Rearrangements

DOI: 10.1002/anie.200906416

Unexpected Electrophilic Rearrangements of Amides: A Stereoselective Entry to Challenging Substituted Lactones**

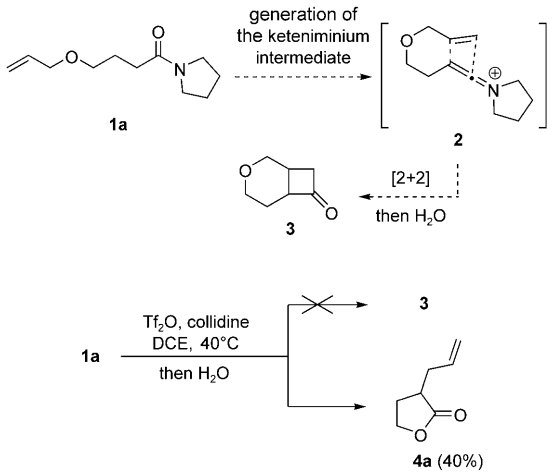
*Claire Madelaine, Viviana Valerio, and Nuno Maulide**

Ever since the original preparation of ketenes and their successful [2+2] cycloaddition with imines reported by Staudinger in 1907,[1] heterocumulenes and their pericyclic reactions have attracted considerable attention. In the latter part of the 20th century, Ghosez and co-workers pioneered the use of keteniminium salts as attractive alternatives to ketenes for cycloadditions with alkenes to give cyclobutanones.[2] Indeed, keteniminium salts are more electrophilic than ketenes, show no tendency towards dimerization, and can be prepared readily by treatment of an amide with collidine and triflic anhydride.[3] In spite of their tremendous potential as easily accessible, highly electrophilic reagents, keteniminium salts generated from tertiary amides have hardly been explored beyond the context of [2+2] cycloadditions.[4]

We became interested in the chemistry of keteniminium salts as part of a research program aimed at the total synthesis of a natural product. Having identified bicyclobutanone **3** (Scheme 1) as a pivotal intermediate in our plan, we envisioned its direct preparation from amide **1a** through a [2+2] cycloaddition of the keteniminium intermediate **2**. In the event, treatment of γ-allyloxyamide **1a** with triflic anhydride and collidine in dichloroethane did not lead to the anticipated product **3**. We were instead surprised to observe the exclusive formation of α-allylbutyrolactone **4a**, after hydrolytic workup, in 40% yield (Scheme 1).

The unexpected skeletal reorganization and the complete absence of any cyclobutanone product in the crude mixture triggered our interest. Furthermore, the observed O-to-C allyl transfer suggested an intermediary [3,3] sigmatropic rearrangement, and the inherent potential of such reactions in the present context decisively warranted further inspection. We present herein an unprecedented "Claisen[5,6]-like" rearrangement of keteniminium salts allowing direct and stereoselective access to challenging substituted lactones.

Systematic variation of the reaction parameters quickly revealed that chlorinated solvents are optimal (Table 1, entries 1–5 and 8). Among the amine bases tested, collidine afforded the best results (Table 1, entries 8–10), whilst triflic anhydride proved to be the most suitable activating agent (Table 1, entries 5 and 6). In accordance with a high energy barrier to the formation of the keteniminium intermediate, higher yields were obtained at temperatures close to reflux (Table 1, entries 5 and 7). Microwave irradiation also proved beneficial; the optimal protocol thus entails microwave irradiation of the reaction mixture in dichloromethane for only 5 min, followed by simple hydrolytic workup with aqueous bicarbonate solution. Under these conditions, α-



Scheme 1. Planned synthesis of compound **3** and unexpected observations. DCE = dichloroethane, Tf = trifluoromethanesulfonate, collidine = 2,4,6-trimethylpyridine.

Table 1: Optimization of the synthesis of **4a** from **1a**[a]

Entry	Solvent	Base	*T* [°C]	Yield of **4a** [%]
1	THF	collidine	40	–
2	pyridine	collidine	40	–
3	toluene	collidine	40	35
4	MeCN	collidine	40	25
5	DCE	collidine	40	40[b]
6	DCE	collidine	40	–[c]
7	DCE	collidine	80	51[b]
8	DCM	collidine	40	55[b]
9	DCM	*i*Pr_2NEt	40	10
10	DCM	DTBMP	40	23
11	DCM	collidine	120[d]	90[b]

[a] All reactions were conducted with 1.2 equivalents of base and 1.05 equivalents of Tf_2O under the reported conditions. Yields were estimated by ^1H NMR analysis unless indicated otherwise. [b] Yield of isolated product. [c] Oxalyl chloride was used instead of Tf_2O. [d] Microwave irradiation for 5 min. DTMBP = 2,6-di-*tert*-butyl-4-methylpyridine.

