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The reactivity of 3-methyl-4-nitro-5-styrylisoxazole with some bis-enolisable ketones

Mauro F. A. Adamo,[a,*] Stefano Chimichi,[b] Francesco De Sio,[b] Donato Donati[c] and Piero Sarti-Fantoni[b]

[a]*Dyson Perrins Laboratory, University of Oxford, South Park Road, Oxford OX1 3QY, UK*
[b]*Dipartimento di Chimica Organica 'U. Schiff', Università di Firenze, Via della Lastruccia 13, 50019 Sesto Fiorentino, Italy*
[c]*Dipartimento di Chimica, Università di Siena, Via Aldo Moro, 53100 Siena, Italy*

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Abstract—The expected Michael adducts and spiroisoxazolines are obtained from the reaction between 3-methyl-4-nitro-5-styrylisoxazole and bis-enolisable ketones. Contrary to reported data, Michael adducts are obtained in good yields only when a substoichiometric amount of base is used, whereas spiroisoxazolines were obtained as the major product when the base is present in a large excess.

Heterocycles are widely utilised compounds in both pharmaceutical and agricultural fields,[1] consequently the development of methodologies useful for the assembly of molecules containing heterocyclic templates continues to attract the attention of both the academic and industrial communities. Among aromatic heterocycles, the isoxazole unit constitutes an easily accessible nucleus that is present in a number of natural and pharmacological compounds.[2]

3-Methyl-4-nitro-5-styrylisoxazole **1** (Fig. 1) represents a versatile building block bearing a number of different functionalities, which can be selectively reacted to generate molecularly diverse products, and several reports have appeared describing the reactivity of isoxazole **1**.[3–7] Basic hydrolysis followed by acidification yielded cinnamic acid **2** (Scheme 1); thus the 3-methyl-4-nitroisoxazol-5-yl group may be considered to be a masked carboxylic acid function.[3] Isoxazole **1** also proved to be an excellent photoreactive substrate, affording the symmetric cyclobutane **3** when irradiated in the solid state (s.s.), whereas additional dimers are also formed in benzene solution (sol.).[4]

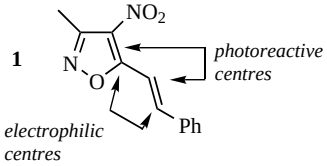

Figure 1.

The high reactivity produced in **1** by the conjugated nitro group renders the styryl moiety susceptible to attack by suitable soft nucleophiles. Rao et al. have reported the Michael addition of acetylacetone (acac)[5] or ethyl acetoacetate (eac)[6] to **1** with triethylamine as the solvent. Considering that it is possible to run the Knoevenagel condensation and Michael conjugate addition in a domino fashion,[7] we envisaged the possibility of building libraries of potentially useful heterocycles using four components in a one-pot assembly procedure (Scheme 2).

In order to investigate this multicomponent procedure we first decided to repeat the reaction between isoxazole **1** and acetylacetone, following the procedure reported by Rao et al. In a first report,[5] the authors state that, under these conditions, a product with the Michael adduct structure **4** (Scheme 1) having mp 170°C was obtained. In a second study the same compound was reported to have a different melting point (155°C).[8]

In our hands the reaction of isoxazole **1** with acetylacetone in triethylamine yielded a solid (A)[9] which, after

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* Corresponding author. Tel.: +44-(0)1865-275650; fax: +44-(0)1865-275674; e-mail: mauro.adamo@chemistry.ox.ac.uk

