Synthesis of Substituted 1,3-Oxazines Using Sulfamic Acid as an Efficient and Eco-Friendly Catalyst

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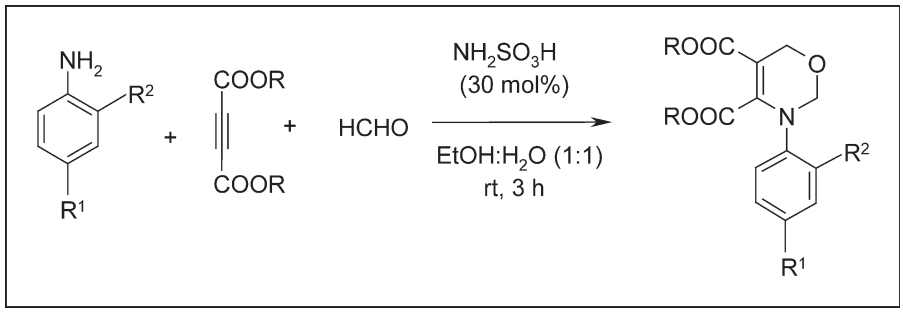

Sulfamic acid catalyzed the synthesis of substituted 1,3-oxazines by one-pot three-component reaction of aniline, alkynoates, and formaldehyde in excellent yields. The catalyst possesses distinct advantages shows ease of handling, good yields, cleaner reactions, nonhygroscopic, noncorrosive, and high activity. Sulfamic acid is a green alternative for metal-containing acidic materials, which are toxic and deleterious for human health and environmental protection.

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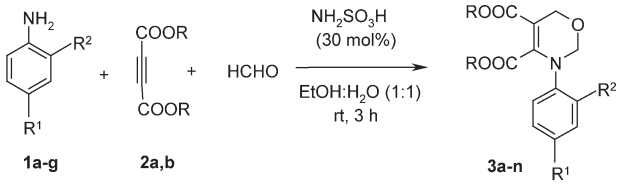
INTRODUCTION

The rapid assembly of molecular diversity is an important goal of synthetic organic chemistry and one of the key paradigms of modern drug discovery. Domino reactions, which result from the combination of multiple transformations in a single pot, are highly efficient means for the improvement of reaction efficiency [1]. Hence, domino reactions and multicomponent reactions (MCRs) [2] involves three or more reactants in a single reaction flask to generate a product incorporating most of the atoms contained in the starting material. Because of intrinsic atom economy, simpler procedure, equipment, time, and energy saving MCRs are gaining much importance in both academia and industry [3]. In domino reactions, each new bond delivers a reactive species, which undergoes further steps without changing the reaction conditions. The main advantage of this strategy is that prefunctionalization of one or both coupling partners are not required; this simplifies the preparation of substrates, shortens the synthetic route, and therefore, minimizes waste production.

Sulfamic acid (NH_2SO_3H) has emerged as a substitute for conventional acidic catalysts and is a dry, nonvolatile, nonhygroscopic, odorless, and white crystalline solid with an outstanding stability. It possesses distinctive catalytic features related to its zwitterionic nature and displays an excellent activity over a vast array of acid catalyzed organic transformations, as witnessed by numerous reports published in the past years [4]. Subsequently, there are reports of sulfamic acid-catalyzed tetrahydropyranylation of hydroxy compounds [5], esterification of cyclic olefins with aliphatic acids under solvent-free conditions [6], and transesterification of β-ketoesters in ionic liquids [7], synthesis of quinoline [8], sulfamic acid is recyclable, easy to handle owing to its immiscibility with common organic solvents and it's intrinsic zwitter ionic property prompted us to explore further applications of NH_2SO_3H as an acidic catalyst in other carbon-heteroatom forming reactions.

