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The convenient synthesis of 4-arylmethylidene-4,5- dihydro-3-phenylisoxazol-5-ones

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Abstract

4-Arylmethylidene-4,5-dihydro-3-phenylisoxazol-5-ones were synthesized by the convenient three-component reaction of ethyl benzoylacetate, hydroxylamine and aromatic aldehydes in the presence of pyridine. The target compounds were also obtained by the reaction between 3-phenylisoxazol-5-one and aromatic aldehydes at 105 °C under solvent free condition. Yields of products depended considerably on the aldehyde used.

Keywords: Isoxazole; One-pot synthesis; Three-component reaction

Isoxazole compound have attracted increasing interest due to their significant pharmaceutical and therapeutic properties, such as hypoglycemic [1], immunosuppressive [2], anti-inflammatory [3], and anti-bacterial activity [4]. Isoxazole derivatives have served as a versatile building block in organic synthesis [5]. In addition, the synthesis of isoxazole derivatives has drawn more attention because of their wide range of application in medicinal chemistry [6].

Being a high efficient and economic method, one-pot synthesis is an important way and become the most popular in heterocyclic chemistry [7]. One-pot synthesis mainly decreases the reaction time as well as cut out purification in reaction process [8]. The traditional synthesis of 4-arylmethylidene-4,5-dihydro-3-phenylisoxazol-5-one was carried out in two steps [9,10]. At first step, ethyl benzoylacetate reacts with hydroxylamine hydrochloride to afford oxime, and further ring closing bring product 3-phenylisoxazol-5-one. And then, the Knoevenagel reactions between 3-phenylisoxazol-5-one and aromatic aldehydes produce 4-arylmethylidene-4,5-dihydro-3-phenylisoxazol-5-ones [10]. As part of our current studies on the development of efficient and simple method for the synthesis of biologically active heterocyclic compounds [11], the current paper reports one-pot synthesis of 4-arylmethylidene-4,5-dihydro-3-phenylisoxazol-5-one through three-component reaction (Scheme 1). In addition, the target products were also prepared by the reaction between 3-phenylisoxazole-5-one and aldehydes *via* heating at 105 °C without solvent and catalyst (Scheme 2). In this study, both methods show various advantages such as shorter reaction time and being environmentally benign.

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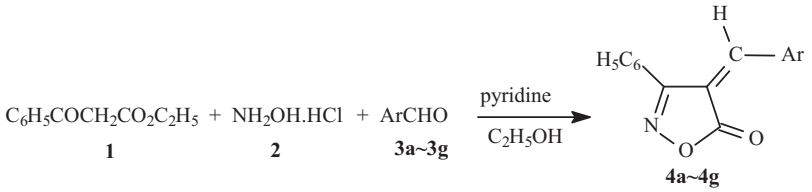
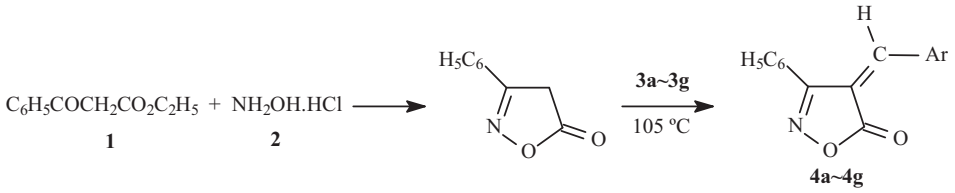


Scheme 1. One-pot synthesis of 4-arylmethylidene-3-phenylisoxazol-5-ones.



Scheme 2. Synthesis of 4-arylmethylidene-3-phenylisoxazol-5-ones under solvent free condition.

1. Experimental

The melting points were recorded on a Sweden BUCHIB 2540 melting point apparatus and uncorrected. Mass spectra were measured with API 2000 spectrometer. The H^1 NMR spectra were determined in $CDCl_3$ solution on a Varian Inova 400 NMR spectrometer using TMS as internal standard. Merck silica gel GF-254 was used for analytical and preparative TLC. All the reagents are of analytical purity.

