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Research Article

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Highly efficient one-pot, three-component synthesis of 1, 5-benzodiazepine derivatives using silver triflate as a catalyst

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ABSTRACT

A general, mild and efficient protocol for the synthesis of 1,5- benzodiazepine derivatives is achieved for first time using Silver triflate as a catalyst by a one pot, three-component condensation of ethylacetoacetate, aldehyde and o-Phenylenediamine. Compared with the conventional synthesis method, this procedure has the advantages of convenient operation, excellent yields, and environmentally benign. The structure of the products is characterized by ¹H NMR, IR, MS and elemental analysis.

Keywords: Silver triflate, ethyl acetoacetate, aldehyde, o-Phenylenediamine

ARTICLE INFO

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1. Introduction

Benzodiazepines constitute an important class of biologically active compounds and their synthesis has been receiving much attention in the field of medicinal chemistry owing to their application as analgesic, antiinflammatory, anticonvulsant, hypnotic and their hypnotic activity [1–6].

In addition, benzodiazepine moiety shows Peripheral cholecystokinin receptor agonists [7], CCKB/ gastrin receptor agonists [8], arginine vasopressin antagonists [9], CNS depressants and antiameobics [10] have been reported. Although, the first benzodiazepine was introduced as a drug

nearly 35 years ago, the research in this area is still very active and is directed toward the synthesis of compounds with enhanced pharmacological activity. Several representative medicinal moieties containing a 1, 5-benzodiazepine scaffold are shown in Figure 1 including compounds I and II,¹¹ two drugs for the treatment of schizophrenia, and compound III,¹² an inhibitor of HIV-1 capsid assembly.

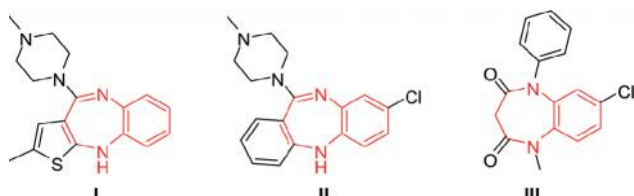


Figure 1: Compounds containing a 1, 5-benzodiazepine Scaffold

Benzodiazepines are the useful precursors for the synthesis of other fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, or furano-benzodiazepines [13–16]. Considering their wide range of applications in biological and industrial synthetic organic chemistry, the development of mild and efficient protocols for the synthesis of 1,5-benzodiazepine analogs continues to be a challenging endeavor.

Benzodiazepines are generally synthesized by the condensation of *o*-phenylenediamine (OPDA) with α , β -unsaturated carbonyl compounds, α -halo ketones or with ketones [17] using acidic catalysts which are critical to enhance the condensation process. Different reagents such as BF_3 -etherate, polyphosphoric acid, NaBH_4 , MgO/POCl_3 , $\text{Yb}(\text{OTf})_3$, $\text{Ga}(\text{OTf})_3$, lead nitrate, L-proline, acetic acid under microwave conditions, molecular iodine and ionic liquids have also been used for the synthesis of benzodiazepines [18–28]. Recently the synthesis of benzodiazepines has also been reported using different solid acid catalysts such as sulfated zirconia, $\text{Al}_2\text{O}_3/\text{P}_2\text{O}_5$, PVP FeCl_3 and zeolite catalysts [29–33]. Such synthesis is traditionally performed through a sequence of separate reaction steps. Unfortunately, many of these catalysts suffer from one or more limitations, such as long reaction times, occurrence of several side reactions, drastic reaction conditions, low yields and tedious workup procedure. These factors stimulate the search for a better catalyst, which should offer a high activity for the synthesis of 1,5-benzodiazepines under mild reaction conditions. These considerations prompt us to develop new methodologies for preparing these important compounds.

Presently, the design, development, and utilization of efficient and environmentally benign synthetic processes have become the conscientious choice of synthesis chemists [34]. One attractive strategy is to design and develop novel, one-pot, multistep syntheses that can help simplify reaction handling and product purification, improve synthesis efficiency, as well as reduce solvent consumption and thereby disposal. Consequently, the consumption of natural resources is reduced, the potential harmful impact of International Journal of Chemistry and Pharmaceutical Sciences

various chemicals on the environment is minimized and sustainability is ultimately improved [35]. The research still continues to have a better methodology for the synthesis of benzodiazepines in terms of simplicity by using Silver triflate.

2. Materials and Methods

Melting points were determined in open-end capillaries and are uncorrected. Compounds were checked for their purity by TLC on silica gel G plates and spots were located by iodine vapors. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz. Chemical shifts are given in ppm (δ) and spectra (^1H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of CDCl_3 -*d* or $\text{DMSO-}d_6$ as the internal standard (^1H NMR: TMS at 0.00 ppm, CDCl_3 at 7.26 ppm, DMSO at 2.50 ppm; ^{13}C NMR: CDCl_3 at 77.16 ppm, DMSO at 40.00 ppm). The IR spectra were recorded on Perkin-Elmer spectrum RX IFT-IR System using KBr pellets.

General Procedure for the Preparation of 1,5-benzodiazepine derivatives:

o-phenyl enediamine (5 mmol), ethyl acetoacetate (5 mmol) were taken into 5 ml of ethanol and to this mixture Silver triflate (10 mol%) was added at room temperature under N_2 and the reaction mixture stirred for 3h. Aryl aldehyde was added to reaction mixture was stirred at 50-60°C. After completion of reaction (monitored by TLC using 30% EtOAc in petroleum ether as eluent), the reaction mixture was diluted with water (25 ml), filter and dried. They were subjected to further purification by chromatography through a column of silica-gel using 20% EtOAc in petroleum ether as eluent and fully characterized.

