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PII:	S0040-4039(17)30858-4
DOI:	http://dx.doi.org/10.1016/j.tetlet.2017.07.019
Reference:	TETL 49101
To appear in:	Tetrahedron Letters
Received Date:	14 June 2017
Revised Date:	24 June 2017
Accepted Date:	3 July 2017



Please cite this article as: Patil, M.S., Mudaliar, C., Chaturbhuj, G.U., Sulfated polyborate catalyzed expeditious and efficient three-component synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(4*H*)-ones, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.07.019

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Graphical Abstract





Tetrahedron Letters

journal homepage: www.elsevier.com

Sulfated polyborate catalyzed expeditious and efficient three-component synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(4*H*)-ones

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ARTICLE INFO

Aldehyde Ethyl acetoacetate ABSTRACT

Article history: Received Received in revised form Accepted Available online Keywords: Sulfated polyborate Isoxazole

Hydroxylamine hydrochloride

A rapid and highly efficient methodology for the synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(4H)-ones has been developed using sulfated polyborate as a catalyst. The multicomponent reaction of an aromatic/heterocyclic aldehyde, hydroxylamine hydrochloride, and ethyl acetoacetate under a solvent free condition at 80 °C is described. This protocol has promising features for the reaction response such as shorter reaction times, easy work-up, ease of separation of pure product with high yields and simplicity in the experimental procedure. The products have been obtained in high yields (80–90 %) and convenient reaction times (15-30 min). The method is operationally simple and eco-friendly.

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Isoxazole and its derivatives are an important class of interesting nitrogen and oxygen-containing heterocyclic compounds with a wide variety of applications in liquid crystalline materials,¹ organic synthesis,² light-conversion molecular devices,³ filter dyes in photographic films,⁴ and optical storage and nonlinear optical research (fig.1).⁵ Several substituted isoxazoles have been shown to have a broad range of biological properties, e.g. anti-obesity,⁶ analgesic,⁷ anti-inflammatory,⁸ and immunosuppressive, antibacterial, antifungal,⁹ anticancer,¹⁰ antitumor,¹¹ and show hypoglycemic activity.^{12,13}

The isoxazole backbone is also a structural component of a variety of natural products and drugs such as muscimol,¹⁴ cycloserine,¹⁵ ibotenic acid, and isoxazole-4-carboxylic acid,¹⁶ Among isoxazoles, 3,4-disubstituted isoxazole-5(4*H*)-ones are active agrochemical compounds, used as fungicides, and insecticides,¹⁷⁻¹⁸ and selective inhibitors of protein kinase C,¹⁹ antiandrogen agents,^{20,21} antidiabetic agents,²² and enzyme inhibitors (fig.1).²³

Thus, synthesis of isoxazole-containing compounds is of considerable interest. There are various methods for synthesis of substituted isoxazole-5(4*H*)-ones, including cyclization of O-propionyl oximes,²⁴ reaction of ethyl acetoacetate and hydroxylamine hydrochloride followed by Knoevenagel condensation with aromatic aldehydes in two steps,²⁵ condensation of substituted benzaldoximes and 1,3-dicarbonyl compounds,²⁶ and reaction of β -ketoesters with hydroxylamine





Fig.1. Representative examples of interesting isoxazol-5(4H)-one containing heterocycles

and sodium hydroxide with subsequent addition of aqueous HCl followed by heating.²⁷

A number of catalysts have been used in one-pot threecomponent reactions toward synthesis of isoxazole-5(4*H*)-one scaffolds including sodium silicate,²⁸ sodium benzoate,²⁹ pyridine,³⁰ sodium citrate,³¹ sodium azide,³² sodium saccharin,³³ 1,4- diazabicyclo[2.2.2]octane (DABCO),³⁴ Ag/SiO₂,³⁵ phthalimide-N-oxyl salts,³⁶ sodium tetraborate,³⁷ sodium sulphide,³⁸ boric acid,³⁹ potassium phthalimide,⁴⁰ glycine,⁴¹ Nbromosuccinimide (NBS),⁴² 2-hydroxy-5-sulfobenzoic acid (2-HSBA),⁴³ potassium hydrogen phthalate (KHP),⁴⁴ Dowex 50WX4,⁴⁵ and tartaric acid.⁴⁶ Furthermore, techniques such as visible light in presence of sodium acetate in aqueous EtOH,⁴⁷ solid-state heating or grinding,⁴⁸ ultrasonic irradiation,^{49,50} and microwave heating⁵¹ have also been reported for the preparation

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Scheme2. Synthesis of various 3-methyl 4-(hetero)arylisoxazol-5(4H)-one derivatives catalyzed by sulfated polyborate.

of isoxazole-5(4H)-ones.

