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Graphical Abstract

Synthesis of 3-methyl-4-arylmethylene isoxazole-5(4H)-ones by visible light in aqueous ethanol

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CH₃ Ar - CHO + $\stackrel{\Theta}{\text{Cl}} \stackrel{\Theta}{\text{NH}_3\text{OH}}$ + $< \stackrel{\text{COCH}_3}{\text{CO}_2\text{C}_2\text{H}_5} = \frac{\text{CH}_3\text{COONa} / \text{aq.C}_2\text{H}_5\text{OH} / \text{hv}}{5-10 \text{ min}}$

Synthesis of 3-methyl-4-arylmethylene isoxazole-5(4H)-ones by visible light in aqueous ethanol

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ABSTRACT

A highly efficient methodology for the synthesis of 3-methyl-4-arylmethylene-isoxazole-5(4H)ones has been developed by visible light induced multicomponent reaction of aromatic aldehydes, ethyl acetoacetate, hydroxylamine hydrochloride and sodium acetate in aqueous ethanol *sans* any phase transfer catalyst or promoter.

Keywords: Multicomponent reaction 3-Methyl-4-arylmethylene-isoxazole-5(4H)-ones Visible light Aqueous ethanol

Isoxazole scaffolds, bearing both oxygen and nitrogen atoms, are important heterocyclic compounds and possess various pharmacological activities. These heterocycles can act as anti-bacterial, immunosuppressive, anti-inflammatory compounds, and show hypoglycemic activity.¹ In addition, several isoxazole derivatives have been employed as versatile building blocks in organic synthesis.² Hence, these molecules are attractive target for the synthesis.³

The traditional procedure for the synthesis of the title compound consists of two consecutive steps⁴ *viz.* a) formation of an oxime by the reaction of ethyl acetoacetate and hydroxylamine hydrochloride followed by ring closure affords 3-methyl-isoxazole-5(4H)-ones; b) a Knoevenagel condensation reaction between 3-methyl-isoxazole-5(4H)-ones and aromatic aldehydes, which finally gives 3-methyl-4-arylmethylene-isoxazole-5(4H)-ones. More recently, several other methodologies involving solid state heating or solid state grinding,⁵ multicomponent reaction,⁶ ultrasonic irradiation⁷ and stirring in water⁸ or ethanol at room

temperature in the presence of catalyst⁹ have also been described. However, in most of the cases either long reaction time or harsh reactive conditions are required.

Photochemical reactions particularly using visible light in organic synthesis in ecofriendly solvents like water or aqueous-ethanol are extremely useful and are generally considered as clean and green procedure. This type of *photo*-activation of substrates very often minimizes the formation of byproducts and requires much lesser time compared to thermal methods; and for this reason, photochemical reactions occupy an interesting position and some fascinating reviews^{10, 11} on this subject are available in the literature.

In connection with our continued interest for the photochemical synthesis of biologically active heterocyclic compounds employing ultraviolet radiation¹² and visible light,¹³ we wish to report here, for the first time, a new, expeditious and eco-friendly visible light induced multi-component reaction in aqueous-ethanol for the synthesis of 3-methyl-4-arylmethylene-isoxazole-5(4H)-ones (Scheme 1).

[Please insert Scheme 1 here]

The present procedure for the multicomponent synthesis of isoxazolone derivatives consists of *photo*-irradiation of aromatic aldehydes, ethyl acetoacetate, hydroxylamine hydrochloride and sodium acetate in aqueous-ethanol for *ca*. 5-10 min only on an average and the products are obtained with an average yield of 56–89%. The utmost advantage of this procedure is that the desired products are obtained in almost analytical grade crystalline form from the reaction mixture either on cooling or by dilution with water and requires no further chromatographic separation. The results of these experiments are given in Table 1. It was also observed that aromatic aldehydes containing electron donating groups smoothly participate in the reaction whereas, under the same reaction condition aromatic aldehydes containing electron withdrawing group (nitro or chloro) failed to afford the desired product; and only the corresponding oxime of the aldehydes such as formaldehyde or acetaldehyde did not participate in the reaction.

