An Efficient Synthesis of Isoxazoles Promoted by Hexamine as an Efficient Organocatalyst

Fahad T. Saleh[1], M. Zameer Ahmed[2], Prashant. D. Netankar[3], Abdul Ahad[4], Syed Ummul Khair Asema[5*]

[1,3,4,5]Department of Chemistry, Maulana Azad College of Arts, Science & Commerce, Rauza Baugh, Aurangabad(M.S),India.

[2]Department of Chemistry, Poona College of Arts, Science & Commerce, Camp, Pune (M.S), India.

Abstract

In the presence of hexamine catalyst in ethanol:water, a clean and efficient multi-component method for the synthesis of biologically important isoxazoles using aryl aldehydes, hydroxyl amine hydrochloride, and ethyl aceto acetate is reported. One-pot reaction, environmentally friendly approach, operational simplicity, broad substrate scope, excellent yields, short reaction time, simple workup procedure and use of hexamine as a non toxic, easily available and safe organocatalyst are the advantages of the current methodology.

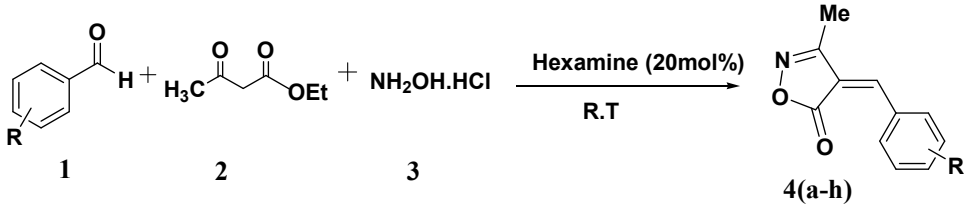
Keywords: Multicomponent reaction, isoxazoles, hexamine catalyst.

1. Introduction

Multicomponent reactions (MCRs) are one of the most efficient tools in modern synthetic organic chemistry because they have all of the characteristics that make for an ideal synthesis such as high atom efficiency, time and energy savings, fast and simple execution, ,environmental friendliness and also offering target and diversity-oriented synthesis [1-2] . Furthermore, combining well-known multicomponent reactions with post-reaction transformations allows for the creation of a wide range of complex and diverse products [3-5]. Isoxazoles are aromatic heterocycles with five membered cyclic ring having neighbouring oxygen and nitrogen atoms. The isoxazole ring system can be found in a wide range of natural products and physiologically active organic molecules [6], Isoxazole derivatives have a wide range of pharmacological and biological properties such as anti-HIV [7], anticonvulsant [8], antimicrobial [9], anticancer [10], analgesic [11] and antiviral [12] etc. According to reported literature the synthesis of one of the isoxazole scaffolds, aryl-3-methylisoxazol-5(4H)-ones performed by combining aromatic aldehydes with ethyl acetoacetate and hydroxylamine. A variety of reagents and catalytic systems in recent years have been utilized for the synthesis of these aryl-3-methylisoxazol-5(4H)-ones , including guanidine hydrochloride [13] [H-Pyrr][H_2PO_4] [14], sodium silicate [15], Nickel [16] pyridine [17], [TMBSED][OMs]$_2$ [18], DOWEX(R)50WX_4 [19].
However, some of the published procedures for the synthesis of arylmethyledene-isoxazole-5(4H)-ones have drawbacks in terms of both economics and the environment. For the first time, we present an efficient, new and environmentally friendly easy synthesis of 4-arylidene-3-phenylisoxazol-5-ones in an ethanol: water (1:1) medium with hexamine as a basic, cost effective and safe organocatalyst. Organocatalysthaving an organic framework, with industrial appeal have piqued the scientific community's interest for a variety of reasons, including their low cost, less sensitive to moisture and air, vast chiral pool, and non-corrosive in nature [3]. The efficiency of hexamine as an organocatalyst has received little attention yet. So in this protocol and in continuation of our previous works towards development of convenient protocols [20-26] here we explore the catalytic activity of hexamine as an efficient organocatalyst.

