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MAGNESIUM BROMIDE AN EFFICIENT CATALYSTS FOR THE SYNTHESIS OF 3,4-DISUBSTITUTED ISOXAZOLE-5(*4H*)-ONES

Yogesh Walunj[a], Pravin Mhaske[a], Pramod Kulkarni[b*]

[a]*Department of Chemistry, Sir Parshurambhau College, Tilak Road, Pune*
(Affiliated to Savitribai Phule Pune University, Pune)
Email: mhaskepc18@gmail.com Cell No.9850577751
[b]*Post graduate center in Organic Chemistry and Department of Chemistry*
Hutatma Rajguru Mahavidyalaya, Rajgurunagar, Pune-410505
Email : pramodskulkarni3@gmail.com Cell No. : 919850658087

Abstract
A one-pot and three component synthesis of 3-mehyl-4-arylmethyleneisoxazol-5(*4H*)-ones was developed in the presence of magnesium bromide as the catalyst. The products were obtained in high yields and short reaction time, with easy workup process. The present method provides an easy and efficient approach for the synthesis of this class of compounds, because of its clean reaction profile and operational simplicity.

Keywords: Multicomponent reaction, 4-aryl-3-methyl isoxazole, magnesium bromide, green chemistry, one-pot, ethanol

Introduction

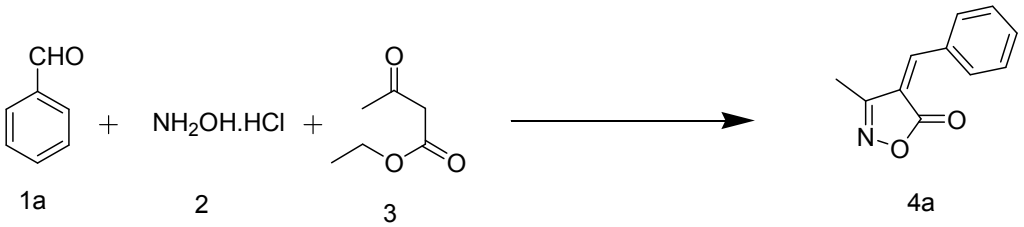
Nitrogen containing heterocycle with an oxygen atom considered as an important class of compounds in medicinal chemistry because of their diversified biological applications. Isoxazole is five member heterocyclic compound containing oxygen and nitrogen atoms in the 1, 2-positions. Isoxazole derivatives possess variety of biological activities.[i-xv] Also, isoxazolone moieties have been used for the design of liquid crystals,[xvi] merocyanine dyes in optical research,[xvii] filter dyes in photographic films,[xviii] light conversion molecular devices,[ixx] optical storage and nonlinear optical research.[xx] Furthermore, 4-(arylmethylene)isoxazol-5-ones are used for the preparation of fused heterocyclic compounds.[xxi-xxiii] The isoxazole backbone is also a structural component of a variety of natural products, for example, muscimol[ixxv], cycloserine,[xxv] ibotenic acid and isoxazol-4-carboxylic acid.[xxvi]

The usual synthesis of 4-arylidene-3-methylisoxazol-5(*4H*)-one to be carried in two steps, in the first step, preparation of oxime[ethyl 3-(hydroxyimino)-3-methylpropanoate] and ring closing of this oxime to afford 3-methylisoxazol-5-one. Then in second step, the Knoevenagel condensation of aryl aldehydes and 3-methylisoxazol-5-one produce 4-arylidene-3-phenylisoxazol-5-ones.[xxvii-xxviii] The three-component reaction of ethyl

