

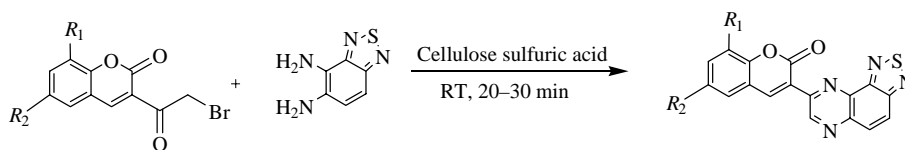
An expeditious synthesis of quinoxalines by using biodegradable cellulose sulfuric acid as a solid acid catalyst

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A simple, efficient and environmentally friendly process for the solid state synthesis of quinoxaline derivatives by the condensation reaction of the benzo[c][1,2,5]thiadiazole-4,5-diamine and 3-(ω -bromoacetyl)-coumarins in the presence of cellulose sulfuric acid by simple physical grinding of reactants using a mortar and pestle at room temperature in good to excellent yields with high purity. The catalyst is recyclable and reusable.



Keywords: quinoxalines; expeditious synthesis; biodegradable; solvent-free synthesis; cellulose sulfuric acid

Introduction

Synthesis of quinoxaline and their derivatives has received much attention from organic and medicinal chemists because of their wide range applications in various fields, such as combinatorial drug discovery libraries [1], dyes [2], organic semiconductors [3], electron luminescent materials [4], cavitands [5], dehydroannulenes [6], DNA cleaving agents [7]. On the other hand, literature surveys show that coumarin ring system [8] is biologically very important pharmacophore. From our laboratories dihydro quinoxaline chromenes [9] were reported under drastic conditions and yields were very poor. A number of methods has been developed for the synthesis of simple and substituted quinoxalines by oxidative coupling [10], MnO_2 [11], POCl_3 [12], ceric ammonium nitrate [13], iodine [14], montmorillonite K-10 [15], $\text{Ga}(\text{OTf})_3$ [16], silica gel [17], citric acid [18], Oxalic acid/ EtOH [19], sulfated TiO_2 [20], sulfated $\text{TiO}_2\text{-P}_{25}$ [21], acetic acid/copper catalyzed oxidative cyclization of α -hydroxy ketones with 1,2-diamines [22]. Nevertheless, most of the reported methods suffer from one or more disadvantages in the process of synthesis which are unsatisfactory yields, longer reaction time, difficulties in product isolation process, moreover the use of highly expensive and detrimental metal precursors, drastic reaction conditions were

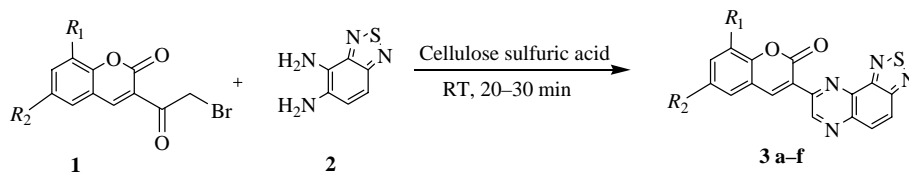
observed and also no agreement with the green chemistry protocols, which limit their use. Hence it is highly essential to develop biodegradable, eco-friendly, green synthesis of quinoxaline.

Cellulose is one of the most abundant natural materials in the world and it has been widely studied during the past several decades because it is a biodegradable material and a renewable resource. Its unique properties make it an alternative to conventional organic or inorganic supports in catalytic applications. Recently, the approach has been shifting more toward eco-friendly and reusable catalysts. Recently, cellulose sulfuric acid has emerged as a solid acid catalyst for acid catalyzed reactions, such as synthesis of α -aminonitriles [23], imidazoazines [24], quinolines [25], aryl-14H-dibenzo [a,j] xanthenes [26], 3,4-dihydropyrimidine-2(1H)-ones [27], Pechmann condensation [28], thiadiazolo benzimidazoles [29], hexahydroxanthene [30], and quinazolines [31]. Cellulose sulfuric acid can be easily prepared by the reaction of inexpensive cellulose with chlorosulfonic acid.

Results and discussion

In continuation of our studies on cellulose sulfuric acid, we attempted the synthesis of quinoxaline derivatives by simple physical grinding of, benzo[c][1,2,5]thiadiazole-4, 5-diamine and 3-(ω -bromoacetyl)-coumarins in

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Scheme 1. A mixture of benzo[*c*][1,2,5]thiadiazole-4,5-diamine (3.0 mmol), 2-(2-Bromo-acetyl)-benzo[*f*]chromen-3-one (3.0 mmol) and cellulose sulfuric acid (0.08g), r.t

the presence of cellulose sulfuric acid using a mortar and pestle at room temperature.