A mixture of 4 mmol ethyl benzoylacetate (**1**), 4 mmol hydroxylamine hydrochloride (**2**) and 4 mmol pyridine in 10 mL ethanol was refluxed for 5 min, after then 4 mmol aromatic aldehyde (**3**) was added, and the mixture was further refluxed for 40–80 min till the completion of the reaction (monitored by TLC). The reaction mixture was cooled to room temperature and allowed to stand overnight. The precipitate was filtered off and washed with water, and recrystallized from EtOH (95%) to afford the pure product **4**.

The aromatic aldehyde (4 mmol) (**3**) and 3-phenylisoxazol-5-one (4 mmol) were grinded in a mortar, and then the mixture was heated in an oil bath at 105 °C for 20 min. The reaction mixture was cooled and washed with water and diethyl ether in order. The crude product was recrystallized from EtOH (95%).

The data of products is as follows:

4-Phenylmethylidene-3-phenylisoxazol-5-one (**4a**). ^{1}H NMR (400 MHz, $CDC1_3$): δ 7.26 (s, 1H, ArCH=), 7.51 (d, 2H, J = 8.4 Hz, ArH), 7.57–7.64 (m, 5H, Ph–H), 8.33 (d, 2H, J = 8.4 Hz, ArH). IR (KBr, cm^{-1}): 3077 (C–H), 1747 (C=O), 1618, 1593, 1569, 1546 (C = N, C = C). ESI-MS *m/z* (%): 272 (M + Na, 100), 250 (M + 1, 68).

4-(4-Methoxyphenyl)methylidene-3-phenylisoxazol-5-one (**4b**). ^{1}H NMR (400 MHz, $CDC1_3$): δ 3.92 (s, 3H, CH_3O), 7.01 (d, 2H, J = 8.8 Hz, ArH), 7.53 (s, 1H, ArCH =), 7.53–7.61 (m, 5H, Ph-H), 8.44 (d, 2H, J = 9.2 Hz, ArH). IR (KBr, cm^{-1}): 3075 (C–H), 1730 (C=O), 1600, 1592, 1558 (C=N, C=C). ESI-MS *m/z* (%): 302 (M + Na, 100), 280 (M + H, 16).

4-(4-Dimethyaminophenyl)methylidene-3-phenylisoxazol-5-one (**4c**). ^{1}H NMR (400 MHz, $CDC1_3$): δ 3.18 (s, 6H, $N(CH_3)_2$), 6.72 (d, 2H, J = 8.4 Hz, ArH), 7.38 (s, 1H, ArCH=), 7.22–7.60 (m, 5H, Ph-H), 8.40 (d, 2H, J = 8.8 Hz, ArH). IR (KBr, cm^{-1}): 3051 (C–H), 1711 (C=O), 1600, 1590, 1562 (C=N, C=C). ESI-MS *m/z* (%): 315 (M + Na, 32), 293 (M + H, 100).

4-(4-Chlorophenyl)methylidene-3-phenylisoxazol-5-one (**4d**). ^{1}H NMR (400 MHz, $CDC1_3$): δ 7.49 (d, 2H, J = 8.8 Hz, ArH), 7.56 (s, 1H, ArCH=), 7.58–7.63 (m, 5H, Ph-H), 8.30 (d, 2H, J = 8.8 Hz, ArH). IR (KBr, cm^{-1}): 3059 (C–H), 1744 (C=O), 1611, 1544 (C=N, C=C). ESI-MS *m/z* (%): 306 (M + Na, 29), 284 (M + H, 100).

4-(4-Methylphenyl)methylidene-3-phenylisoxazol-5-one (**4e**). ^{1}H NMR (400 MHz, $CDC1_3$): δ 7.38 (d, J = 8.8 Hz, 2H, ArH), 7.59 (s, 1H, ArCH=), 7.61–7.73 (q, 5H, Ph-H), 8.34 (d, J = 8.8 Hz, 2H, ArH), 2.45 (s, 3H, CH_3). IR (KBr, cm^{-1}): 3069 (C–H), 1746 (C=O), 1613, 1546, 1517 (C=N, C=C). ESI-MS *m/z* (%): 286 (M + Na, 36), 264 (M + 1, 100).

Table 1
Reaction conditions and results.

