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Conversion of *N*-Acyl-4-acyloxy-β-lactams into 1,3-Oxazin-6-ones: Two Consecutive Pseudopericyclic Processes

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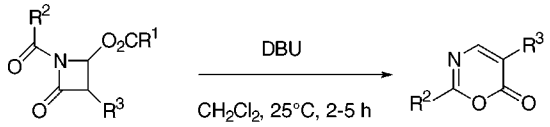
ABSTRACT

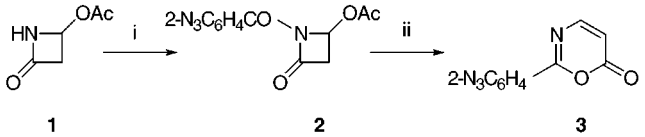


***N*-Acyl-4-acyloxy-β-lactams are converted into 1,3-oxazin-6-ones under basic conditions. This transformation is believed to proceed via *N*-acylazetones, which rearrange to the final products by a sequence of two electrocyclic processes. The calculated (RHF and B3LYP) transition structures of both concerted reactions are shown to present characteristic pseudopericyclic orbital topologies.**

In the course of our recent work on the intramolecular aza-Wittig reaction of the β-lactam carbonyl group,[1] we required a number of *N*-(2-azidobenzoyl)-β-lactams which were prepared by acylation of *N*-unsubstituted β-lactams with 2-azidobenzoyl chloride in the presence of Et_3N. In one of such reactions, that in which the substrate was 4-acetoxy-β-lactam (**1**), we noted the appearance of trace amounts of an unidentified byproduct which seemed to derive from the action of the base (Et_3N) on the acylated lactam **2**, as its relative proportion in the final reaction mixture increased by using more equivalents of base and extended reaction times. Herein we disclose the structure of that byproduct, 2-(2-azidophenyl)-1,3-oxazin-6-one (**3**) (Scheme 1), describe a new general method for the preparation of 1,3-oxazin-6-ones by the action of organic bases on *N*-acyl-4-acyloxy-β-lactams, and discuss a reasonable mechanistic explanation of such transformations.

The structural elucidation of the 1,3-oxazin-6-one **3** was straitghtforward from its analytical and spectral data.[2] A careful exploration of the reaction conditions (organic base, solvent, temperature) for the conversion of **2** to **3** revealed DBU (2 equiv) to be the base of choice and CH_2Cl_2, 25 °C, and 2 h as the optimal conditions for obtaining the best yield of **3** (78%). Moreover, we found that 1,3-oxazin-6-one **3** could be also efficiently obtained (41% yield) in one experimental step when **1** was reacted with 2-azidobenzoyl chloride (2 equiv) by using an excess of DBU (5 equiv) under similar reaction conditions.

Scheme 1



1 **2** **3**

(i) 2-$N_3C_6H_4COCl$, Et_3N, CH_2Cl_2, 25°C; (ii) Et_3N, CH_2Cl_2, 25°C

The validity of this one-step method for the preparation of 1,3-oxazin-6-ones was checked for a number of combinations of two different 4-acyloxy-β-lactams **4** with several

(1) Alajarín, M.; Molina, P.; Vidal, A.; Tovar, F. *Synlett* **1998**, 1288.
(2) See Supporting Information.

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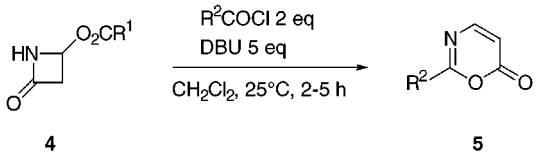
acyl chlorides (aroyl, heteroaroyl, alkenoyl and alkanoyl) and resulted in compounds of general applicability (Scheme 2 and Table 1).

Scheme 2



1,3-Oxazin-6-ones are versatile intermediates in heterocyclic chemistry, and their synthesis and reactivity have been reviewed.[3] Compounds **5a**, **5b**, **5e**, and **5f** have been previously synthesized by other methodologies.[4] Their reported analytical and spectral data were fully coincident with those of the titled compounds here prepared. For most of the entries in Table 1, the intermediate *N*-acyl-β-lactams could be isolated when the reactions were run using Et_3N instead of DBU and then cleanly converted into the corresponding **5** by the action of this last base.

