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Application of Michael Reaction on 2-Phenyl-5-Oxazolone

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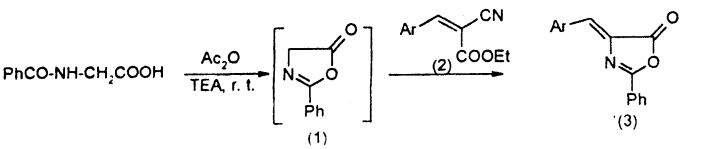
Michael reaction has been applied on 2-phenyl-5-oxazolone ring (1), which was used as Michael donor with arylmethylene-cyanoacetic acid ethyl ester (2) as Michael acceptor. The Michael adducts had not been isolated but arylmethylene-2-phenyl-5-oxazolone (3) have been separated.

Key Words: Michael reaction, 2-Phenyl-5-oxazolone.

INTRODUCTION

Oxazolones have been used as intermediate in syntheses of amino acids, peptides, arylacetic acids and many natural products[1]. Michael addition had been applied to unsaturated azlactones* (3), which was used as Michael acceptor with arylmagnesium halides and phenyllithium[2,3]. Also compound (3) was reacted with ethylcyanoacetate to give oxonitrile compound[4]. Unsaturated azlactones also reacted as Michael acceptors with enamines to give respective amides[5]. In this paper we have reported the reaction of compound (1) (which was obtained by cyclization of hippuric acid in acetic anhydride)[6,7] as Michael donor with aryl-methylene cyanoacetic acid ethyl ester (2), **Scheme-1.**



a = Phenyl
b = *p*-Methoxyphenyl
c = *p*-Nitrophenyl
d = *o*-Nitrophenyl
e = *p*-Hydroxyphenyl

Scheme-1

EXPERIMENTAL

All chemicals used are of chemically pure grade. m.p.s were determined on Griffin apparatus and were uncorrected. ^{1}H NMR spectra were recorded on

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Brucker 200 MHz instrument, in $CDCl_3$ solution. Chemical shifts are given in δ values against TMS as internal standard. IR spectrum of compound (3a) was measured on Maltson 5000 FT-IR spectrometer as KBr pellets. Microanalyses were performed by C.S.I.C. Raslanoff Company.

Arylmethylenecyanoacetic acid ethyl esters (2a–e) were prepared according to the reported method[8] and crystallized from ethanol.

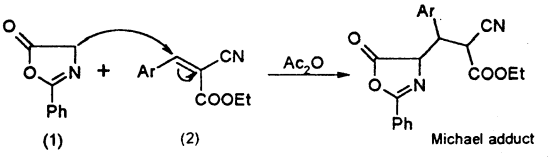
Syntheses of unsaturated azlactones (3a–e): Hippuric acid (0.01 mol) was suspended in 15 mL acetic anhydride; 3–4 drops of triethylamine were added. The reaction mixture was stirred for 15 min at room temperature, then 0.01 mol of compound (2) was added gradually. The stirring of reaction mixture was continued until the completion of reaction was observed; then the solvent was evaporated under vacuum and the product was filtered and crystallized from benzene.

RESULTS AND DISCUSSION

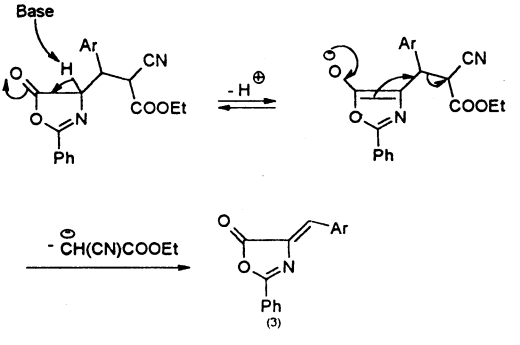
4-Arylmethylene-2-phenyl-5-oxazolone (3) was prepared by refluxing hippuric acid in presence of sodium acetate with arylaldehyde[6, 7]. The same product was also obtained when compound (1) was reacted with compound (2) at room temperature in presence of acetic anhydride and few drops of triethylamine. The structures of compound (3a–e) were confirmed by satisfactory elemental analyses, IR and ^1H NMR spectra (Tables 1 and 2).

