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Reactions of an imidazo[4,5-*c*]isoxazole-6-carboxylate with electron deficient acetylenes

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Abstract

The synthesis of the first examples of the imidazo[4,5-*c*]isoxazole ring system has recently been reported,[2] but little is known about the chemistry of this heterocycle. In this paper we describe our investigation into the behaviour of an imidazo[4,5-*c*]isoxazole-6-carboxylate ester with acetylenic esters and ketones. A complex reaction sequence is found to occur, involving addition of two molecules of alkyne followed by ring opening and fragmentation, leading to the formation of 2-pyrrol-2-yl imidazoles in moderate yield. The mechanism and scope of the reaction is discussed.

1. Introduction

We have been interested in the chemistry of fused [5,5] ring heterocycles since the strain in such molecules frequently leads to interesting ring opening and rearrangement reactions. Many [5,5] fused ring compounds[1] have been used in the construction of larger, ring expanded heterocycles.

Tennant and co-workers[2] have demonstrated the strain inherent in the imidazo[4,5-*c*]isoxazole ring system, e.g. the 6-carboxylate derivative **1** (Scheme 1), by the easy reductive cleavage of the N–O bond in the isoxazole ring and the easy hydrolytic opening of the imidazole ring. We have obtained an X-ray crystal structure† of **1**, the first for an imidazo[4,5-*c*]isoxazole and this is shown in Fig. 1. We expected that the strain present in the isoxazole ring would make compounds of this class reactive towards dienophiles, and we considered that the imidazo[4,5-*c*]isoxazole ring might undergo hetero-Diels–Alder reaction with acetylenic esters to generate imidazo-fused bicyclic compounds such as **2**, or more likely, imidazo[4,5-*c*]pyridine-*N*-oxides such as **3**, which would arise through ring opening of the oxygen bridged structure **2**. Similar processes are well known[3] for benzofurans, but few examples have been reported for 2,1-benzisoxazoles (anthranils). The quinoline-*N*-oxide **7** has been synthesised[4] by reaction

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† X-Ray crystal structure data has been deposited at the Cambridge Crystallographic Database.

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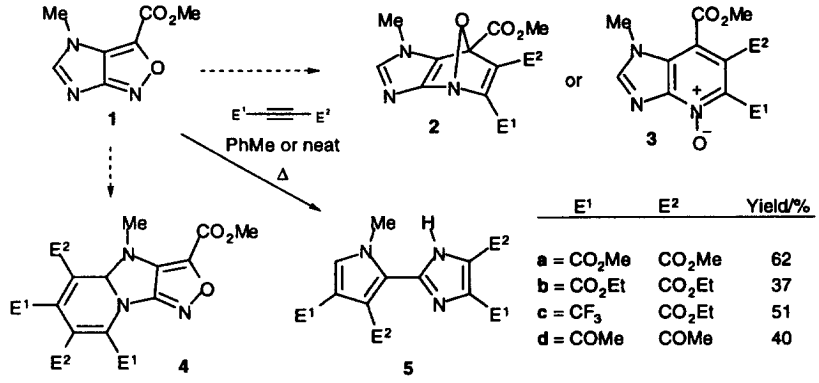
of 2,1-benzisoxazole **6** with dimethyl acetylenedicarboxylate (DMAD) (Scheme 2) and quinolines and acridines have been synthesised[5] by heating anthranils with ketones; the reaction is believed to proceed by cycloaddition of the enol form of the ketone to the isoxazole ring. Subsequent ring opening and dehydration then leads to formation of a pyridine ring. We considered that a similar type of reaction might occur with imidazo[4,5-*c*]isoxazoles which would provide a useful route to biologically interesting imidazo[4,5-*c*]pyridine derivatives (deazapurines). Alternatively, it was thought that reaction may occur at the imidazole ring, since the isoxazole ring bears an electron withdrawing ester substituent, which would hinder reaction with an electron deficient dienophile. The fused pyridine **4** was considered a possible product; simple imidazoles such as **8** (Scheme 3) are transformed[6] into imidazo[1,2-*a*]pyridines, e.g. **9** on treatment with DMAD in ether at room temperature.



	E^1	E^2	Yield/%
a	CO_2Me	CO_2Me	62
b	CO_2Et	CO_2Et	37
c	CF_3	CO_2Et	51
d	COMe	COMe	40

Scheme 1.