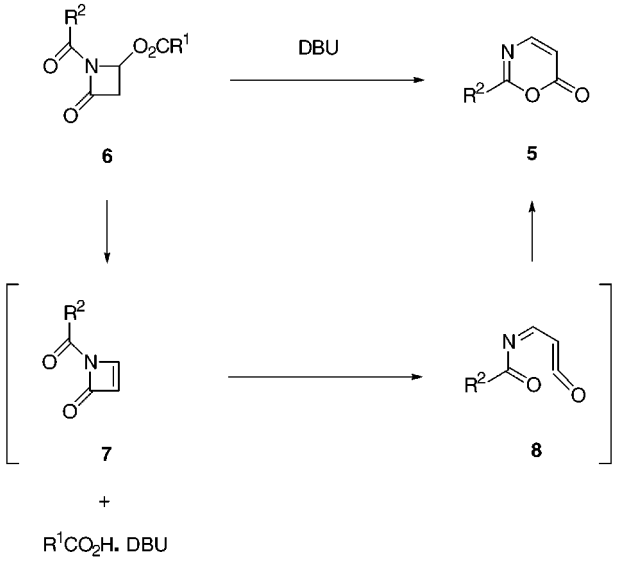
Table 1. One-Step Preparation of 2-Substituted 1,3-Oxazin-6-ones **5** from 4-Acyloxy-β-lactams **4**

entry	R^1	R^2	product	(%) yield[a]
1	CH_3	C_6H_5	**5a**	69
2	CH_3	4-Cl-C_6H_4	**5b**	58
3	C_6H_5	2-furyl	**5c**	44
4	C_6H_5	(*E*)-C_6H_5-CH=CH	**5d**	50
5	C_6H_5	$(CH_3)_3C$	**5e**	76
6	C_6H_5	C_2H_5	**5f**	40
7	C_6H_5	4-Br-C_6H_4	**5g**	53

[a] Isolated yield.

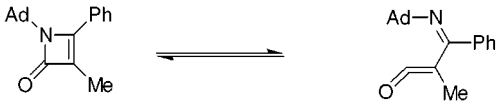
A reasonable mechanistic explanation for the conversion of *N*-acyl-4-acyloxy-β-lactams **6** into 2-substituted 1,3-oxazin-6-ones **5** by the action of DBU is the following: first, the organic base promotes the β-elimination of 1 equiv of carboxylic acid R^1CO_2H across the C3−C4 bond of the β-lactam ring, giving rise to the highly strained *N*-acylazetone **7**, which was not stable enough to survive in the reaction conditions and rapidly experienced a four-centered electrocyclic ring opening to the *N*-acylimidoylketene **8**, which in turn was transformed into the final 1,3-oxazin-6-one **5** through a six-centered electrocyclic ring closure (Scheme 3).

Scheme 3



This mechanism is supported by the following: First, the most general methods for the synthesis of 1,3-oxazin-6-ones have been proposed to involve, as immediate precursors, ring-opened valence tautomers such as acyliminoketene type **8**,[3] although they have never been isolated or detected by spectroscopic means. The two most recent reports on this theme are coincident in that proposal.[4a,5]

Second, concerning the putative intermediate *N*-acylazetone **7**, it is worth pointing out that azetones have occasionally been proposed in the literature as highly reactive intermediates.[6] Resonance of their carbonyl group leads to formally antiaromatic structures. They have only been well-characterized in their benzo-fused forms,[7] whereas Wentrup and co-workers claimed the isolation of an *N*-adamantylazetone in an Ar matrix at 77 K together with its ring-opened valence tautomer imidoylketene.[8]



Ab initio calculations (HF/6-31G*) carried out by Nguyen showed that ring opening of the parent azetone to the unsubstituted imidoylketene is exothermic by 12 kcal/mol.[9]

The previous literature report more closely related to the present work is due to Pericás et al.[10] These authors attempted

(3) Steglich, W.; Jeschke, R.; Buschmann, E. *Gazz. Chim. Ital.* **1986**, *116*, 361.