Many of these methods have some limitations and drawbacks, such as the use of toxic reagents, strongly acidic or basic conditions, costly reagents and catalysts, stringent reaction conditions, tedious steps, and low product yields and/or long reaction times, which restrict their scope in practical applications. Therefore, a novel protocol with good and inexpensive catalyst demanding short reaction times and high yield is desirable.

Having the above points in mind, herein we report a rapid and efficient synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(4*H*)-ones catalyzed of sulfated polyborate under solvent-free conditions.

A literature search revealed that boric acid catalyzes many useful organic transformations above $100^{\circ}C$.^{52,53} Boric acid dehydrates above $100^{\circ}C$ and turns to its polymeric forms, which could be the active species catalyzing the reaction.⁵⁴ Dehydrative polymerization of boric acid liberates water molecules which may hamper the progress of the reaction.

This persuades us to develop a polymeric boric acid catalyst with mild Bronsted acidity. To accomplish this boric acid was dehydrated at 200 °C to convert it into its polymeric Lewis acid form and then sulfonated to introduce the mild Bronsted acid character.⁵⁵ Boron being an electron deficient element and electron withdrawing effect of adjacent sulfate enhances its Lewis acidity; hence the sulfated catalyst is acting as a Lewis/Bronsted acid. (Scheme 1).

The development of the green, practical, and convenient catalytic methods for the commercial process of current interest and organic synthesis is valuable. Hence, the sulfated polyborate was prepared from readily available boric acid, as economic and non-toxic starting material, characterized and effectively applied for various organic transformations.⁵⁵⁻⁶⁴ Herein we report its applicability in the promotion of the synthesis of 3-methyl 4-(hetero)arylisoxazol-5(4H)-ones. All reactions are performed under mild conditions during relatively short reaction time in good to high yields (Scheme 2).

To initiate our study, we checked the three-component reaction of benzaldehyde, hydroxylamine hydrochloride, and ethyl acetoacetate as a model reaction. The effects of the amounts of catalyst and temperature were investigated; the experimental results are summarized in (Table 1). Yields of the product were traces, 30, 50, 70 and 90 % with 0, 2.5, 5, 7.5 and 10 wt% loading of sulfated polyborate, respectively (Table 1, entries 1-5).

Table 1

Effect of catalyst loading and temperature for the synthesis of 3-methyl-4-phenylmethylene isoxazole-5(4H)-one ^a

Entry	Catalyst	Temperature	Time	Yield ^b
	(wt %)	(°C)	(min)	(%)
1	-	80	60	traces
2	2.5	80	45	30
3	5	80	30	50
4	7.5	80	30	70
5	10	80	15	90
6	15	80	30	80
7	10	r.t.	60	NR ^c
8	10	50	30	45
0	10	50	50	45

^a Reaction conditions: benzaldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol), ethyl acetoacetate (1 mmol)^b Isolated yield. ^cNo Reaction

Table 2

The effect of the solvents on the synthesis of 3-methyl-4-phenylmethylene isoxazole-5(4H)-one ^a

Entry	Solvent	Temperature (°C)	Time (min)	Yield ^b (%)
1	Solvent free	100	15	90
2	EtOH	reflux	60	70
3	MeCN	reflux	60	50
4	THF	reflux	60	30
5	Water	reflux	60	30
6	Toluene	reflux	60	NR ^c
7	DMF	100	60	NR ^c
D C	1.6 1 111 1 (1	1) 1 1 1 1	1 1 11 11	(1 1)

^a Reaction conditions: benzaldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol), ethyl acetoacetate (1mmol)^b Isolated yield. ^cNo Reaction

Based on reaction time (15 min) and yield (90 %), 10 wt% of catalyst provided the best result and was thus selected as the optimum quantity for the promotion of the reaction. Use of larger amounts of sulfated polyborate resulted decreased the product yield (Table 1, entries 6).

Temperature played an important role in the synthesis of 3methyl-4-phenyllmethylene isoxazole-5(4H)-one (Table 1, entry 7 - 8). The temperature effect was examined at ambient, 50 and 80 °C under the solvent free condition with sulfated polyborate as a catalyst. The reaction proceeds very slow at room temperature. while increasing temperature to 80 °C resulted in increased product yield in shorter reaction time (Table 1, entries 6, 7 and 8). Therefore, this was the optimum temperature for performing the reaction.