acetoacetate, hydroxylamine hydrochloride and various aryl aldehydes for the synthesis of isoxazole-5(4H)-one have been reported by the use of boric acid,[xxix] Dowex(R)50WX4/H_2O,[xxx] Phthalimide-N-oxyl salts,[xxxi] Sodium Saccharin,[xxxii] Dowex1-x8OH in water,[xxxiii] sodium sulphide,[xxxiv] sodium silicate,[xxxv] sodium benzoate,[xxxvi] N-bromosuccinimide,[xxxvii] Ag/SiO_2,[xxxviii] Starch solution,[xxxix] potassium phthalimide,[xl] 2-Hydroxy-5-sulfobenzoic acid(2-HSBA),[xli] tartaric acid,[xlii] 1,4-diazabicyclo[2.2.2](DABCO),[xliii] $Ni(OAc)_2.H_2O$,[xliv] sodium ascorbate,[xlv] nanoMgO,[xlvi]sodium citrate,[xlvii] tetrabutylammonium perchlorate, sodium oxalate, glycine.[xlviii] Also some methods has been carried out at high temperature and long reaction times,[xlix] with moderate yields, or under unconventional energy sources such as ultrasound irradiation,[l] visible light,[li] and microwave irradiation,[lii] solid state heating or grinding.[liii] These reported methods have their own merits and demerits. Some of these methods have disadvantage such as catalyst preparation required, long reaction time, low yield, expensive catalyst. On the other hand, multi-component reactions (MCRs) have been used as very powerful method for the synthesis of a variety of molecules in one-pot reactions. This type of reactions is important in the synthesis of natural products and biologically active compounds, because they have many advantages such as excellent functional group compatibility, minimization of waste, versatility, atom economy, environmentally friendly and easy work-up.[liv] Magnesium bromide is used as a catalyst for the synthesis of dihydropyriminones,[lv] acylation of alcohols,[lvi] and effecting various transformation[lvii-lx] such as condensation reaction cyclization reaction, polymerization, Diels-Alder reactions.

Results and Discussion

The condensation of ethyl acetoacetate, hydroxylamine hydrochloride and benzaldehyde was selected as a model reaction. Initially we have various metal salts such as potassium chloride, potassium bromide, sodium acetate, sodium oxalate, zinc acetate, calcium chloride, calcium nitrate, potassium acetate, magnesium bromide hexahydrate, magnesium chloride, magnesium nitrate, ammonium acetate, potassium nitrate, calcium oxalate, manganese acetate, calcium nitrate, potassium oxalate as catalyst for the condensation reaction in 15mL as solvent at room temperature and results are summarized in table (**Table 1)**. The model reaction is performed in 50mL RB flask using 1mmol of ethyl acetoacetate, 1mmol of hydroxylamine hydrochloride, 1mmol of benzaldehyde and 0.2mmol of catalyst in 5ml ethanol under stirring condition at 60ºC (Scheme 1). From **Table 1** it was observed that magnesium bromide was found an efficient catalyst for synthesis of 4-aryl-3-methyl isoxazole with 96% yield. Zinc acetate, potassium nitrate, calcium oxalate, did not give the desire product while ammonium acetate and manganese acetate afford the unidentified product.



Scheme 1: Model reaction for optimization of reaction condition

Table 1. Screening of catalyst for condensation reaction between ethyl acetoacetate, hydroxylamine hydrochloride and benzaldehyde in 5mL EtOH under stirring condition[a]

Sr. No	Catalyst	Product **4a**	Time in h	% yield [b]
1	KCl	**4a**	2	55
2	KBr	**4a**	2	70
3	NaOAC	**4a**	3.56	65
4	Sodium oxalate	**4a**	3.20	74
5	$Zn(OAc)_2$	**4a**	4.10	No reaction
6	$CaCl_2$	**4a**	8.00	82
7	KOAc	**4a**	3.10	76
8	$MgBr_2$	**4a**	2.0	96
9	$MgCl_2$	**4a**	5.45	83
10	$MgNO_3$	**4a**	3.56	80
11	NH_4OAc	**4a**	-	unidentified product
12	KNO_3	**4a**	-	unidentified product
13	Calcium oxalate	**4a**	-	No Reaction
14	$Mn(OAc)_2$	**4a**	-	unidentified product
15	Calcium nitrate	**4a**	2.20	78
16	Potassium oxalate	**4a**	2.5	67

a: Reaction conditions are: 1 mmol of ethyl acetoacetate, 1 mmol of hydroxylamine hydrochloride, 1mmol benzaldehdye and 0.2 mmol of catalyst in 5mL EtOH under stirring condition at 60ºC. b: Isolated yield after purification