(4) (a) McNab, H.; Withell, K. *Tetrahedron* **1996**, *52*, 3163. (b) Stajer, G.; Szabo, A. E.; Fülop, F.; Bernath, G. *Synthesis* **1984**, 345.

(5) Millan, D. S.; Prager, R. H.*J. Chem. Soc., Perkin Trans. 1* **1998**, 3245.

(6) Kato, H.; Wakao, K.; Yamada, A.; Mutoh, Y. *J. Chem. Soc., Perkin Trans. 1* **1988**, 189. Kappe, T.; Zadeh, R. K. *Synthesis* **1975**, 247. Micetich, R. G.; Maiti, S. N.; Tanaka, M.; Yamazaki, T.; Ogawa, K. *J. Org. Chem.* **1986**, *51*, 853.

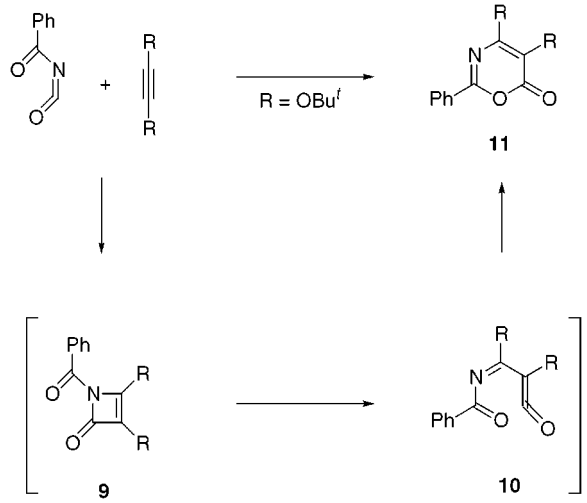
(7) Olofson, R. A.; Van der Meer, R. K.; Hoskin, D. H.; Bernheim, M. Y.; Stournas, S.; Morrison, D. S.*J. Org. Chem.* **1984**, *49*, 3367. Wentrup, C.; Gross, G. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 543.

(8) Kappe, C. O.; Kollenz, G.; Netsch, K.-P.; Leung-Toung, R.; Wentrup, C. *J. Chem. Soc., Chem. Commun.* **1992**, 488.

(9) Nguyen, M. T.; Ha, T.; O'Ferral, R. A. M. *J. Org. Chem.* **1990**, *55*, 3251.

(10) Pericás, M. A.; Serratosa, F.; Valentí, E.; Font-Altaba, M.; Solans, X. *J. Chem. Soc., Perkin Trans. 2* **1986**, 961. In the context of the present work, it is remarkable that the title of this article starts with the sentence "Can *N*-acylazetones ever be obtained?"

to prepare *N*-acylazetones **9** by [2 + 2] cycloaddition of benzoyl isocyanate with di-*tert*-butoxyethyne, obtaining the 1,3-oxazin-6-one **11** as the main reaction product. They rationalized the formation of **11** through the sequence depicted below, involving the transient formation of azetone **9** and *N*-acylimidoylketene **10**, a mechanism similar to the one here proposed for the conversion of **7** into **5**.



Following semiempirical MNDO calculations, the authors of that work concluded that "... the conversion of *N*-acylazetones into 1,3-oxazin-6-ones is predicted to take place easily and completely, even at low temperatures, owing to the important difference in thermodynamic stability between the compounds."

Finally, a brief comment on the β-elimination reaction of *N*-acyl-4-acyloxy-β-lactams **6** presumably leading to *N*-acylazetones **7**. Although 4-acyloxyazetidinones are widely employed synthetic materials,[11] to our knowledge there are no previous reports on elimination of carboxylic acids from *N*-substituted substrates, whereas *N*-unsubstituted derivatives are believed to undergo displacement of the 4-acyloxy group by different *O*-, *N*-, and *S*-centered nucleophiles through the intermediacy of the 1-azetin-4-one **12**.[11,12]

