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ONE POT SYNTHESIS OF ISOXAZOLONE DERIVATIVES USING IONIC LIQUID AS AN EFFICIENT CATALYST VIA MULTICOMPONENT REACTION

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Abstract: A simple and convenient route for the synthesis of isoxazol-5(4*H*)-one derivatives is described via multi-component condensation of aryl aldehyde, ethyl acetoacetate and hydroxyl amine under the influence of 1-butyl-3-methyl-imidazolium hexafluoro phosphate [BMIM][PF_6] ionic liquid as an efficient, cheaper and eco-friendly catalyst under conventional reflux condition in ethanol. The present protocol has several beneficial things such as simple work-up process, a cleaner reaction, optimum reaction time and good to excellent yields.

Keywords: Aryl aldehyde, ethyl acetoacetate, ionic liquid, [BMIM][PF_6], isoxazolone, multicomponent reaction, etc.

Introduction:

In the recent era, ionic liquids (ILs) have developed more attention in the area of synthetic organic chemistry because of noteworthy eco-friendly properties like adequate ionic conductivity, extensive liquid range, non-flammability, low vapor pressure, and ability to dissolve a wide range of organic solids[i-iii]. They are effectively employed in many organic transformations such as biginelli reaction, epoxidation reaction, hantzsch reaction, hydroformylation reaction, oxa-michael addition and prins reaction[iv-ix].

The isoxazol-5(4*H*)-one nucleus containing nitrogen and oxygen atoms which shows significant pharmaceutical as well as biological activities such as antibacterial, anticancer, anti-HIV, antifungal, anti-inflammatory, analgesic, anti-mycobacterial, antioxidant, antitumor, antiprotozoal, anti-tubercular, CDP-ME kinase inhibitor, nematicidal, larvicidal activity and antiviral activities[x-xviii]. The some important example of isoxazol-5(4*H*)-one nucleus containing active agents are shown in **Figure I**.

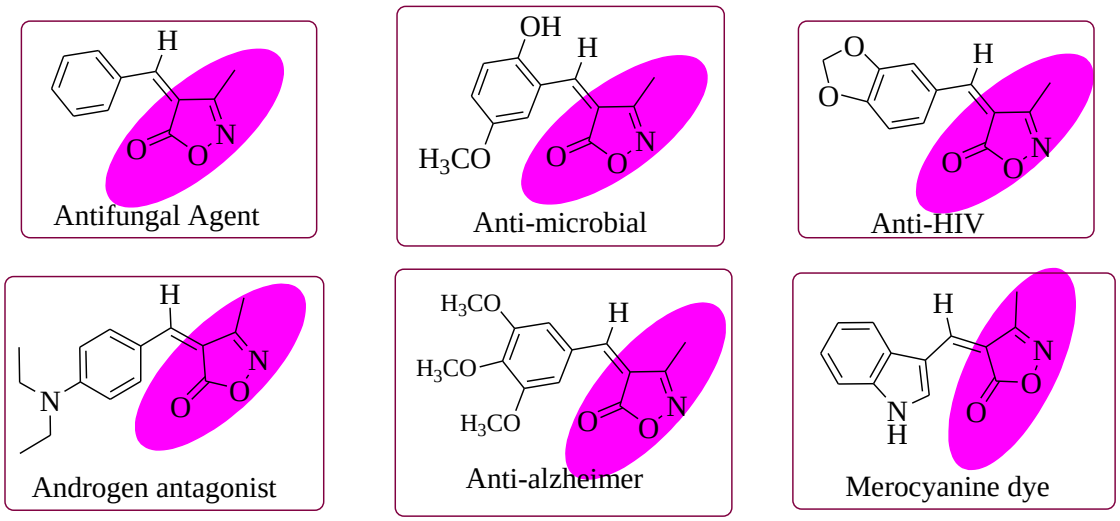


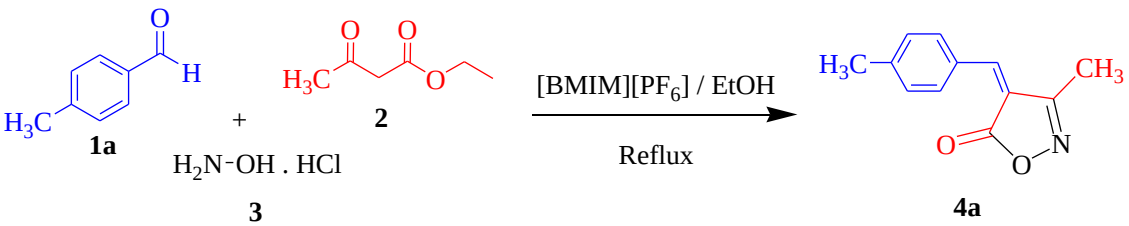
Figure 1: Some illustrations of drugs containing isoxazol-5(4*H*)-one nucleus