The effect of various solvents on time and yield of the reaction was ascertained (Table 2, entire 2-7). In ethanol, the reaction proceeds smoothly with high yield (Table 2, entire 2). While in MeCN, THF, and water reaction proceed lower yields (Table 2, entire 3,4, and 5). In DMF and toluene reaction does not proceed (Table 2, entire 6,7). None of the solvents presented the advantage of time and yield over solvent free condition. Hence, the solvent free condition was regarded as best for the cost and environmental acceptability. In all the experiments, the products were isolated by aqueous quenching followed by filtration and recrystallized from methanol.

Table 3

Sulfated polyborate catalyzed synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(4H)-ones ^{a 65}

H_∕O .		u u u u u u u u u u u u u u u u u u u	lfated polyborate	R
+ R	NH20H.HCI + /	so y	lvent free, 80 °C	010
Entry	R	Product	Time (min)	% Yield
1	C ₆ H ₅		15	90
2	2-HO-C ₆ H ₄	OH OH OH	20	85
3	2- O ₂ N-C ₆ H ₄		30	traces
4	3-Cl-C ₆ H ₄	CI	20 0	85



^a Reaction conditions: aldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol), ethyl acetoacetate (1 mmol) and sulfated polyborate 10 wt%, ^b Isolated yield. ^cNo Reaction

To study the substrate scope, optimized reaction condition was applied to various aromatic/heterocyclic aldehydes with hydroxylamine hydrochloride and ethyl acetoacetate.⁶⁵ All the substrate variants reacted well and afforded high yields of the corresponding 3-methyl-4-(hetero)arylmethylene isoxazole-5(4H)-ones derivatives within shorter reaction time (Table 3) except 2- and 4-nitrobenzaldehydes (Table 3, entries 3 and 12). Several electron-releasing or electron-withdrawing substituents at *ortho, meta* and *para* positions of aromatic aldehydes showed no significant effect on product yield and time. This protocol is also extendable to heteroaromatic α/β unsaturated (Table 3, entries 13-16) which also reacted very well and afforded good to high yields of the corresponding 3-methyl-4-(hetero)arylmethylene



Fig. 2. Reusability of the catalyst.

isoxazole-5(4*H*)-ones. We have also attempted applying the optimized reaction condition to the aliphatic and alicyclic aldehyde with no success.

Recyclability of the catalyst is an important attribute for the industrial suitability. Therefore, reusability of the catalyst in the model reaction under optimized reaction condition was evaluated. In this study, after completion of each reaction cycle, water was added and the product was filtered off. The filtrate was evaporated in vacuum rotary evaporator to recover catalyst. Recovered catalyst was recycled for four times with no significant loss in catalytic activity (Fig. 2).

A plausible mechanism sulfated polyborate catalyzed the synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(4*H*)-ones is as suggested in Scheme 3. The mechanism might begin with the acid catalyzed oximation of ethyl acetoacetate to produce [C], followed by Knoevenagel condensation of the activated aldehyde [2] with the tautomer [D] of [C] to produce intermediate [F] via intermediate [E]. Further intramolecular cyclization of ethanol to obtain target compound. The Bronsted acid sites of the catalyst not only activates carbonyl of aldehyde but also interacts with all other intermediates in the stated mechanism.

Conclusion

We have developed a rapid, simple, efficient, and environmentally benign one-pot three-component protocol for the synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(4*H*)ones with good to excellent yields. The new homogeneous catalyst, sulfated polyborate is simple, highly efficient and recyclable in this protocol. The main advantages of this approach are a solvent free condition, cheap raw materials, easy workup, non-hazardous and environment-friendly reaction conditions, recyclable catalyst, excellent yields, and short reaction time.

Acknowledgements

Authors are thankful to Department of Science and Technology, India for their financial support.



Scheme 3. A plausible mechanism for sulfated polyborate catalyzed synthesis of 3-methyl-4-phenylmethylene isoxazole-5(4H)-ones.

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- 65. General procedure for the synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(4H)-ones. A mixture of equimolar quantities of hydroxylamine hydrochloride (1 mmol) and ethyl acetoacetate (1 mmol) and 10 wt% sulfated polyborate were stirred at 80 °C in an oil bath. Then, added aromatic/heterocyclic aldehyde (1 mmol) and the reaction mixture was stirred. The reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and quenched in water; solid precipitated was filtered at the pump, washed with water (3 X 5 mL), dried under

vacuum and recrystallized from methanol to afford the pure product.

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Highlights:

- Sulfated polyborate catalyzed preparation of • substituted isoxazole-5(4H)-ones.
- An accelerated procedure under solvent free • condition.
- • Key advantages are high yields, short reaction time and simple work-up procedure.
- Catalyst is recyclable with no significant ٠ loss in activity.
- Method tolerates a variety of functionality ٠ with multiple substrates extendibility.