J IRAN CHEM SOC
DOI 10.1007/s13738-014-0423-9

ORIGINAL PAPER

Si-OSO_3H catalyzed one-pot three-component synthesis of 1,3-oxazines

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Received: 14 March 2013 / Accepted: 31 January 2014

Abstract A simple and an efficient method for the synthesis of six membered nitrogen containing heterocyclic compounds—1,3-oxazines from diethyl acetylene dicarboxylate, substituted anilines or amines and formaldehyde is reported. A versatile, economical and eco-friendly heterogeneous reagent silica sulfuric acid (Si-OSO_3H) is used as a catalyst for this reaction.

Keywords DEAD · MCR · Silica sulfuric acid · 1,3-oxazines

Introduction

Oxazine and its derivatives are structurally important motifs which possess a wide range of biological activities including anti-tumor, analgesic, anti-convulsant, anti-malarial, anti-anginal, anti-hypertensive and non-nucleoside reverse transcriptase inhibitor activities [1–3]. They are also used as organic dyes with interesting photophysical and lasing properties [4]. The 1,3-oxazines are generally constructed by hydroamination/Prins reaction/cyclization/dehydration reactions.

Multi-component reactions (MCRs) are defined as one-pot reactions in which three or more substrates combine either simultaneously or through a sequential procedure to form products that contain significant portions of all the reactants. MCRs are considered to be economical as the number of reaction steps and waste production are reduced; MCRs are best employed for diversity-oriented synthesis [5–7]. Though there are reports on this MCR in the literature, [8–10] use of a heterogeneous catalyst for the synthesis of this important six membered heterocyclic molecule will be of greater advantage.

Heterogeneous catalysts in organic synthesis offer diverse applications, the solid acid catalysts compared to their homogeneous counterparts have many advantages such as ease in handling and environmental compatibility [11, 12]. Silica sulfuric acid (Si-OSO_3H) acts as a heterogeneous catalyst for MCRs in a much more profitable manner because of its low cost, ease of preparation and catalyst recycling; and catalytic amounts of nano silica sulfuric acid has been used recently in the synthesis of 1,3,5-triarylbenzenes under microwave irradiation [13] and in the one-pot multi-component reactions [14]. In continuation of our work on the use of silica sulfuric acid as catalyst in organic synthesis, [15, 16] herein, we report the synthesis of 1,3-oxazines from diethylacetylene dicarboxylate (DEAD), substituted anilines/amines and formaldehyde in ethanol in the presence of catalytic amounts of silica sulfuric acid at 26 °C as shown in the Scheme 1.

Results and discussion

At the onset of this reaction, various Lewis acid catalysts were tested, 1 mmol of DEAD and 1 mmol of aniline were

Electronic supplementary material The online version of this article (doi:10.1007/s13738-014-0423-9) contains supplementary material, which is available to authorized users.

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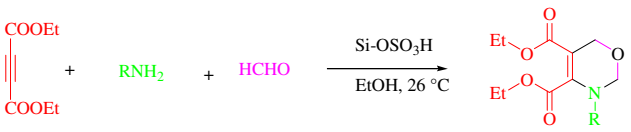
Published online: 23 February 2014



R= Phenyl, aryl, cyclohexyl

Scheme 1 One-pot three-component synthesis of 1,3-oxazines

Table 1 Optimization of catalyst for the one-pot, three-component synthesis of 1,3-oxazine

Sl. No	Catalyst	Yields (%)
1	Zinc chloride[a]	15
2	Zinc bromide[a]	20
3	Lithium perchlorate[a]	15
4	Ceric ammonium nitrate[a]	40
5	Cuprous Chloride[a]	20
6	Silica sulfuric acid (Si-OSO_3H)[b]	70

Reaction condition: standard conditions as given in general procedure for a time period not more than 7 h

[a] 10 mol %

[b] 100 mg

taken in ethanol (3 mL), to this 3.5 mmol of formaldehyde was added, and stirred at 26 °C for about 10 h. The reaction was considered as the standard reaction for the optimization of the catalyst, and the results of catalyst optimization are presented in the Table 1. It is clear from this Table that, silica sulfuric acid is a better catalyst for this reaction. After finding out the suitable catalyst for our reaction, we then studied the quantity of catalyst required to carry out the reaction i.e., the catalyst loading was tested and 100 mg of the catalyst was sufficient to catalyze the reaction and excessive loading was found to be futile (Table 2). Encouraged by these finding we continued to explore the reaction with various amines.

A series of aromatic amines were tested with DEAD and formaldehyde to get the corresponding 1,3-oxazines in good yield, the reaction proceeded smoothly with aliphatic amine like cyclohexyl amine and aromatic amines bearing electron releasing and electron withdrawing groups. The small library of 1,3-oxazines thus synthesized is presented in Table 3. The substituents present on the phenyl ring did not impart much on the rate of the reaction; all the

Table 2 Optimization of Si-OSO_3H load for the reaction

Sl. No	Catalyst (mg)	Yield[a] (%)
1	200	40
2	100	75
3	50	50
4	25	40

[a] Isolated yield

reactions containing electron donating and electron withdrawing anilines proceeded with the same ease to give the corresponding products in high yield. We expect the reaction to proceed by the hydroamination of amine (**2**) with DEAD (**1**) to give intermediate **I** which may then react with two molecules of formaldehyde (**3**) to give the desired product (**4**) as shown the Scheme 2.

