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Access to arylmethylidene-isoxazol-5(4H)-ones and benzylidenemalononitriles promoted by imidazole as an efficient organocatalyst

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Abstract: Synthesis of Arylmethyledene-isoxazole-5(4H)-ones have been achieved via one pot reaction of various aromatic aldehydes, hydroxylamine hydrochloride and ethyl acetoacetate promoted by imidazole as an efficient organocatalyst in ethanol: water medium. In mild basic condition, this protocol is useful for easy access to arylmethylidene-isoxazol-5(4H)-ones, which are having potential utility in the field of medicinal chemistry. Encouraged by this, the same protocol has been utilized for the synthesis of benzylidenemalononitriles by the Knoevenagel condensation reaction between various aldehydes and malonitrile. Both the protocols offer cost effectiveness and operational simplicity for the synthesis of isoxazoles and benzylidenemalononitriles in environment-friendly reaction conditions.

Keywords: Arylmethyledene-isoxazole-5(4H)-ones, Benzylidenemalononitriles, Imidazole, Aqueous ethanol medium.

Introduction

Organocatalysts having industrial interest have attracted scientific community in many aspects such as they are less expensive, provide a large chiral pool, insensitive to moisture and air and non-toxic in nature. Organocatalysts are catalysts having an organic framework that does not contain any metal and which can accelerate reactions in substoichimetric amounts. Not much work has been done on the efficiency of imidazole as an organocatalyst. Imidazole having unique reactivity pattern contains two nitrogen atoms, one pyridine like and another pyrrole like. The mild basicity character of imidazole is due to its pyridine like nitrogen. The catalytic activity of imidazole has been studied by different groups. Recently it has been used for the synthesis of multisubstituted 2-amino thiophenes [1], monoacylatedc symmetrical diamines [2], 3, 4-dihydropyridi-2-one derivatives [3], polysubstituted cyclohexene [4] and 2-amino-4H-chromene derivatives [5]. Herein, we had the opportunity to further exploration of the catalytic activity of imidazole.

The isoxazole scaffold constitutes is a privileged structure of many pharmaceutical drugs attracting considerable interest in the field of medicinal chemistry. It has shown numerous activities such as anti-inflammatory [6], antibacterial [7], anticonvulsant [8], antituberculosis [9], antiviral [10], anticancer [11] and anti protein-tyrosine phosphate 1B inhibitory [12]. Over the past few years arylmethylene isoxazol-5(4H)-ones were prepared by using different catalytic system such as DABCO [13], pyridine [14], boric acid [15], sodium benzoate [16], sodium sulfide [17], sodium silicate [18] tetrabutyl ammonium perchlorate (TBAP) and sodium oxalate or glycine [19].

The carbon-carbon bond formation using the Knoevenagel condensation reaction between aldehydes

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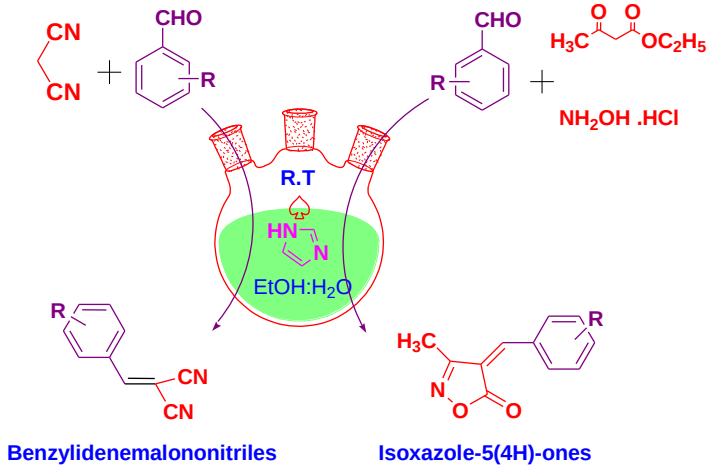
and compounds with activated methylene groups(C–H acidic methylene) is one of the most useful and highly preferred methods, with numerous applications in the synthesis of different chemicals such as drugs, cosmetics and many biologically active heterocyclic compounds [20-22]. Conventionally, this reaction is catalyzed by weak bases like primary, secondary and tertiary amines under various conditions. Numerous synthetic protocols have been developed for this reaction [23-35].