In the literature various catalytic materials have been reported for the synthesis of isoxazolones derivative such as nano-MgO[xix], Cu/TCH-pr@SBA-15 nano-composite[xx], Ag/SiO_2[xxi], boric acid[xxii], citric acid[xxiii], *N*-bromosuccinimide[xxiv], $H_3PW_{12}O_{40}$, clinoptilolite, nano Fe_2O_3[xxv], NaOAc/visible light[xxvi], NaH_2PO_4[xxvii], phthalimide-*N*-oxyl salts[xxviii], pottasium phthalimide[xxix], pyridine/ultrasound irradiation[xxx], pyridine/reflux[xxxi], sodium benzoate[xxxii], sodium saccharin[xxxiii], sodium sulfide[xxxiv], L-valine[xxxv], $KBr.6H_2O/MW$[xxxvi], Sn^{II}-montmorillonite/US[xxxvii], Pyruvic acid/US[xxxviii], 4-(N,N-Dimethylamino)pyridinium Acetate[xxxix], $[HNMP][HSO_4]$[xl] etc.

In continution of our work in the field of ionic liquid catalyzed reaction[xli]; we have investigated new protocol for the synthesis of isoxazolone derivatives by three component condensation of aryl aldehyde **(1)**, ethyl aceto acetate (**2**), hydroxylamine hydrochloride (**3**) and 150 mg of ionic liquid $[BMIM][PF_6]$ under reflux condition.

Results and Discussion:

Initially, the optimal reaction conditions were studied using the model reaction between *p*-methyl benzaldehyde **1a,** ethyl acetoacetate **2** and hydroxyl amine hydrochloride **3** under solvent-free conditions and with solvent in presence of varying amounts of $[BMIM][PF_6]$ as a catalyst. The model reaction was also carried out in absence of catalyst **(Table 1, Entry 1 and 2)**. The best result was obtained, when the reaction were conducted under reflux conditions with loading 150 mg $[BMIM][PF_6]$ for a relatively short period of time **(Table 2, Entry 4)**. Optimization reactions were carried out at reflux condition. The results were not obtained when carrying out the reaction at room temperatures with grinding and stirring.



Scheme 1. Model reaction for synthesis of isoxazolone derivative (**4a)**

Table 1: Optimization of reaction condition to synthesize isoxazolone derivative (**4a**)

Entry	Catalyst/ Solvent	Reaction Condition	Time	Yield
1	No catalyst/ Solvent free	Grinding	1 h	NR
2	No catalyst/ EtOH	Stirring at RT	1 h	NR
3	150 mg [BMIM][PF_6] / SF	Grinding	1 h	NR
4	150 mg [BMIM][PF_6] / EtOH	Stirring at RT	1 h	NR
5	150 mg [BMIM][PF_6] / EtOH	Reflux	1 h	85 %

Reaction Condition: Aryl aldehyde **1a** (2 mmol), Ethyl acetoacetate **2** (2 mmol), hydroxyl amine hydrochloride **3** (2 mmol) and 150 mg [BMIM][PF_6]

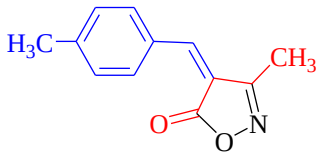
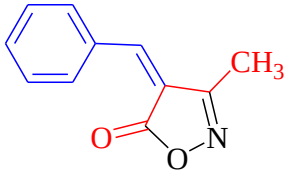
Table 2: Optimization of the amount of catalyst on the synthesis isoxazolone derivative (**4a**)

