IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
Volume 12, Issue 4, December 2021
Impact Factor: 5.731

A Convenient Green Protocol for the Synthesis of 4-Arylmethylidene-3-substituted-isoxazol-5(4H)-ones catalysed by Dimethylaminopyridine (DMAP)

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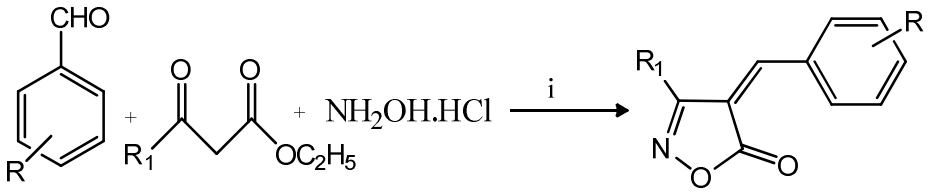
Abstract: *Isoxazolemotif containing heterocyclic compounds are important for their wide range of biological activities. Therefore, in the present article, I report a convenient and green protocol for the synthesis of 4-arylmethylidene-3-substituted-isoxazol-5(4H)-ones by the one pot three component reaction of aldehydes, β-keto ester and hydroxylamine hydrochloride catalyzed by Dimethylaminopyridine (DMAP).*



1 (a-i) 2(a-b) 3 (4a-f), (5a-i)

Scheme 1: Reagent and conditions:(i) Dimethylaminopyridine (DMAP), H_2O (5 mL), 70- 80^{0}C, 6 to 25 min.

Keywords: Aldehyde, β-keto Ester, Hydroxylamine Hydrochloride, DAMP

I. INTRODUCTION

Nitrogen-containing heterocycles are of high importance. Isoxazole is one of the nitrogen containing moiety which represent a unique class of pharmacophores, which constituents a diverse range of therapeutic agents[1]. In the past decades, studies have been carried out on isoxazole scaffold and noticed to be vital building block in several fields including medicine, agrochemicals and industry[2], optical recording and nonlinear optical research[2,3].Isoxazole derivatives were found to exhibit various biological and pharmaceutical activities including antifungal[4], antimicrobial[5], metastatic activities[6], anticancer[7], anti-inflammatory[6], hypoglycemic[8], analgesic[9], HIV-inhibitory[9], antioxidant[10], antinociceptive, antimycobacterial, nematicidal, antituberculosis, COX-2 inhibitory, neurotoxic, antiepileptic, cytotoxic, anticonvulsant, HDAC inhibitory, arthritis and leishmaniasis[11-13].Some of the representative examples are shown in Figure 1. Being omnipresent medicinal value, hetereocyclic drug moieties containing isoxazole nucleus has accomplished a leading role in pharmaceutical market. Valedecoxib, Leflunomide, Cycloserine, Zonisamide, Drazoxol and Acetylsulfisoxazole are some of the popular drugs of this class[14].

Due to outstanding importance of isoxazole-5(4*H*)-ones, various synthetic approaches have been developed for their synthesis. Different methods were employed for the synthesis of substituted isoxazole-5(4*H*)-ones which includescondensation of substituted benzaldoximes and 1,3-dicarbonyl compounds[15], reaction between alkynes, hydroxyl amine hydrochloride and different aldehydes[16]. One-pot three component synthesis involving β-ketoester, hydroxylamine hydrochloride and diverse aldehydes has been considered as a unique and attractive approach to access this significant class of heterocycles. This method is widely accessed world-wide catalyzed by sodium benzoate[17], sodium sulfide[18], sodium silicate[19], DABCO[20], sodium ascorbate[21], sodium citrate[22], citric acid[23], sodium saccharin[24], sodium tetraborate[25], sodium azide[26], boric acid[27], potassium phthalimide (PPI)[28], potassium hydrogen phthalate (KHP)[29], phthalimide-N-oxyl salts[30], NaH_2PO_4[31], DOWEX 50WX4[32a],Dowex1-x8OH[32b], tartaric acid[33], N-

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bromosuccinimide[34], 2-hydroxy-5-sulfobenzoic acid[35], nano-Fe_2O_3[36], clinoptilolite[37], $H_3PW_{12}O_{40}$[38], Ag/SiO_2[39], visible light/sodium acetate[40]and Iodine[41] etc.