[*] Dr. C. Madelaine, V. Valerio, Dr. N. Maulide
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 45470 Mülheim (Germany)
Fax: (+49) 208-306-2999
E-mail: maulide@mpi-muelheim.mpg.de
Homepage: http://www.kofo.mpg.de/maulide

[**] This work was supported financially by the Deutsche Forschungsgemeinschaft (grant MA4861/1-1). We are grateful to the Max-Planck Society and the Max-Planck Institut für Kohlenforschung for generous funding of our research programs. Dr. C. Wirtz is kindly acknowledged for skillful NMR assistance.

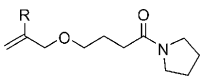
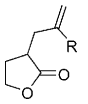
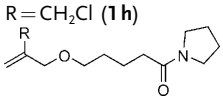
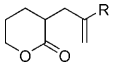
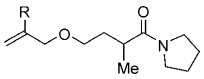
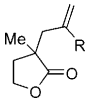
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200906416.

allylbutyrolactone **4a** was generated in an excellent 90% yield. It is worth mentioning that during this optimization we never detected even traces of the [2+2] cycloadduct **3** or related isomers.

Applying the optimized conditions for this skeletal rearrangement, we then proceeded to examine its scope and functional-group tolerance (see Table 2). A wide variety of allyloxyamides could be converted into the corresponding lactones in good to excellent yields. Ester, nitrile, and halide functionalities are well tolerated, and oxygenated substrates were also amenable to this reaction (Table 2, entries 3–8). Isomeric [2+2] cycloaddition products were never detected in the crude mixtures. This suggests that the electronic properties of the allyl moiety do not affect the reaction. It is interesting to note that the length of the tether could be increased with only a slight decrease in yield (Table 2, entry 9). Moreover, this reaction has the potential to generate products containing all-carbon-substituted quaternary centers (Table 2, entries 10 and 11).

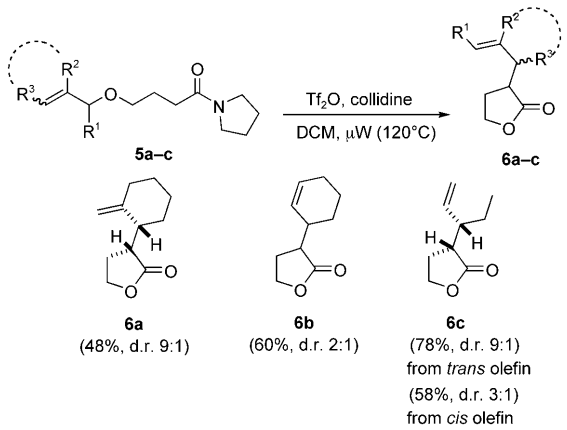
Table 2: Scope of the rearrangement reaction.[a]

1a–k **4a–k**

Entry	Substrate	Product	Yield [%][b]
			
1	R = H (**1a**)	**4a**	90
2	R = Me (**1b**)	**4b**	61[c]
3	R = CO_2Et (**1c**)	**4c**	78
4	R = CH_2OMe (**1d**)	**4d**	50
5	R = CH_2OAc (**1e**)	**4e**	54
6	R = CN (**1f**)	**4f**	65
7	R = Br (**1g**)	**4g**	33
8	R = CH_2Cl (**1h**)	**4h**	75[d]
			
9	R = H (**1i**)	**4i**	57
			
10	R = H (**1j**)	**4j**	50
11	R = CO_2Et (**1k**)	**4k**	49

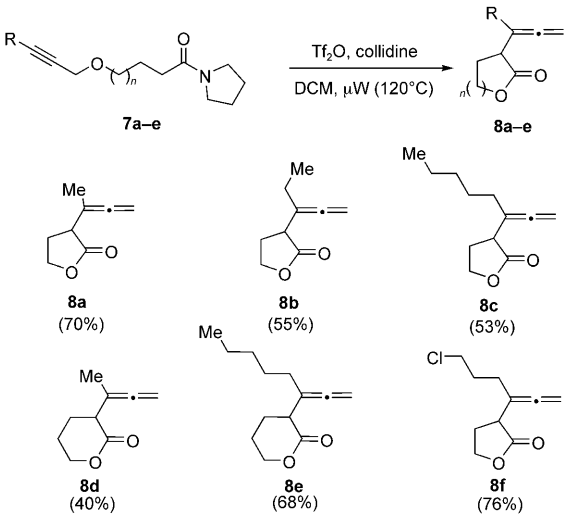
[a] All reactions were conducted with 1.2 equivalents of base and 1.05 equivalents of Tf_2O unless otherwise noted. [b] Yield of isolated product. [c] 3 equivalents of base used. [d] 1.5 equivalents of Tf_2O used.