2. Results and Discussion

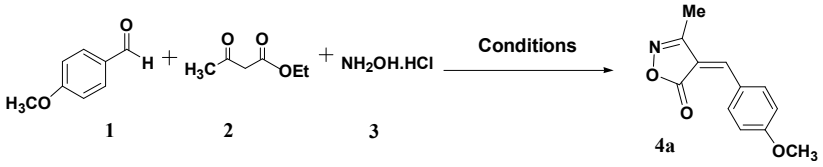
A one-pot multicomponent reaction was utilized to obtain the desired aryl-3-methylisoxazol-5(4H)-ones by using appropriate substrates catalyzed by hexamine in aqueous ethanol medium (Scheme 1).



Scheme: 1. Hexamine promoted synthesis of arylmethyledene-isoxazole-5(4H)-ones

Initially, a model reaction was set up with p-methoxy benzaldehyde, ethyl acetoacetate and hydroxylamine (Scheme 1). Different parameters such as solvent and temperature were investigated to develop optimized reaction conditions for the model reaction. The focus for the optimization of the reaction was to incorporate green and safer medium and catalyst for the synthesis of these isoxazoles. After screening, it was observed that hexamine catalyst has a unique capability to enhance the rate of reaction in water: ethanol (1:1). In addition to this, other solvents like acetonitrile and methanol and were also studied. In the beginning a mixture of 4- OMe-benzaldehyde, ethyl acetoacetate and hydroxyl amine hydrochloride and 20 mol% hexamine in 5ml ethanol afforded the corresponding isoxazole with 91% yield in 75min (Table **1**, entry 1). When the same reaction is performed in water: ethanol (1:1) the reaction gave similar yield as compared to ethanol alone (Table **1**, entry 2), whereas if the water ratio is doubled then the yield of the product decreases (Table **1**, entry 3). When water alone was investigated as reaction medium, the yield was only 60%, which may be owing to poor solubility of the material in water (Table 1, entry 4). Other solvents such as methanol and acetonitrile gave poor yield of the products at room temperature (Table 1, entries 4-5).

Table 1 Optimization of reaction conditions for the synthesis of arylmethyledene-isoxazole-5(4H)-one



Entry	Solvents [a]	Hexamine	Temperature (°C)	Time (min)	Yield (%)[b]
1	EtOH	20 mole%	R.T	75	91
2	EtOH:H_2O (1:1)	20 mole%	R.T	75	91
3	EtOH:H_2O (1:2)	20 mole%	R.T	80	82
4	H_2O	20 mole%	RT	100	60
5	MeOH	20 mole%	RT	240	65
6	ACN	20 mole%	RT	240	55

[a] 5mL, [b]Isolated yields.

Different derivatives are prepared, as shown in Table 2, to investigate the efficiency and scope of the developed process, and it was found that this new procedure works with a variety of substrates. The reaction was carried out with seven different types of substituted aromatic aldehydes, while all of the

aldehydes produced the corresponding products in good to excellent yields where as aromatic aldehydes with electron donating substituents produced the products in comparatively high yields.

Table 2 Hexamine catalyzed synthesis of arylmethyledene-isoxazole-5(4H)-ones

Entry	R	P	Yield (%)[a]	Time (min)	M. p (°C)	
					Observed	Literature
1	4-CH_3O	4a	91	75	175-178	175-177 [15]
2	4-NO_2	4b	88	85	180-182	183-184 [6]
3	2-NO_2	4c	80	80	138-140	----
4	4-CH_3	4d	90	70	131-133	132-134 [3]
5	4-OH	4e	89	70	220-225	213-215 [18]
6	H	4f	85	80	138-140	141-143 [15]
7	2-OH	4g	87	65	196-198	197-199 [21]
8	4-Cl	4h	86	75	124-126	128-130 [18]

[a]Isolated yields.