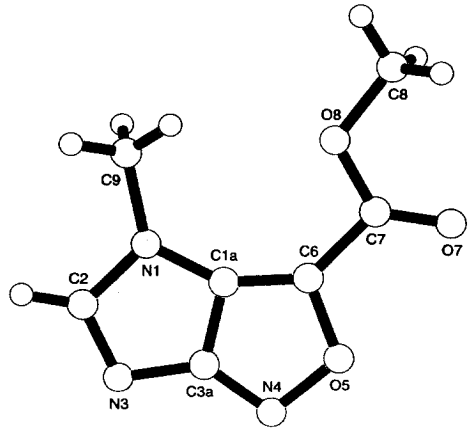
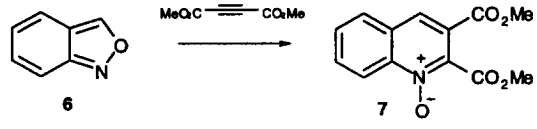
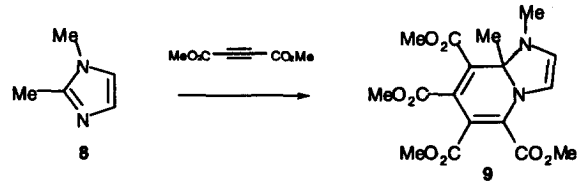


Figure 1.



Scheme 2.



Scheme 3.

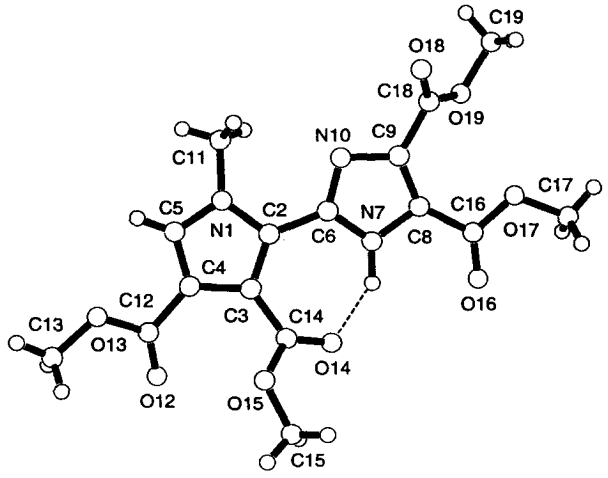


Figure 2.