The synthesis of 1,3-oxazines has attracted attention in the past because of their potential as antibiotics [9], antitumor [10], analgesics [11], and anticonvulsants [12]. 1,3-Oxazines have generated great interest as antipsychotic agents and as possible effectors for serotonin and dopamine receptors [13]. The ring-chain tautomeric interconversion of N-unsubstituted 1,3-*N*-*O*-heterocycles and the corresponding hydroxyalkylimines can often be exploited advantageously in different areas of organic synthesis. Hence, synthesis of these derivatives is of considerable interest. The synthesis of dihydro-2*H*-1,3-oxazines was reported using hydrochloric acid as catalyst [14]. The disadvantage of this methodology is longer reaction time and hazardous acid catalyst. In a broad program of developing efficient eco-friendly synthetic method for pharmacologically important moieties, we

Scheme 1. Sulfamic acid-catalyzed synthesis of substituted 1,3-oxazines at room temperature.



explored an alternative procedure, which resulted in an operationally efficient process. More recently we have reported the synthesis of heterocyclic compounds promoted by sulfamic acid [15]. In our ongoing efforts on one-pot multicomponent synthesis [16] and organic synthesis using solid acid catalysts [17], herein we report the synthesis of 3,4,5-trisubstituted-3,6-dihydro-2*H*-1,3-oxazines using sulfamic acid as catalyst. The reactions proceeded in short reaction times. The catalytic activity of sulfamic acid showed enhanced effect in 1:1 mixture of ethanol and water.

RESULTS AND DISCUSSION

The reactions were carried out using aniline **1a** (1 eq.), diethyl acetylenedicarboxylate **2a** (1 eq.), and formaldehyde (3 eq.) in the presence of 20 mol % sulfamic acid in 1:1 mixture of ethanol and water (Scheme 1). It was found that all the reactions proceeded rapidly and afforded the desired products in 70% yield. It was also found that increasing the amount of sulfamic acid (20–40 mol %.) increased the yield of the reaction. Further, increasing the amount of sulfamic acid (40–60 mol %) did not affect the rate of the reaction as well as yield. We tried using different acid catalysts, such as $KClO_4$, $Ce(SO_4)_2$, $Cd(OAc)_2$, tetrabutylammmoniumhydrogen suphate, and oxalic acid (Table 1) and found that sulfamic acid is the most effective catalyst in terms of reaction time as well as yield (80%) (Table 2), whereas in presence of other catalysts formed the products with varying yields (0–40%).

Table 1

Screening of different catalysts on the synthesis of substituted 1,3-oxazine **3a** at room temperature in EtOH/H_2O (1:1).

Entry	Catalyst	Time (h)	Yield (%)
1	NH_2SO_3H	3	80
2	$KClO_4$	12	20
3	Oxalic acid	12	40
4	TBAHS	12	trace
5	$Ce(SO_4)_2$	12	trace
6	$Cd(OAc)_2$	12	No product

Table 2

Solvent effect on the synthesis of substituted 1,3-oxazine **3a** catalyzed by sulfamic acid at room temperature.

Entry	Solvent	Time (h)	Yield (%)
1	EtOH/H_2O (1:1)	3	80
2	EtOH	12	70
3	MeOH	12	50
4	CH_3CN	12	50
5	Toluene	12	trace
6	$CHCl_3$	12	30
7	DCM	12	45

Also it has been observed that 1:1 mixture of ethanol and water is the best solvent for carrying out this reaction using sulfamic acid (30 mol %) (Table 3). For reaction of dimethyl acetylenedicarboxylate **2b**, aniline **1a** and formaldehyde, similar yields were obtained (Table 3, entries 1–7).

An evident electronic effect was observed on the yields of the products **(3a–n)**. The yield of the products decreased when electron donating groups were present on the phenyl ring. When diethyl acetylenedicarboxylate was used, there was no change in yields (Table 3, entries 8–14).

