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Thermal rearrangements of α-(ω-azidoalkyl) enones

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Abstract—The thermal rearrangement of α-(ω-azidoalkyl) enones has been investigated. A variety of these substrates were synthesized and subjected to thermal rearrangement to investigate the scope and generality of their transformation to bicyclic lactams. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Nitrogen heterocycles comprise the vast majority of medicinals on the market today. With this in mind, we began investigations into the scope and mechanism of the thermal rearrangement of α-(ω-azidoalkyl) enones, a reaction that provides ready access to unsaturated bicyclic lactams. To our knowledge, there have been relatively few investigations into the thermal rearrangements of α-(ω-azidoalkyl) α,β-unsaturated enones. Notable exceptions are the studies of Aubé,[1] Schultz,[2] and Sha.[3–5] The rearrangements reported herein provide products that are complementary to those provided by the Lewis acid catalyzed rearrangement described by Aubé[1] and two substrates were investigated that gave different products from those reported by Sha under both disparate and similar conditions (vide infra).

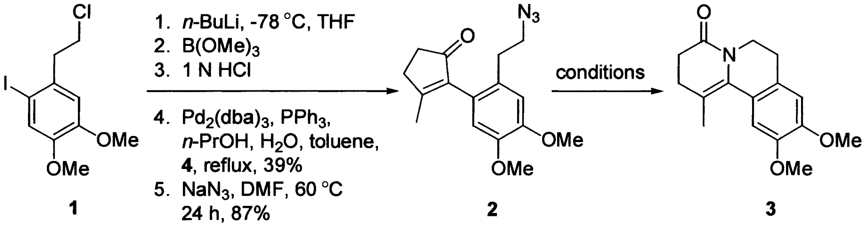
Table 1. Effect of solvent on the thermal rearrangement of **2**

Entry	Conditions	% Isolated yield of **3**
1	DMF, reflux, 15 h	76
2	Xylenes, reflux, 15 h	65
3	DMSO, 145°C, 15 h	45
4	DMSO, 110°C, 48 h	0
5	Neat, 145°C	0

2. Results and discussion

Aromatic α-(ω-azidoalkyl) enone **2** (Eq. (1)) was the first substrate we subjected to thermal rearrangement conditions. We selected this compound based on its similarity to an intermediate that had undergone an analogous thermal rearrangement in our synthetic route to the natural product cephalotaxine.[6] Substrate **2** was synthesized via a Suzuki coupling[7] of known substrates **1** and 2-iodo-3-methylcyclopent-3-en-1-one, **4**, followed by treatment of the coupled alkyl chloride with NaN_3 in DMF.

We initially tested several temperatures and solvents to optimize the reaction conditions for the rearrangement (**2** to **3**, Eq. (1)) as outlined in Table 1. Both DMF and xylenes worked reasonably well. Performing the reactions in DMSO or neat led to dramatic decreases in the



(1)

Keywords: triazoline; rearrangement; α-(ω-azidoalkyl) enone.

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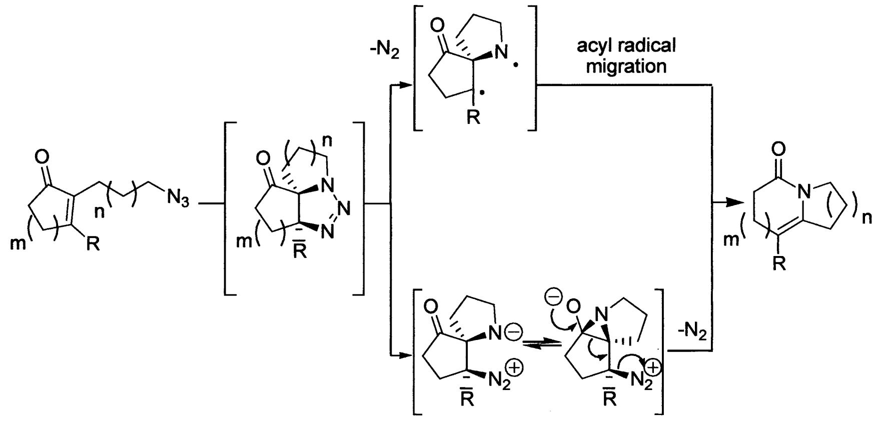


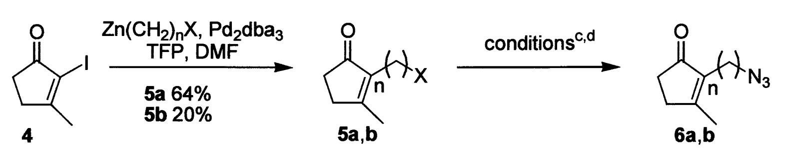
Scheme 1.

yields. Although the yield of the reaction in xylenes was slightly less than the yield of the reaction in DMF, we used xylenes during our subsequent studies because we found the products difficult to separate from DMF.