After the completion of the reaction, the catalyst was filtered, washed with minimum quantity of ethanol and dried at 100 °C for about 3 h, this was then used for the next reaction. To check the reproducibility of silica sulfuric acid, the standard reaction was carried out using the recovered catalyst and it can be seen from Graph 1 that, the catalyst can be used for nearly thrice without the loss of its activity.

Experimental section

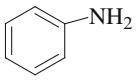
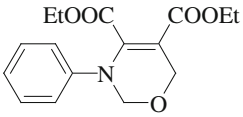
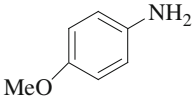
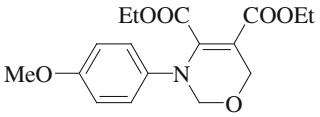
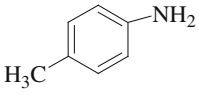
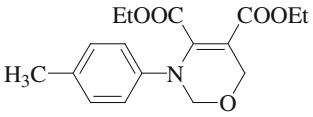
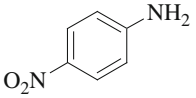
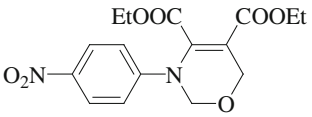
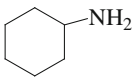
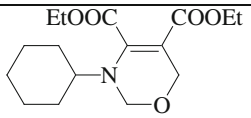
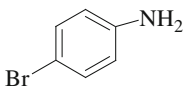
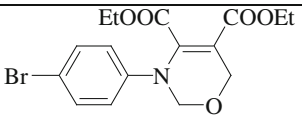
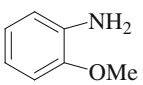
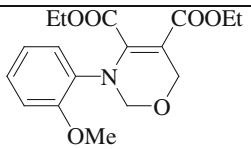
Synthesis

DEAD (1 mmol) and aniline (1 mmol) were taken in a RB flask containing ethanol (3 mL), and stirred for 10 min, to this formaldehyde (3.5 mmol) and Si-OSO_3H (100 mg) were added and stirring was continued till the formation of the product at 26 °C (TLC, 5–7 h). After the completion of the reaction, the solid catalyst was filtered and was washed with ethanol (5 × 3 mL) and dried at 100 °C for about 3 h and reused. All the organic portions were combined and evaporated to get the crude product, which was then purified by silica gel column chromatography.

Synthesis of the catalyst

The catalyst silica sulfuric acid was prepared by known methods as shown in the Scheme 3 [13–15].

Table 3 Si-OSO_3H catalyzed synthesis of 1,3-oxazines

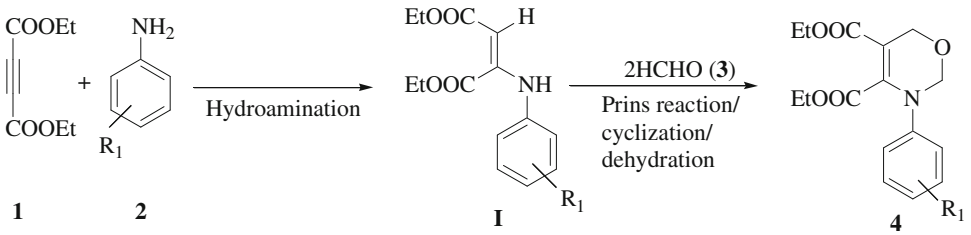
Sl. No.	Aniline/amine (**2**)	Product (**4**)	Yield[b] (%)	M.p[c] (°C)
a			75	235
b			70	189–192
c			75	195–200
d			72	245–249
e			70	199–203
f			70	189–192
g			65	170

All reactions were performed using DEAD (1 mmol), amine (1 mmol), formaldehyde (3.5 mmol) and silica sulfuric acid (100 mg) in ethanol (3 mL)

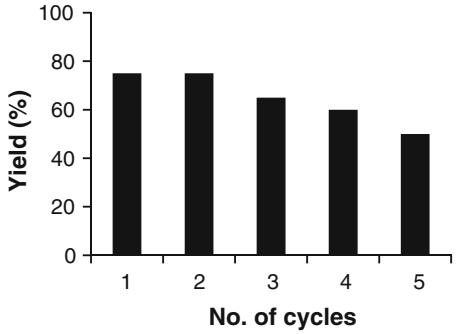
[a] Isolated yield; all the synthesized compounds are known, and physical properties agree with the reported values. Mass spectral data of all the products match with the reported data

[b] Observed melting points comply with the literature Melting point [10–12]

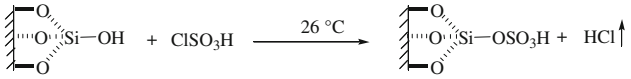
Scheme 2 Proposed pathway for the formation of oxazines



1 **2** **I** **4**



Graph 1 Reusability of Si-OSO_3H



Scheme 3 Synthesis of silica sulfuric acid catalyst from chlorosulfonic acid and silica gel

Conclusion

To summarize, silica sulfuric acid acts as a versatile, reusable heterogeneous catalyst for the present one-pot three-component reaction of DEAD, an amine/aniline and formaldehyde to give biologically important 1,3-oxazines in high yields.

Acknowledgments The authors are grateful to the University Grants Commission, INDIA for the financial support through the major research project [UGC No. F. No. 37-71/2009 (SR)].

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