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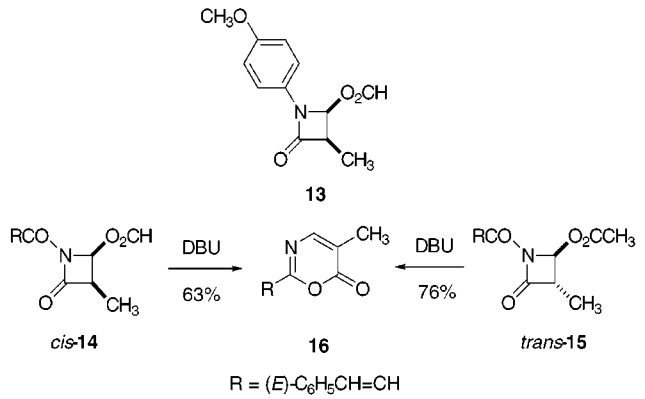
We carried out some additional experiences (Scheme 4) in relation to this first step of the mechanism in Scheme 3. *N*-Aryl-4-formyloxy-β-lactam **13** remained unchanged in the presence of DBU (CH_2Cl_2, 25 °C, or toluene, 110 °C). We believe that the suitability of the *N*-acylated derivatives **2** and **6** to undergo β-elimination along its C3−C4 bond is due to the enhancing of the acidity of H-3 by the electron-withdrawing *N*-acyl group, which makes the β-lactam

Scheme 4



carbonyl group more "ketone-like". The absence of this effect explains why more common *N*-alkyl- or -aryl-substituted 4-acyloxy-β-lactams, e.g., **13**, do not undergo such elimination.

The conversions of 3-monosubstituted β-lactams *cis*-**14** and *trans*-**15** into 1,3-oxazin-6-one **16** were easily achieved, in comparable yields (Scheme 4). The fact that the 3,4-elimination is amenable irrespective of the relative *cis* or *trans* relationship between the groups being eliminated, and apparently at similar rate, is indicative, but not yet conclusive, of an E1cB-like mechanism.

At the present we are carrying out ab initio calculations, at different levels of theory, on the full reaction path leading from *N*-formylazetone to the simplest 1,3-oxazin-6-one (a simplified model of the conversion **7** to **5**), which will be fully reported in due course. We here show the geometries of the so far calculated transition states of the two exothermic electrocyclic processes (ring opening and ring closure), as they revealed orbital topologies different from the ones expected for classical pericyclic reactions (Figure 1).

Whereas $TS_1^{\ddagger}$ was located at both levels of theory studied, RHF and B3LYP, $TS_2^{\ddagger}$ could only be located at the RHF level.[13] The energy barriers for both reactions were notably small (see Figure 1), particularly that of the ring closure reaction. This value could explain why all attempts to locate $TS_2^{\ddagger}$ at the B3LYP level led directly to the ring-closed oxazinone. Notably, both transition states $TS_1^{\ddagger}$ and $TS_2^{\ddagger}$ show essentially planar geometries, proving to be *nonrotatory*, that is, *not* to be of a classic, 4π conrotatory or 6π disrotatory

(11) Wild, H. In *The Organic Chemistry of β-Lactam Antibiotics*; Georg, G. I., Ed.; VCH: New York, 1993; Chapter 2.

(12) Attrill, R. P.; Barret, A. G. M.; Quayle, P.; van der Westhuizen, J.; Betts, M. J. *J. Org. Chem.* **1984**, *49*, 1679 and references therein.

(13) The ring closure of a similar system, 5-oxo-2,4-pentadienal, was calculated to have no barrier at the MP2/6-31G* level: Birney, D. M. *J. Org. Chem.* **1996**, *61*, 243.

(14) Ross, J. A.; Seiders, R. P.; Lemal, D. M. *J. Am. Chem. Soc.* **1976**, *98*, 4325.

(15) Birney, D. M.; Xu, X.; Ham, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 189. Birney, D. M.; Xu, X.; Ham, S.; Huang, X. *J. Org. Chem.* **1997**, *62*, 7114. Birney, D. M.; Ham, S.; Unruh, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 4509. Ham, S.; Birney, D. M. *J. Org. Chem.* **1996**, *61*, 3962. Wagenseller, P. E.; Birney, D. M.; Roy, D. *J. Org. Chem.* **1995**, *60*, 2853. Birney, D. M.; Wagenseller, P. E. *J. Am. Chem. Soc.* **1994**, *116*, 6262.