CONCLUSIONS

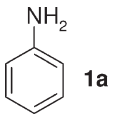
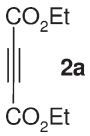
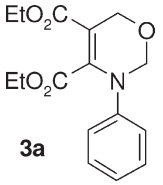
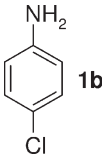
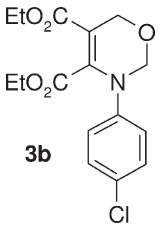
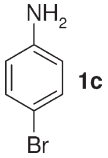
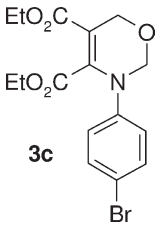
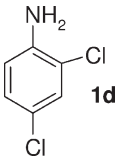
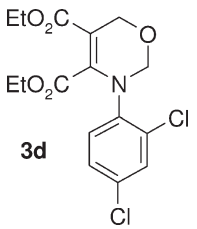
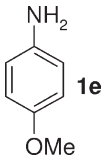
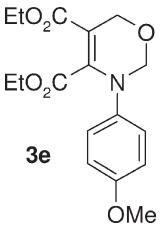
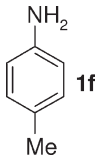
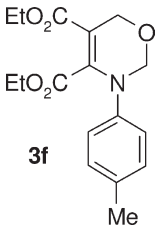
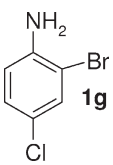
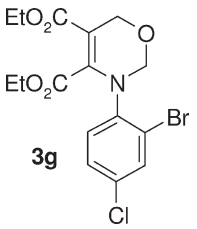
We have developed a novel and highly efficient method for the synthesis of 3,4,5-trisubstituted-1,3-oxazine from alkynoates, amines, and formaldehyde with a simple experimental workup procedure. Sulfamic acid has proved to be an efficient catalyst and green alternative for metal-containing acidic materials, which are toxic and deleterious for human health and environmental protection.

EXPERIMENTAL

Materials and methods. $CDCl_3$ and DMSO-d_6 was purchased from Aldrich. IR measurements were done using Perkin Elmer Spectrum RXI FT-IR. The ^1H and ^{13}C NMR were recorded in $CDCl_3$ with JEOL 500 MHz high resolution NMR spectrometer. $CDCl_3$ was used as the solvent for the NMR spectral measurements and spectra were recorded in ppm with TMS as internal standard. The mass spectra were recorded by using an Electrospray Ionization method with Thermo Finnigan mass spectrometer and EI method with JEOL DX-303 mass spectrometer. Melting points were determined in capillary tubes and were uncorrected. Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany). Elemental analysis data were recorded using a Thermo Finnigan FLASH EA 1112 CHN analyzer.

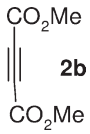
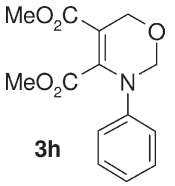
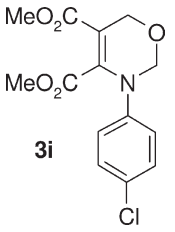
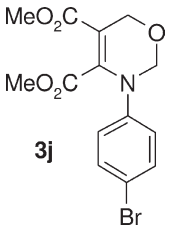
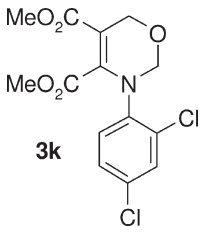
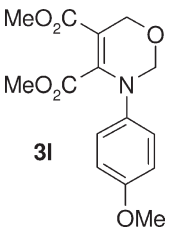
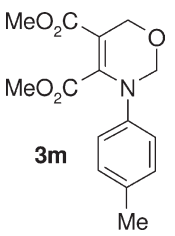
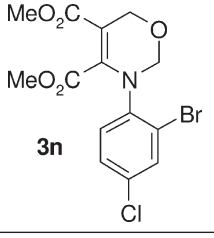
Table 3

Sulfamic acid-catalyzed synthesis of substituted 1,3-oxazines at room temperature.