In the mechanism the amino group of hydroxyl amine hydrochloride attacks the carbonyl carbon of ethyl acetoacetate to form an oxime intermediate. Hexamine abstracts the proton from the active methylene position of the oxime intermediate to form a carbanion, which attacks the electrophilic carbonyl carbon atom of aldehydes via the Knoevenagel condensation reaction. The oxygen atom of the oxime group attacks the carbon atom of the ester, followed by proton transfer and elimination of the ethanol molecule resulting in isoxazole-5(4H)- ones (Figure: 1).

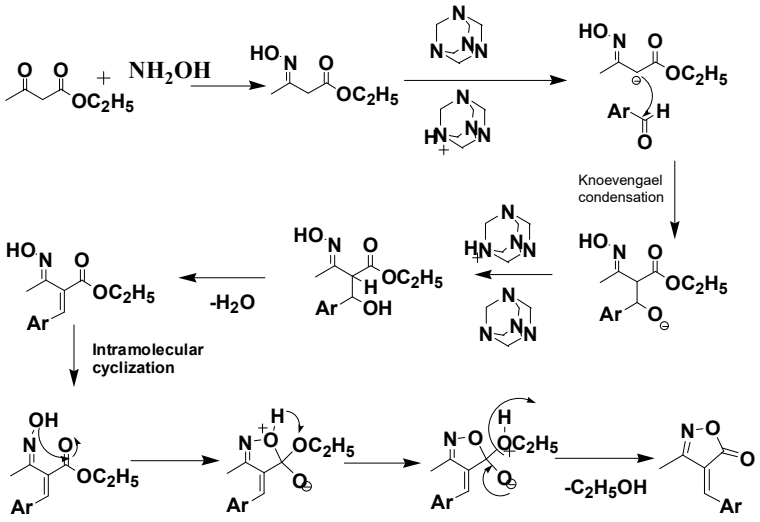


Figure1: Possible Mechanism for the hexamine catalyzed synthesis of isoxazole-5(4H)-ones

3. Experimental

Chemicals were purchased from SD Fine Chemical Companies. The physical properties of the synthesized derivatives were confirmed by comparing the physical data of those described in the literature. A Bruker Advance DPX-250 was used to record NMR spectra. Mass spectra were recorded on the Waters GC-MS spectrophotometer. Silica gel TLC plated were used to monitor the reactions' and the product's purity.

2.1. Typical Procedure for the synthesis of arylmethylidene-isoxazol-5(4H)-ones (4a-h)

Aromatic aldehyde (1 mmol) was added to a stirred mixture of ethyl acetoacetate (1 mmol), hydroxylamine hydrochloride (1 mmol), and hexamine (20 mol%) in EtOH: H_2O (5 mL, 1:1), and the mixture was agitated at room temperature for the necessary amount of time and monitored by TLC (ethyl acetate:hexane, 2:8). After indication of reaction completion, 5 mL of water was added, and the resulting solid crude precipitate was filtered. To obtain the pure product, the crude product was recrystallized from EtOH-H_2O (4:1).

2.2. **Spectral data**

3-Methyl-4-(4-methoxyphenyl)methylene-isoxazole-5(4H)-one (4a) M.p. 175-178 ºC; ^{1}H NMR (500 MHz, DMSO-d6) δ(ppm): 2.27 (3H, s, CH3), 3.90 (3H, s, OCH3), 7.17 (2H, d, J = 8.9 Hz, HAr), 7.87 (1H, s, =CH), 8.53 (2H, d, J = 8.9 Hz, HAr); ^{13}C NMR(125 MHz, DMSO-d6) δ(ppm): 11.16, 56.9, 114.57, 115.13, 125.69,136.79, 151.13, 162.28, 164.15, 169.77;Mass, m/z: 218.10 [M+1].

3-Methyl-4-(4-hydroxyphenyl)methylene-isoxazole-5(4H)-one (4e) M.p. 220-225 ºC; ^{1}H NMR (500 MHz, DMSO-d6)δ(ppm): 2.23 (3H, s, CH3),6.94 (2H, d, J = 8.8 Hz, HAr), 7.74 (1H, s, = CH),8.43 (2H, d, J = 8.7 Hz, HAr), 11.00 (1H, s, OH);^{13}C NMR(125 MHz, DMSO-d6) δ(ppm): 11.16, 113.79, 116.05, 124.48, 137.42, 151.31, 162.11, 163.75, 168.72;Mass, m/z: 204.07 [M+1].