In previous investigations, Sha had ruled out a nitrene mechanism in these reactions in favor of a 1,3-dipolar mechanism that involved a triazoline intermediate (Scheme 1).[4] During the course of the current investigations, we used React-IR® to follow the disappearance of the azide absorption at about 2100 cm^{-1}, with concomitant formation of an amide carbonyl stretch at 1660 cm^{-1}. On the basis of the NMR experiments of Aubé[1] and the dipolar cycloaddition mechanism put forth by Sha,[4,5] we had expected to observe the appearance of an absorbance at 1620 cm^{-1} corresponding to a transient triazoline.[8] This intermediate could decompose via a diradical process based on acyl radical migration or via a process involving discrete betaine intermediates (Scheme 1).[4,5] However, no absorbance at this frequency was observed during any of the experiments listed in Table 1, indicating that the triazoline, if formed, decomposed immediately on formation under the reaction conditions.

After studying the effect of solvent and temperature on this test substrate, we set out to elucidate the scope of this rearrangement by synthesizing a variety of suitable azides. In general, we synthesized the corresponding alkyl chloride or alkyl mesylate, which yielded the desired substrates upon treatment with NaN_3 in DMF at 60°C. Compounds **5a**,**b** (Eq. (2)) were synthesized according to a previously conveyed protocol.[6] Substrates **8a**–**c** (Eq. (3)) were constructed according to the method of Majetich.[9] Enones **15** and **17** were accessed according to the method of Johnson et al.[10] γ-Substituted enone **23** was prepared by treatment of the corresponding alkyl chloride with NaI in acetone at reflux followed by treatment with NaN_3 in DMF at room temperature. Azide **13** is known[1] and was acquired by adapting the method of Gassman[11] for the preparation of α-substituted α-phenylthiocycloalkanones, followed by oxidation with *m*-CPBA and treatment with NaN_3 in DMF at 60°C. The starting material **25** has been previously reported[4] and was available from ongoing studies in our laboratory.

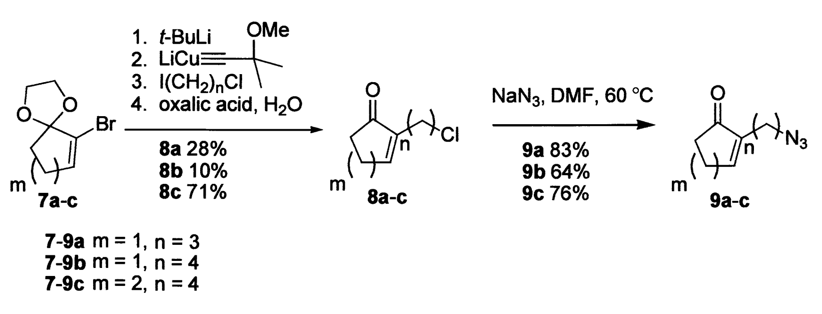
Table 2 summarizes the results of our investigation into the thermal rearrangement of the α-(ω-azidoalkyl)



(2)

5a, **6a** : X = Cl, n = 4
5b, **6b** : X = OTBS, n = 3

c) **6a**: NaN_3, DMF, 60 °C, 95%
d) **6b**: 1. HCl: MeCN 1:5, 85%
2. MsCl, Et_3N, CH_2Cl_2
3. NaN_3, DMF, 60 °C, 80% two steps

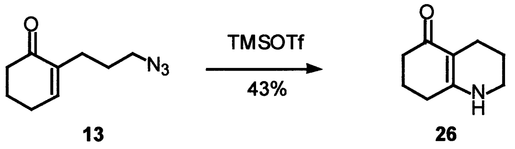


(3)

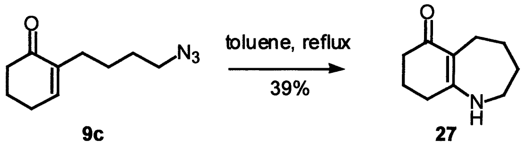
7-9a m = 1, n = 3
7-9b m = 1, n = 4
7-9c m = 2, n = 4

enones. Of special interest are entries 7 and 8, in which the enamide isomerizes, presumably through an iminium ion intermediate. Entry 8 diverges from the reactivity reported by Sha[4] for his thermal rearrangement of **9c** (Eq. (5)). Entry 9 is noteworthy because it reveals that this isomeric triazoline is stable under the reaction conditions. The result in entry 10 complements the investigations of Sha,[3–5] who reported the same product, **26**, but as a minor constituent when the rearrangement was performed in the polar solvents MeOH or DMF. We were not able to isolate any other products during this experiment.