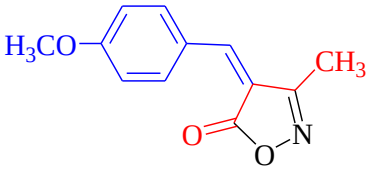
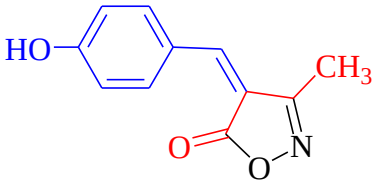
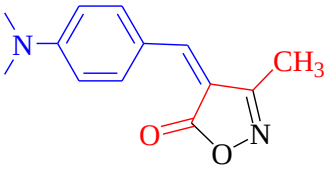
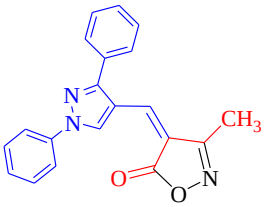
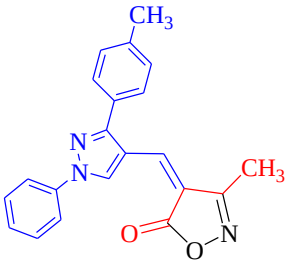
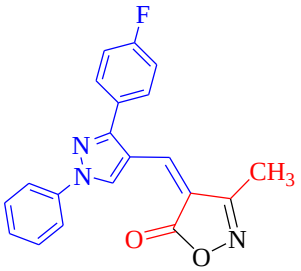
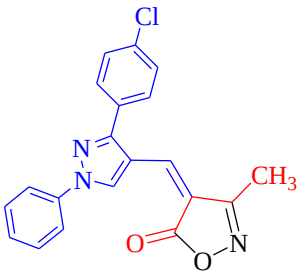
Entry	Amount of Catalyst	Reaction Condition	Time	Yield
1	75 mg [BMIM][PF_6]	Reflux in EtOH	1 h	40 %
2	100 mg [BMIM][PF_6]	Reflux in EtOH	1 h	55 %
3	125 mg [BMIM][PF_6]	Reflux in EtOH	1 h	70 %
4	150 mg [BMIM][PF_6]	Reflux in EtOH	1 h	85 %
5	175 mg [BMIM][PF_6]	Reflux in EtOH	1 h	85 %

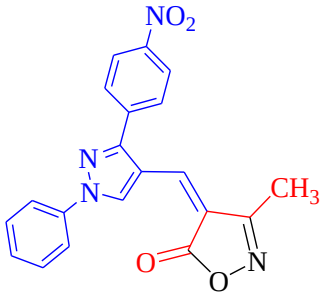
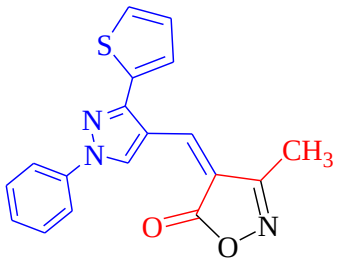
Reaction Condition: Aryl aldehyde **1a** (2 mmol), Ethyl acetoacetate **2** (2 mmol), hydroxyl amine hydrochloride **3** (2 mmol) and [BMIM][PF_6]

After the selection of optimized reaction conditions, the divergent derivatives of 3,4-disubstituted isoxazole-5(4*H*)-ones (**4a–k**) were synthesized from the reaction of hydroxylamine hydrochloride, ethyl acetoacetate with various aryl and heteroaryl aldehydes with electron-donating and electron-withdrawing substituent in the presence of 150 mg [BMIM][PF_6] ionic liquid in ethanol under reflux conditions. The results are summarized in **Table 3**.

Table 3: Data of synthesized isoxazolone derivatives (**4a-k)** using [BMIM][PF_6] as a catalyst

Entry	Iso-oxazolone derivative	Color	Time in hrs.	Yield in (%)	M.P. in (^oC)	
					Observed	Reported
4a		Yellow	01	85	132	136-137[xxxvi]
4b		Yellow	01	80	138	140-141[xxxvi]

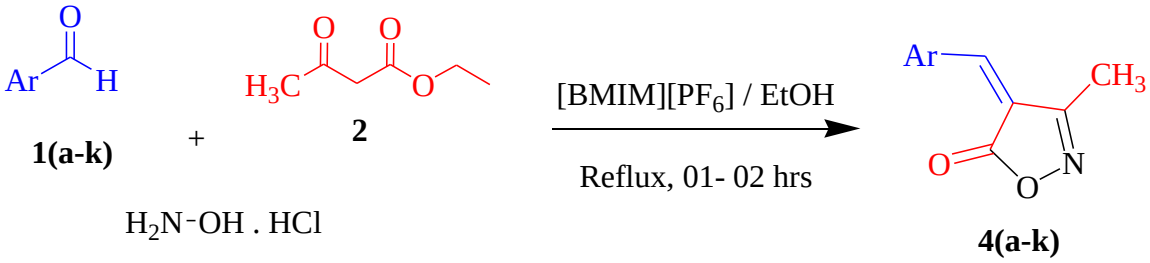
4c		Yellow	01	80	172	177-179[xxxvi]
4d		Faint Orange	01	85	206	214-215[xxxvii]
4e		Red	01	85	218	226-227[xxxvi]
4f		Yellow	01	75	202	208[xl]
4g		Yellow	02	75	216	210[xl]
4h		Yellow	02	75	214	204[xl]
4i		Yellow	02	70	234	228[xl]

