylic acid **9**, which was coupled with dibenzylamine, ozonized and olefinated.[14] Finally, a 6-*exo* cyclization model substrate (**14**) was built by addition of the iodosilyl ether branch **12**[15] to *N*-methylpyrrolidinone enolate, followed by methanolysis of the silyl ether, oxidation and silylation.

Endo types of cyclizations were also investigated. N-Alkylation of pyrrolidinone with iodides **15**[16] or **12** followed by the usual sequence furnished the 5-*endo* and 6-*endo* cyclization precursors **18** and **19** (Scheme 3). A formamide substrate **22** was also prepared using the usual route.

Scheme 3. Syntheses of 5- and 6-*endo* Cyclization Substrates

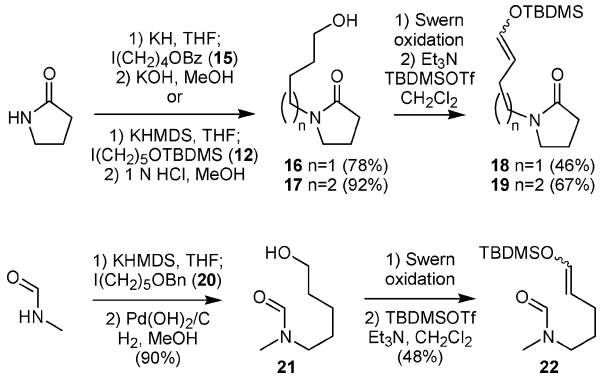


Table 1 shows the variety of nucleophiles that all gave 5-*exo* cyclizations upon amide activation. Among the as-

(5) For addition of heteroatomic nucleophiles to activated amides, see: (a) Charette, A. B.; Chua, P. *Synlett* **1998**, 163. (b) Charette, A. B.; Chua, P. *Tetrahedron Lett.* **1997**, *38*, 8499. (c) Charette, A. B.; Chua, P. *J. Org. Chem.* **1998**, *63*, 908. (d) Charette, A. B.; Grenon, M. *Tetrahedron Lett.* **2000**, *41*, 1677. (e) Sforza, S.; Dossena, A.; Corradini, R.; Virgili, E.; Marchelli, R. *Tetrahedron Lett.* **1998**, *39*, 711. (f) Thomas, E. W. *Synthesis* **1993**, 767. (g) Smith, D. C.; Lee, S. W.; Fuchs, P. L. *J. Org. Chem.* **1994**, *59*, 348.

(6) Typically the Bischler−Napieralski cyclization: Bischler, A.; Napieralski, B. *Chem. Ber.* **1893**, *26*, 903.

(7) (a) Marson, C. M. *Tetrahedron* **1992**, *48*, 3659. (b) Martinez, A. G.; Alvarez, R. M.; Barcina, J. O.; Cerero, S. M.; Vilar, E. T.; Fraile, A. G.; Hanack, M.; Subramanian, L. R. *J. Chem. Soc., Chem. Commun.* **1990**, 1571.

(8) For various amide activation conditions, see references cited in ref 5g and in: Kuhnert, N.; Clemens, I.; Walsh, R. *Org. Biomol. Chem.* **2005**, *3*, 1694, See also: Nishiyama, H.; Nagase, H.; Ohno, K. *Tetrahedron Lett.* **1979**, *48*, 4671. Keck, G. E.; McLaws, M. D.; Wager, T. T. *Tetrahedron* **2000**, *56*, 9875.

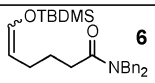
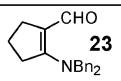
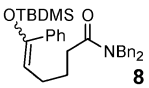
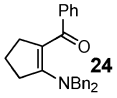
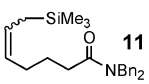
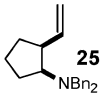
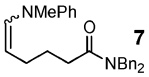
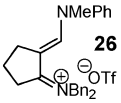
(9) For the use of enaminones in natural product synthesis, see: Michael, J. P.; de Koning, C. B.; Gravestock, D.; Hosken, G. D.; Howard, A. S.; Jungmann, C. M.; Krause, R. W. M.; Parsons, A. S.; Pelly, S. C.; Stanbury, T. V. *Pure Appl. Chem.* **1999**, *71*, 979.