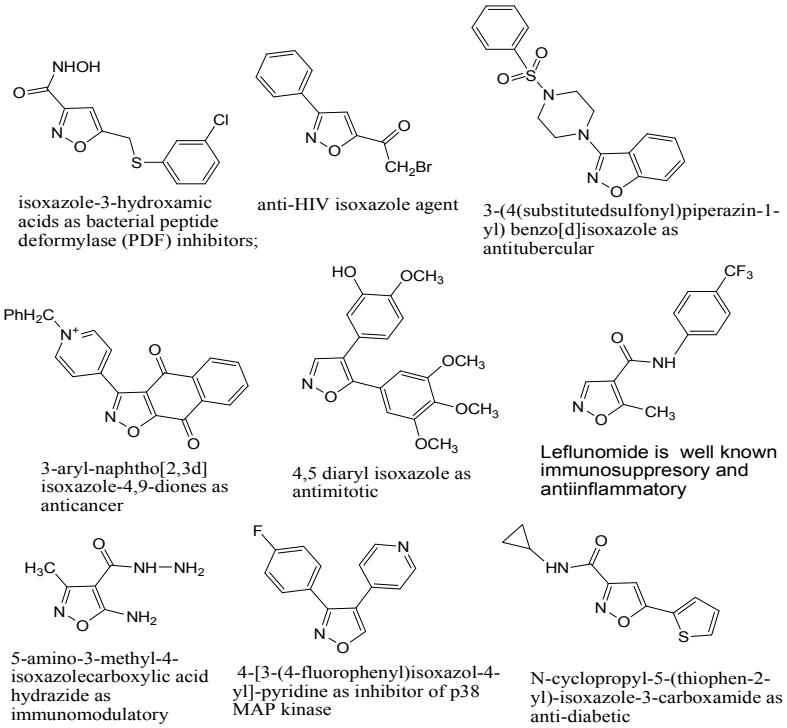

Figure 1: Some representative moieties containing isoxazole nucleus.

The above reported methodologies for synthesis of 4-arylmethylidene-3-substituted-isoxazol-5(4H)-ones derivatives have shown good results in many instances. However, some of synthetic strategies also have limitations in terms of expensive reagents, long reaction time, environmentally hazardous, harsh reaction conditions, tedious work-up procedure and unsatisfactory yield. 4-(Dimethylamino) pyridine (DMAP) is a catalyst of outstanding utility in a variety of group-transfer reactions, such as the acylation of alcohols and amines.[42-46]. Despite the frequent use of DMAP itself and the recent development of chiral DMAP derivatives for applications in stereoselectivecatalysis[47-51]. The mechanisms of even the simplest DMAP-catalyzed reactions, such as the acetylation of alcohols with acetic anhydride, have not yet been studied in detail. A recent review of the mechanistic characteristics of this reaction highlighted the importance of the deprotonation step as well as the influence of the auxiliary base on the catalytic activity of DMAP[44]. Hence we were interested in the synthesis of 4-Arylmethylidene-3-substituted-isoxazol-5(4H)-ones using DMAP as versatile catalyst. In the search of better reaction condition for the synthesis of 4-Arylmethylidene-3-substituted-isoxazol-5(4H)-ones, we have developed water mediated synthetic protocol with excellent yield using DMAP catalyst.

II. Results and Discussion

Major efforts were taken to optimize the suitable reaction conditions.In the beginning, a solvent-free reaction of ethyl acetoacetate (1 mmol), hydroxyl amine hydrochloride (1 mmol) and p-dimethyl amino benzaldehyde (1 mmol) was performed at room temperature (entry 1, **Table 1**), low yield was observed. Then, the reaction mixture was heated for 2 h and 21% yield was found. Further, I studied the effect of solvent and various amounts of DAMP catalyst on the model reaction.

The same reaction was performed using different solvents such as H_2O, EtOH, CH_3CN, CH_2Cl_2 under heating for about 40-80^{0}C with more time and low yield (entry 2-4, Table 1). As it can be seen that the results were obtained by performing the reaction in the presence of 5-10 mol% at 70-80^{0}C water (entry 6-7, Table 1).The more yield was observed using 10 mol% DAMP in about 6 min. (entry 5, Table 1).