(16) Fabian, W. M. F.; Kappe, C. O.; Bakulev, V. A. *J. Org. Chem.* **2000**, *65*, 47. Fabian, W. M. F.; Bakulev, V. A.; Kappe, C. O. *J. Org. Chem.* **1998**, *63*, 5801. Liu, R. C.-Y.; Lusztyk, J.; McAllister, M. A.; Tidwell, T. T.; Wagner, B. D. *J. Am. Chem. Soc.* **1998**, *120*, 6247. Luo, L.; Bartberger, M. D.; Dolbier, W. R. *J. Am. Chem. Soc.* **1997**, *119*, 12366.

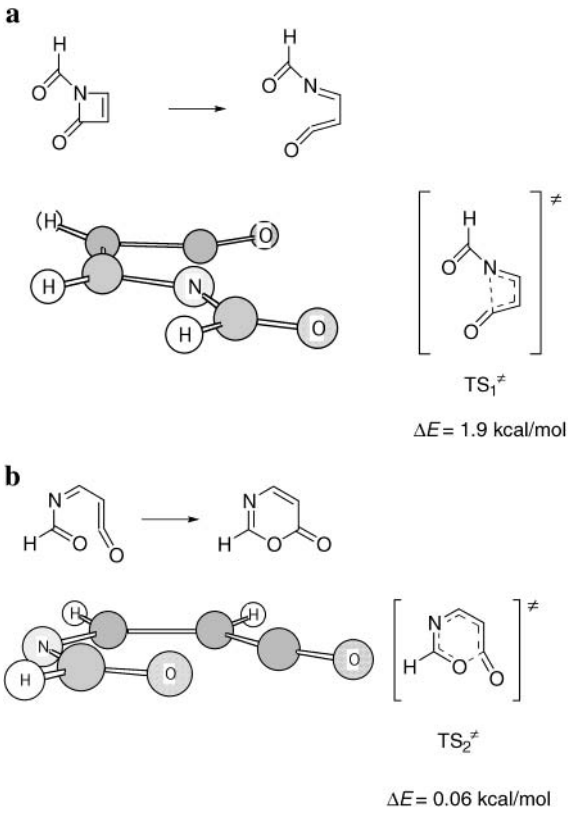


Figure 1. (a) Calculated (B3LYP/6-311++G**) transition state $TS_1^{\ddagger}$ for the concerted ring opening. **(b)** Calculated (RHF/6-31G*) transition state $TS_2^{\ddagger}$ for the concerted ring closure. The ΔE values contain a ZPVE correction, computed at the same level of theory.

electrocyclic nature, respectively. This means that the orbitals interactions must be qualitatively different from those commonly encountered in pericyclic reactions. Thus, the N−C σ-bond being broken in $TS_1^{\ddagger}$ is giving rise to an sp^2-orbital on the nitrogen (not a p-orbital of the N═C π-bond) and to a p-orbital of the carbonyl π-bond, rather than to that of the cumulated C═C π-bond. Similarly, in $TS_2^{\ddagger}$ the σ-bond being formed is due to the interaction between an sp^2-orbital of the formyl oxygen atom and a p-orbital of the cumulated carbonyl π-bond, both in the molecular plane, instead of involving the two parallel p-orbitals of the reactant, on the extremes of the cyclic array of six atoms. In both cases, nonbonded pairs become bonded pairs as the new σ-bond is broken or formed, thus giving rise to "disconnections" in the cyclic array of overlapping orbitals because the atomic orbitals which are switching functions are mutually orthogonal.

All these characteristics of the transition structures $TS_1^{\ddagger}$ and $TS_2^{\ddagger}$, corresponding to the two reactions shown in Figure 1, are consistent with Lemal's definition of a *pseudopericyclic* process,[14] a subset of pericyclic reactions that remained almost ignored for about 20 years but which has been placed on a solid foundation by the recent publications of Birney[13,15] and others.[16]

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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