[Please insert Table 1 here]

In order to check the efficacy of the photochemical reaction as compared to thermal reaction, the multicomponent reaction was performed with 4-methoxybenzaldehyde, ethyl acetoacetate, hydroxylamine hydrochloride and sodium acetate in aqueous-ethanol under refluxing condition for 4 h. The reaction mixture became a sticky reddish oily material after dilution with water and 3-methyl-4-(4-methoxyphenyl) methylene-isoxazole-5(4H)-one (4c) was obtained by chromatography in only 18% yield. However, the same combination of substrates under identical condition in the presence of light afforded 4c in much higher yield (82%) in a significantly lesser time (10 min), in purely crystalline form after dilution of the reaction mixture. Similar experiment with indole-3-aldehyde for 2 h afforded 4i in 51% yield, whereas photochemical reaction using the same substrate for only 18 min yielded 56% of the product. This clearly shows that the present photochemical method is much superior to the conventional thermal one.

It has been reported⁹ by Liu and Hou that the formation of the title compound proceeds through the intermediacy of a Knoevenagel adduct of the preformed oxime of ethyl acetoacetate followed by ring closure in the presence of sodium sulphide. We, therefore, tried first to prepare the Knoevenagel condensation product with ethyl acetoacetate and 4-methoxybenzaldehyde in the presence of sodium acetate in refluxing aqueous ethanol. However, the condensation product was not obtained. This, therefore, led us, in the present instance, to speculate that the reaction may plausibly be initiated by an electron transfer from hydroxylamine in the presence of light to the carbonyl group of ethyl acetoacetate to produce a radical anion (I) that subsequently transforms to oxime (II). The intermediate (II) then undergoes a *photo*-lactonization by a SET pathway through (III) to generate isoxazolone (IV) which on further reaction with aldehydes affords **4** *via* a *photo*-Knoevenagel reaction^{13b} as depicted in Scheme 2.

[Please insert Scheme 2 here]

The structure of 3-methyl-4-(4-methoxyphenyl) methylene-isoxazole-5(4H)-one (**4c**) was confirmed by X-ray crystallography and the ORTEP view is presented in Figure 1. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 924978.

[Please insert Figure 1 here]

Single crystals of suitable quality for X-ray diffraction study of compound, 3-methyl-4-(4-methoxyphenyl) methylene-isoxazole-5(4H)-ones (**4c**), were grown by slow evaporation from acetone hexane mixture (1:1 ν/ν). The X-ray intensity data were measured at 296 K on Bruker AXS SMART APEX CCD diffractometer (Mo K_a λ = 0.71073 Å). The detector was placed at a distance 6.03 cm from the crystal. The data were reduced in SAINTPLUS¹⁴ and empirical absorption correction was applied using the SADABS package.¹⁴ All the non hydrogen atoms were located by Direct Methods. The structures were refined by full matrix least-square procedure on F^2 . All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were added theoretically and riding on the concerned atoms. Calculations were performed using the SHELXTL v.6.14^{15, 16} program package. Molecular structure plots were drawn using ORTEP.¹⁷ Relevant crystal data are given in Table 2,

[Please insert Table 2 here]

In conclusion, we have developed an efficient, environment-friendly, high yielding and one-pot three-component reaction for the synthesis of 3-methyl-4-arylmethylene-isoxazole-5(4H)-ones in aqueous ethanol. This new method¹⁸ is devoid of any unwarranted side reactions and may be considered as an excellent improvement over the existing methods.