We then investigated the efficiency of the cellulose sulfuric acid compared to various sulfur analog acidic catalysts. The results are summarized in Table 2. Cellulose sulfuric acid was found to be the most effective catalyst based on the product yield. The reaction did not proceed in the absence of catalyst (yield less than 15%).

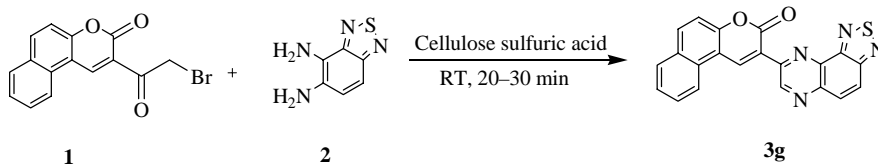
We examined the amount of catalyst in this reaction. The best results were obtained using 0.08 g of catalyst (96%). Using lower amounts of catalyst resulted in lower yields, in the absence of catalyst the yield of the product was found to be very low (Table 3).

Experimental

Melting points are uncorrected and were determined in open capillaries. The reactions were monitored by thin layer chromatography (TLC) and visualized with UV light. IR spectra (KBr) were recorded on Shimadzu FTIR model 8010 spectrometer and the ¹H NMR spectra on Varian Gemini 200 MHz spectrometer using TMS as an internal standard. Mass spectra were recorded on a JEOL JMS D-300 Spectrometer. The elemental analysis of the compounds was done on a Carlo Erba Model EA1108. All solvents and reagents were purchased from Aldrich and Fluka firms.

General procedure

A mixture of benzo[*c*][1,2,5]thiadiazole-4,5-diamine (3.0 mmol), 3-(ω-bromoacetyl)-coumarin (3.0 mmol) and cellulose sulfuric acid (0.08 g) was taken in a mortar, grinding with a pestle at room temperature for the appropriate time, as shown in Table 1.



Scheme 2. A mixture of benzo[*c*][1,2,5]thiadiazole-4,5-diamine (3.0 mmol), substituted 3-(ω-bromo acetyl)-coumarins (3.0 mmol) and cellulose sulfuric acid (0.08g), r.t, 30min

Completion of the reaction was indicated by TLC (2:8, ethyl acetate:hexane) monitoring. After completion of the reaction, ethyl acetate (10 mL) was added and the reaction mixture was washed with water (6 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to dryness, and the crude solid product was further purified by column chromatography (hexane/ethyl acetate, 8:2). The aqueous layer containing the catalyst could be evaporated under reduced pressure to give a white solid. The recovered catalyst was washed with CH₂Cl₂, dried in an oven (50 mm Hg pressure) at 60°C for 5 h under high-pressure prior to use in the other reaction. The recovered catalyst can be reused at least three additional times in subsequent reactions without significant loss in product yield (Table 4).

Product characterization data

3-([1,2,5]thiadiazolo[3,4-*f*]quinoxalin-8-yl)-2H-chromen-2-one (3a)

Mp 245°C. IR (KBr, cm⁻¹): 1610, 1720. ¹H NMR (CDCl₃): δ = 7.31–7.85 (m, 6H), 8.18 (s, 1H), 9.18 (s, 1H); MS (EI): *m/z* = 332(M). Anal. Calcd. for C₁₇H₈N₄O₂S: C, 61.44; H, 2.43; N, 16.86; Found: C, 61.32; H, 2.40; N, 16.92.

3-([1,2,5]thiadiazolo[3,4-*f*]quinoxalin-8-yl)-8-bromo-2H-chromen-2-one (3b)

Mp 215°C. IR (KBr, cm⁻¹): 1607, 1735. ¹H NMR (CDCl₃): δ = 7.28–7.84 (m, 5H), 8.39 (s, 1H), 9.13 (s, 1H); MS (EI): *m/z* = 411(M). Anal. Calcd. for C₁₇H₇BrN₄O₂S: C, 49.65; H, 1.72; N, 13.62; Found: C, 49.76; H, 1.79; N, 13.55.

3-([1,2,5]thiadiazolo[3,4-*f*]quinoxalin-8-yl)-6,8-dichloro-2H-chromen-2-one (3c)

Table 1. Yields of cellulose sulfuric acid catalyzed synthesis of quinoxalines.

