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Synthesis of 4-Oxo-3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazole-3-carboxylic Acid Esters

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ABSTRACT

3-Imidazoline 3-oxides react regioselectively with 3-phenylpropanoic acid alkyl esters to give the corresponding 2-phenyl-3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazole-3-carboxylic acid alkyl esters. This adducts convert to imidazole and the corresponding alkyl 3-oxo-3-phenylpropanoic acid esters when treated with alkoxides or heated under vacuum. Attempts to oxidise the carbon–carbon double bond using $KMnO_4$–$FeSO_4$ led to the formation of heretofore unknown 4-oxo-3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazoles.

Key Words: Imidazole; Heterocycles; Adducts; Nitrones.

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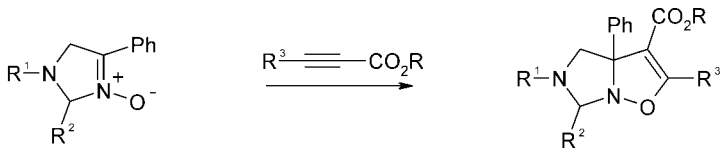
RESULTS AND DISCUSSIONS

The nitrones make possible the derivatisation of carbonyl compounds through forming a five-membered heterocycles and their decomposition. They readily undergo cycloaddition reactions with a wide variety of carbon–carbon, carbon–nitrogen, carbon–sulphur, and nitrogen–phosphorus multiple bond systems to provide various heterocyclic five-membered ring systems.[1–4] The cycloadducts of cyclic nitrones[5] **1** with variety of dipolarophiles[6] give bicyclic compounds with potentially interesting biological activity.[a] On the other hand, they are sours of new heterocyclic compounds via interesting ring-opening reactions.[7]

We report herein the regioselective 1,3-dipolar cycloaddition of cyclic nitrones **1** to give 3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazoles **2** (Sch. 1, Table 1). Their oxidation to 4-oxo-3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazoles with $KMnO_4$–$FeSO_4$ mixture and the thermal and base induced ring-opening reactions will also be reported.

Cyclic nitrones **1** were refluxed in toluene in the presence of equimolar amounts of alkyl phenylpropinoates for 24 hr to give regioselectively the corresponding 2-phenyl-3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazoles **2**. The structure was deduced from their IR and ^{1}H NMR spectra. IR (KBr) spectra of adducts **2** show a $\nu_{C=O}$ at 1700 cm^{-1} and $\nu_{C=C}$ at 1660 cm^{-1}. Characteristic singlets at 3.59 (3H) in the spectra of **2c** and **d** correspond to the ester methoxy group linked to C-3. This is in agreement with the assignments in the spectra of DMAD adducts. Parts of the two AB systems corresponding to C-4 and C-6 are appearing at 3.69 (1H, d, $J = 9.9$), 4.40 (1H, d, $J = 10.4$), 4.75 (1H, d, $J = 9.9$), 5.10 (1H, d, $J = 10.4$).



1 **2**

Scheme 1.

[a]A series of tetrahydroimidazo compounds were tested for their anticancer activity and found to be quite active at 10^{-5} molar concentrations.

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Table 1. 3a,4,5,6-Tetrahydroimidazo[1,5-*b*]isoxazoles.

	R	R^1	R^2	R^3	Yield (%)	Mp (°C)
2a	Et	4-MeC_6H_4	H	Ph	90	117–120
2b	Et	4-$MeOC_6H_4$	H	Ph	92	110–114
2c	Me	4-MeC_6H_4	H	Ph	90	137–138
2d	Me	4-$MeOC_6H_4$	H	Ph	95	109–110
2e	Me	4-MeC_6H_4	Ph	CO_2Me	97	129 lit.[6e] mp 129
3a	Et	4-MeC_6H_4	H	Ph	60	Oil
3b	Et	4-$MeOC_6H_4$	H	Ph	65	Oil
3e	Me	4-MeC_6H_4	Ph	CO_2Me	55	Oil
4a	Et	4-MeC_6H_4	H	Ph	90[a] (95)[b]	131 lit.[7a] mp 134–135
4b	Et	4-$MeOC_6H_4$	H	Ph	92[a] (96)[b]	103 lit.[7a] mp 100–101

[a]Yields of the base induced ring-opening.
[b]Yields of the thermal ring-opening.

Adducts **2** were heated under vacuum for 15 min to give the corresponding imidazoles[7a] and alkyl 3-oxo-3-phenylpropanoate which is a further evidence for the formation of 2-phenyl regioisomer (Sch. 2).[b]

The treatment of adducts **2** with an excess of $KMnO_4$–$FeSO_4$ at ice cooling for short time led to the formation of products having a second carbonyl absorption in their IR spectra at 1750, beside the absorptions at 1710 cm^{-1} corresponding to the ester carbonyl and $\nu_{C=C}$ at 1660 cm^{-1}. The AB system centred at 4.52 ppm assigned to C-6 methylene remains unchanged as well as remains the peak at 73.5 ppm in the ^{13}C NMR spectrum assigned to C-6. The ^1H NMR spectrum of the oxidation product of adduct **2e** shows only a singlet at 6.18 corresponding to C-6 proton and the carbonyl absorption is again at 1760 cm^{-1}.