Acknowledgments

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- 18. Method: Equivalent amounts (10 mmol) of different aromatic aldehydes, ethyl acetoacetate, hydroxylamine hydrochloride and sodium acetate were taken in aqueousethanol mixture (20 mL, 1:1 v/v) and irradiated with a 150W tungsten lamp (Philips India Ltd). The reaction time varied on an average from 5-10 min (monitored by TLC after 5 min. interval). Upon completion of the reaction, the reaction mixture was cooled and the crystalline product so obtained was filtered, washed with water and dried in *vacuo*. The desired compounds, 3-methyl-4-arylmethylene-isoxazole-5(4H)-ones (**4**) were isolated in high yields in essentially pure form.

3-Methyl-4-(2, 4-dimethoxyphenyl) methylene-isoxazol-5-(4H)-one (**4e**): Yellow needle shaped crystal. Yield: 87%; mp. 191°C. IR (KBr) v_{max} 3447, 2947, 2366, 1746, 1730, 1590, 1472, 1424, 1382, 1305, 1281, 1217 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 22°C) δ 2.27 (s, 3H), 3.91 (s, 6H), 6.43 (d, *J* = 2.3Hz, 1H), 6.63 (dd, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, J = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, J = 9.0 Hz, 2.3 Hz, 1H), 7.97 (s, 1H), 9.22 (d, J = 9.0 Hz), 9.0 Hz, 9.0 Hz,

1H) ppm; ¹³C NMR (75 MHz, CDCl₃, 22°C) δ 169.3, 166.9, 162.2, 161.8, 143.0, 136.1, 115.5, 114.7, 105.9, 97.7, 55.9, 55.8, 11.6 ppm; HRMS (ESI) m/z [M⁺⁺ + H] 248.0334.

3-Methyl-4-(3, 4-dimethoxyphenyl) methylene-isoxazol-5-(4H)-one (**4f**): Yellow needle shaped crystal. Yield: 83%; mp. 135°C. IR (KBr) v_{max} 2938, 2836, 1729, 1587, 1554, 1519, 1439, 1376, 1336, 1279, 1213 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 22°C) δ 2.26 (s, 3H), 3.98 (s, 6H), 6.94 (d, *J* = 8.4 Hz, 1H), 7.31 (s, 1H), 7.58 (dd, *J* = 8.4 Hz, 1.8 Hz, 1H), 8.72 (s, 1H) ppm; HRMS (ESI) m/z [M⁺⁺ + H] 248.2197.

3-Methyl-4-(3, 4-methylynedioxyphenyl) methylene-isoxazol-5(4H)-one (4g): Yellow needle shaped crystal. Yield: 79%; mp. 204°C. IR (KBr) v_{max} 3448, 3085, 2912, 2369, 1730, 1608, 15984 1498, 1452, 1278 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 22°C) δ 2.27 (s, 3H), 6.11 (s, 2H), 6.93 (d, J = 8.23 Hz, 1H), 7.29 (s, 1H), 7.68 (d, J = 9.6 Hz, 1H), 8.42 (d, J = 1.4 Hz, 1H) ppm; ¹³C NMR (75 MHZ, CDCl₃, 22°C) δ 168.5, 161.1, 153.1, 149.2, 148.5, 132.8, 127.4, 116.8, 112.3, 108.7, 102.4, 11.5 ppm; HRMS (ESI) m/z [M⁻⁺ + H] 231.7979.

3-Methyl-4-(2-thiaphenyl) methylene-isoxazol-5(4H)-one (**4h**): Yellow needle shaped crystal. Yield: 89%; mp. 147°C (lit.^{9c} mp. 145-147°C). ¹H NMR (300 MHz, CDCl₃, 22°C) δ 2.29 (s, 3H), 7.27 (dd, *J* = 4.9, 4.0 Hz, 1H), 7.61 (s, 1H), 7.93 (d, *J* = 5.0 Hz, 1H), 8.11 (d, *J* = 3.5 Hz, 1H) ppm; ¹³C NMR (75 MHz, CDCl₃, 22°C) δ 168.6, 160.6, 141.4, 139.5, 139.1, 136.5, 128.9, 114.6, 11.4 ppm; HRMS (ESI) m/z [M⁺ + H] 194.0270.