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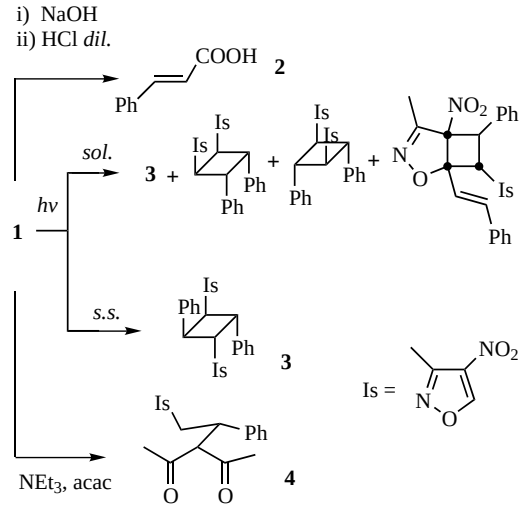
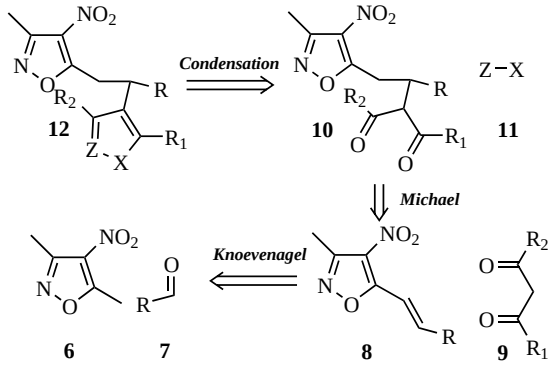


Scheme 1.



Scheme 2.

crystallisation from ethanol, showed mp 155°C. Treatment of solid A with dilute acid gave a solid compound (B) which after crystallisation from ethanol showed mp 170–171°C (B).[10]

Elemental analysis for solid A was in agreement with the empirical formula $C_{23}H_{33}N_3O_5$. The ^{1}H NMR spectrum indicated the presence of two non-equivalent methyl groups, and in the IR spectrum the diagnostic absorption expected for the 4-nitroisoxazole group (ca. 1600 cm^{-1}) was absent. Based on the chemical behaviour and spectroscopic data,[9] the structure assigned to solid A was that of 8-acetyl-9-phenyl-3-methyl-7-oxo-1-oxa-2-azaspiro[4.5]dec-2-ene-4-nitronate triethylammonium salt **13** (Fig. 2). X-Ray crystallographic analysis confirmed the structure **13** for solid A and allowed the determination of the relative configurations of the three stereocentres.[11]

The mass spectrum of solid B showed a signal at m/z 330, as expected for a 1:1 adduct between isoxazole **1** and acetylacetone, elemental analysis confirmed the empirical formula of this compound to be $C_{17}H_{18}N_2O_5$. The ^{1}H NMR and ^{13}C NMR spectra indicated the presence of two methyl groups while in the IR spectrum the absorption characteristic of the 4-nitroisoxazole group near 1600 cm^{-1} was again absent. On the basis of this data the structure assigned to solid B was that of 8-acetyl-3-methyl-4-nitro-9-phenyl-1-oxa-2-aza-spiro-[4.5]dec-2-en-7-one **14**.[10]

However, when isoxazole **1** was reacted with acetylacetone and a substoichiometric amount of piperidine in ethanol, a new compound (C)[12] was obtained, with mp 121–122°C. Elemental analysis again confirmed this product to be a 1:1 adduct between isoxazole **1** and acetylacetone, but in this case the ^{1}H NMR and ^{13}C NMR spectra indicated the presence of three non-equivalent methyl groups and the IR showed the presence of the 4-nitroisoxazole group.[12] The structure of solid C was therefore assigned as the expected Michael adduct **4**, and this was confirmed by X-ray crystallographic analysis.

