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Ultrasound Assisted an Expeditious Synthesis of 1,5-Benzodiazepine Catalyzed by Cellulose Sulphuric Acid

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Abstract: The article describes simple, rapid and highly effective method for the synthesis of 1,5-benzodiazepines from *o*-phenylenediamine and different ketones using biosupported cellulose sulphuric acid (CSA) as a catalyst under ultrasound irradiation at room temperature. The synthesis method seems to be mild reaction conditions, good to excellent yield, easy workup and the selected catalyst can be easily separated from the reaction mixture and reused in subsequent reaction.

Keywords: 1,5-Benzodiazepines, cellulose sulphuric acid, ketones, ultrasound irradiation

Introduction:

In the past decades benzodiazepines compounds have gained the remarkable importance due to their widespread biological activities such as anticonvulsant, analgesic, hypnotic, sedative and anti-depressive agents [1]. Moreover, benzodiazepine derivatives are commercial importance as dyes for acrylic fibers in photography [2]. Furthermore, 1,5-benzodiazepines are also used as a starting material for the synthesis of some fused ring systems such as triazole-, furano-, oxazino-, oxadiazolo- or triazolo-benzodiazepines [3]. Thus, the synthesis of benzodiazepines is of prime importance, hence a number of methods have been developed for the synthesis of 1,5-benzodiazepines from condensation reactions of *o*-phenylenediamines with various ketones using different catalyst [4]. Although, there are specific merits to each of these methods, different kinds of drawbacks include prolonged reaction time, expensive catalyst, higher temperature, use of solvents and exotic reaction condition. Therefore, search for a safe and mild protocol for synthesis of 1,5-benzodiazepines molecules is important.

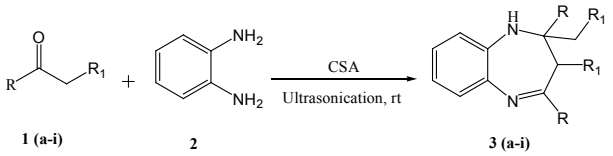
Heterogeneous solid acids are advantageous over conventional homogeneous acid catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be re-used

after activation or without activation thereby making the process economically more viable. Cellulose sulphuric acid (CSA), has widely been reported in the literature for the synthesis of various heterocyclic compounds [5] to be an efficient heterogeneous catalyst, which is non-toxic, easily available, reusable and solid support biodegradable acid catalyst.

Ultrasound has been increasingly used in organic synthesis in the last three decades due to shorter reaction time, or milder conditions and many homogeneous and heterogeneous reactions can be conducted smoothly to provide improved yields and increased selectivities [6].

Result and discussion:

In present work, we wish to report a simple, convenient and solvent-free method for the synthesis of 1,5-benzodiazepines from *o*-phenylenediamine and different ketones in the presence of CSA as a catalyst under ultrasound at room temperature (**Scheme 1)**.



Scheme 1

Initially, the reaction of acetone **1a** with *o*-phenylenediamine **2** was selected as model under ultrasound irradiation at room temperature. To determine the appropriate ratio of the CSA, we investigated the model reaction at different proportions including 0.1, 0.2, 0.3, 0.4, 0.5 and 0.6 g (Table **1**). The 1,5 benzodiazepines product formed in 83%, 87%, 90%, 93%, 98% and 98% yield, respectively, indicating that 0.5 g of CSA is sufficient (Table **1**, entry 5). This result indicates that CSA exhibit a high catalytic activity in this transformation. Encouraged by this success, we extended the reaction of *o*-phenylenediamine with range of other ketones under similar conditions and the optimized results are summarized in Table **2**.

We have developed a newer route for the synthesis of 1,5 benzodiazepines in the presence of CSA under solvent-free conditions using ultrasound irradiation at room temperature. In this methodology, condensation reactions were completed in a shorter time (10-15 min) and with good to excellent yields (70-98%). The reactions were compatible with various substituents such as, nitro, methyl, chloro, methoxy *etc.* Thus, this is an excellent method for the synthesis of 1,5 benzodiazepines.

The reusability of the catalyst was investigated for the model reaction in the presence of 0.5 g CSA. The results illustrated in Table **3** showed that the catalyst could be used three times without any loss of activity.

Table 1 : Optimization quantity of cellulose sulphuric acid[a]

Entry	CSA (g)	Time (min)	Yield(%)[b]
1	0.1	15	83
2	0.2	15	87
3	0.3	15	90
4	0.4	10	93
5	**0.5**	**10**	**98**
6	0.6	10	98

[a]Reaction condition: acetone **1a** (2 mmol), *o*-phenylenediamine **2** (1 mmol) under ultrasonication at room temperature; [b]Isolated yield.

Table 2: Syntheses of 1,5-benzodiazepines using CSA as catalyst under ultrasonication at room temperature

Entry	R	R_1	Time (min)	Yield[a]	M. P.(°C) / Lit.[4e]
3a	CH_3	H	10	98	134-136
3b	C_2H_5	CH_3	20	70	140-142
3c	C_6H_5	H	10	97	150-152
3d	3-$NO_2C_6H_4$	H	10	85	151-152
3e	4-$NO_2C_6H_4$	H	10	82	154-156
3f	4-ClC_6H_4	H	15	77	142-144
3g	4-MeC_6H_4	H	10	90	98-100
3h	Cyclopentanone		15	86	138-140
3i	Cyclohexanone		20	88	136-138

[a]Isolated yields.