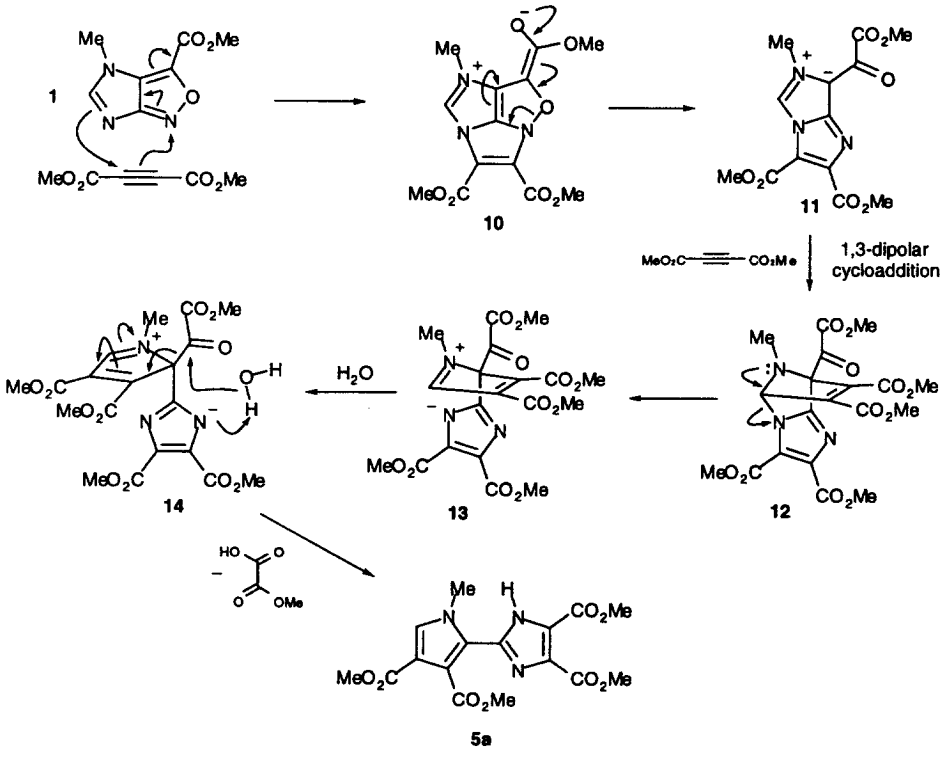
2. Results and discussion

When the imidazo[4,5-*c*]isoxazole **1** (Scheme 1) was treated with DMAD in boiling toluene, a crystalline compound‡ analysing for $C_{16}H_{17}N_3O_8$ was obtained in a moderate yield of 62%. The ^1H NMR spectrum of this compound showed four methyl ester signals, a single aromatic proton at δ 7.25 and a three hydrogen singlet corresponding to a methyl attached to nitrogen. A broad signal at δ 12.9 suggested the presence of a NH group in the molecule. When the reaction was repeated using diethyl acetylene dicarboxylate, a similar compound was obtained in low yield (37%) which exhibited signals due to four ethyl esters, but no methyl ester, suggesting that both the methyl ester at C-6 and the ring oxygen of the imidazoisoxazole had been lost during the reaction, and that two molecules of the acetylenic ester had been incorporated into the product. We were able to obtain crystals of the dimethyl acetylenedicarboxylate adduct; X-ray diffraction analysis of the compound‡ showed it to be the 2-pyrrol-2-yl imidazole **5a** (Fig. 2).

We have proposed a mechanism to account for the formation of ester **5a** and this is outlined in Scheme 4. We believe that nucleophilic addition of the imidazoisoxazole to the acetylenic ester occurs through *N*-3 and subsequent attack of the vinyl anion at *N*-4 of the imidazoisoxazole leads to the tricyclic intermediate **10**. Ring opening of the isoxazole by cleavage of the N–O bond would then form **11** setting up a 1,3-dipole across atoms 1,2 and **6a** of the original bicycle. Cycloaddition of a second molecule of the acetylenic ester would generate the bridged intermediate **12**, which can fragment by elimination of an imidazolyl anion. Aromatisation of the pyrrole ring may then occur by loss of the keto-ester side chain. This most likely occurs through a retro-Claisen reaction mediated by traces of water in the reaction

‡ All new compounds exhibited satisfactory analytical, spectrocopic and mass spectrometric data.

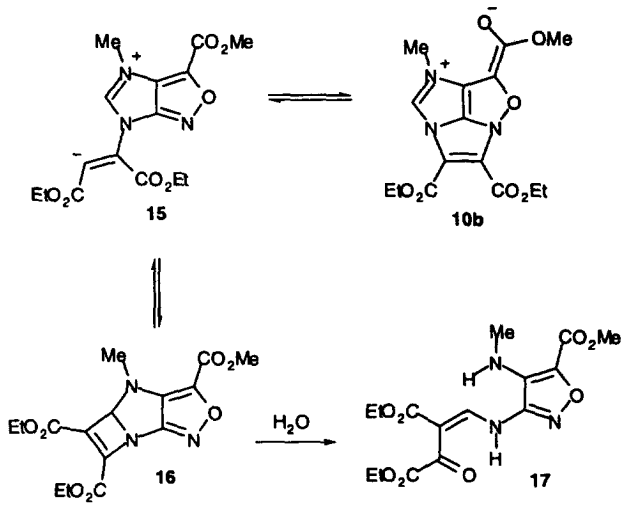
mixture or present during isolation. Water is also required to protonate the newly formed imidazole ring. We have not been able to determine the fate of the keto ester group. No mono-methyl oxalate was isolated during chromatographic separation of the products. Hydrolysis of the ester and decarboxylation and decarbonylation could also account for side chain loss and aromatisation of the pyrrole ring.



Scheme 4.

Some evidence for the proposed mechanism has been obtained from the reaction involving diethyl acetylenedicarboxylate. An orange crystalline compound analysing for $C_{15}H_{17}N_3O_7$ believed to be betaine **10b** (Scheme 5) was also obtained in 48% yield and corresponds to the adduct derived from addition of a single molecule of diethyl acetylenedicarboxylate. In an attempt to obtain crystals suitable for X-ray diffraction analysis, the substance was allowed to crystallise slowly from light petroleum and ethanol. The diffraction analysis however showed the compound[‡] to be the substituted isoxazole **17** (Fig. 3) with molecular formula $C_{15}H_{19}N_3O_8$, indicating that hydration of the molecule had occurred during the crystallisation process. The presence of the intact isoxazole ring in this compound indicates that the substance initially isolated cannot be **11**, and is most likely **10b**. If the addition of the vinyl anion **15** to the isoxazole ring is reversible, addition of the anion could also occur onto the iminium ion of the imidazole ring, to form **16**, albeit via a 4-*exo*-trig cyclisation (assuming a resonance structure involving the lone pair of the imidazole *N*-1 is important). Addition of water to the unsaturated azetine ring, and subsequent hydrolytic opening of the four-membered ring and the aminal of the imidazole ring, then account for formation of the vinylogous amide side chain in the product isoxazole **17**.