4. Conclusion

We have developed a new procedure for the synthesis of different substituted isoxazole derivatives (4a-4h) by one-pot three-component reaction between substituted aldehydes, ethyl acetoacetate and hydroxylamine hydrochloride in the presence of hexamine as an efficient organocatalyst in aqueous ethanol medium. The current methodology has numerous benefits, such as simple process, use of safe and easily accessible hexamine oraganocatalyst and ethanol:water as green medium, less reaction time and maximum yields.

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4. References

[1] J. Zhu, H. Bienayme., Eds. Multicomponent Reactions; Wiley-VCH: Weinheim, Germany (2005).
[2] S. G. Cedric, V. R. Felipe, R. R. Kamilla and E. K. Arthur, Multicomponent Reactions for the Synthesis of Bioactive Compounds: A Review, Curr. Org. Synth., 16 (6), **(2019)**, 855-899.
[3] A. Ahad and F. Maqdoom, Access to arylmethylidene-isoxazol-5(4H)-ones and benzylidenemalononitriles promoted by imidazole as an efficient organocatalyst, Iran J. Org. Chem., 8 (1), **(2016)**, 685-1691.
[4] P. A.Wender, Toward the ideal synthesis and molecular function through synthesis-informed design, Nat. Prod. Rep., 31, (**2014),** 433-444.
[5] A. Ahad and F. Maqdoom, An Efficient ultrasound Assisted multicomponent synthesis of 1-Amido alky 2-Naphthols, Int. J. Chem. Sci., 10(4), **(2012)**, 2165-2170.
[6] B. Hamid, K.D. Mahboubeh, A. Reza, G. Behzad, M. Z. Mohammad and M. M. Mohammadreza, Green multicomponent synthesis, antimicrobial and antioxidant evaluation of novel 5-amino-isoxazole-4-carbonitriles, Chem. Cent. J., 12, 114, **(2018)**, 1-8.
[7] B. L. Deng, M. D.Cullen, Z. Zhou , T. L. Hartman, R. W. Buckheit Jr, C. Pannecouque, E. De Clercq, P.E. Fanwick, M. Cushman, Synthesis and anti-HIV activity of new alkenyldiarylmethane (ADAM) non-nucleoside reverse transcriptase inhibitors (NNRTIs) incorporating benzoxazolone and benzisoxazole rings, Bioorg. Med. Chem., 7, **(2006)**, 2366-2374
[8] S. Balalaei, A. Sharifi, B. Ahangarian, Solid phase synthesis of isoxazole and pyrazole derivatives under microwave irradiation, Indian J. Heterocycl. Chem., **(2000)**, 10, 149-150.