Product	R ₁	R ₂	Time (min)	Yield (%)	Melting point
3a	H	H	20	96	245
3b	Br	H	20	94	215
3c	Cl	Cl	25	92	280
3d	Br	Br	20	91	268–269
3e	CH ₃	H	30	92	225–226
3f	Cl	H	20	93	210
3g	–	–	30	89	153–155

Table 2. Effect of catalysts on yield.

Entry	Catalyst	Yield ^a (%)
1	Cellulose sulfuric acid	96
2	Silica sulfuric acid	92
3	Methane sulfonic acid	85
4	Sulfuric acid in acetic acid	55
5	No catalyst	15

^aYields refer to the pure isolated recovered catalyst.

Mp 280°C. IR (KBr, cm⁻¹): 1604, 1734. ¹H NMR (CDCl₃): δ = 7.24–7.88 (m, 4H), 8.33 (s, 1H), 9.14 (s, 1H); MS (EI): *m/z* = 401(M). Anal. Calcd. for. C₁₇H₆Cl₂N₄O₂S: C, 50.89; H, 1.51; N, 13.96; Found: C, 50.84; H, 1.61; N, 13.82.

3-([1,2,5]thiadiazolo[3,4-f]quinoxalin-8-yl)-6,8-dibromo-2H-chromen-2-one (3d)

Mp 268–269°C. IR (KBr, cm⁻¹): 1612, 1738. ¹H NMR (CDCl₃): δ = 7.26–7.91 (m, 4H), 8.35 (s, 1H), 9.17 (s, 1H); MS (EI): *m/z* = 490(M). C₁₇H₆Br₂N₄O₂S: Anal. Calcd. for C, 41.66; H, 1.23; N, 11.43; Found: C, 41.62; H, 1.31; N, 11.55.

Table 3. Influence of the catalytic amounts of cellulose sulfuric acid.^a

Entry	Catalyst (grams)	Time (min)	Yield ^b (%)
1	None	60	Trace
2	0.01	20	28
3	0.03	20	51
4	0.05	20	79
5	0.08	40	96
6	0.08	20	96

^aHere we observed variation in yields by loading catalyst (0.01 g, yield; 28%), (0.03 g, yield; 51%), (0.05 g, yield; 79%), (0.08 g, yield; 96%).

^bisolated yield.

Table 4. Yields of recovered catalyst.

Run	Cycle	Yield ^a (%)
1	0	96
2	1	95
3	2	90
4	3	82

^aYields refer to the pure isolated recovered catalyst.

3-([1,2,5]thiadiazolo[3,4-f]quinoxalin-8-yl)-8-methyl-2H-chromen-2-one (3e)

Mp 225–226°C. IR (KBr, cm⁻¹): 1626, 1724. ¹H NMR (CDCl₃): δ = 2.35 (s, 3H), 7.15–7.92 (m, 5H), 8.24 (s, 1H), 9.1 (s, 1H); MS (EI): *m/z* = 346(M). C₁₈H₁₀N₄O₂S: Anal. Calcd. for. C, 62.42; H, 2.91; N, 16.18; Found: C, 62.51; H, 2.84; N, 16.32.

3-([1,2,5]thiadiazolo[3,4-f]quinoxalin-8-yl)-8-chloro-2H-chromen-2-one (3f)

Mp 210°C. IR (KBr, cm⁻¹): 1602, 1733. ¹H NMR (CDCl₃): δ = 7.26–7.82 (m, 5H), 8.38 (s, 1H), 9.11 (s, 1H); MS (EI): *m/z* = 366(M). C₁₇H₇ClN₄O₂S: Anal. Calcd. for. C, 55.67; H, 1.92; N, 15.28; Found: C, 55.78; H, 1.81; N, 15.41.

2-([1,2,5]thiadiazolo[3,4-f]quinoxalin-8-yl)-3H-benzo[f]chromen-3-one (3g)

Mp 153–155°C. IR (KBr, cm⁻¹): 1600, 1731. ¹H NMR (CDCl₃): δ = 7.01–7.87 (m, 8H), 8.55 (s, 1H), 9.24 (s, 1H); MS (EI): *m/z* = 382(M). C₂₁H₁₀N₄O₂S: Anal. Calcd. for. C, 65.96; H, 2.64; N, 14.65; Found: C, 65.79; H, 2.57; N, 14.78.

Conclusion

In conclusion, cellulose sulfuric acid is found to be an excellent catalytic system for the synthesis of quinoxaline derivatives at RT under solvent-free conditions. This method is found to be more advantageous than the previously reported methods. This catalyst could be directly reused at least three additional times. We claim that cellulose sulfuric acid is a stable and green catalyst.

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