Having realized that this unusual reaction is indeed general, we proceeded to probe substrates containing more challenging allyl moieties. Since the starting allyloxyamides are accessible by simple allylation of the corresponding hydroxy derivatives, a range of substrates could be synthesized readily (Scheme 2).[7] In the event, lactones bearing branched allyl substitutents in the α position were generated as the exclusive reaction products—a consequence of the allyl inversion expected from a [3,3] sigmatropic shift.[8,9] More importantly, high diastereoselectivities were observed in most cases.[10] For instance, our system is able to effectively differentiate between ethyl and vinyl substituents as in product **6c**, and easily generate nearly diastereopure lactone **6a**. Both of these products would be almost impossible to prepare by direct alkylation of the corresponding allylic halides. It is therefore not surprising that such simple compounds are, to the best of our knowledge, unknown in the chemical literature.



Scheme 2. Results with differently substituted allyl moieties.

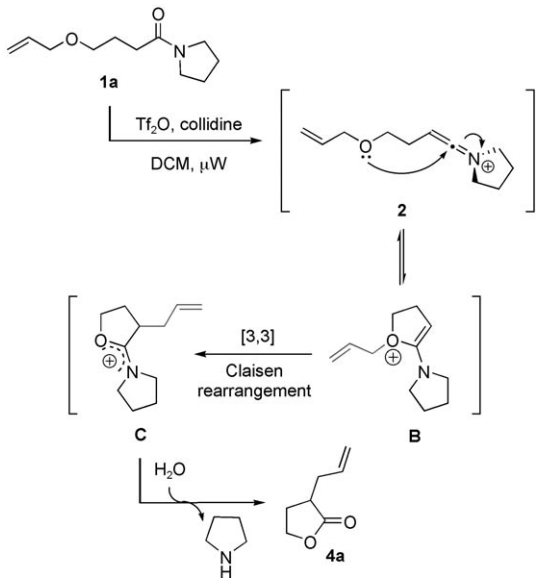
At this juncture, we became intrigued with the possibility of extending the substrate scope to propargyl ethers. The preparation of allenes through the thermal, metal-free [3,3] sigmatropic rearrangement of alkynes is known to be difficult.[11,12] We thus awaited the outcome of the reaction of propargyl ether **7a** with some trepidation (Scheme 3). In the event, alkyne **7a** smoothly rearranged to α-allenyl lactone **8a** in an excellent yield for such a challenging transformation. Neither the isomeric propargylated butyrolactone nor [2+2] cycloadducts were detected in the reaction mixture. As can be further inferred from Scheme 3, this reaction also appears



Scheme 3. Synthesis of α-allenyl lactones.

quite general with respect to the acetylenic component. In each case, the crude reaction mixtures are extremely clean and the allenes are the only products detected; only their pronounced volatility precluded higher yields of isolated products. To our knowledge, all of these products were hitherto unknown in the chemical literature. Indeed, and despite their apparent structural simplicity, straightforward routes to such compounds are not particularly easy to conceive.

Our mechanistic rationale for this transformation is depicted in Scheme 4. After initial activation of the amide

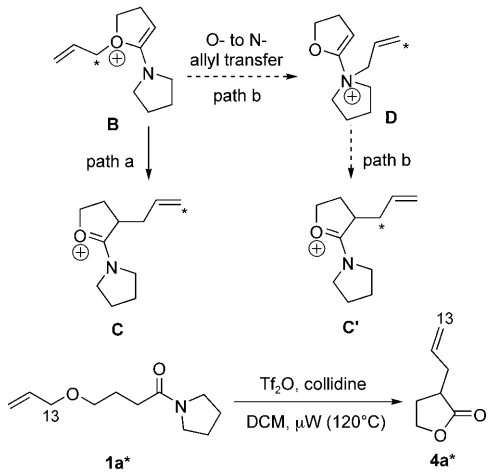


Scheme 4. Proposed reaction mechanism.

