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Fast and Efficient Synthesis of 4-Arylidene-3-phenylisoxazol-5-ones

MARYAM MIRZAZADEH* and GHOLAM HOSSEIN MAHDAVINIA

*Department of Chemistry, Firoozabad Branch
Islamic Azad University, Fars, Iran
Department of Chemistry, Marvdasht Branch
Islamic Azad University, Fars, Iran
mirzazadeh_maryam@yahoo.com

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Abstract: A convenient and easy synthesis of 4-arylidene-3-phenylisoxazol-5-ones by the three-component reaction of hydroxylamine, ethyl benzoylacetate and aromatic aldehydes in the presence of DABCO in refluxing ethanol is reported.

Keywords: One-pot, Isoxazole, DABCO, MCRs

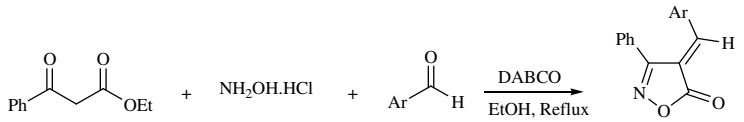
Introduction

Isoxazoles and its derivatives represent useful synthetic building blocks[1]. They are an important class of heterocycles compounds, which are employed in the area of pharmaceuticals and therapeutic such as antimicrobial, antifungal[2], anticancer[3], ulcerogenic[4] and anti-inflammatory[5]. Therefore, various synthetic methods have been reported to access the isoxazole derivatives[6].

Multicomponent coupling reactions (MCRs) involving domino processes, in which several reactions are combined into one synthetic operation have emerged as a powerful valuable synthetic tool in organic synthesis[7]. MCRs have some advantages over classical multistep syntheses, including cost-effective, requiring a minimum of time, simple procedures, high degrees of atom economy, the possibility for combinatorial surveying of structural variations and environmental friendliness[8]. The preparation of heterocyclic systems using MCRs often involves classical carbonyl condensation chemistry. Among various carbonyl structures, 1,3-dicarbonyl compounds constitute important synthetic building blocks and intermediates, incorporating multiple functionalities that can be involved either as nucleophilic or electrophilic species in a variety of synthetic transformations[9]. Thus, the high synthetic potential of these easily accessible reagents has found numerous applications, especially for the synthesis of heterocyclic structures[10].

The conventional synthesis of 4-arylidene-3-phenylisoxazol-5-one to be fulfilled in two steps, in the first step, preparation of oxime [ethyl 3-(hydroxyimino)-3-phenylpropanoate] and ring closing of this oxime to afford 3-phenylisoxazol-5-one. Then in second step, the Knoevenagel condensation of aryl aldehydes and 3-phenylisoxazol-5-one produce 4-arylidene-3-phenylisoxazol-5-ones[11,12].

Recently one-pot synthesis of these compounds catalyzed by pyridine is reported[13]. However, the use of toxic reagent (pyridine), long reaction time, low yields are among the drawbacks of this reported method. We herein described a facile synthesis of 4-arylidene-3-phenylisoxazol-5-one derivatives by three-component condensation of ethyl benzoylacetate, hydroxylamine and aldehyde, in ethanol using DABCO, as weak and safe base, at reflux condition (Scheme 1).



1 **2** **3** **4**

Scheme 1. DABCO-promoted synthesis of 4-arylidene-3-phenylisoxazol-5-ones

Experimental

A mixture of 2 mmol ethyl benzoylacetate (**1**), 2 mmol hydroxylamine hydrochloride (**2**) and 1.1 mmol DABCO in 4 mL ethanol was refluxed for 3 min, after then 2 mmol aromatic aldehyde (**3**) was added and the mixture was further refluxed for 1-15 min. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and the resulting crystal product (**4**) was collected by filtration and washed with water. The product was found to be pure and no further purification was necessary.

Results and Discussion

In our initial experiments toward the development of this reaction, we have reacted 4-methoxybenzaldehyde (1.0 mmol) with hydroxylamine hydrochloride (1.0 mmol) and ethyl benzoylacetate (1.0 mmol) in ethanol, but no resulting product has been found at room temperature and reflux conditions. It was observed that the same reaction proceeded when we use DABCO in ethanol at room temperature yielding the corresponding 4-arylidene-3-phenylisoxazol-5-one in 43% yield after 30 min. When we attempted the same reaction in ethanol at reflux condition, the reaction proceeded to completion within 4 min and yielded the corresponding 4-arylidene-3-phenylisoxazol-5-one in 90% yield. Encouraged by this result we have explored the efficiency of various bases on the reaction. Among the bases tested for this condensation reaction to yield 4-(4-methoxybenzylidene)-3-phenylisoxazol-5-one, are triethyl amine (65%), pyridine (77%)[13], piperidine (75%), DBU (78%) and DABCO (82%). However DABCO gave excellent yields.