EXPERIMENTAL

Melting points were taken on an electrothermal digital melting point apparatus. Infrared spectra were recorded on a Mattson 1000 FTIR. Proton

[b]The spectra of alkyl 3-oxo-3-phenylpropanoates were compared with the IR spectra of those obtained by Jons oxidation of the 3-hydroxy-3-phenylpropanoates. The latter were prepared from the Reformatsky reaction of alkyl bromoacetates and benzaldehyde.

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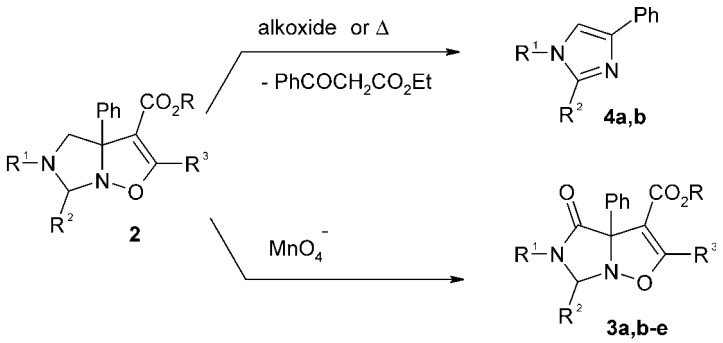

Scheme 2.

magnetic resonance spectra were recorded on a Bruker Dpx 400 MHz spectrometer. All spectra were taken in deuteriochloroform. Mass spectra were routinely recorded at 70 eV by electron impact. Visualisation was effected with UV light. Freshly prepared imidazoline 3-oxides were used after recrystallization from either ethanol or acetone.

Tetrahydroimidazo[1,5-*b*]isoxazolines 2. General Procedure

To a solution of imidazoline 3-oxide **1** (5 mmol) in toluene (20 mL) alkyl phenylpropinoate (5.2 mmol) was added. The mixture was refluxed for 24 hr. The solvent was removed under vacuum. The product was recrystallised from ethanol.

Ethyl-2,3a-diphenyl-5-(*p*-tolyl)-3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazole-3-carboxylate 2a. Yield 90%; mp: 117–120°C; IR (KBr) $\nu_{C=O}$ 1700 cm^{-1}; $\nu_{C=C}$ 1660 cm^{-1}. Anal. Calcd for $C_{27}H_{26}N_2O_3$ (426.52) C, 76.03; H, 6.14; N, 6.57; Found C, 76.10; H, 6.15; N, 6.55.

Ethyl 2,3a-phenyl-5-(*p*-methoxyphenyl)-3a,4,5,6-tetrahydroimidazo [1,5-*b*]isoxazole-3-carboxylate 2b. Yield 92%; mp: 110–114°C; IR (KBr) $\nu_{C=O}$ 1700 cm^{-1}; $\nu_{C=C}$ 1660 cm^{-1}. Anal. Calcd for $C_{27}H_{26}N_2O_4$ (442.52) C, 73.29; H, 5.92; N, 6.33; Found C, 73.35; H, 5.90; N, 6.38.

Methyl-2,3a-diphenyl-5-(*p*-tolyl)-3a,4,5,6-tetrahydroimidazo[1,5-*b*] isoxazole-3-carboxylate 2c. Yield 92%; mp: 137–138°C; IR (KBr) $\nu_{C=O}$ 1700 cm^{-1}; $\nu_{C=C}$ 1660 cm^{-1}. ^1H NMR δ 2.34 (3H, s), 3.59 (3H, s), 3.69 (1H, d, $J = 9.9$), 4.40 (1H, d, $J = 10.4$), 4.75 (1H, d, $J = 9.9$), 5.10 (1H, d, $J = 10.40$), 6.79 (2H, d, $J = 8.3$), 7.15 (2H, d, $J = 8.3$), 7.27–7.52 (6H, m), 7.66 (2H, d, $J = 7.4$), 7.72 (2H, d, $J = 7.6$). Anal. Calcd for

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$C_{26}H_{24}N_2O_3$ (412.49) C, 75.71; H, 5.86; N, 6.79; Found C, 75.68; H, 5.89; N, 6.81.