Similarly, ethyl acetoacetate (1 mmol), hydroxylamine hydrochloride (1mmol) and benzaldehyde (1mmol) were selected as the model substrates to optimize the amount of magnesium bromide hexahydrate. The catalyst loading was optimized by increasing the amount of magnesium bromide hexahydrate from 5 mol% to 40 mol% for 1mmol scale reaction. When the reaction was carried in the absence of catalyst, the product formed in minor quantity and time required to form product is long (**Table 2, entries 1**). The yield increased with the increase in catalyst amount (**Table 2, entries 2-6**). Nevertheless, there was a very minor increase in the yield when the catalyst loading has increased from 30 mol% to 40 mol%. From table it was observed that 30 mol% of the catalyst was sufficient to obtain the best yield. Although reaction has also well proceeded with 5 mol%, 10mol% and 20 mol% of catalyst, but to achieve good yields require longer time.

Table 2.Optimising amount of catalysts for synthesis of 4-aryl-3-methyl isoxazole[a]

Entry	Catalyst/Mol%	Time h	% yield[b]
1	0(without catalyst)	5. 17	No reaction
2	5	4. 10	45
3	10	3. 30	68
4	20	3. 10	84
5	30	2.00	96
6	40	2.00	96

[a]:Ethyl acetoacetate (1 mmol), hydroxylamine hydrochloride (1mmol) and benzaldehyde (1mmol) in 5mL EtOH were used [b]: Isolated yield after purification

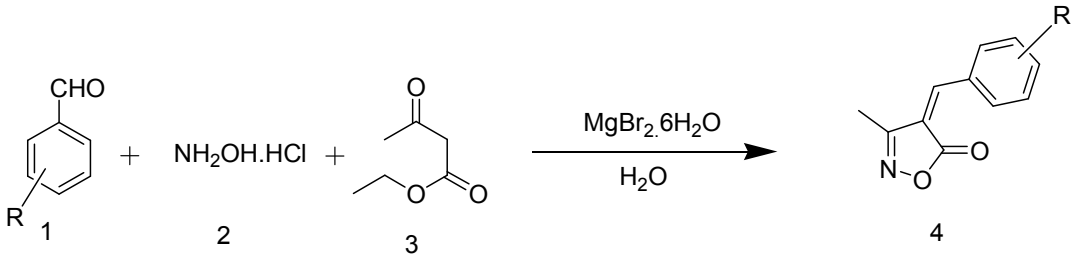
In addition, to search for the optimal solvent, the synthesis of 4a was accomplished by using solvents like ethanol, water, DMF, DMSO, acetonitrile, toluene, carbon tetrachloride, and solvent free condition at room temperature (**Table 3, entries 1-8**). As can be seen in Table 3, the reaction in ethanol was selected as the suitable solvent. Therefore, all further reactions were carried out using 30 mol% of magnesium bromide in ethanol at 60ºC.

Table 3. Optimiatization of solvent for synthesis of 4-aryl-3-methyl isoxazole[a]

Entry	Solvent	Time h	% yield[b]
1	Water	2.00	90
2	DMF	7.05	20
3	CCl_4	4.05	35
4	Ethanol	2 .00	96
5	CH_3CN	3. 32	45
6	Toluene	3. 45	-
	DMSO	3. 10	-
	Solvent free	1.10	50

[a]:Reaction conditions are: 1 mmol of ethyl acetoacetate, 1 mmol of hydroxylamine hydrochloride, 1mmol benzaldehdye and 0.3 mmol of catalyst in 5mL above solvent under stirring condition at 60ºC. [b]: Isolated yield after purification

With the optimized reaction conditions in hand, convenience of the method was well evaluated using a variety of aryl aldehydes and a series of compounds **4** were synthesized with this simple approach. The results are summarized in Table 4. The nature and position of the functional groups on the phenyl ring affected the reaction time and yields of product. The results indicated that aromatic aldehydes bearing electron-donating groups such as –OCH_3, -CH_3, -OH, and π-excessive heterocyclic systems such as Indole-3-carbaldehyde reacted with EAA and hydroxyl amine hydrochloride to afford high yields of products. On other hand, aryl aldehydes containing electron-withdrawing groups such as –Cl, Br or NO_2 reacted with EAA and hydroxylamine hydrochloride to afford low yields of product. 2-Hydroxybenzaldehyde derivative yielded the corresponding isoxazol-5(*4H*)-one derivative in moderate yield of the desired product presumably due to its higher crowded steric effect.



