MECHANISTIC INVESTIGATION OF AN INTRAMOLECULAR REARRANGEMENT IN A HETEROCYCLIC ALLYLOXY IMINIUM COMPOUND

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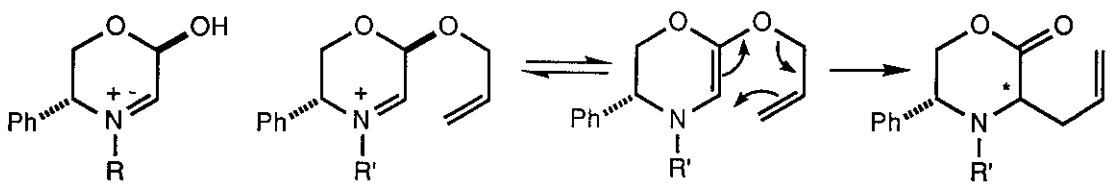
Abstract - A new rearrangement involving an ene iminium system derived from a homochiral 2-allyloxy-3-phenylthiomorpholine is reported.

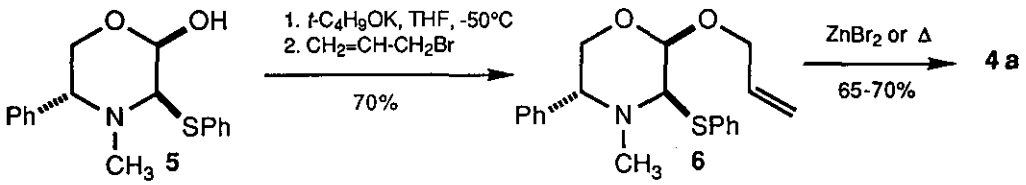
Claisen rearrangements have found widespread use for the stereoselective transformation of organic molecules.[1] The increasing attention being devoted to the application of this process in heterocyclic chemistry is focusing principally in aromatic compounds.[2] Our interest in the synthetic potential of chiral glycine cation equivalents (**1a**) and (**1b**) which have been used respectively in the enantioselective syntheses of acyclic[3] and cyclic[4] α-amino acids led us to investigate the reactivity of iminium ions (**2**). These substrates are well suited for a transformation into the allyloxyenamines (**3**) *via* the classical[5] enamine-iminium ion tautomerism. [3,3]-Sigmatropic rearrangements of compounds (**3**) would thus give access to lactones (**4**) which are precursors of unsaturated α-amino acids.



1a R = CH_3 **2a** R' = CH_3 **3** **4**

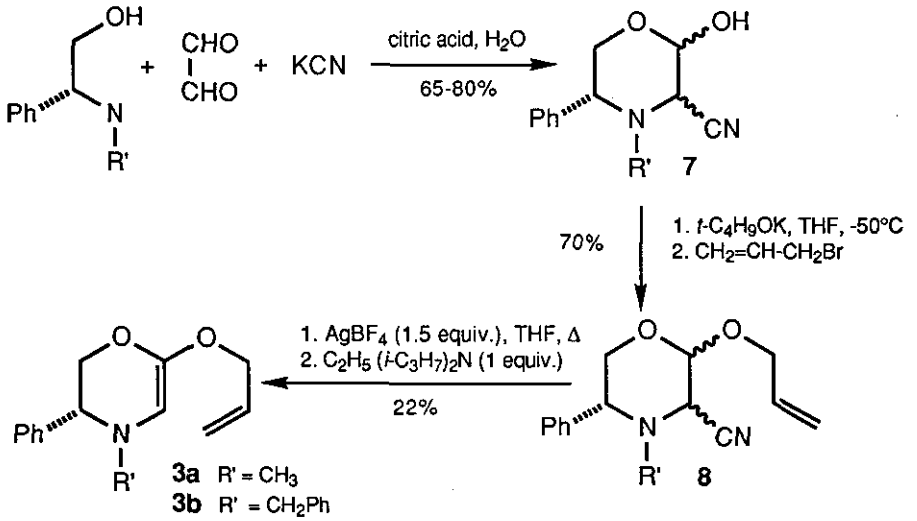
1b R = $CH_2CH_2CH{=}CH_2$ **2b** R' = CH_2Ph

Amino thio ether (**6**) was synthesized from the chiral tetrahydrooxazine (**5**): [6]



Refluxing a THF solution of compound (**6**) in the presence of zinc bromide (1 equiv.)[7] afforded lactone (**4a**) (yield: 65%); comparison of its ^{1}H nmr spectrum with previous data[8] showed that this lactone was formed with a 70% diastereoselectivity in favor of the *trans* isomer.

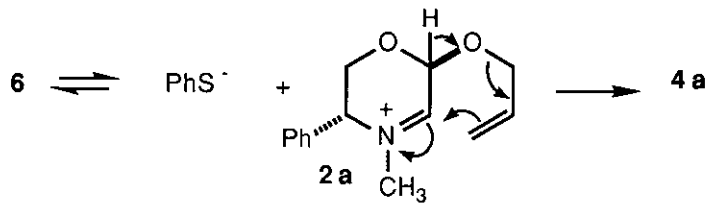
As regards the mechanism of the formation of the lactone (**4a**) from morpholine derivative (**6**), it is clear that iminium ion (**2a**) is involved since amino thio ethers are well-known precursors of such ions. However this transformation may not necessarily imply the enamine (**3a**) as an intermediate. In order to see to it that this really occurs, enamines (**3a**)[9] and (**3b**)[10] were synthesized as depicted on the following scheme: [11]



Unexpectedly, none of these enamines (**3a,b**) yielded the corresponding Claisen-rearranged lactones. These compounds remain unchanged whatever the experimental conditions: refluxing in toluene solution with or without a transition metal catalyst[13] ($PdCl_2(CH_3CN)_2$) or a Lewis acid catalyst[14] ($ZnBr_2$).