Entry	Aniline (**1**)	Alkynoates (**2**)	Product (**3**)	Yield (%)[a]
1	 **1a**	 **2a**	 **3a**	80
2	 **1b**	**2a**	 **3b**	82
3	 **1c**	**2a**	 **3c**	85
4	 **1d**	**2a**	 **3d**	80
5	 **1e**	**2a**	 **3e**	72
6	 **1f**	**2a**	 **3f**	70
7	 **1g**	**2a**	 **3g**	82

(*Continued*)

Table 3
(*Continued*)

Entry	Aniline (**1**)	Alkynoates (**2**)	Product (**3**)	Yield (%)[a]
8	**1a**	 **2b**	 **3h**	70
9	**1b**	**2b**	 **3i**	78
10	**1c**	**2b**	 **3j**	80
11	**1d**	**2b**	 **3k**	80
12	**1e**	**2b**	 **3l**	76
13	**1f**	**2b**	 **3m**	70
14	**1g**	**2b**	 **3n**	85

[a] Isolated yield.

Representative procedure for the synthesis of 3,4,5-trisubstituted-3,6-dihydro-2*H*-1,3-oxazines 3a–n. To a mixture of diethyl acetylenedicarboxylate **2a** (1 mmol) and aniline **1a** (1 mmol), ethanol (3 mL) was added. The mixture was stirred at room temperature for 10 min. Subsequently, sulfamic acid (30 mmol %) and formaldehyde (3.5 mmol) were added. After 30 min, water (3 mL) was added and stirring was continued for 3 h. After completion of the reaction, the reaction mixture was extracted with diethyl ether (3 × 15 mL) and organic layer was separated and the combined extract was dried with anhydrous Na_2SO_4. Solvent was removed, and the residue was separated by column chromatography on silica gel (Merck, 100–200 mesh), ethyl acetatepetroleum ether (20:80) to obtain pure product **3a**. ^{1}H NMR, ^{13}C NMR, IR, and mass data of the products **3a–c**, **3e**, **3f**, **3h–j**, **3l**, and **3m** are in full agreement with those reported previously (Ref. 14).

Diethyl 3,6-dihydro-3-phenyl-2H-1,3-oxazine-4,5-dicarboxylate 3a (Table 3, entry 1). Brown viscous oil; IR (neat): 2981, 2930, 1728, 1603, 1488, 1227 cm^{-1}. ^{1}H NMR δ: 1.23 (t, 6H, J = 6.9 Hz), 3.30 (s, 3H), 3.87 (d, 1H, J = 9.1 Hz), 3.98 (d, 2H, J = 9.1 Hz), 4.19–4.26 (m, 1H), 4.50 (d, 1H, J = 10.4 Hz), 7.29 (t, 1H, d, 1H, J = 6.9 Hz), 7.45 (t, 2H, J = 8.4 Hz), 7.84 (d, 2H, J = 8.4 Hz); ^{13}C NMR δ: 14.0, 29.7, 49.0, 59.6, 63.0, 72.9, 119.6, 127.1, 129.4, 138.4, 156.4, 165.9, 193.5; ms (EI) m/z = 306 (M^+); *Anal*. Calcd for $C_{16}H_{19}NO_5$: C 62.94, H 6.27, N 4.59 Found: C 62.80, H 6.31, N 4.65.

Diethyl 3-(2,4-dichlorophenyl)-3,6-dihydro-2H-1,3-oxazine-4,5-dicarboxylate 3d (Table 3, entry 4). Yellow solid. mp.: 78–80°C; IR (KBr): 2994, 2983, 1752, 1698, 1501, 890 cm^{-1}. ^{1}H NMR δ: 1.28–1.38 (m, 6H), 3.47 (q, 2H, J = 6.9 Hz), 4.13–4.21 (m, 5H), 4.47 (d, 1H, J = 9.9 Hz), 7.38 (d, 1H, J = 8.4 Hz), 7.56 (d, 1H, J = 6.9 Hz), 7.74 (d, 1H, J = 2.0 Hz); ^{13}C NMR δ: 13.9, 14.3, 27.2, 52.0, 54.4, 60.3, 63.8, 119.0, 127.3, 129.1, 138.7, 153.9, 163.7, 187.7; ms (EI) m/z = 374 (M^+), 376 (M^{+2}), 378 (M^{+4}); *Anal*. Calcd for $C_{16}H_{17}Cl_2NO_5$: C 51.35, H 4.58, N 3.74. Found: C 50.27, H 4.60, N 3.71.