carbonyl by the electrophilic reagent, elimination to form keteniminium **2** probably takes place. The enhanced electrophilicity of this intermediate then triggers an unusual nucleophilic attack of the ether, which may be reversible. This addition, however, generates a vinyl allyl oxonium intermediate **B**. Such a species should be ideally poised to undergo a "Claisen-like" [3,3]-sigmatropic rearrangement, leading to the stabilized carbenium ion **C**, hydrolysis of which then accounts for the formation of lactone **4a**. From a mechanistic point of view, this reaction is reminiscent of the Claisen–Eschenmoser–Ficini–Bellus rearrangements.[13–16] However, and in stark contrast to the latter, the reactive intermediates herein are generated from stable, easily handled amides under essentially neutral conditions.

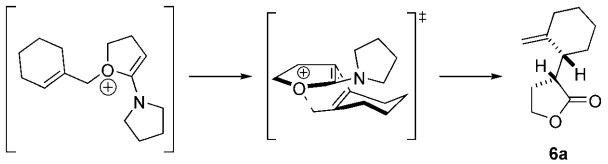
From the outset, we were aware of possible, alternative mechanisms to account for the transfer of the allyl moiety (Scheme 5). Two such mechanisms in particular appeared plausible: a direct or stepwise 1,3-allyl migration (not shown) and a nitrogen-assisted allyl transfer proceeding via a quaternary allylammonium species **D** (path b in Scheme 5).[17] For geometric reasons, the latter process should take place with double allylic inversion.

Our results with substrates having more complex allyl (and propargyl) residues already strongly argue against such a



Scheme 5. Unambiguous distinction between allyl transfer pathways in the rearrangement of **1a**.

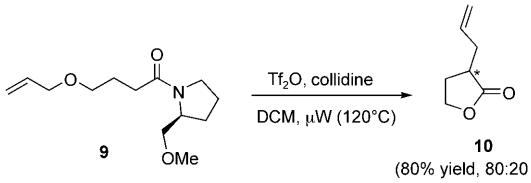
mechanistic scenario. Further evidence in support of the direct [3,3] shift was obtained in experiments with the ^{13}C-labeled allyl ether **1a*** (Scheme 5). Upon rearrangement, the lactone **4a*** bearing the label exclusively at the unsaturated terminus of the allyl group was obtained as the only reaction product (NMR analysis of the crude reaction mixture).[7] This unambiguous result lends further support to a direct "Claisen-like" sigmatropic rearrangement (Scheme 5, path a). Based on such a mechanistic rationale, we propose that the highly stereoselective reorganization of substrates **5a** and **5c** proceeds through a boatlike transition-state structure (Scheme 6), in order to minimize eclipsing interactions between the allyl substituent(s) and the dihydrofuran ring.[10]



Scheme 6. Mechanistic proposal for diastereoselectivity.

Finally, we evaluated a possible asymmetric version (Scheme 7). Our initial results were promising: the reaction of the readily available chiral amide **9** led to lactone **10** in high yield and 80:20 e.r.[7,18] This preliminary result opens up exciting vistas for this chemistry.

In summary, we have developed an efficient synthesis of challenging substituted lactones of different ring sizes. This



Scheme 7. Preliminary experiments towards an asymmetric variant.

unprecedented "Claisen-like" rearrangement draws from the high electrophilicity of keteniminium derivatives and completely disrupts their well-known propensity to undergo [2+2] cycloaddition reactions with olefins. The reaction proceeds under essentially neutral conditions and tolerates a variety of useful functionalities. Furthermore, it allows the generation of all-carbon quaternary centers, as well as the stereoselective formation of conjugate C–C bonds and (perhaps most strikingly) α-allenyl lactones; most of the compounds reported herein would be very difficult to access by other routes. Evidence in support of a [3,3]-sigmatropic mechanism has been garnered. Additionally, promising results indicate the potential for the development of an asymmetric version. Efforts aimed at broadening the scope of this methodology, elucidating mechanistic intricacies, and developing highly enantioselective asymmetric versions are currently underway in our laboratories.