In order to determine the most appropriate choice of solvent system for this DABCO-promoted synthesis of 4-arylidene-3-phenylisoxazol-5-ones, we have screened the solvents such as methanol (70%), ethanol (82%) and water (52%). Of the solvents tested in the screening we got the maximum yield of the product in shorter reaction times, when we use ethanol as solvent.

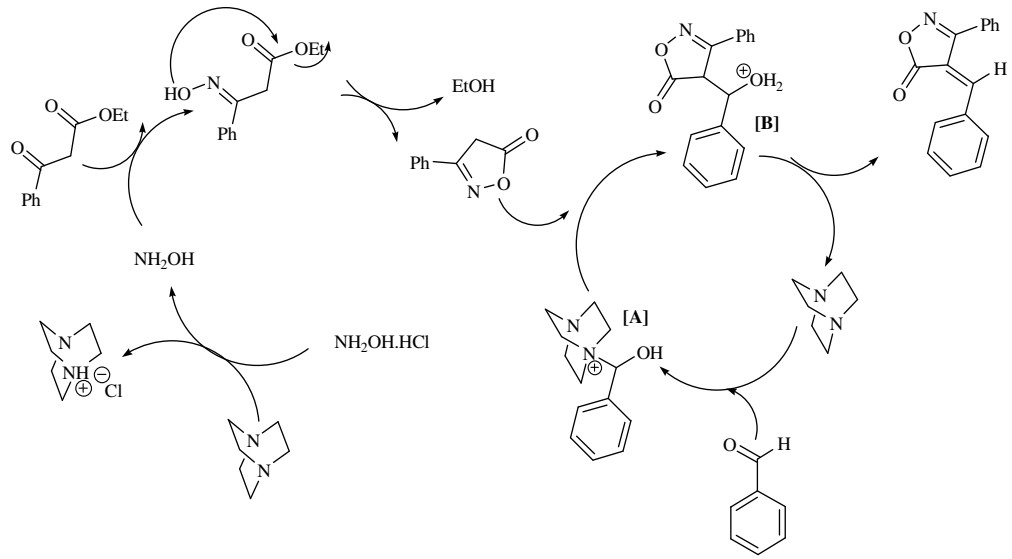
In order to determine the scope of this reaction, we have synthesized differently substituted 4-arylidene-3-phenylisoxazol-5-ones by varying differently substituted aldehydes including both electron-donating and electron-withdrawing groups. It is observed

that the reaction gave good yields of products with faster reaction rate when the aldehydes bearing electron-donating group is used compared to the aldehydes with electron-withdrawing groups. The corresponding results are tabulated in Table 1.

Table 1. Preparation of 4-arylidene-3-phenylisoxazol-5-ones

Entry	Ar	Product	Time, min	Yield, %	Mp, ºC	Lit. Mp, ºC
1	C_6H_5	**4a**	12	70	210-212	215-216[13]
2	4-Cl	**4b**	15	65	171-173	175-176[13]
3	4-Br	**4c**	15	60	175-177	---
4	4-CH_3	**4d**	10	80	187-188	189-191[13]
5	4-OCH_3	**4e**	4	82	165-167	168-169[13]
6	4-OH	**4f**	4	75	210	---
7	4-Me_2N-C_6H_4	**4g**	4	85	195-196	194-196[13]
8	2-OCH_3	**4h**	6	78	162-164	---
9	2-Naphthyl	**4i**	10	70	184-186	---
10	2,4-OCH_3	**4j**	1	85	210-213	---
11	2,4-OH	**4k**	1.5	80	259(dec.)	---
12	PhCH=CH_2	**4l**	15	65	156	---

The plausible mechanism for the synthesis of 4-arylidene-3-phenylisoxazol-5-ones in the presence of DABCO involves the initial reaction of DABCO with hydroxylamine hydrochloride for repudiation of hydroxylamine which attacked to ethyl benzoylacetate to the formation of oxime then ring closing of oxime gives 3-phenylisoxazol-5-one. Reaction of DABCO with aldehyde leading to the formation of intermediate **(A)**, which attacked by the 3-phenylisoxazol-5-one gives another intermediate **(B)** with subsequent elimination of H_2O leads to the desired product (Scheme 2). All the unknown products were characterized by ^1H, ^{13}C NMR and IR



Scheme 2. Plausible mechanistic pathway for the formation of 4-arylidene-3-phenylisoxazol-5-ones

Spectral Data

*4-(4-Bromobenzylidene)-3-phenylisoxazol-5-one (**4c**)*

IR (KBr): 3100, 1745, 1613, 1545, 1488,1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (s, 1H, ArCH=), 7.61-7.53 (m, 5H, Ph-H), 7.64 (d, 2H, J = 8.4 Hz, ArH), 8.19 (d, 2H, J = 8.4 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 119.39, 127.15, 128.18, 128.74, 128.95, 129.39, 129.64, 130.87, 131.14, 131.65, 132.43, 133.38, 135.19, 151.09, 163.92, 168.00.

