Sequential Addition of 2-Potassio-2-nitropropane and Oxygen to 4-Arylidene-oxazol-5-ones: A New Method for 2-Aryl Butenoic Acid Imides†

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The regiospecific addition of 2-potassio-2-nitropropane to the 4-arylidene-oxazol-5-ones followed by oxygenation led to 2-arylbutenoic acid imides, the key intermediate for several pharmacodynamic compounds in high yields.

The versatility of 4-arylidene-oxazol-5-ones, commonly known as azlactones, as useful synthons for several biologically active compounds including cyclopropane carboxylic acid derivatives has been well recognised.[1] We previously reported the triethylamine-mediated stereospecific cyclopropanation of azlactones with diphenyl diazomethane.[2] In continuation of our interest in making cyclopropane carboxylic acid derivatives that contain a *gem*-dimethyl group from azlactones, we have searched for alternative cyclopropanating agents. It has been shown by Krief *et al.*[3] that the reaction of 2-metallo-2-nitropropane with electron-deficient alkenes gives the corresponding cyclopropane derivative. When this strategy was adopted with azlactones, we obtained 2-arylbutenoic acid imides instead of the desired cyclopropanation.

Treatment of (*Z*)-2-phenyl-4-benzylidene-oxazol-5-ones‡ **1a** with 2-potassio-2-nitropropane **2** (generated *in situ* with KOH in DMSO) gave a single product **3** as colourless solid (90% yield) m.p. 180 °C.§ Elemental analyses coupled with CI mass spectral data¶ led to the formula $C_{18}H_{18}N_2O_4$, indicating the addition of a nitropropyl group to the azlactone and loss of one carbon. Finally the structure of the product has been shown to be *N*-benzoyl-3-methyl-3-nitro-2-phenylbutanoic acid imide **3a** on the basis of IR and NMR data.‖ Compound

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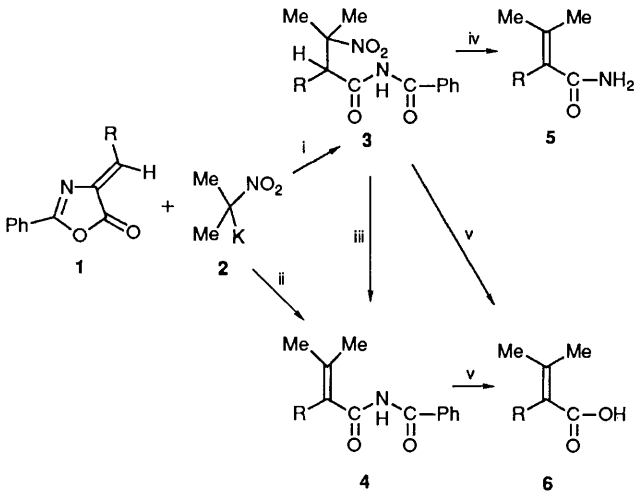
‡ Compound **I** was synthesised by treating the corresponding aldehyde (ref. 5) with benzoyl glycine in acetic anhydride and sodium acetate (freshly fused).

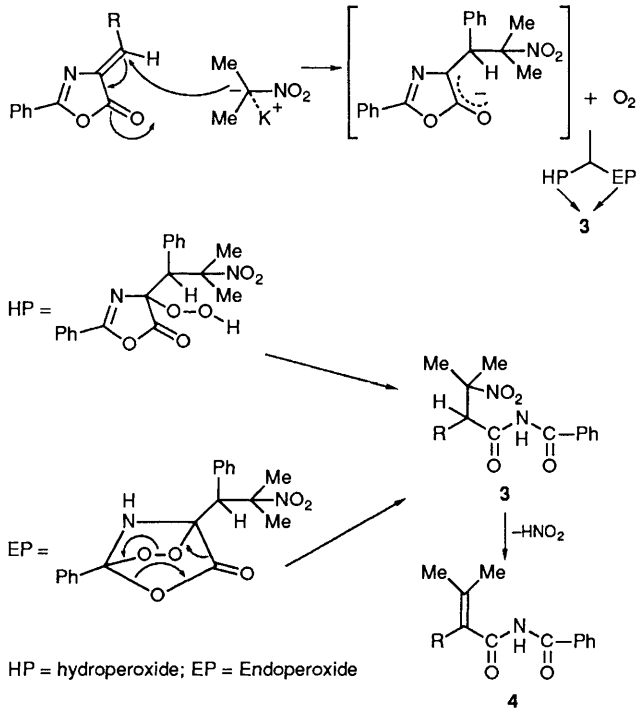
§ Typical reaction conditions were azlactone **1** (5 mmol dm^{-3}), 2-nitropropane (Fluka grade, freshly distilled, 5 mmol dm^{-3}), KOH (5 mmol dm^{-3}), TEBA (2 mol%) in 80 ml benzene under oxygen atmosphere were stirred at ambient temperature. The reactions (**1–3**) generally proceeded to completion in 5–8 h. The reaction was monitored by TLC using benzene as an eluent.

¶ The mass spectrum observed for compound **3** (measured on Micromass 7070 H model) at 70 and 20 eV indicated M^+ at 271 ($M - HNO_2$) but under CI conditions gave (M + 1) at 327 which exactly matched with elemental analysis.