Scheme 2: Synthesis of arylmethylene-isoxazol-5(*4H*)-ones catalyzed by magnesium bromide

Table 4. Synthesis of arylmethylene-isoxazol-5(*4H*)-ones (**4**) catalyzed by magnesium bromide[a]

Entry	Aldehyde	Product (**4**)	Time in hr	%Yield[b]	M. P.ºC
1	Benzaldehyde	**4a**	2	96	142-144
2	3,4-diemthoxy benzaldehyde	**4b**	1.45	92	177-180
3	2,4,6-trimethoxy benzaldehyde	**4c**	1.40	91	210-216
4	2,4-diemthoxy benzaldehyde	**4d**	2.30	82	240-242
5	3,4,5-trimethoxy benzaldehyde	**4e**	2.15	92	180
6	2,5-dimethoxy benzaldehyde	**4f**	2.30	84	180-182
7	4-hydroxy-3-methoxy benzaldehyde	**4g**	2.15	81	230-234
8	2-hydroxy-3-methoxy benzaldehyde	**4h**	2.15	78	240-242
9	3-hydroxy-4-methoxy benzaldehyde	**4i**	3.30	75	170
10	4-hydroxy benzaldehyde	**4j**	2.00	92	213-215
11	3-hydroxy benzaldehyde	**4k**	5.10	93	211-215
12	N,N-dimethyl benzaldehyde	**4l**	2.00	92	225-227
13	Salicylaldhyde	**4m**	3.30	68	130-132
14	5 bromo -2- methyl benzaldhyde	**4n**	4,15	78	180-184
15	4-Diethylamine salicylaldehyde	**4o**	4.10	65	108 -112
16	5-Nitrosalicylaldehyde	**4p**	4.30	60	132
17	Indole-3-carbaldeyde	**4q**	2.15	75	130-132
18	Cinnamaldehyde	**4r**	3.15	85	210-225
19	Crotonaldehyde	**4s**	3:15	50	180-182
20	2-bromo benzaldehyde	**4t**	4.10	45	102
21	4-nitrobezaldehyde	**4u**	3.15	48	103-107
22	2-nitrobenzaldehyde	**4v**	4.10	40	132
23	4-chloro benzaldehyde	**4w**	4.10	55	105-107
24	2 –chloro benzaldehyde	**4x**	2.15	40	76
25	Acetaldehyde	**4y**	3.10	25	140
26	Formldehyde	**4z**	4.15	30	110-112

[a]Reaction conditions: Ethyl acetoacetate (1 mmol), aromatic aldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol) in EtOH (5 mL) stirring at 60ºC. [b] All yields are of pure products, after filtrated and recrystallization from ethanol.

Conclusions

In this paper, we reported an efficient synthesis of arylmethylene-isoxazol-5(*4H*)-ones using solid magnesium bromide hexahydrate as catalyst. The efficiency of the method has been demonstrated by synthesizing various substituted isooxazole derivative. The merit of this method is high yield, hazardous chemical avoided, easy work up, eco-friendly method, easily available and inexpensive catalyst.

Experimental Section

General

All the reagents and chemicals were obtained from commercial sources and used without further purification. Melting points were measured open capillary method and are uncorrected. IR spectra were recorded on alpha T BRUKER model. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature on a BRUKER AVANCE DRX-400 MHz spectrophotometer using $CDCl_3$ or DMSO-d6 as the solvent and TMS as an internal standard. The purity of newly synthesized compounds and the development of reactions were monitored by thin layer chromatography (TLC) on Merck pre-coated silica gel 60 F254 aluminum sheets, visualized by UV light.

General procedure for preparation of 4H-isoxazole-5(*4H*)-ones (4a-z):

A mixture of ethyl acetoacetate (1 mmol), hydroxylamine hydrochloride (1 mmol) and magnesium bromide (30 mol%) in 5 mL of ethanol was stirred at room temperature for 5min, then corresponding aromatic aldehyde (1 mmol) was added to the mixture. The reaction mixture was stirred at 60ºC for mentioned time in Table 4. The progress of the reaction was monitored by TLC. After completion of reaction, the precipitate was filtered off, and washed with cold distilled water and dried in air to get pure products. The product was purified by recrystallization in the ethanol.

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