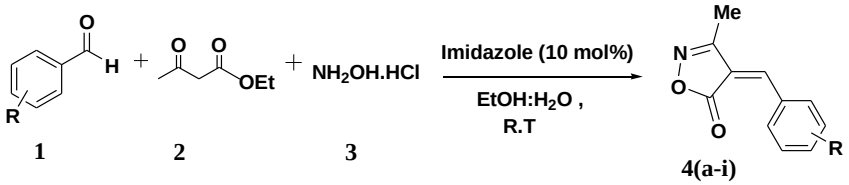
However, many of the reported methods for the synthesis of arylmethyledene-isoxazole-5(4H)-ones and benzylidenemalononitriles, have some demerits from both economic and environmental viewpoints. We herein wish to describe, for the first time, an efficient, novel and eco-friendly facile synthesis of 4-arylidene-3-phenylisoxazol-5-ones and benzylidene malononitriles in ethanol: water (1:1) medium using imidazole as a mild basic and safe organocatalyst (Scheme **1**).



Scheme 1: Synthesis of isoxazol-5(4H)-ones and benzylidene malononitriles.

Results and discussion

Optimization of the reaction conditions was carried out by a test reaction using p-methoxy benzaldehyde, ethyl acetoacetate and hydroxylamine hydrochloride, using imidazole as a catalyst (Scheme **2**). At first, we focused on the optimization of the amount of the catalyst, it was observed that optimal quantity of 10 mol % of the catalyst gave maximum yield in minimum time period. Initially, stirring a mixture of 4-OMe-benzaldehyde, ethyl acetoacetate and hydroxyl amine hydrochloride and 5 mol% imidazole in 4ml ethanol afforded the corresponding isoxazole with 65% yield in 70 min (Table **1**, entry 1). Increasing the catalyst amount up to 10 mol % gave the highest yield of 4b with 90 % yield in 60 min (Table **1**, entry 2). The effect of solvent was observed by carried out the reaction in either ethanol alone or in ethanol and water mixture (Table **1**). It was observed that use of water: ethanol (1:1) gave similar yield as compared to ethanol alone (Table **1**, entries 2&4), while reaction in which water was used in double ratio gave lower yield (Table **1**, entry 5), So we choose for all the reactions water : ethanol (1:1) as the optimized medium in regards with economic and environmental aspects (Table**1**, entry 4). Rather than employing hazardous organic solvents, the use of EtOH/water advantageous in terms of cost and toxicity.



Scheme 2: Synthesis of arylmethyledene-isoxazole-5(4H)-ones.

With the optimized reaction conditions in hand, we tested the variability of aromatic aldehydes with different substituent's under the similar reaction condition and the results are summarized in Table **2**. It was found that aldehydes having electron releasing substituent furnished the products in high yields

comparable to other electron withdrawing substituent (Table **2**, entries 1-9). However α, β unsaturated aldehyde, i.e cinnamaldehyde gave good yield of the corresponding product.

Table 1: Model reaction and optimization under various conditions for the synthesis of arylmethyledene-isoxazole-5(4H)-one[a].

Entry	Catalyst	Solvent[b]	Temp ^{0}C	Time (min)	Yield (%)[c]
1	5mol%	EtOH	R.T.	70min	65
2	10mole%	EtOH	R.T.	60min	90
3	15mol%	EtOH	R.T.	50min	90
4	10mol%	EtOH/H_2O(1:1)	R.T.	50min	90
5	10mole%	EtOH/H_2O(1:2)	R.T.	60min	88

[a]*Reaction Conditions*: ethyl acetoacetate (1mmol), 4-OMe benzaldehyde (1mmol), hydroxylamine hydrochloride (1mmol), [b] 4 mL, [c] isolated yield.