‖ The structure was confirmed by spectral and analytical data. M.p. 180 °C (1.467 g, 90% yield), Mass (M^+) 326; IR($CHCl_3$): 3300, 1710, 1675, 1535 and 1230 cm^{-1} PMR (δ, $CDCl_3$): 1.65 and 1.80 (s, 3H, 3H of CH_3), 7.11–7.72 (m, 10H, Ar*H*), 8.44 (br., 1H, N*H*) and 5.84 (s, 1H, C_6H_5CHCOR).



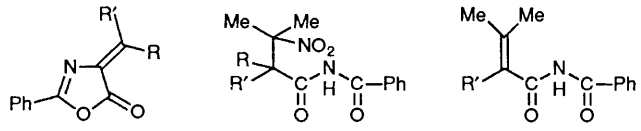
Scheme 1 *Reagents and conditions*: i, DMSO, 28 °C, O_2, 5 h; ii, benzene, TEBA (1 mol%), 6–12 h, with an excess of alkali and O_2; iii, KOH in methanol at room temp.; iv, sodium borohydride in dry methanol for ½ h; v, KOH aq. (40%) refluxing for 2–5 h



Scheme 2 Sequential Michael addition of 2-potassio-2-nitropropane and oxygen to the azlactone **1**

3a on treatment with alkali at ambient temperature gave the corresponding butenoic acid imide **4a** with loss of HNO_2 but at refluxing temperature smoothly converted to the acid **6**. Reaction of **3** with sodium borohydride in dry methanol, resulted in the partial cleavage of the imide linkage giving the methyl atropic amide **5** as evidenced by mass, IR and NMR data. The structure of **5** has further been substantiated by establishing its identity with authentic material made from benzyl cyanide and acetone.[4] The reaction of **2** with **1** proceeds smoothly in other solvents such as tetrahydrofuran and acetonitrile (slower). However, when the reaction was carried out in benzene using a phase-transfer catalyst, the triethyl benzylammonium chloride (TEBA) afforded **4** directly in 80% yield.

Table 1 Formation of novel imides **3** and **4** under different reaction conditions



Entry	R	R′	Reaction conditions[a]	*t*/h	Yield (%) **3**	Yield (%) **4**
a	H	Ph	*A*	5	90.0	—
			B	8	—	90.0
b	Ph	H	*A*	5	90.0	—
			B	8	—	90.0
c	H	*p*-$MeOC_6H_4$-	*A*	6	80.0	—
			B	8	—	80.0
d	H	*p*-Cl-C_6H_4-	*A*	6	80.0	—
			B	8	—	80.0
e	H	*p*-NO_2-C_6H_4-	*A*	10	—	40.0
			B	12	—	60.0
f	H	2-Furyl	*A*	10	—	20.0
			B	12	—	40.0

[a] Method *A*: dimethyl sulphoxide/28 °C/O_2/2-potassio-2-nitropropane salt (1 mol). Method *B*: benzene/TEBA/28 °C/O_2/2-nitropropane/potassium hydroxide (2 mol).

Formation of **3** and **4** appears to be dependent on the availability of oxygen in the medium. This was indicated when the unreacted azlactone **1** was recovered without any product formation under a nitrogen atmosphere, while application of a slow stream of oxygen to the reaction medium gave **3** or **4** more quickly (5 h completion point is extended to 8 h in the presence of air). The present investigation provides a facile method for making butenoic acid derivatives in a single pot reaction starting from easily accessible azlactones.[5] The compounds prepared, **3** and **4**, by this reaction are listed in Table 1.

It is reasonable to assume that the Michael type addition of the 2-nitropropane anion to the ylidene double bond of **1** is the initial step of the mechanism to give **A**. The resonance stabilised anion **A** then reacts with the molecular oxygen leading to the hydroperoxide/endoperoxide intermediate (HP or EP) which can subsequently fragment to the product **3** and carbon dioxide. Controlled experiments have shown a rapid absorption of oxygen during the reaction and in fact a stoichiometric quantity of carbon dioxide was isolated as potassium carbonate.

This mechanism finds precedence in the literature where the saturated azlactones react with oxygen in the presence of Pd–C to give the acyclic imides.[6] Only one report of the oxygenation of unsaturated azlactones by Warnhoff *et al.*[7] describes the formation of imide as one of the products (40% yield) in the presence of triethylamine, invoking hydroperoxide (HP)/endoperoxide (EP) intermediates. It is pertinent to note that normally azlactones do not react with oxygen except as shown in a recent report on the photooxygenation of 2-oxazol-5-ones.[8] Though a few oxygenations of azlactones as mentioned above have been cited in the literature, the sequential Michael addition and oxygenation observed in the present investigation is the first in the chemistry of azlactones.

Preliminary screening of the new imides reported herein indicate encouraging antibacterial action against Gram positive and negative strains.**

** The new compounds prepared **3a–f** and **4a–f** have shown significant antibacterial activity against *B. subtilis*.

Work is in progress to obtain an insight into the mechanistic aspects and apply this reaction for the synthesis of other biologically active molecules such as Ibuprofen.

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