Claisen rearrangements of acyclic allyloxyenamines were observed by Barluenga *et al.*,[15] however our substrates actually show an extra enol ether moiety and, in view of the very intricate effects of substituents on Claisen rearrangements,[16] it would be hazardous to rationalize the lack of reactivity of enamines (**3**).

Therefore it appears that an enamine is not implied during the **6** → **4a** transformation. It could be assumed that the iminium ion (**2a**) resulting from (**6**) undergoes an ene-iminium rearrangement as shown below :



The major isomer produced by this reaction, that is *trans* (**4a**), corresponds to an axial attack onto the C=N$^+$ double bond of compound (**2a**). The same *anti* attack in relation to the phenyl group was already observed for the ene-iminium cyclization of substrate (**1b**); it could noted that (**1b**) and (**2a**) essentially differ by the position of the tethered unsaturated chain.

References and notes

1. R. K. Hill, 'Asymmetric Synthesis: Chirality Transfer via Sigmatropic Rearrangements', Vol. 3, ed. by J. D. Morrison, Academic Press, Inc., London, 1984, pp. 503-572.
2. C. J. Moody, 'Advances in Heterocyclic Chemistry: Claisen Rearrangements in Heteroaromatic Systems', Vol. 42, ed. by A. R. Katrizky, Academic Press, Inc., London, 1987, pp. 203-244.
3. C. Agami, F. Couty, B. Prince, and C. Puchot, *Tetrahedron*, 1991, **47**, 4343.
4. C. Agami, F. Couty, M. Poursoulis, and J. Vaissermann, *Tetrahedron*, 1992, **48**, 431.
5. P. W. Hickmott, *Tetrahedron*, 1982, **38**, 3363.
6. C. Agami, F. Couty, L. Hamon, B. Prince, and C. Puchot, *Tetrahedron*, 1990, **46**, 7003.
7. In the absence of $ZnBr_2$, with a protracted reaction time, the amino thio ether (**6**) gave the same ratio of *cis* and *trans* lactones (**4a**) (yield: 70%). It has been checked that no epimerization took place when either *cis* or *trans* (**4a**) were separately treated with zinc bromide.

8. ^{1}H Nmr signals (200 MHz, $CDCl_3$ solution) of the N-CH_3 moiety appear respectively at 2.16 and 2.30 ppm respectively for *cis* and *trans* (**4a**) (see ref.3).

9. ^{1}H Nmr (200 MHz, $CDCl_3$): 2.87 (s, 3H), 3.65 (d, J = 11.7, 1H), 4.1-4.3 (m, 3H), 4.61 (dd, J = 3.8 and 11.7 Hz, 1H), 5.10 (s, 1H), 5.2-5.4 (m,2H), 5.9-6.0 (m, 1H), 7.2-7.4 (m, 5H). ^{13}C Nmr (50 MHz, $CDCl_3$): 33.1, 62.1, 62.7, 69.4, 94.8, 118.1, 126.6, 128.2, 128.8, 133.5, 138.2, 164.6.

10. ^{1}H Nmr (200 MHz, $CDCl_3$): 3.39 (d, J = 14.7 Hz, 1H), 3,62 (d, J = 9.8 Hz, 1H), 4.2-4.3 (m, 3H), 4.44 (dd, J = 3.7 and 11.7 Hz, 1H), 5.20 (s, 1H), 5.25-5.5 (m, 2H), 5.56 (d, J = 14.7 Hz, 1H), 5.9-6.1 (m, 1H), 7.2-7.4 (m, 10H). ^{13}C Nmr (50 MHz, $CDCl_3$): 47.2, 58.4, 63.3, 69.7, 95.0, 118.3, 127.1, 127.8, 128.4, 128.6, 126,8, 129.0, 133.8, 136.2, 138.4, 164.8.

11. The key-step of this sequence is the treatment[12] of the amino nitrile (**8**) with $AgBF_4$ followed by a tertiary amine-mediated deprotonation of the resulting iminium ion.

12. L. Guerrier, J. Royer, D. S. Grierson,and H. P. Husson, *J. Am. Chem. Soc.*, 1983, **105**, 7754.

13. J. L. van der Baan and F. Bickelhaupt, *Tetrahedron Lett.*, 1986, **27**, 6267.

14. K. Maruyama, N. Nagai, and Y. Naruta, *J. Org. Chem.*, 1986, **51**, 5083 and references cited therein.

15. J. Barluenga, F. Aznar, R. Liz, and M. Bayod, *J. Chem. Soc., Chem. Commun.*, 1984, 1427.

16. R. M. Coates, B. D. Rogers, S. J. Hobbs, D. R. Peck, and D. P. Curran, *J. Am. Chem. Soc.*, 1987, **109**, 1160.

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