Entry	Ar	m.p. (°C)	Product	Time (min)/yield[a] (%)	Time (min)/yield[b] (%)
1	C_6H_5	215–216	**4a**	70/72	20/60
2	4-$H_3COC_6H_4$	168–169[10]	**4b**	60/77	20/69
3	4-$(CH_3)_2NC_6H_4$	194–196	**4c**	40/87	20/74
4	4-ClC_6H_4	175–176[10]	**4d**	60/65	20/65
5	4-$H_3CC_6H_4$	189–191	**4e**	50/74	20/68
6	4-$O_2NC_6H_4$	179–181	**4f**	80/58	20/45
7	Thienyl	226–228	**4g**	80/61	20/48
8	Furyl	183–184	**4h**	80/59	20/51

[a] Three-component reaction.
[b] Heating at 105 °C.

4-(4-Nitrophenyl)methylidene-3-phenylisoxazol-5-one (**4f**). ^{1}H NMR (400 MHz, $CDC1_3$): δ 7.40 (d, 2H, J = 9.2 Hz, ArH), 7.73 (d, 2H, J = 9.2 Hz, ArH), 7.62 (s, 1H, ArCH=), 7.63–7.75 (q, 5H, Ph-H), 8.34 (d, 2H, J = 9.2 Hz, ArH). IR (KBr, cm^{-1}): 3068 (C–H), 1745 (C=O), 1610, 1539, 1523 (C=N, C=C). ESI-MS *m/z* (%): 317 (M + Na, 36), 295 (M + 1, 100).

4-(2-Thienyl)methylidene-3-phenylisoxazol-5-one (**4 g**). ^{1}H NMR (400 MHz, $CDC1_3$): δ 7.27 (dd, 1H, J = 4.0 Hz, J = 5.2 Hz, thiophene-H), 7.57–7.64 (m, 5H, Ph-H), 7.79 (s, 1H, thiophene-CH=), 7.99 (d, 1H, J = 5.2 Hz, thiophene-H), 8.07 (d, 1H, J = 4.0 Hz, thiophene-H). IR (KBr, cm^{-1}): 3060 (C–H), 1743 (C=O), 1611, 1544, 1515 (C=N, C=C). ESI-MS *m/z* (%): 278 (M + Na, 22), 256 (M + H, 100).

4-(2-Furyl)methylidene-3-phenylisoxazol-5-one (**4 h**). ^{1}H NMR (400 MHz, $CDC1_3$): δ 6.72 (d, 1H, J = 2.8 Hz, furan-H), 7.21 (dd, 1H, J = 6.8 Hz, J = 7.6 Hz, furan-H), 7.43–8.07 (m, 5H, Ph-H), 8.82 (d, 1H, J = 3.6 Hz, furan-H). IR (KBr, cm^{-1}): 3055 (C–H), 1740 (C=O), 1613, 1546, 1518 (C=N, C=C). ESI-MS *m/z* (%): 293 (M + Na, 45), 271 (M + H, 100).

2. Results and discussion

As part of our interest on developing efficient route for the synthesis of β-unsaturated isoxazolone, we reported a convenient and rapid method for the synthesis of 4-arylmethylidene-4,5-dihydro-3-phenylisoxazol-5-ones from available starting materials. Pyridine being an organic base plays a significant role in the formation of products. This synthetic method is an easy and simple procedure for the synthesis of target compound. In addition, we have tried heating the mixture of 3-phenylisoxazol-5-one and aromatic aldehyde at 105 °C under solvent free condition without catalyst, and obtained products in moderate yields. Both methods indicated that the reactivity and yields are better when an electron donating group is attached to an aromatic ring of arylaldehyde (Table 1).

In order to investigate completion time of the reaction, the reaction was carried out for 30–120 min by continues TLC checking, previously. As indicated in Table 1, the substituent at aromatic ring has played a major role in completion of the reaction. For example, compound **4c** was formed in 40 min due to the electron-donating property of dimethylamino group at phenyl ring. While the reaction between 3-phenylisoxazol-5-one and arylaldehyde carried out under solvent free condition *via* heating at 105 °C was completed in 20 min, and products were obtained in moderate yield (Table 1).

In conclusion, the present work describes an efficient and simple method for the syntheses of 4-arylmethyl- idene-4,5-dihydro-3-phenylisoxazol-5-ones in moderate yield *via* one-pot synthetic route. The target products were also prepared under solvent free condition. This method has the advantage for its simple manipulation or green procedure which is useful for the syntheses of β-unsaturated isoxazolone derivatives.

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