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The first examples of di- and *cis* triaryl-3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazoles and their ring-opening reactions

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Abstract

The Δ^3-imidazoline 3-oxides **1** undergo diastereoselective cycloaddition with dimethyl acetylenedicarboxylate **2** to give 3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazoles **3**. Thermal and base induced ring-opening reactions of compounds **3** were demonstrated.

The inter- and intramolecular 1,3-dipolar cycloadditions of nitrones with different dipolarophiles provide valuable routes leading to many heterocyclic compounds. The cycloaddition of nitrones with a variety of alkynes is used in the synthesis of isoxazolines.[1–3] The intramolecular 1,3-dipolar cycloaddition of acetylenic nitrones leading to bicyclic nitrogen heterocycles has been investigated.[4] Intermolecular 1,3-dipolar cycloaddition of acyclic[5–8] and cyclic nitrones[9–12] with DMAD have been reported. Dihydroazet-1-oxide,[9] dihydro-β-carboline *N*-oxide,[10] and 3,4-dihydro-2*H*-pyrrole 1-oxide derivatives[11,12] are the few known heterocyclic nitrones which have been used in 1,3-dipolar cycloaddition reactions with DMAD. The synthesis of the first examples of the 4*H*-imidazo[4,5-*c*]isoxazole ring system was recently reported.[13]

As part of a continuing study into new tetrahydroimidazole containing ring systems[14,15] possessing antibacterial and anticancer activity we have used imidazoline *N*-oxides as cyclic nitrones and DMAD as a dipolarophile to prepare the corresponding tetrahydroimidazoisoxazole bicyclic system. We report herein a diastereoselective synthesis of a new class of 3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazole by cycloaddition of Δ^3-imidazoline 3-oxides with dimethyl acetylenedicarboxylate as well as their thermal and base induced ring opening reactions (Scheme 1).

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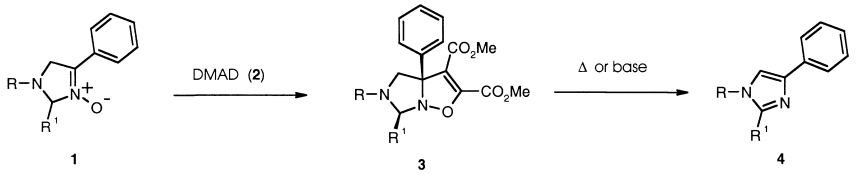

entry	R	R^1	yield of **3** (%)	yield of **4** (%) thermal	piperidine	triethylamine	mp of **3** (°C)
a	4-MeC_6H_4	H	98	85	80	85	134.8
b	4-$MeOC_6H_4$	H	99	72	73	70	116
c	4-ClC_6H_4	H	97	91	85	80	135.5
d	4-MeC_6H_4	Ph	97	68	65	no reaction	129
e	4-$MeOC_6H_4$	Ph	95	67	70	no reaction	104-105.3

Scheme 1.

The reaction of the nitrones **1a–e** with dimethyl acetylenedicarboxylate in benzene at reflux gave the corresponding imidazoisoxazolines **3** in almost quantitative yields.[17] Nitrones **1d**,**e** reacted with dimethyl acetylenedicarboxylate with high diastereoselectivity. A tentative *cis* configurational assignment[11,12] for compounds **3d**,**e** was made on the basis of ^{1}H NMR spectroscopic data and NOESY experiments. We have observed the same diastereoselectivity as has been observed in the reaction of imidazoline oxides **1** with aryl isocyanates and styrene.[14–16]

Thermal treatment of compounds **3a–e** in the condensed phase under vacuum led to the formation of the imidazoles. This was in contrast with the behaviour of the imidazoline 3-oxides' adducts formed from isocyanates and styrene where thermal treatment led to retro 1,3-dipolar cycloaddition.

In the case of *cis* 3a,6-diaryltetrahydroimidazo[1,5-*b*][1,2,4]oxadiazol-2(1*H*)-ones we have found that secondary amines open the ring producing imidazole while tertiary amines led to retro 1,3-dipolar cycloaddition giving the starting cyclic nitrone.[18] The adducts obtained from the same imidazoline oxides and styrene did not undergo reaction with secondary and tertiary amines. This reaction would have been useful in distinguishing the diastereomers obtained from the reaction of

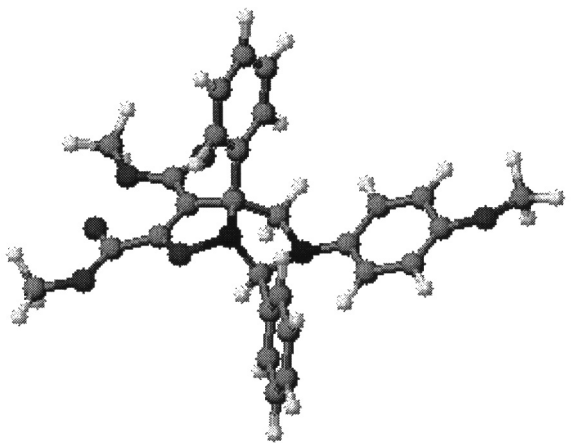

Figure 1. 3D Perspective view of the crystal structure of **3e**

imidazoline 3-oxides and isocyanates, the *cis* configuration was assigned tentatively on the basis of NOE experiments and the second diastereomer was not available by cycloaddition reaction. The adducts **3** were subjected to the same amine test and showed surprisingly similar behaviour to the imidazooxadiazolones. Compounds **3a**–**e** were converted to imidazoles **4a**–**e** and dimethyl oxaloacetate in refluxing acetonitrile in the presence of an excess of piperidine. Compounds **3d**–**e** were converted to the corresponding imidazoles in the presence of piperidine but remain unchanged in the presence of triethylamine under the same reaction conditions. The easy ring-opening of adducts **3** led us to suspect an abnormality in their formation. Such an abnormal adduct would be formed if imidazoline 3-oxides react via their rearranged oxaziridinoimidazole[16] form to give dimethyl 5,6,7,7*a*-tetrahydroimidazo[5,1-*b*][1,3]oxazole-2,3-dicarboxylates. The IR and ^{1}H NMR spectra were consistent with both structures therefore we needed to elucidate this structure by an X-ray diffraction method. The adduct is proved unequivocally to be the *cis*-isomer by X-ray crystallographic analysis. A 3D perspective view of the crystal structure of **3e** is shown in the Fig. 1. Thus the configuration of adducts **3d**,**e** has to be *cis* for the double *cis* elimination with secondary amines.

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17. Compound **3a**; IR (KBr) $n_{C=O}=1750$, 1716; $n_{C=C}=1665$ cm^{-1}; ^{1}H NMR $CDCl_3$ δ 2.27 (3H, s), 3.42 (1H, d, $J=11$), 3.64 (3H, s), 3.87 (3H, s), 4.19 (1H, d, $J=11$), 4.65 (1H, d, $J=11$), 5.05 (1H, d, $J=11$), 6.71 (2H, d, $J=8$), 7.08 (2H, d, $J=8$), 7.28–7.39 (3H, m), 7.60 (2H, d, $J=8$); MS m/z 394 (M^+).
18. Coşkun, N. unpublished results.