*4-(4-Hydroxybenzylidene)-3-phenylisoxazol-5(4H)-one (**4f**)*

IR (KBr): 3357, 3050, 1725, 1580, 1531, 1448, 1375, 1301, 1225 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 6.92 (d, 2H, J = 8.8, ArH), 7.56-7.65 (m, 6H, Ph-H, ArCH=), 8.41 (d, 2H, J = 8.8, ArH), 11.12 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 113.22, 116.62, 124.89, 127.94, 129.30, 129.69, 131.27, 136.88, 138.52, 153.74, 164.76, 169.39.

*4-(2-Methoxybenzylidene)-3-phenylisoxazol-5-one (**4h**)*

IR (KBr): 3065, 1739, 1587, 1543, 1476, 1365, 1251, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 3H, OMe), 6.93 (d, 1H, J = 8.4 Hz, ArH), 7.08 (t, 1H, J = 7.6 Hz, ArH), 7.24-7.28 (m, 1H, ArH), 7.53-7.6 (m, 5H, Ph-H), 8.25 (s, 1H, ArCH=), 8.85 (d, 1H, J = 8.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.93, 117.14, 119.70, 121.82, 127.72, 127.90, 128.55, 128.76, 129.19, 130.37, 130.93, 133.45, 136.56, 147.33, 160.05, 164.21, 168.58.

*4-(Naphthalen-2-ylmethylene)-3-phenylisoxazol-5(4H)-one (**4i**)*

IR (KBr): 3050, 1743, 1592, 1542, 1377, 1269, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54-7.94 (m, 11H, Ph-H, ArH), 8.46 (dd, 1H, J = 8.6 Hz, J = 1.2 Hz, ArH), 8.80 (s, 1H, ArCH=); ^{13}C NMR (100 MHz, $CDCl_3$): δ 118.54, 127.13, 127.50, 127.86, 128.28, 128.59, 128.74, 128.84, 128.88, 129.36, 129.72, 129.98, 130.21, 131.05, 132.75, 135.82, 137.11, 152.75, 164.19, 168.32.

*4-(2,4-Dimethoxybenzylidene)-3-phenylisoxazol-5(4H)-one (**4j**)*

IR (KBr): 3072, 1741, 1572, 1534, 1504, 1473, 1428, 1379, 1272, 1213,1083 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.80(s, 3H, OMe), 3.91 (s, 3H, OMe), 6.39 (d, 1H, J = 2.0 Hz, ArH), 6.64 (dd, 1H, J = 9.1 Hz, J = 2.0 Hz, ArH), 7.53-7.63 (m, 5H, Ph-H), 8.18 (s, 1H, ArCH=), 9.21 (d, 1H, J = 9.1 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.88, 55.99, 97.75, 105.99, 113.53, 115.67, 127.98, 128.20, 128.72, 128.85, 129.06, 130.63, 136.36, 146.15, 162.59, 164.68, 167.30, 169.64.

*4-(2,4-Dihydroxybenzylidene)-3-phenylisoxazol-5(4H)-one(**4k**)*

IR (KBr): 3339, 3095, 1726, 1625, 1581, 1537, 1476, 1391, 1317, 1242, 1190, 1092 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 6.37 (d, 1H, J= 1.6 Hz, ArH), 6.37 (dd, 1H, J = 9.0 Hz, J = 1.6 Hz, ArH), 7.59 (s, 5H, Ph-H), 8.05 (s, 1H, ArCH=), 9.04 (d, 1H, J = 9.0 Hz, ArH), 11.09 (s, 2H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 102.10, 109.80, 113.82, 128.46, 129.27, 129.62, 131.16, 136.01, 146.59, 164.06, 165.33, 167.74, 170.09.

*3-Phenyl-4-(-3-phenylallylidene) isoxazol-5(4H)-one (**4l**)*

IR (KBr): 3080, 1747, 1610, 1535,1493, 1445, 1392, 1175, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, 1H, , J= 15.6 Hz, =CH) 7.40-7.46 (m, 3H, ArH, Ph-H), 7.50 (d, 1H, J= 12 Hz, ArCH=), 7.55-7.66 (m, 7H, ArH, Ph-H), 8.43 (dd, 1H, J= 15.6 Hz, J= 12 Hz, CH=); ^{13}C NMR (100 MHz, $CDCl_3$): δ 116.53, 122.78, 127.53, 128.22, 128.60, 129.09, 129.24, 129.29, 131.01, 131.63, 131.71, 135.00, 148.40, 150.08, 151.41, 152.33, 162.29, 169.31.

Conclusion

In conclusion, we have developed a clean, efficient, convenient, simple and fast method for the synthesis of 4-arylidene-3-phenylisoxazol-5-ones in good yield *via* one-pot synthetic route. Present methodology offers very attractive features such as reduced reaction times, higher yields, easy work-up and economic viability of the promoter, when compared with conventional methods as well as with other catalysts.

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