Pergamon

Tetrahedron Letters 41 (2000) 9319–9321

TETRAHEDRON LETTERS

Reactions of an imidazo[4,5-*c*]isoxazole-6-carboxylate with dimethyl acetylenedicarboxylate; formation of the first example of a [1,4]diazepino[2,3-*c*]isoxazole

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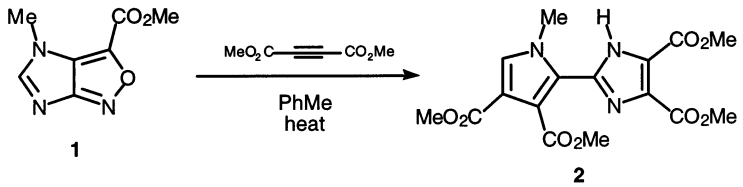
Received 10 August 2000; revised 20 September 2000; accepted 27 September 2000

Abstract

The synthesis of the first example of a [1,4]diazepino[2,3-*c*]isoxazole derivative is reported. Reaction of an imidazo[4,5-*c*]isoxazole with acetylenic esters has been shown to lead to the formation of 2-pyrrol-2-yl imidazoles. Here we report an alternative reaction pathway in which the fused imidazole ring adds a molecule of acetylenic ester, and undergoes ring expansion to a fused [1,4]diazepine. A mechanism for the reaction is discussed.

We recently reported[1] the reaction of the imidazo[4,5-*c*]isoxazole-6-carboxylate **1** with acetylenic esters and other electron deficient alkynes to give 2-pyrrol-2-yl imidazole derivatives e.g. **2** (Scheme 1). The reaction involved the overall addition of two molecules of alkyne, and loss of the elements $C_3H_2O_3$ from the fused isoxazole. These atoms may have been lost as a molecule of formaldehyde and two molecules of carbon dioxide, or alternatively, as a methyl oxalate derivative in a de-acylation process by attack of a nucleophile such as water. We have not yet been able to identify the fragments lost. Also isolated from this reaction in low yield was an orange–red crystalline compound[†] which corresponded to the addition product of a single



Scheme 1.

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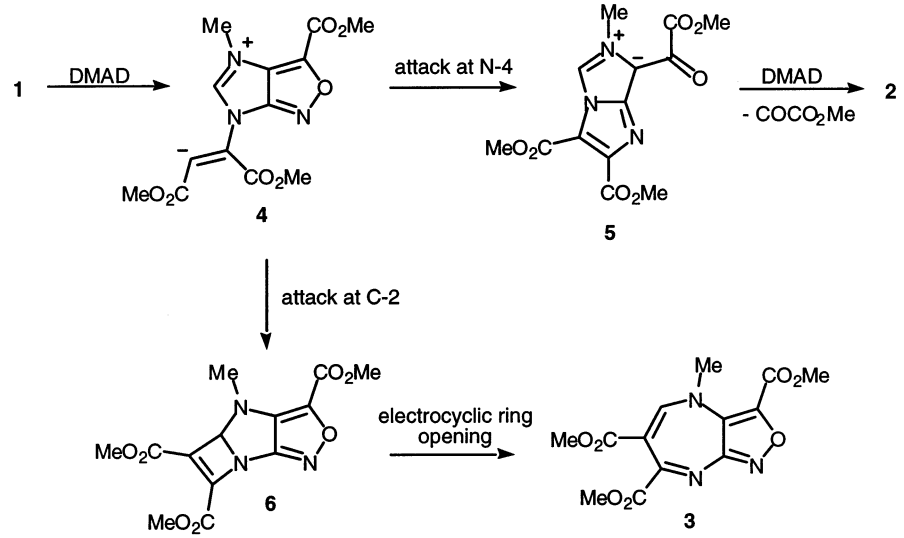
† All new compounds exhibited satisfactory analytical, spectroscopic and mass spectrometric data.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01682-8

molecule of acetylenic ester. This compound was initially thought to be an intermediate in the reaction, namely the imidazo[3,4-*a*]imidazolium betaine **5** (Scheme 2). We now report the structure of this compound as the first example of a derivative of the [1,4]diazepino[2,3-*c*]isoxazole ring system **3** (mp 102–103°C). The isolation of this compound demonstrates the existence of an alternative pathway for the reaction between dimethyl acetylenedicarboxylate and the imidazo[4,5-*c*]isoxazole derivative **1**. The structure of the compound was determined by X-ray crystallography[‡] and is shown in Fig. 1. We believe this compound is formed by the mechanism outlined in Scheme 2. Nucleophilic addition of the imidazole nitrogen of **1** to the acetylenic ester would generate intermediate **4**. Cyclisation of the anion onto the N-4 atom of the fused isoxazole, and ring opening of the isoxazole would produce the betaine **5**. Dipolar cycloaddition of a second molecule of alkyne would lead to the pyrrol-2-yl imidazole as described in our earlier paper. The second cycloaddition is likely to be faster than the initial addition step, meaning **5** does not accumulate in the reaction mixture. Alternatively, intermediate **4** can ring close onto the imidazole C-2 carbon atom to form the tricyclic fused compound **6**. Electrocyclic ring opening of the strained azetine ring[2] would then produce the [1,4]diazepine ring in the product **3**. The ring opening of **6** should be a conrotatory process, and unfavourable



Scheme 2.