No compounds of the type **4** (Scheme 1) were isolated, in which two molecules of the acetylenic ester had added consecutively to form a six-membered ring fused across the 2,3 bond of the imidazole ring. This is a common pathway for reaction of imidazoles, pyridines and other heterocycles[7] with DMAD



Scheme 5.

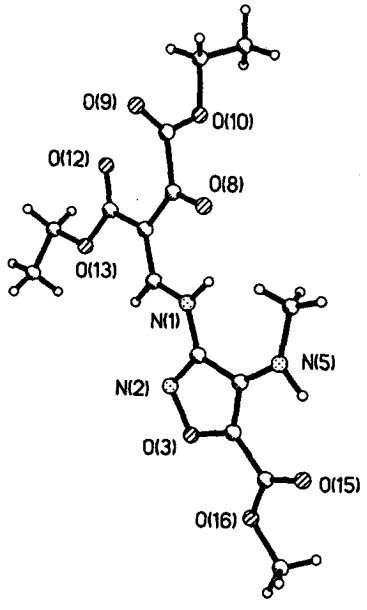
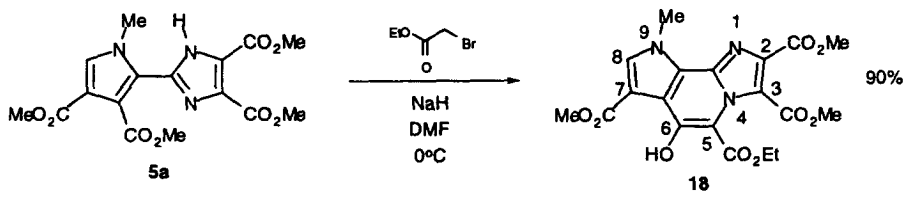


Figure 3.

and it is not clear why cyclisation of the intermediate **15** occurs to form the four-membered ring required to account for production of the vinylogous amide **17**.

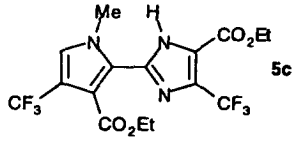
Support for the structure of the pyrrol-2-yl imidazoles also comes from the ready conversion of the ester **5a** into the novel 9*H*-imidazo[1,2-*a*]pyrrolo[2,3-*c*]pyridine-2,3,7-tricarboxylate **18** (Scheme 6) on treatment with sodium hydride and ethyl bromoacetate in DMF; the tricycle being formed in 90% yield and existing as the fully aromatic tautomer with a hydroxyl group at *C*-6.

In an attempt to extend the scope of this reaction we have investigated the use of other electron deficient alkynes. Mono-substituted alkynes appear not to be effective and the imidazoisoxazole **1** was recovered unchanged in high yield after heating with phenylacetylene or with methyl propiolate. Success was obtained with ethyl 4,4,4-trifluorobut-2-ynoate and 2,5-dioxohex-3-yne and the pyrrolyl imidazoles

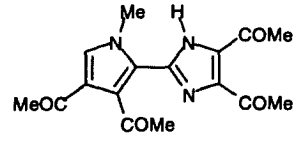


Scheme 6.

5c and **5d** were obtained in moderate yields of 51% and 40%, respectively. The regio chemistry of the former compound was determined by ^{13}C NMR spectroscopy. Although no fluorine coupling could be seen to the pyrrole *H*-5 hydrogen atom in the ^{1}H NMR spectrum, the signal for the carbon atom at *C*-5, δ 128.3, was split into a quartet, with a three bond coupling constant, $^{3}J_{CF}$, of 6 Hz. The *C*-5 carbon was identified by proton–carbon correlation; the opposite α-carbon of the pyrrole ring resonating at a similar chemical shift of 127.8 ppm. The signal for the C-4 carbon of the pyrrole ring also showed a quartet splitting (q, $^{2}J_{CF}$, 40 Hz) at δ 115, not very far down field from a typical pyrrole β-carbon signal at δ 108. The C-4(5) carbon of the imidazole ring was also easily identified by the signal at δ 135.2 by fluorine coupling (q, $^{2}J_{CF}$, 40 Hz). None of the alternative regioisomer was isolated. The reactions with the highly electron deficient dicyano acetylene and cyanotrifluoromethyl acetylene were not successful and the imidazoisoxazole was recovered unchanged. This may have been due to rapid decomposition of the former, and the high volatility of the latter, precluding them from reacting with the substrate compound.



5c



5d

Reaction with electron deficient alkenes can be expected to lead to saturated imidazo[1,2-*c*]imidazoles, while alkenes such as enol ethers, may be expected to form imidazopyridine-*N*-oxides if the conventional Diels–Alder mode of addition operates with electron rich dienophiles. Studies with alkenes and further investigation into the mechanism of this reaction are currently under way and will be reported in due course.

Acknowledgements

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