Received: November 13, 2009
Published online: February 2, 2010

Keywords: Claisen rearrangement · keteniminium ions · lactones · rearrangement · stereoselective synthesis

[1] H. Staudinger, *Justus Liebigs Ann. Chem.* **1907**, *356*, 51.
[2] For leading references from the Ghosez group, see: a) L. Ghosez, J. Marchand-Brynaert, in *Iminium Salts in Organic Chemistry*, *Part 1* (Eds.: H. Böhme, H. G. Viehe), Wiley, New York, NY, **1976**, pp. 421; b) J.-B. Falmagne, J. Escudero, S. Taleb-Sahraoui, L. Ghosez, *Angew. Chem.* **1981**, *93*, 926; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 879; c) L. Ghosez, I. Marko, A.-M. Hesbain-Frisque, *Tetrahedron Lett.* **1986**, *27*, 5211; d) C. Schmit, J. B. Falmagne, J. Escudero, H. Vanlierde, L. Ghosez, *Org. Synth.* **1990**, *69*, 199; e) C. Genicot, B. Gobeaux, L. Ghosez, *Tetrahedron Lett.* **1991**, *32*, 3827.
[3] For a review on keteniminium chemistry, see: a) B. B. Snider, *Chem. Rev.* **1988**, *88*, 793. For further examples, see: b) B. B. Snider, R. A. H. F. Hui, *J. Org. Chem.* **1985**, *50*, 5167.
[4] For a Pictet–Spengler cyclization of a keteniminium salt, see: Y. Zhang, R. P. Hsung, X. Zhang, J. Huang, B. W. Slafer, A. Davis, *Org. Lett.* **2005**, *7*, 1047.
[5] L. Claisen, *Chem. Ber.* **1912**, *45*, 3157.
[6] For reviews, see: a) G. B. Bennett, *Synthesis* **1977**, 589; b) F. E. Ziegler, *Chem. Rev.* **1988**, *88*, 1423; c) S. Blechert, *Synthesis* **1989**, 71; d) U. Nubbemeyer, *Synthesis* **2003**, 961; e) A. M. Martin Castro, *Chem. Rev.* **2004**, *104*, 2939. See also: f) *The Claisen Rearrangement: Methods and Applications* (Eds.: M. Hiersemann, U. Nubbemeyer), Wiley-VCH, Weinheim, **2007**, and references therein.
[7] See the Supporting Information for details.
[8] In contrast to other related reactions: a) A. Fürstner, H. Szillat, F. Stelzer, *J. Am. Chem. Soc.* **2000**, *122*, 6785; b) A. Fürstner, F. Stelzer, H. Szillat, *J. Am. Chem. Soc.* **2001**, *123*, 11863.
[9] Y.-J. Li, Y.-K. Chang, G.-M. Ho, H.-M. Huang, *Org. Lett.* **2009**, *11*, 4224.
[10] For further discussion of the diastereoselectivity of this reaction and additional experiments, see the Supporting Information.
[11] For a metal-catalyzed propargyl-Claisen rearrangement, see: B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 15978.
[12] M. O. Frederick, R. P. Hsung, R. H. Lambeth, J. A. Mulder, M. R. Tracey, *Org. Lett.* **2003**, *5*, 2663.
[13] a) J. Ficini, C. Barbara, *Tetrahedron Lett.* **1966**, *7*, 6425; b) J. Ficini, N. Lumbroso-Bader, J. Pouliquen, *Tetrahedron Lett.* **1968**, *9*, 4139; c) P. A. Bartlett, W. F. Hahne, *J. Org. Chem.* **1979**, *44*, 882.
[14] A. E. Wick, D. Felix, K. Steen, A. Eschenmoser, *Helv. Chim. Acta* **1964**, *47*, 2425.
[15] J. A. Mulder, R. P. Hsung, M. O. Frederick, M. R. Tracey, C. A. Zificsak, *Org. Lett.* **2002**, *4*, 1383.
[16] a) R. Malherbe, G. Rist, D. Bellus, *J. Org. Chem.* **1983**, *48*, 860; b) J. Gonda, *Angew. Chem.* **2004**, *116*, 3600; *Angew. Chem. Int. Ed.* **2004**, *43*, 3516, and references therein. For other mechanistically related reactions, see e.g.: c) D. J. Pollart, H. W. Moore, *J. Org. Chem.* **1989**, *54*, 5444.
[17] A reviewer suggested an alternative possible scenario: the formation of a triflyl-enamine and its subsequent intramolecular attack onto the allyl (or propargyl) moiety in S_N2' fashion, followed by cyclization of the resulting alcohol. We believe that the implied seven- or eight-membered-ring transition-state structure for the S_N2' attack might be considerably higher in energy than the rationale presented herein.
[18] To our knowledge, the only alternative reported synthesis of enantioenriched (ca. 85:15 e.r.) **10** entails five steps from commercially available substances: A. I. Meyers, E. D. Mihelich, *J. Org. Chem.* **1975**, *40*, 1186.