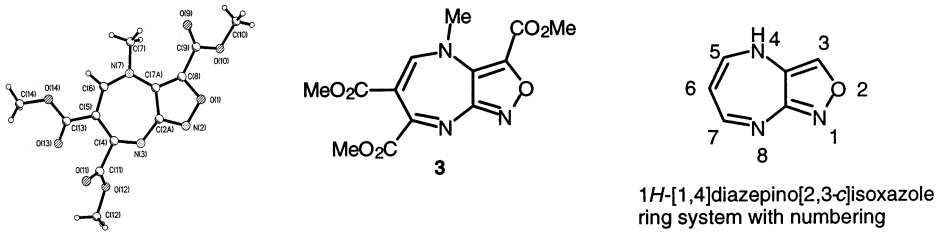
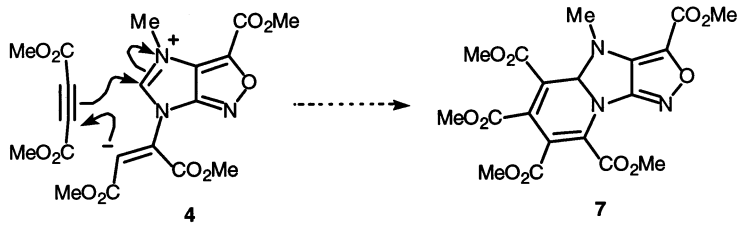


Figure 1. X-ray crystal structure of [1,4]diazepino[2,3-*c*]isoxazole **3**

[‡] X-ray crystallographic data have been deposited at the Cambridge Crystallographic Database.

as a thermal reaction for a fused azetine unless permitted by inversion at nitrogen. Ring opening of a 1,2-diazabicyclo[3.2.0]hept-2-en-6-one, and its reversion to the starting 1,2-diazepin-6-one after photochemical cyclisation has been reported,[3] as have other disrotatory ring opening reactions of fused 2-azetines.[4,5] The different stereochemical outcome of azadiene–azetine interconversion has been attributed to a shift in the nodal position in the HOMO of the azadiene system.[6]

It is not clear why the fused four-membered ring is produced initially; most intermediates of the type **4** (Scheme 3) add to a second molecule of the unsaturated ester, before undergoing ring closure to form six-membered fused products.[7] No compounds of the type **7** have been isolated during our studies. The fused azetine **6** may, alternatively, be formed in a 2+2 cycloaddition between the acetylenic ester and the 2,3 C=N bond of the imidazoisoxazole **1**. Further studies on the mechanism of this reaction are in progress.



Scheme 3.

Diazepines are important pharmacologically active compounds,[8] and the isoxazolo-fused system **3** represents a useful building block for the synthesis of potentially biologically active molecules of this class. The ester substituted isoxazole ring in this molecule is a useful group for further elaboration, for example by reductive ring opening to give adjacent amino and keto-ester substituents. The synthesis of further examples of this ring system and study of their chemistry is in progress.

Acknowledgements

We thank the EPSRC for a Quota studentship (to A.T.) and Loughborough University and Pfizer Central Research for financial support.

References

1. Taher, A.; Slawin, A. M. Z.; Weaver, G. W. *Tetrahedron Lett*. **1999**, 8157.
2. Davies, D. E.; Storr, R. C. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 7, Chapter 5.09, p. 237; De Klimpe, N. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Elsevier Science: Oxford, 1996; Vol. 1B, Chapter 1.18, p. 507.
3. Theuer, W. J.; Moore, J. A. *J. Chem. Soc., Chem. Commun*. **1965**, 468.
4. Adger, B. M.; Rees, C. W.; Storr, R. C. *J. Chem. Soc., Perkin Trans 1* **1975**, 45.
5. Völker, E. J.; Pleiss, M. G.; Moore, J. A. *J. Org. Chem*. **1970**, *35*, 3615.
6. Snyder, J. P. *J. Org. Chem*. **1980**, *45*, 1344.
7. Acheson, R. M.; Elmore, N. F. *Adv. Heterocyclic Chem*. **1978**, *23*, 263.
8. Fryer, R. I. In *Comprehensive Medicinal Chemistry*; Hansch, C., Ed.; Pergamon: New York, 1990; Vol. 3, p. 539.