(10) The use of *exo* and *endo* in this manuscript refers to the amide portion of the substratres. For a more appropriate description of cationic cyclizations involving π-nucleophiles, see: (a) Ben-Ushai, D. *J. Chem. Soc., Chem. Commun.* **1980**, 687. (b) Lochead, A. W.; Proctor, G. R.; Caton, M. P. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2477.

(11) Huang, P.-Q.; Zheng, X.; Deng, X.-M. *Tetrahedron Lett.* **2001**, *42*, 9039.

(12) Enamine **7** was unstable and had to be used without further purification in the cyclization step.

Table 1. 5-*exo* Cyclizations of Various Tethered Nucleophiles on Activated *N*,*N*-Dibenzylamides

entry	substrate	activation condition[a]	product	quench (overall yield)[b]
1	 **6**	**A**	 **23**	Pyr·HF[c] (85%)
2	 **8**	**A**	 **24**	1 N NaOH[d] (80%)
3	 **11**	**A**	 **25**	$NaBH(OAc)_3$[e] (81%)
4	 **7**	**B**	 **26**	concentrate (74% from **5**)[f]

[a] Activation conditions: (A) Tf_2O (1.1 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (1.1 equiv), CH_2Cl_2, 0 °C, 20 min; (B) Tf_2O (2.5 equiv), $^iPr_2NEt$ (3.0 equiv), $CHCl_3$, 0 °C, 20 min. [b] Yields of isolated product. [c] Pyr·HF, 0 °C, 20 min. [d] Concentrated and then diluted in 1 N NaOH, THF, 25 °C, overnight. [e] $NaBH(OAc)_3$, −78 °C to rt, overnight. An inseparable 94:6 mixture of *Z*/*E*-**25**, respectively, as established by nOe. [f] Concentrated and then purified directly.

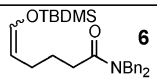
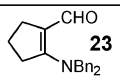
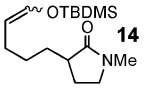
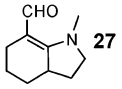
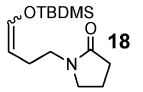
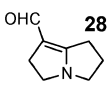
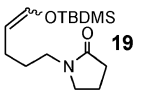
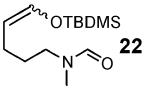
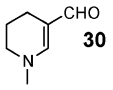
sortment of amide activating agents we surveyed, triflic anhydride (Tf_2O) is the reagent of choice and gave reproducible results with all of the substrates tested. $POCl_3$ and triphosgene led to the cleavage of the silyl enol ethers (the corresponding aldehydes were recovered), whereas TMSOTf and TFAA gave undesired side products.

The amide activation with Tf_2O was always completed within 20 min at 0 °C[17] in the presence of 2,6-di-*tert*-butyl-4-methylpyridine or di-isopropylethylamine to prevent the generation of triflic acid. These rather mild conditions were tolerated by TBDMS enol ethers from aldehydes or from ketones (Table 1, entries 1 and 2 respectively), as well as by allylic trimethylsilane (entry 3) and *N*-methyl-*N*-phenylenamine (entry 4). The aldehyde TBDMS enol ether **6** gave the highest yield, cyclizing in 85% yield (entry 1). The phenyl ketone analogue **8** was also successfully cyclized even though the yields were slightly lower (entry 2 versus 1), presumably because of a higher steric congestion developed during cyclization. When the allylsilane **11** was cyclized (entry 3), a reductive quench ($NaBH(OAc)_3$) was necessary, since the iminium ion resulting from the cyclization was not stable.[18] An overall yield of 81% was obtained for the cyclization−reduction sequence.

Finally, upon activation of amide **7**, we were able to isolate and characterize the vinylogous amidinium ion **26**. As the conversion of aldehyde **5** to enamine **7** was estimated at 80−85%[17] and the overall yield of **26** from aldehyde **5** is 74%, the cyclization yield from **7** to **26** is evaluated at around 85%. This means that silyl enol ethers, allylsilanes, and enamines add to activated amides with comparable ease and yields under mild conditions.