3-Methyl-4-(3-indolyl) methylene-isoxazol-5(4H)-one (**4i**): Orange needle shape crystal. Yield: 56%; mp. 240°C (lit.^{6b} mp. 239-241 ° C). ¹H NMR (300 MHz, CDCl₃, 22°C) δ1.99 (s, 3H), 6.97 (m, 2H), 7.19 (m, 1H), 7.52 (d, *J* = 5.3 Hz, 1H), 7.55 (s, 1H), 9.26 (d, *J* = 3.4 Hz, 1H) ppm; ¹³C NMR (75 MHz, CDCl₃, 22°C) δ175.6, 165.9, 143.9, 143.8, 141.1, 132.9, 128.7, 127.6, 122.86, 117.9 117.7, 114.1, 16.3 ppm; HRMS (ESI) m/z [M^{.+} + H] 227.0204.



Scheme 1. Photochemical synthesis of 3-methyl-4-arylmethylene-isoxazol-5(4H)-ones



Scheme 2. Plausible mechanistic pathway for the photochemical synthesis of 3-methyl-4arylmethylene isoxazole-5(4H)-ones

MA

Table 1

Results of visible light promoted synthesis of **3-methyl-4-arylmethylene-isoxazole-5(4H)-ones**

Entry	Reactant	Product ^a	Mp.	Time	Yield ^b
				(min.)	(%)
1	CHO 1a	4a O O N	139°C (lit. ⁸ mp. 141-143°C)	15	61
2	HO 1b	HO $ CH_3$ 4b O O N	196°C (lit, ⁸ mp. 214-216°C)	10	66
3	H ₃ CO 1c	$H_3CO - CH_3$ 4c O O N	176°C (lit. ⁸ mp. 175-177°C)	10	82
4	HO CHO OCH ₃ Id	H ₃ CO HO 4d O O N	212°C (lit. ⁸ mp. 211-214°C)	10	68
5	H ₃ CO CHO OCH ₃ 1e	H ₃ CO 4e O N	191°C	5	87
6	H ₃ CO If	H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3CO H_3C	135°C	4	83
7	O Ig	4g O O N CH ₃	204°C	3	79



^a: All products were characterized by their satisfactory spectral data and also by comparison with literature data; ^b: Yield refers to combined amounts of first and second crops of crystallized products.

.... amounts of fi

Table 2

Crystal data and structure refinement parameters for **3-methyl-4-(4-methoxyphenyl)** methylene-isoxazole-5(4H)-ones (4c)

3-Methyl-4-(4-methoxyphenyl)-methylene-isoxazole-5(4H)-ones (4c)				
formula	C ₁₂ H ₁₁ NO ₃			
$F_{ m W}$	217.22			
crystal system	Monoclinic			
space group	P21/c			
<i>a</i> [Å]	12.8059(5)			
<i>b</i> [Å]	6.9143(3)			
c [Å]	12.7500(5)			
α [°]	90.00			
$oldsymbol{eta}$ [°]	111.890(2)			
γ[°]	90.00			
V[Å ³]	1047.54(7)			
Z	4			
Dcalcd [mg m ³]	1.377			
μ [mm ⁴]	0.100			
$oldsymbol{ heta}$ [°]	1.71, 27.59			
T [K]	296(2)			
Unique Reflections/Rint	2027/0.0649			
$R1^{a} wR2^{b} [I > 2 \phi I)]$	0.0649, 0.1470			
GOF on F^2	1.127			

^a R1 = |Fo| - |Fc| |Fo| |Fo| $|WR2 = [W(Fo^2 - Fc^2)^2 / W(Fo^2)^2]^{1/2}$



Figure 1. ORTEP view of 3-Methyl-4-(4-methoxyphenyl) methylene-isoxazole-5(4H)-ones (4c) is represented by 35% thermal probability ellipsoid.