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Table 1: Optimization of reaction conditions

Entry	Solvent	Catalyst (mol%)	Temperature (^{0}C)	Time (min.)	Yield (%)
1	None	-	70-80	120	21
2	EtOH	10	70-80	10	86
3	CH_3CN	10	70-80	30	66
4	CH_2Cl_2	10	40	40	68
5	**H_2O**	**10**	**70-80**	**6**	**85**
6	H_2O	5	70-80	11	82
7	1:1 EtOH	10	70-80	10	85

A series of reactions were carried out using diversely substituted aromatic aldehydes under identical reaction conditions as in entry 5, table 1. All these reactions afforded good to excellent yield of 4-arylmethylidene-3-substituted-isoxazol-5(4H)-one derivatives (4a-4f and 5a-5i). (**entries 1-15, Table 2**). It is found that the aldehydes with electron donating groups gave superior yield in short reaction time than those with electron withdrawing groups require high time period with low yield of the product. The above reaction is environmentaly benign because of the use of water as solvent, short reaction time, easy work-up and good to high yield of the product.

Table 2: One pot synthesis of 4-arylmethylene-3-substituted isoxazol-5(4H) one derivatives

Entry	aromatic aldehyde (1a-i)	β-keto ester (2a-b)	Product (4a-f), (5a-i)	Time (min.)	Isolated yield[b] (%)	Mp (^{0}C)
1	4-dimethyl amino benzaldehyde	ethyl acetoacetate	4a	6	91	220-222[41]
2	4-hydroxy benzaldehyde	ethyl acetoacetate	4b	7	88	211-212[41]
3	4-methyl benzaldehyde	ethyl acetoacetate	4c	8	87	136-138[41]
4	4-methoxy benzaldehyde	ethyl acetoacetate	4d	7	90	175-178[41]
5	Pyrrol 2-carboxaldehyde	ethyl acetoacetate	4e	12	84	--
6	5-bromo thiophene 2-carboxaldehyde	ethyl acetoacetate	4f	22	82	--
7	4-dimethyl amino benzaldehyde	ethyl benzoyl acetate	5a	6	90	194-196[36b]
8	3,4-dihydroxy benzaldehyde	ethyl benzoyl acetate	5b	6	88	--
9	3,4-dimethoxy benzaldehyde	ethyl benzoyl acetate	5c	6	90	--[24]
10	4-methyl benzaldehyde	ethyl benzoyl acetate	5d	8	85	188-191[36b]
11	Salicyaldehyde	ethyl benzoyl acetate	5e	12	87	--[24]
12	Pyrrol 2-carboxyaldehyde	ethyl benzoyl acetate	5f	14	85	150-152

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13	5-bromo thiophene 2-carboxyaldehyde	ethyl acetate	benzoyl	5g	25	83	--
14	4-methoxy benzaldehyde	ethyl acetate	benzoyl	5h	8	90	166-167[36b]
15	4-bromo benzaldehyde	ethyl acetate	benzoyl	5i	38	82	176-177[24]

[a]substituted aromatic aldehyde (1 mmol), β-keto ester (1.1 mmol), hydroxyl amine hydrochloride (1.1 mmol), 10 mg Cu-NP/C,water:ethanol (1:1) (5 ml) under reflux.
[b]isolated yield

III. EXPERIMENTAL

3.1 General details

All chemicals were purchased from Sigma Aldrich and Spectochem companies and used without further purification. Reactions were monitored on TLC using aluminium sheets 20 x 20 cm, Silica gel 60 F_{254} ,Merck grade plates. Products were characterized by ^{1}H NMR and ^{13}C NMR spectra recorded onBruker spectrometer using $CDCl_3$ or DMSO-d_6 as a solvent and tetramethylsilane as the internal standard. Mass spectrometric data was recorded by an electron spray ionisation (ES) technique on a Q-tof-micro quadruple mass spectrometer (Micro mass). Melting points were determined on DBK-programmable melting point apparatus.