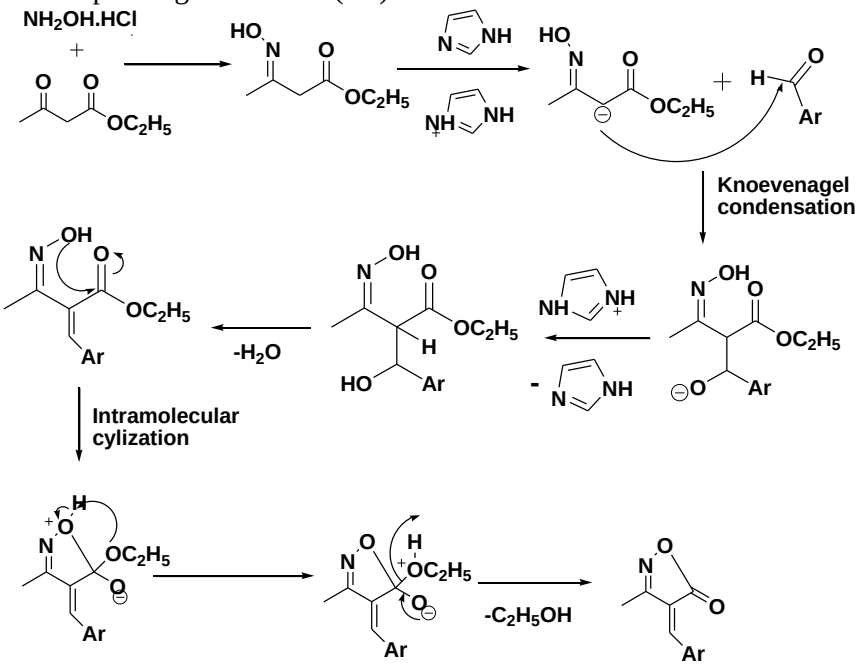
Table 2: Synthesis of Arylmethyledene-isoxazole-5(4H)-ones[a].

Entry	Ar	Product	Yield (%)[b]	Time(min)	m. p (^{o}C)		
					Found	Reported	Ref
1	2-OHC_6H_4	4a	92	60min	197-199	198-201	[16]
2	4-$CH_3OC_6H_4$	4b	90	50min	172-174	175-177	[16]
3	C_6H_5	4c	90	55 min	138-140	141-143	[16]
4	4-$NO_2C_6H_4$	4d	40	80min	178-180	--------	-----
5	4-OHC_6H_4	4e	90	70min	212-214	210-211	[19]
6	N,N$(CH_3)_2C_6H_4$	4f	89	80min	222-225	220-221	[19]
7	3-OCH_3,4-OHC_6H_3	4g	45	80min	210-212	212-215	[16]
8	4-CH_3 C_6H_4	4h	93	70min	132-134	135-135	[19]
9	C_6H_5CH=CH	4i	92	65min	174-176	171-173	[16]

[a]*Reaction Conditions*: ethyl acetoacetate (1mmol), aldehydes(1mmol), hydroxylamine hydrochloride(1mmol), imidazole(20mol%), EtOH:H_2O(1:1/4ml),R.T, [b]Isolated yield.

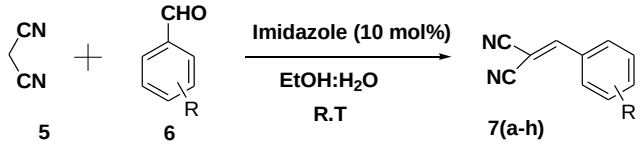
Mechanistically, in the beginning, the hydroxyl amine hydrochloride provides amino group, which attack on carbonyl carbon of ethyl acetoacetate to generate an oxime intermediate. Imidazole abstract proton from the active methylene position of oxime intermediate to generate a carbanion, which attack on the electrophilic carbonyl carbon atom of aldehydes via the Knoevenagel condensation reaction. The oxygen atom of oxime group attacks on the carbon atom of ester, in which after proton transfer followed by

removal of ethanol molecule through intramolecular cyclization affords the corresponding isoxazole-5(4H)-ones (Scheme **3**).