4j		Brown	02	75	230	268[xl]
4k		Orange	02	70	198	192[xl]

Reaction Condition- Aryl aldehyde **1** (2 mmol), Ethyl acetoacetate **2** (2 mmol), hydroxyl amine hydrochloride **3** (2 mmol), 150 mg [BMIM][PF_6] and 10 mL ethanol.

Experimental:

The physical constants were recorded in an open capillary and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectrums were recorded on a Brucker Avance II 500MHz in $CDCl_3$. Mass spectra were recorded on a Finnigan Mass spectrometer. TLC was carried out on pre-coated silica gel on aluminum plates to study the formation of the product.



Scheme 1: Synthesis of isoxazolone derivatives **(4a-k)**

General procedure for the synthesis of isoxazolone derivatives 4(a-k)

A mixture of the aryl aldehyde **1** (2 mmol), ethyl aceto acetate **2** (2 mmol), hydroxyl amine hydrochloride **3** (2 mmol) and 150 mg of [BMIM][PF_6] was taken in a 100 mL round bottom flask containing 10 mL of ethanol. Then it was refluxed for 1-2 hrs until all the components were consumed. The progress of the reaction was monitored by TLC. After completion of the reaction, the content were cooled to room temperature, solid product thus obtained was separated by filtration. The crude product was purified by recrystallization using ethanol to get pure product.

Discussion of spectral data of synthesized compounds:

Compound 4a: 4-(4-methylbenzylidene)-3-methylisoxazol-5(4*H*)-one

Yellow Solid; M.P. 132˚C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.26 (s, 3H, -CH_3), 2.45 (s, 3H, -CH_3), 7.32 (d, 2H, Ar-H), 7.39 (s, 1H, vinyl proton), 8.28 (d, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ: 11.63, 22.06, 118.43, 129.73, 129.88, 129.95, 131.02, 134.14, 145.72, 149.96, 161.21, 168.21; MS: m/z= 202.1084 $[M+1]^+$.

Compound 4c: 4-(4-methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one
Yellow Solid; M.P. 172˚C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.28 (s, 3H, -CH_3), 3.92 (s, 3H, -OCH_3), 7.01 (m, 2H, Ar-H), 7.34 (s, 1H, vinyl proton), 8.44 (d, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ: 11.64, 55.72, 114.66, 116.36, 125.83, 136.96, 149.33, 161.28, 164.61, 168.77; MS: m/z= 218.0780 $[M+1]^+$.
Compound 4f: 4-(4-(dimethylamino)benzylidene)-3-methylisoxazol-5(4*H*)-one
Reddish Solid; M.P. 218˚C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.24 (s, 3H, -CH_3), 3.15 [s, 6H, -$N(CH_3)_2$], 6.74 (d, 2H, Ar-H), 7.21 (s, 1H, vinyl proton), 8.40 (d, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ: 11.70, 40.22, 111.43, 111.72, 121.78, 137.57, 149.18, 154.09, 161.54, 170.05; MS: m/z= 231.1062 $[M+1]^+$.

Conclusion:
We have investigated a simple and convenient route for the synthesis of isoxazol-5(4*H*)-one derivatives via multi-component condensation of aryl aldehyde, ethyl acetoacetate and hydroxyl amine under the influence of [BMIM][PF_6] ionic liquid as an efficient, cheaper and eco-friendly catalyst under conventional reflux condition in ethanol. The present protocol has offered several beneficial things such as non-toxicity of the catalyst, simple work-up process, a cleaner reaction, optimum reaction time and good to excellent yields which lead to the contribution in green chemistry.

Abbreviations:
SF : Solvent Free,
[BMIM][PF_6] :1-butyl-3-methyl-imidazolium hexafluoro phosphate
MCRs : Multicomponent Reactions,
RT : Room Temperature,
NR : No Reaction

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