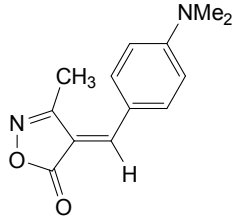
General procedure for the synthesis of 4-(arylmethylidene)-3-methylisoxazol-5(4*H*)-ones and 4-(arylmethylidene)-3-phenylisoxazol-5(4*H*)-ones:

A mixture of β-ketoester (1.1mmol), hydroxylamine hydrochloride (1.1mmol), aromatic aldehyde (1 mmol), and 10 mol% DAMP were added in 5 mL of 1:1 water and refluxedat 70-80^{0}for 6 to 25 minutes (**Table 2**). Progress of the reaction was monitored by Thin Layer Chromatography. After completion of reaction there was generation of a precipitate. While hot, the precipitate was filtered and washed with hot water thrice. Finally, to obtain the products in maximum purity recrystallization was done in hot ethanol. The isolated products were characterized by various spectroscopic techniques. Spectral data for some of the representative compounds are given below.

IV. CONCLUSION

- Require very short reaction time period for completion of reaction.
- Environmental friendly method.
- Method gives high reaction yield.

4.1 Characterisation Data



4-(4-(Dimethylamino) benzylidene)-3-methyl Isoxazol-5(4H)-one (4a)[65]: M.P.- 220-222.**IR** (KBr, v/cm) : 590, 772, 943, 993, 1031, 1198, 1222, 1353, 1373, 1410, 1439, 1558, 1582, 1711, 2851, 2919;
^{1}H NMR- (300 MHz, $CDCl_3$) : δ (ppm) 2.4 (s, 3H, CH_3), 3.4 (s, 6H, NMe_2), 6.75 (d, 2H, ArH), 7.23 (s, 1H, =CH), 8.40 (d, 2H, ArH);
^{13}C NMR- (300MHz, $CDC1_3$+DMSO d_6) δ (ppm): 11.6, 40.0, 111.4, 121.4, 137.5, 149.2, 154.1, 161.5, 170.0;
ESI-MS: calculated for $C_{13}H_{14}N_2O_2$is 230, found-231 (M+1).

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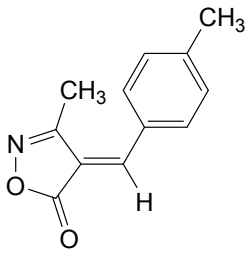
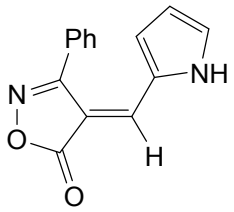


3-Methyl-4-(4-methylbenzylidene) isoxazol-5(4H)-one (4c)[65]: M.P.- 136-138.
IR (KBr, v/cm): 667, 742, 928, 1215, 1435, 1517, 1599, 3019;
^{1}H NMR (300 MHz, $CDC1_3$) δ (ppm): 2.32 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 7.36 (m, 4H, ArH), 8.3 (s, 1H, =CH);
^{13}C NMR (300MHz, $CDC1_3$) δ (ppm): 11.6, 22.0, 118.3, 129.8, 134.0, 145.6, 149.8, 161.1, 168.1;
ESI-MS: Calculated for $C_{12}H_{11}NO_2$is 201, found-202 (M+1).



3-phenyl 4-((1H-pyrrol-2-yl) methylene) isoxazol-5(4H)-one (5f): M.P.- 150-152^{0}C
IR (KBr, v/cm): 651, 694, 754, 871, 970, 1043, 1081, 1117, 1246, 1323, 1336, 1385, 1430, 1473, 1492, 1521, 1538, 1598, 1701, 3099, 3109, 3371;
^{1}H NMR (400 MHz, $CDC1_3$+DMSO d_6): δ (ppm): 6.56 (m, 1H, ArH), 7.0 (m, 1H, ArH), 7.40 (s, 1H, =CH), 7.5 (m, 1H, ArH), 7.6(m, 5H, ArH);
^{13}C NMR (500MHz, DMSO d_6) δ (ppm):114.57, 128.42, 129.08, 130.50, 137.30 and 163.63.
ESI-MS: calculated for $C_{14}H_{10}N_2O_2$ is 238, found - 239 (M+1).

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