A mechanistic rationale for the formation of products **4**, **13**, and **14** can be proposed (Scheme 3): initial Michael addition of acetylacetone to **1** gives the

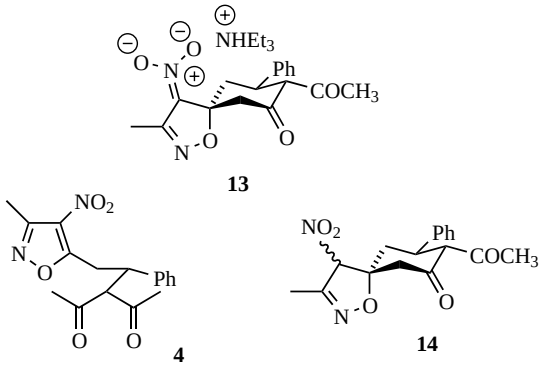
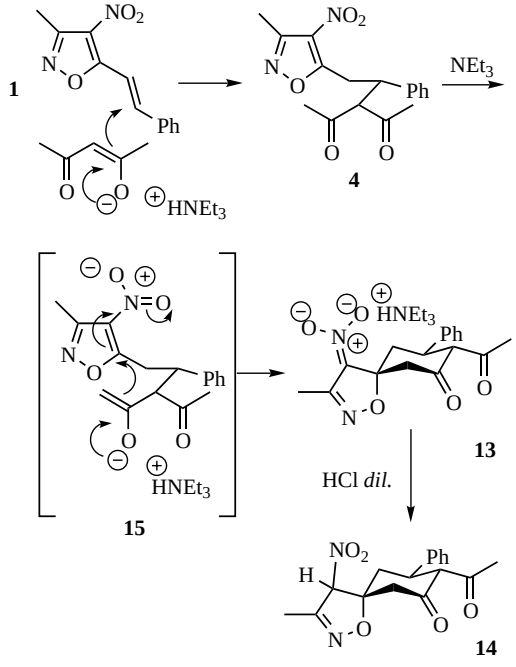


Figure 2.



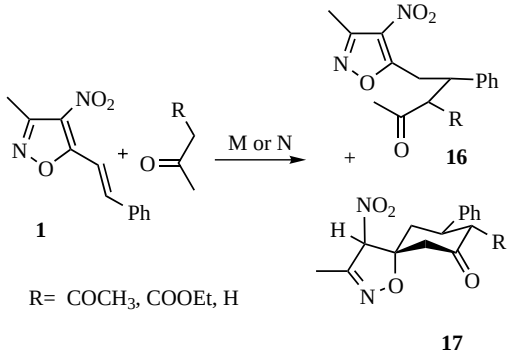
Scheme 3.

expected adduct **4** which, in the presence of a large excess of base (triethylamine) is enolised to give intermediate **15**, which subsequently cyclises to yield the stable spiroisoxazoline nitronate **13**. Treatment of nitronate **13** with dilute acid then gives isoxazoline **14**. Evidence for this proposal includes the fact that when a sample of pure Michael adduct **4** was treated with triethylamine, nitronate **13** was formed in 76% yield.

Ethyl acetoacetate and acetone behave similarly yielding **16** and **17** (Scheme 4) in different yields depending on the experimental conditions (Table 1).

The results indicate that the reaction of alkene **1** with bis enolisable ketones preferentially leads to Michael adducts **16** when the base is present in a substoichiometric amount (Table 1, entries 1, 3 and 5), while spiroisoxazolines **17** are obtained in moderate to good yields in the presence of a large excess of base (Table 1, entries 2, 4 and 6).

It is noteworthy that in compound **13** three chiral centres are introduced in a single step with a high degree of stereoselectivity; indeed only one racemate out of four possibilities was formed. This remarkable feature is probably related to the relative thermodynamic stability of spirocycle **13**, in which the phenyl and the acetyl group both occupy equatorial positions in the six-membered ring. In addition, molecular modelling energy calculations suggest that the nitronate group is orientated in the less hindered position.[13]



Scheme 4.

Table 1. Yields of **16** and **17** under conditions M[a] or N[b]

Entry	Conditions	Donor	% Yield of **16**[c]	% Yield of **17**[d]
1	M	acac	75	16
2	N	acac	20	75
3	M	eac	85	13
4	N	eac	31	56
5	M	Acetone	22	10
6	N	Acetone	6	21

[a] Conditions M: ratio acceptor:donor (1:10), ethanol, piperidine (0.3 equiv.), 65°C, 3 h.
[b] Conditions N: ratio acceptor:donor (1:10), triethylamine as solvent, 65°C, 6 h.
[c] Yield of isolated products after column chromatography.
[d] Yield of isolated products after crystallisation.