Table 3: The effect of reusability of cellulose sulfuric acid catalyst on the product **3a**[a]

Entry	Cycle	Yield[a]
1	0	98
2	1	94
3	2	93
4	3	93

[a]Reaction condition: **1a** (2 mmol), **2** (1 mmol) and CSA (0.5 g) under ultrasound irradiation at room temperature; [b]Reaction time 10 min; [c]Isolated yield.

Experimental

The uncorrected melting points of compounds were taken in an open capillary in a paraffin bath. IR spectra were recorded on Perkin-Elmer FT spectrophotometer in KBr disc. ^{1}H NMR spectra were recorded on an 300 MHz FT-NMR spectrometer in $CDCl_3$ as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard. Bandelin Sonorex (35 kHz) ultrasonic bath was used for ultrasonic irradiation.

General procedure for the synthesis of f 1,5-benzodiazepines (3a-i)

Mixture of *o*-phenylenediamine (1 mmol), ketone (2 mmol) and CSA (0.5 g) were taken in single neck round bottom flask and the reaction mixture was immersed into the water bath of an ultrasonic cleaner at room temperature for the prescribed time (Table **2**). The reaction mass was diluted with ethyl acetate (20 mL), washed with saturated $NaHCO_3$ solution (3 × 15 mL) and then with brine (3 × 10 mL). The organic layer was dried over anhydrous sodium sulphate. Evaporation of the solvent gave the crude product which was purified by recrystallization from ethyl acetate: hexane mixture. The products **3(a-i)** were confirmed by comparisons with authentic samples, ^{1}H NMR,^{13}CNMR, mass and melting points.

Spectral data of principal compounds

(3a): ^{1}H-NMR δ 7.13–7.12 (m, 1H), 7.00–6.96 (m, 2H), 6.74–6.72 (m, 1H), 2.97 (br s, 1H, NH), 2.37 (s, 3H), 2.23 (s, 2H), 1.32 (s, 6H); ^{13}C-NMR δ 172.4, 140.8, 137.9, 126.9, 125.5, 122.1, 121.7, 68.2, 45.2, 30.5, 29.9; MS (EI) m/z 188 (M+ , 38), 173 (100), 133 (39), 132 (50).

(3b): ^{1}H-NMR δ 7.36 (dd, 1H, J = 7.9, 1.1 Hz), 6.97 (t, J = 8.1 Hz, 1H), 6.74 (t, J = 7.1 Hz, 1H), 6.62 (dd, J = 8.0, 0.5 Hz, 1H), 3.86 (br s, 1H, NH), 2.85 (q, J = 7.0 Hz, 1H), 2.60–2.49 (m, 2H), 1.60–1.51 (m, 2H), 1.37 (q, J = 7.4 Hz, 2H), 1.24 (t, J = 7.4 Hz, 3H), 0.96–0.88 (m, 6H), 0.79 (t, J = 7.3 Hz, 3H); ^{13}C-NMR δ 173.8, 139.0, 132.8, 132.2, 126.6, 117.9, 117.5, 60.3, 46.1, 35.7, 28.4, 28.0, 12.3, 11.5, 7.8, 7.3; MS

(EI) m/z 244 (M+, 14), 216 (12), 215 (100), 147 (23).

(3e): ^{1}H-NMR δ 8.05 (d, J = 8.5 Hz, 4H), 7.75 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 7.6 Hz, 1H), 7.16 (t, J = 7.5, 7.4 Hz, 1H), 7.09 (t, J = 7.6, 7.3 Hz, 1H), 6.91 (d, J = 7.7 Hz, 1H), 3.67 (br s, 1H), 3.31 (d, J = 13.6 Hz, 1H), 3.00 (d, J = 13.6 Hz, 1H), δ 1.84 (s, 3H); ^{13}C-NMR δ 164.1, 154.2, 148.6, 147.1, 144.9, 138.0, 137.4, 129.8, 127.9, 127.7, 127.0, 123.7, 123.6, 122.3, 121.5, 73.5, 43.1, 30.4; MS (EI) m/z 402 (M+ , 18), 387 (17), 280 (18), 239 (100), 193 (20).

(3f): ^{1}H-NMR δ 7.52–7.46 (m, 4H), 7.28 (d, J = 2.1 Hz, 1H), 7.21–7.18 (m, 4H), 7.08–7.04 (m, 2H), 6.83 (d, J = 8.8 Hz, 1H), 3.43 (br s, 1H, NH), 3.08–3.04 (d, J = 13.2 Hz, 1H), 2.87 (d, J = 13.1 Hz, 1H), 1.72 (s, 3H); ^{13}C-NMR δ 166.0, 145.8, 139.9, 137.7, 137.6, 135.0, 133.0, 128.6, 128.3, 128.2, 127.0, 126.6, 122.0, 121.5, 73.4, 42.9, 29.7; MS (EI) m/z 380 (M+ , 4), 365 (5), 231 (18), 230 (40), 229 (60), 228 (100), 193 (12), 137 (12), 133 (11).

Conclusion:

In conclusion, CSA as an stable, efficient and recyclable catalyst was prepared and employed for the solvent-free synthesis of 1,5-benzodiazepine derivatives *via* the condensation of *o*-phenylenediamine and various ketone under ultrasound irradiation at room temperature. The prominent merits offered by this new catalytic methodology are mild reaction conditions, simple procedures, cleaner reactions, short reaction times, and good to excellent yields of products.

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