Diethyl 3-(2-bromo-4-chlorophenyl)-3,6-dihydro-2H-1,3-oxazine-4,5-dicarboxylate 3g (Table 3, entry 7). Brown solid. mp 83–85°C. IR (KBr): 3024, 2970, 1766, 1694, 1501, 722 cm^{-1}. ^{1}H NMR δ: 1.19–1.23 (m, 6H), 3.43 (q, 2H, J = 6.9 Hz), 4.12–4.22 (m, 5H), 4.47 (d, 1H, J = 9.9 Hz), 6.94 (d, 1H, J = 9.2 Hz), 7.55 (d, 1H, J = 8.4 Hz), 7.74 (d, 1H, J = 1.7 Hz); ^{13}C NMR δ: 14.1, 14.9, 31.4, 50.2, 59.5, 62.0, 70.9, 120.1, 127.0, 128.1, 137.2, 150.9, 165.4, 196.3; ms (EI) m/z = 418 (M^+), 420 (M^{+2}), 422 (M^{+4}); *Anal*. Calcd for $C_{16}H_{17}BrClNO_5$: C 45.90, H 4.09, N 3.35. Found: C 45.86, H, 4.12, N 3.37.

Dimethyl 3-(2,4-dichlorophenyl)-3,6-dihydro-2H-1,3-oxazine-4,5-dicarboxylate 3k (Table 3, entry 11). Yellow soild. 77–79°C; IR (KBr): 3010, 2925, 1773, 1554, 1481, 1009 cm^{-1}. ^{1}H NMR δ: 3.31 (s, 3H), 3.77 (s, 3H), 3.90 (d, 1H, J = 9.2 Hz), 4.09 (d, 1H, J = 9.5 Hz), 4.20 (d, 1H, J = 10.8 Hz), 4.48 (d, 1H, J = 10.4 Hz), 7.51 (d, 1H, J = 8.6 Hz), 7.79 (d, 1H, J = 8.8Hz), 7.88 (d, 1H, J = 1.5 Hz); ^{13}C NMR δ: 48.8, 52.3, 55.6, 59.5, 70.9, 119.0, 128.1, 138.7, 155.9, 164.4, 193.6; ms (EI) m/z = 311 (M^+), 313 (M^{+2}), 315 (M^{+4}); *Anal*. Calcd for $C_{14}H_{13}Cl_2NO_5$: C 48.58, H 3.79, N 4.05. Found: C 48.66, H 3.75, N 4.02.

Dimethyl 3-(2-bromo-4-chlorophenyl)-3,6-dihydro-2H-1,3-oxazine-4,5-dicarboxylate 3n (Table 3, entry 14). Brown solid. mp 83–85°C; IR (KBr): 3031, 2985, 1706, 1677, 1481, 915 cm^{-1}. ^{1}H NMR δ: 3.34 (s, 3H), 3.38 (s, 3H), 4.02 (d, 1H, J = 9.2 Hz), 4.41 (d, 1H, J = 9.2 Hz), 4.52 (d, 1H, J = 10.6 Hz), 4.79 (d, 1H, J = 10.2 Hz), 7.00 (d, 1H, J = 6.8 Hz), 7.55 (d, 1H, J = 7.2 Hz), 7.89 (d, 1H, J = 1.6 Hz); ^{13}C NMR δ: 47.8, 53.3, 55.6, 58.5, 71.9, 118.2, 127.1, 136.7, 156.9, 164.4, 194.0; ms (EI) m/z = 390 (M^+), 392 (M^{+2}), 394 (M^{+4}); *Anal*. Calcd for $C_{14}H_{13}BrClNO_5$: C 43.05, H 3.35, N 3.59. Found: C 43.10, H 3.32, N, 3.61.

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