Significant is the fact that the substitution pattern of the resultant products from these thermal rearrangements differs from that obtained by Aubé[1] in his Lewis acid catalyzed rearrangement of **13** (Eq. (4)). In general, the thermal rearrangements produce enamide substrates whose structure can be predicted by the mechanism described previously (Scheme 1). In the specific case where **13** was subjected to the rearrangement conditions (entry 4), we obtained a complex mixture which contained neither **14** nor **26**.



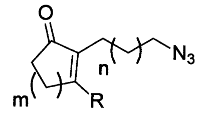
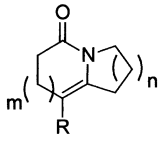
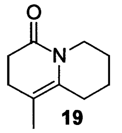
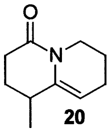
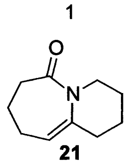
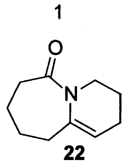
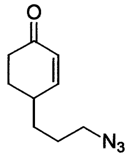
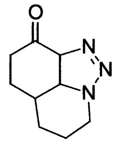
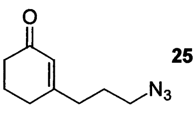
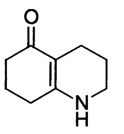
(4)



(5)

In conclusion, the thermal rearrangement of a variety of different α-(ω-azidoalkyl) enones has been performed. The products of these reactions are comple-

Table 2. Thermal rearrangement of α-(ω-azidoalkyl) enones

entry	substrate	product(s)	isolated yield (%)[a]
			
1	R = Me, m = 1, n = 1, **6b**	R = Me, m = 1, n = 1, **10**	80
2	R = H, m = 1, n = 2, **9b**	R = H, m = 1, n = 2, **11**	70
3	R = H, m = 1, n = 1, **9a**	R = H, m = 1, n = 1, **12**	0
4	R = H, m = 2, n = 1, **13**	R = H, m = 2, n = 1, **14**	0
5	R = Me, m = 2, n = 2, **15**	R = Me, m = 2, n = 2, **16**	48
6	R = Me, m = 2, n = 1, **17**	R = Me, m = 2, n = 1, **18**	83
7	R = Me, m = 1, n = 2, **6a**	 **19**  **20** 1 : 1	67
8	R = H, m = 2, n = 2, **9c**	 **21**  **22** 6 : 1	73
9	 **23**	 **24**	83
10	 **25**	 **26**	71

[a]In each case, a 0.10 M solution of substrate in xylenes was heated at reflux for 18-24 h.

mentary to those provided by the Lewis-acid promoted processes previously developed by Aubé. The reaction is of synthetic value, and may be a useful tool in assembling nitrogen heterocyclic intermediates for the total synthesis of natural products.

Acknowledgements

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References

1. Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449.
2. Schultz, A. G. *Adv. Cycloaddition* **1988**, *1*, 53.
3. Sha, C.-K.; Yuang, J.-J.; Ouyang, S.-L. *Heterocycles* **1984**, 566.
4. Sha, C.-K.; Ouyang, S.-L.; Hsieh, D.-Y.; Chang, R.-C.; Chang, S.-C. *J. Org. Chem.* **1986**, *51*, 1490.
5. Sha, C.-K.; Ouyang, S.-L.; Hsieh, D.-Y.; Hseu, T.-H. *Chem. Commun.* **1984**, 492.
6. Molander, G. A.; Hiersemann, M. *Tetrahedron Lett.* **1997**, *38*, 4347.
7. Black, W. C.; Brideau, C.; Chan, C.-C.; Charleson, S.; Chauret, N.; Claveau, D.; Ethier, D.; Gordon, R.; Greig, G.; Guay, J.; Hughes, G.; Jolicoeur, P.; Leblanc, Y.; Nicoll-Griffith, D.; Ouimet, N.; Riendeau, D.; Visco, D.; Wang, Z.; Xu, L.; Prasit, P. *J. Med. Chem.* **1999**, *42*, 1274.
8. Kadaba, P. K.; Stanovnik, B.; Tisler, M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed. Δ^2-1,2,3-Triazolines; Academic Press: Orlando, 1984; Vol. 37, p. 217.
9. Majetich, G.; Leigh, A. J.; Condon, S. *Tetrahedron Lett.* **1991**, *32*, 605.
10. Johnson, W. S. Alkinyl [sic] terminating groups in biogenetic-like cyclizations to steroids. U.S. Patent 4,189,431, August 3, 1977.
11. Gassman, P. G.; Richmond, G. D. *J. Chem. Soc.*, *Perkin Trans. I* **1966**, 2355.