[9] Y. Prashanthi, K. Kiranmai, N. Subhashini, Synthesis, Potentiometric and Antimicrobial Studies on Metal Complexes of Isoxazole Schiff Bases, Spectrochim. Acta, Part A, 70(1), **(2008)**, 30-35.
[10] J. Y. C. Wu, W. F. Fong, J. X. Zhang, C. H. Leung, H. L. Kwong, M. S. Yang, D. Li, H. Y. Cheung, Reversal of multidrug resistance in cancer cells by pyranocoumarins isolated from Radix Peucedani, *Eur. J. Pharmacol, 473*, *(***2003)**, 9-17.
[11] H. Kano, I. Adachi, R. Kido, K. Hirose, Synthesis and analgesic activity of 2-substituted isoxazoline, *J. Med. Chem,* 10(3), *(***1967)**, 411.
[12] Y. S. Lee, S. M. Park, B. H. Kim, Synthesis of 5-Isoxazol-5-yl-2'-deoxyuridines Exhibiting Antiviral Activity against HSV and Several RNA Viruses, *Bioorg. Med. Chem. Lett., 19, (***2009)**, 1126-1128.
[13] A. B. Barkule, Y. U Gadkari, V. N. Telvekar, One-Pot Multicomponent Synthesis of 3-Methyl-4-(Hetero)Arylmethylene Isoxazole-5(4H)-Ones Using Guanidine Hydrochloride as the Catalyst under Aqueous Conditions, Polycycl. Aromat. Compd., 24(9), **(2022)**.
[14] S**.** K. Asadi, G. Aleabaa, N. Daneshvar, F. Shirini, Sustainable and green synthesis of 3-methyl-4-arylmethylene-isoxazole-5(4H)-one derivatives under mild conditions using a novel phosphoric acid-based molten salt as catalys, Sustain. Chem. Pharm, 21, **(2021)**, 100442.
[15] Q. Liu, R.T. Wu, Facile synthesis of 3-methyl-4-arylmethylene-isoxazol-5(4H)- ones catalysed by sodium silicate in an aqueous medium, J. Chem. Res., 35, **(2011)**, 598-599.
[16] H. Kiyani, H. A. Samimi, Nickel-catalyzed One-pot, three-component synthesis of 3,4-disubstituted Isoxazole-5(4H)-ones in aqueous medium, Chiang Mai J. Sci., 44, (2017), 1011-1021.
[17] K. Ablajan, H. Xiamuxi,The convenient synthesis of 4-arylmethylidene-4, 5-dihydro-3-phenylisoxazol-5-ones, Chin. Chem. Lett, 22, **(2011)**, 151-154.
[18] N. Irannejad-Gheshlaghchaei, Z. Abdolkarim, S. S. Sajadikhah & A. Banaei, A novel dicationic ionic liquid as a highly effectual and dual-functional catalyst for the synthesis of 3-methyl-4-arylmethylene-isoxazole-5(4H)-ones, Res. Chem. Intermed, 44, **(2018)**, 6253-6266.
[19] D. Setamdideh, DOWEX(R)50WX$_4$/H$_2$O: A Green System for a One-pot and Three-Component Synthesis of isoxazol-5(4H)-one Derivatives, J. Mex. Chem. Soc, 59(3), **(2015)**, 191-197.
[20] A. Ahad and F. Maqdoom, Glycine catalyzed synthesis of 3-Indole derivatives mediated by PEG-400 in water, Chem. Sci.Trans, 5 (1), **(2016)**, 202-206.
[21] A. Ahad and F. Maqdoom, Choline chloride and urea based deep eutectic solvent promoted synthesis of arylmethylidene-isoxazol-5(4H)-ones, Int. J. Chemtech Res., 10 (6), **(2017)**, 269-273.
[22] A. Ahad and F. Maqdoom, An efficient synthesis of 3-amino alkylated indole Via A Mannich-Type reaction catalyzed by SiO_2-I, Heterocyc. Lett., 7 (4), **(2017)**, 953-958
[23] A. Ahad and F. Maqdoom, Pot, atom and step economic (PASE) synthesis of 2-amino-3, 5-dicarbonitrile-6-thio-pyridines in aqueous PEG-400 promoted by sodium benzoate, Int. J. Chem. Sci., 14,3, **(2016)**,1789-1796.
[24] A. Ahad and F. Maqdoom, Organocatalyzed domino reactions: Diversity oriented synthesis of pyran-annulated scaffolds using in situ-developed benzylidenemalononitriles, Res. Chem. Intermed., 43 (4), **(2016)**, 2445-2455.
[25] A. Ahad and F. Maqdoom, Hydroquinolines via the Hantzsch reaction promoted by SiO_2-I, Org. Prep. Proced. Int, Organic Preparations and Procedures International, 48 (4), **(2016)**, 371-376.
[26] A. Ahad and F. Maqdoom, Recyclable Amberlite IR-120 catalyzed synthesis of 3-substituted indoles, Chemistry & Biology Interface., 5(5), **(2015)**.