Considering that isoxazolines are versatile synthetic precursors[14] and that spiroisoxazolines themselves display interesting biological properties, including herbicidal, plant hormonal and antitumoural activity,[15] the easy and stereocontrolled access to multi-functionalised spiroisoxazolines via reaction of **1** with bis-enolisable ketones may be of interest in many fields of synthetic organic chemistry.

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9. **Triethylammonium 8-acetyl-9-phenyl-3-methyl-7-oxo-1-oxa-2-azaspiro[4.5]dec-2-ene-4-nitronate 13**: mp 155°C (acetone); IR: 3100–2300 cm^{-1} broad, 1725 cm^{-1} strong, 1697 cm^{-1} strong; ^1H NMR (200 MHz, $CDCl_3$) δ 7.4–7.2 (5H, m), 4.0–3.9 (2H, m), 3.1–2.9 (7H, m), 2.6–2.5 (1H, m), 2.2 (3H, s), 2.1–2.0 (2H, m), 2.0 (3H, s), 1.2 (9H, m). Anal. calcd for $C_{23}H_{33}N_3O_5$: C, 64.03; H, 7.65; N, 9.74; Found: C, 63.77; H, 7.92; N, 9.90.
10. **8-Acetyl-3-methyl-4-nitro-9-phenyl-1-oxa-2-aza-spiro[4.5]-dec-2-en-7-one 14**: mp 170–171°C (acetone); IR: 1710 cm^{-1} strong, 1702 cm^{-1} strong, 1575 cm^{-1} strong. m/z: 330, 287, 242, 187, 145, 131. ^1H NMR (200 MHz,

$CD_3CO\ CD_3$) δ 7.5–7.2 (5H, m), 5.9 (1H, s), 4.38 (1H, d, $J=12.6$), 3.77 (1H, td, $J=12.6$, $J=12.6$, $J=3.8$), 3.30 (1H, d, $J=14.3$), 2.70 (1H, dd, $J=14.3$, $J=2.7$), 2.59 (1H, t, $J=12.6$), 1.98 (3H, s), 2.12 (3H, s), 1.88 (1H, ddd, $J=12.6$, $J=3.8$, $J=2.7$). ^{13}C NMR (80 MHz, CD_3COCD_3) δ 204.1, 203.5, 151.7, 142.4, 129.6, 128.2, 128.0, 99.8, 89.4, 67.8, 49.9, 45.3, 42.1, 31.1, 12.0. Anal. calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.45; N, 8.48; Found: C, 61.77; H, 5.48; N, 8.21%.

11. Full details of the crystal and molecular structure will be published elsewhere.
12. **4-Methyl-3-[2-(3-methyl-4-nitro-isoxazol-5-yl)-1-phenyl-ethyl]-pent-4-en-2-one 4**: mp 121–122°C; IR: 1705 cm^{-1} strong, 1600 cm^{-1} strong, 1520 cm^{-1} medium, 1375 cm^{-1} medium. m/z: 287, 245, 147, 103. ^1H NMR (200 MHz, $CDCl_3$) δ 7.3–7.1 (5H, m), 4.3 (1H, d, $J=12$), 4.2–4.1 (1H, m), 3.6–3.3 (2H, m), 2.45 (3H, s), 2.3 (3H, s), 1.9 (3H, s). ^{13}C NMR (80 MHz, $CDCl_3$) δ 199.2, 198.5, 172.3, 158.1, 138.7, 131.4, 129.3, 128.2, 128.0, 127.8, 75.4, 43.4, 32.1, 30.7, 12.7. Anal. calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.45; N, 8.48; Found: C, 61.58; H, 5.24; N, 8.28.
13. AM1 calculations performed using the MOPAC package implemented in ChemOffice 6.0, CambridgeSoft.Com.
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