Scheme 3: Suggested mechanism for the formation of isoxazole-5(4H)-ones.

Encouraged by these results, we used the present protocol and same reaction conditions for the Knoevenagel condensation reaction between aldehydes and malonitrile (Scheme **4**). Surprisingly, in this case also the reaction worked smoothly and the corresponding Knoevenagel products were obtained in good yields (Table **3**, entries 1–8). The main step of this reaction is the generation of a carbanion from an active methylene compound provided by malonitrile. The imidazole catalyzed the knoevenagel condensation with aldehydes takes place smoothly at room temperature in a short time period giving maximum yields.



Scheme 4: Synthesis of benzylidenemalononitriles by the Knoevenagel condensation.

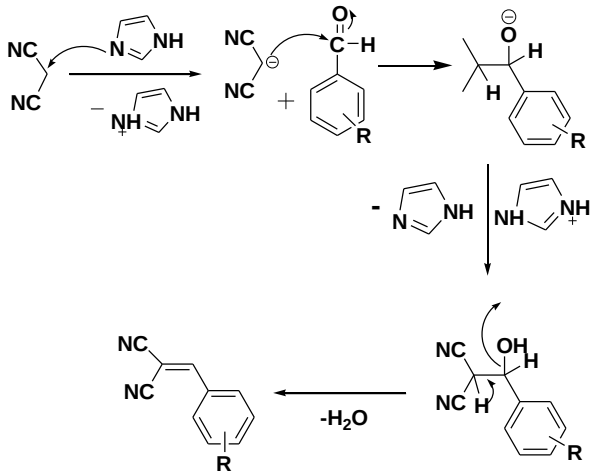
The reaction performed well in the case of aromatic aldehydes tethered with different groups either activating or deactivating in nature (Table **3**, entry 1-8). Here also imidazole, which is acting as a mild base, abstracts proton from active methylene position of malonitrile to generate a carbanion which attack on the electrophilic carbon atom of the aldehydes (Scheme **5**). So imidazole, acted as a base due to pyridine like nitrogen atom efficiently and catalyzed the reactions.

Table 3: The Knoevenagel condensation reactions between aromatic aldehydes and malononitrile [a].

Entry	Ar	Product	Yield (%)[b]	Time (min)	m. p. (°C) Observed	Reported	Ref
1	3-OHC_6H_4	7a	96	5	146-148	148-150	[31]
2	4-$OCH_3C_6H_4$	7b	98	5	109-111	110-112	[31]

3	C_6H_5	7c	92	7	78-80	80-81	[31]
4	4-ClC_6H_4	7d	94	6	151-152	153-155	[31]
5	4-OH C_6H_4	7e	97	5	175-177	177-179	[31]
6	4-$NO_2C_6H_4$	7f	98	10	152-154	155-157	[31]
7	2-ClC_6H_4	7g	96	10	90-92	92-94	[31]
8	2-$OMeC_6H_4$	7h	95	5	78-80	79-80	[31]

[a] Reaction condition: aromatic aldehyde (1mmol), malononitrile (1mmol) and imidazole (10mol%) in EtOH:H_2O (1:1/4ml) , R.T , [b]Isolated yield .



Scheme 5: Suggested mechanism for the Knoevenagel condensation.

Conclusion

New protocols have been developed for the synthesis of arylmethyledene-isoxazole-5(4H)-ones (**4a-i)** and benzylidenemalononitriles (**7a-h**) catalyzed by imidazole in aqueous ethanol medium. Both reactions proceeded smoothly in the EtOH : Water solution, considered to be the best solvent system owing to the advantages of being eco-friendly and low cost. The imidazole catalyzed protocols may be considered as great improvements over the previously reported methods such as operationally simple, mild conditions, absence of hazardous organic solvents, maximum yields with no need of column chromatography and use of imidazole as low cost, non toxic organo-catalyst.