The formation of unsaturated azlactones (3) can be explained by the attack of nucleophilic carbon in compound (1) on the β-carbon in α,β-unsaturated system of compound (2) giving Michael adducts, which had been further reacted by losing ethylcyanoacetate forming unsaturated azlactones (3). These steps are illustrated in **Scheme-2**:

Step (1): Michael Addition Reaction:

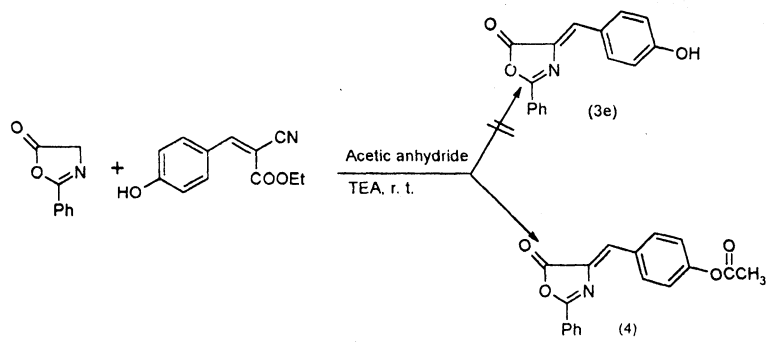


Step (1): Retro Michael Reaction:



Scheme-2

Although the method of preparation of unsaturated azlactones **(3)** *via* Michael reaction was quite general for all arylmethylenecyanoacetic acid ethyl ester **(2),** it has been noted that the substitution on aromatic ring of compound **(2)** have a considerable effect on the reaction time and the yield of the products **(3).** However, *p*-nitrophenylmethylenecyanoacetic acid ethyl ester **(2c)** was reacted with compound **(1)** to give **(3c)** in the highest yield and consumed the least reaction time. The reactivity of **(2c)** is due to the electron withdrawing effect of the nitro group which lower the electron density of the double bond[9], which facilitate the Michael addition. Reaction of **(1)** with p-hydroxyphenylmethylene-cyanoacetic acid ethyl ester **(2e),** the expected 4-(*p*-hydroxyphenylmethylene)-2-phenyl-5-oxazolone **(3e)** was not isolated, but instead the 4-(p-acetoxyphenyl-methylene)-2-phenyl-5-oxazolone **(4)** was obtained, **Scheme-3.**



Scheme-3

TABLE-1
ANALYTICAL AND PHYSICAL DATA OF THE COMPOUNDS

Compd.	m.p. (°C)	Yield (%)	m.f. (mol. mass)	Analyses %, Found (Calcd.)		
				C	H	N
3a	162	74	$C_{16}H_{11}NO_2$ (249.27)	76.77 (77.10)	4.47 (4.45)	5.46 (5.62)
3b	149–150	65	$C_{17}H_{13}NO_3$ (279.29)	73.23 (73.11)	4.66 (4.69)	4.70 (5.02)
3c	229	87	$C_{16}H_{10}N_2O_4$ (294.27)	64.89 (65.31)	3.42 (3.43)	9.23 (9.52)
3d	210–212	73	$C_{16}H_{10}N_2O_4$ (294.27)	5.05 (65.31)	3.53 (3.43)	9.25 (9.52)
4	179–179	61.50	$C_{18}H_{13}NO_4$ (307.30)	70.29 (70.35)	4.26 (4.26)	4.49 (4.56)

Compound **(4)** was formed through acylation of the phenolic group of compound **(2e).** This acylation process was confirmed by the presence of singlet

signal at $\delta = 2.32$ ppm for 3H of $OOCC\underline{H}_3$ group. Also the melting point of compound **(4)** is (178–179°C) which is not identical with compound **(3e)** (109°C)[10].

TABLE-2
SPECTROSCOPIC DATA OF THE PRODUCTS

Compd.	Spectroscopic Data (^{1}H NMR and IR)
3a	$\delta = 8.20$–8.30 (m, 4H, ArH), 7.40–7.60 (m, 6H, ArH), 7.30 (s, 1H, CH) ν_{max} (cm^{-1}) = 3063 (=CH, ArH), 1790 (C=O cyclic ester), 1651 (C=C and/or C=N), 1162 (C—O), 751 an 686 (mono substituted aromatic).
3b	$\delta = 8.15$–8.25 (m, 4H, ArH), 7.45–7.60 (m, 3H, ArH), 7.25 (s, 1H, CH), 7.0 (d, 2H, ArH), 3.90 (s, 3H, OCH_3).
3c	$\delta = 8.0$–8.30 (m, 5H, ArH), 7.60–7.80 (m, 4H, ArH), 7.20 (s, 1H, CH).
3d	$\delta = 8.30$–8.10 (m, 4H, ArH), 7.4–7.6 (m, 5H, ArH), 7.22 (s, 1H, CH).
4	$\delta = 8.10$–8.25 (m, 4H, ArH), 7.50–7.70 (m, 3H, ArH), 7.15–7.30 (m, 3H, ArH) and (s, 3H, $OOCCH_3$).

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