Methyl-2,3a-phenyl-5-(*p*-methoxyphenyl)-3a,4,5,6-tetrahydroimidazo [1,5-*b*]isoxazole-3-carboxylate 2d. Yield 95%; mp: 109–110°C; IR (KBr) $\nu_{C=O}$ 1700 cm^{-1}; $\nu_{C=C}$ 1660 cm^{-1}. ^1H NMR δ 3.45 (3H, s), 3.50 (1H, d, $J = 9.8$), 3.69 (3H, s), 4.20 (1H, d, $J = 10.4$), 4.58 (1H, d, $J = 9.8$), 4.94 (1H, d, $J = 10.4$), 6.71 (2H, d, $J = 8.9$), 6.78 (2H, d, $J = 8.9$), 7.13–7.42 (6H, m), 7.54 (2H, d, $J = 7.3$), 7.58 (2H, d, $J = 7.7$). Anal. Calcd for $C_{26}H_{24}N_2O_4$ (428.49) C, 72.88; H, 5.65; N, 6.54; Found C, 72.80; H, 5.61; N, 6.55.

Oxidation of Tetrahydroimidazo[1,5-*b*]isoxazoles with Potasium Permanganate. General Procedure[8]

To the powdered mixture of $KMnO_4$ (2 g, 12 mmol) and $FeSO_4 \cdot 7H_2O$ (1 g, 4 mmol) in a reaction flask water (0.1 mL) and dichloromethane (10 mL) was added. The mixture was cooled in an ice bath. Tetrahydroimidazo[1,5-*b*]isoxazole (1 mmol) dissolved in 0.5 mL *t*-BuOH was added and the mixture stirred for 15 min. The ice cooling was removed and after addition of 15 mL of ether the mixture was stirred for more 15 min at room temperature. The reaction mixture was filtered through a celite bad and dried over anhydrous Na_2SO_4. The solvent was evaporated on a rotary evaporator and the residue was subjected to silica gel packed column. Ethyl acetate petroleum ether was used as eluent.

2,3a-Diphenyl-5-*p*-tolyl-4-oxo-3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazole-3-carboxylic acid ethyl ester 3a. Yield 60%; IR (film); $\nu_{C=O}$ 1750, 1710 cm^{-1}, $\nu_{C=C}$ 1660 cm^{-1}. ^1H NMR δ 0.96 (3H, t, $J = 7.1$), 2.18 (3H, s), 3.93 (2H, q, $J = 7.1$), 4.08 (1H, d, $J = 9.8$), 4.97 (1H, d, $J = 9.8$), 7.04 (2H, d, $J = 8.5$), 7.17–7.33 (6H, m), 7.41 (2H, d, $J = 8.5$), 7.58 (2H, d, $J = 7.4$), 7.62 (2H, d, $J = 7.4$); ^{13}C NMR δ 14.2, 21.2, 52.7, 61.0, 73.5, 106.7, 119.4, 126.0, 126.7, 128.1, 128.7, 129.2, 130.1, 131.1, 132.1, 135.2, 135.9, 141.5, 160.3, 163.3, 165.6. MS $C_{27}H_{24}N_2O_4$ (440.50) m/z 440 (M^+).

5-(4-Methoxy-phenyl)-4-oxo-2,3a-diphenyl-3a,4,5,6-tetrahydroimidazo [1,5-*b*]isoxazole-3-carboxylic acid ethyl ester 3b. Yield 65%; IR (film); $\nu_{C=O}$ 1750, 1710 cm^{-1}, $\nu_{C=C}$ 1660 cm^{-1}; ^1H NMR δ 1.15 (3H, t, $J = 7.1$), 3.82 (3H, s), 3.93 (2H, q, $J = 7.1$), 4.26 (1H, d, $J = 9.8$), 5.14 (1H, d, $J = 9.8$), 6.98 (2H, d, $J = 8.5$), 7.20–7.50 (6H, m), 7.61 (2H, d, $J = 8.5$), 7.73–7.80 (4H, m) MS $C_{27}H_{24}N_2O_5$ (456.50) m/z 456 (M^+).

4-Oxo-3a-phenyl-5-*p*-tolyl-3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazole-2,3-dicarboxylic acid dimethyl ester 3e. Yield 55%; IR (neat); $\nu_{C=O}$ 1760, 1710 cm^{-1}, $\nu_{C=C}$ 1660 cm^{-1}. ^1H NMR δ 2.28 (3H, s), 3.72 (3H, s), 3.95 (3H,

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s), 6.18 (1H, s), 7.12 (2H, d, $J = 8.2$), 7.20–7.34 (10H, m), 7.76 (2H, d, $J = 8.2$) MS $C_{28}H_{24}N_2O_6$ (484.51) m/z 456 ($M^+ - 28$).

Base Induced Ring-Opening Reactions of Isoxazoles 2

To a solution of sodium alkoxide in methanol (30 mL, 9.5 mmol Na, 0.219 g) 3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazole-3-carboxylate **2** (3.17 mmol) was added. The mixture was refluxed for 2 hr. The solvent was evaporated and water was added to the residue and extracted with chloroform. The products were separated by column chromatography.

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