The Pyr·HF (or NaOH as found in Table 2)[19] quench is essential to cleave the TBDMS group still attached to the carbonyl when enol ethers were cyclized.[17] Such a detail is highly important: regardless of the tethered nucleophile used, there is always an activated species in solution before quenching the reaction.

Table 2. 5-*exo*, 6-*exo*, 5-*endo*, and 6-*endo* Cyclizations of Tethered TBDMS Enol Ethers on Activated Amides and Lactams[a]

entry	substrate	cyclization type	product	quench (overall yield)[b]
1	 **6**	5-*exo*	 **23**	1 N NaOH[c] (89%)
2	 **14**	6-*exo*	 **27**	Pyr·HF[d] (81%)
3	 **18**	5-*endo*	 **28**	1 N NaOH[c] (35%)
4	 **19**	6-*endo*	 **29**	1 N NaOH[c] (93%)
5	 **22**	6-*endo*	 **30**	1 N NaOH[c] (78%)

[a] Activation conditions: Tf_2O (1.1 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (1.1 equiv), CH_2Cl_2, 0 °C, 20 min. [b] Yields of isolated product. [c] Concentrated and then diluted in 1 N NaOH, THF, 25 °C, overnight. [d] Pyr·HF, 0 °C, 20 min.

A study comparing ring sizes as well as *endo* and *exo* cyclizations was also performed with aldehyde silyl enol ethers. The 5-*exo* and the 6-*endo* cyclizations of alkylamides **6** and **19** gave the highest yields (Table 2, entries 1 and 4 respectively), followed by the 6-*exo* cyclization of **14** (entry 2). As expected, the 5-*endo* cyclization of substrate **18** was quite difficult, which is in accordance with the Baldwin rules,[10,20] but nonetheless successful (35% yield, entry 3). Surprisingly, the 6-*endo* cyclization of the less congested iminium ion upon formamide **22** activation gave lower conversion than the cyclization of pyrrolidinone **19**. This could be due to a lower stability of the iminium ion derived from **22**.

In summary, we demonstrated for the first time that activated amides could be trapped with various tethered nonaromatic carbon nucleophiles very efficiently. The resulting enaminals cover a wide range of skeletons of various

(13) The phenyl was essential since we had to control on which side the ketone would enolize during the final silyl enol ether preparation.
(14) Fleming, I.; Paterson, I. *Synthesis* **1979**, 446.
(15) Deng, Y.; Salomon, R. C. *J. Org. Chem.* **1998**, *63*, 3504.
(16) Ott, M. M.; Little, R. D. *J. Org. Chem.* **1997**, *62*, 1610.
(17) As observed by ^1H NMR.
(18) The resulting iminium ion after the cyclization was not conjugated with the remaining alkene according to ^1H NMR spectroscopy, presumably because of high allylic strain resulting from conjugation.
(19) The quench procedure has a crucial influence on the cyclization yield that we do not yet fully understand. Investigation in that direction is underway and will be published in due course.
(20) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.

ring sizes containing either an *endo*- or *exo*-cyclic nitrogen. The alkenes of the enaminals are either tetra- or trisubstituted depending on whether the initial amide carbonyl was alkylated or not. Ultimately, upon double nucleophilic additions, related systems (such as **1**, Scheme 1) could lead to quaternary or tertiary centers α to nitrogen (such as **3**). Moreover, we also demonstrated that the intermediates obtained before quenching of the cyclization reaction were still iminium ions, thus conferring optimistic perspective to our planned biscyclization with two nucleophilic moieties tethered to the amide. Work in that direction is currently in progress.

Acknowledgment. We thank Ghislain Boucher for his early work on this project. This research was supported by the Natural Science and Engineering Research Council (NSERC) of Canada, FQRNT (Québec), the Canadian Fund for Innovation (CFI), and the Université de Sherbrooke. NSERC doctoral fellowship to R.L.-G. and NSERC predoctoral fellowship to F.B. are also gratefully acknowledged.

Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra for compounds **5**−**8**, **10**, **11**, **13**, **14**, **16**−**19**, and **21**−**30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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