Experimental

General:

Chemicals were purchased from SD Fine Chemical Companies. All the products are known and their physical data is confirmed by comparison with those reported in the literature. The NMR spectra were recorded on a Bruker Advance DPX-250. Mass spectra were recorded on Waters GC-MS spectrophotometer. The progress of the reactions and the purity of the products were observed by TLC on silica-gel.

General procedure for the synthesis of 4-arylmethylene-3-methyl-isoxazol-5(4H) ones:

A 25 mL round-bottomed flask was charged with a mixture of ethyl acetoacetate (1mmol), hydroxylamine hydrochloride (1mmol) and imidazole (10 mol %) in 1:1 / EtOH: H_2O (4 mL) mixture and stirred for ten minutes. Then the aldehyde (1mmol) was added and the mixture was stirred for the appropriate time (Table **2**, entry 1-9). After completion of the reaction as indicated by TLC (ethyl acetate-hexane, 2:8), the reaction mixture was poured into ice cold water and the obtained solid precipitate was collected by suction. Then it was washed with cold water (20mL) and

recrystallized from EtOH-H_2O (4:1), to afford the pure product.

Selected spectral data:

*4-benzylidene-3-methylisoxazol-5(4H)-one (**4c**):*

M.p.:138-140^{o}C; ^{1}H NMR ($CDC1_3$, 400 MHz): 7.62–7.65 (m, 1H), d2.32 (s, 3H), 7.42 (s, 1H), 8.38 (dd, J=1.3, 7.5 Hz, 2H), 7.53 (t, J=7.8 Hz, 2H); MS(m/z): 188.1.

*3-Methyl-4(4-methylbenzylidene)isoxazol-5(4H)one (**4h**):*

M.p.: 132-134^{o}C; ^{1}HNMR ($CDC1_3$, 400MHz): 7.33 (d, J=8Hz, 2H), 8.34(d, J=8.3Hz, 2H), 2.32 (s, 3H), 2.46 (s, 3H), 7.41(s, 1H); MS(m/z): 202.1.

General procedure for the Knoevenagel condensation for the Synthesis of benzylidenemalononitriles:

A 25 mL round-bottomed flask was charged with aldehydes (1mmol), malonitrile (1mmol) and imidazole (10mol %) in 4 mL 1:1 / EtOH: H_2O medium. The mixture was stirred for the appropriate time (Table **3**). After completion of the reaction as monitored by TLC (ethyl acetate-hexane, 2:8), the reaction mixture solidified in the round-bottomed flask. The solid was filtered and washed with cold water (20mL), then recrystallized from ethanol-water (4:1), to afford the pure product.

Selected spectral data:

*2-(4-methoxybenzylidene) malononitrile (**7b**):*

M.p.: 109-111°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87(d, 2H, J= 8.91 Hz), 7.63 (s, 1H),7.01 (d, 2H, J= 8.91 Hz), 3.92(s, 3H), MS(m/z):185.1.

*2-benzylidenemalononitrile (**7c**):*

M.p.: 78-80°C; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ*7.92 (d, 2H, *J*=7.8 Hz), 7.82 (s, 1H), 7.66 (t, 1H, *J*=7.31 Hz), 7.53 (t, 2H, *J*= 7.7 Hz); MS(m/z):155.1.

*2-(4-chlorobenzylidene) malononitrile (**7d**):*

M.p.: 151-152°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84 (d, 2H, J= 8.3 Hz), 7.73 (s, 1H), 7.52 (d, 2H, J= 8.3 Hz,); MS(m/z):190.1.

*2-(4-nitrobenzylidene) malononitrile (**7f**):*

M.p.: 152-154°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.73(s,1H), 8.42 (d, 2H, J= 8.7 Hz), 8.11 (d, 2H, J= 8.8 Hz); MS (m/z): 200.1.

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