3. Results and Discussion

The one-pot, three-component reaction of *o*-phenylenediamine **1** with ethylacetoacetate **2** and various aromatic aldehydes **3** in the presence of Silver triflate catalyst proceeded rapidly in ethanol solvent at 50-60°C to afford 1,5-benzodiazepine derivatives **4** in good yields (Table 2). We performed the solvent effect on the outcome of the reaction. The model reaction was carried out in solvents such as DCE, $\text{C}_2\text{H}_5\text{OH}$, CH_2Cl_2 , and ACN. It was observed that ethanol was the most effective solvent, and the reaction proceeded efficiently, giving the maximum yield (Table 1).

Any excess of Silver triflate (10 mol%) beyond this loading did not show any substantial improvement in the yield. So 10 mmol of Silver triflate chosen as the optimal loading of the catalyst. To generalize the proposed method, a series of aromatic aldehydes were used (Table 2). The results indicated that a wide range of structurally varied aromatic aldehydes reacted smoothly to give the 1,5-benzodiazepine derivatives good yields (scheme 1).

Spectral data for selected compound:

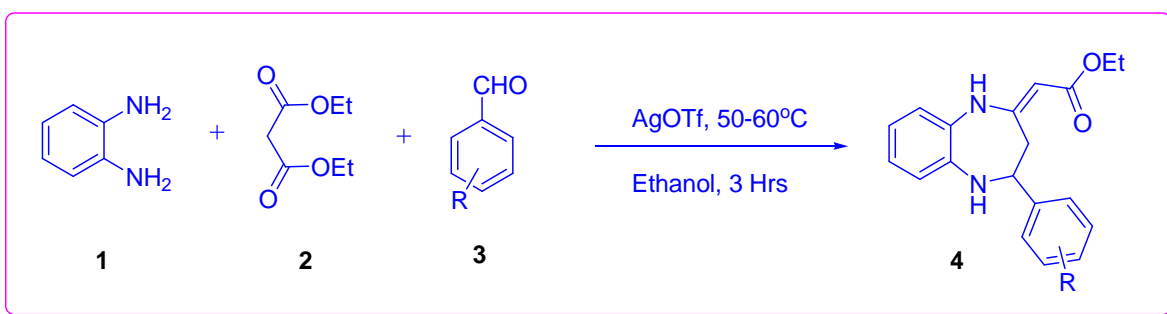
4a: (E)-ethyl 2-(2,3-dihydro-2-phenyl-1H-benzo[b][1,4]diazepin-4(5H)-ylidene) acetate: Yellow solid; MP 74-78°C. IR (KBr): 1158, 1454, 1618, 1638, 2923, 3415, 3467 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 1.29 (t, J = 7.2 Hz,

3H, -CH₃), 2.54(dd, J= 14, 4.4 Hz, 1H, -CH₂), 2.70(dd, J= 14, 9.2 Hz, 1H, -CH₂), 3.7 (br s, 1H, -NH), 4.1-4.3 (m, 2H, -OCH₂), 4.61 (s, 1H, =CH), 4.85 (dd, J= 9.2, 4Hz, 1H, -CH), 6.77-7.39 (m, 9H, Ar-H), 10.24 (s, 1H, -NH). ¹³C

NMR (100 MHz, CDCl₃): = 14.75, 40.52, 59.05, 65.34, 82.42, 121.01, 121.81, 122.74, 125.9, 126.29, 126.3, 128.18, 129.03, 129.1, 130.11, 138.11, 145.07, 158.83, 170.53. MS (EI, m/z): 309.15 (M⁺, 100).

Table 1: Effect of solvent on reaction

S.No	Solvent	Time (hr)	Temperature(°C)	Yield (%)
1	Ethanol	3	60	77
2	Dichloromethane	6	40	61
3	1,2-Dichloroethane	8	60	21
4	Acetonitrile	9	60	37



Scheme 1: Synthesis of 1,5-benzodiazepine derivatives in a one pot, three-component using Silver triflate as a catalyst.

Table 2: Synthesis of 1,5-benzodiazepine derivatives (4a-l)

S.No	Ar	Product	Time (Hrs)	Yield (%)
1	Ph	4a	3	77
2	3-MeC ₆ H ₄	4b	3.5	78
3	4-MeC ₆ H ₄	4c	3	74
4	2-FC ₆ H ₄	4d	3	79
5	4-FC ₆ H ₄	4e	3.5	71
6	4-ClC ₆ H ₄	4f	3	78
7	3-BrC ₆ H ₄	4g	3.5	77
8	2-ClC ₆ H ₄	4h	3.5	71
9	4-MOC ₆ H ₄	4i	3	81
10	3-MOC ₆ H ₄	4j	3.5	78
11	2-Naphthyl	4k	4	77
12	1-Naphthyl	4l	4	76

4. Conclusion

In conclusion we have developed a simple methodology for the preparation of 1,5-benzodiazepine derivatives by using Silver triflate (10 mol%) as efficient catalyst. The advantage of this method are extremely mild reaction conditions, short reaction time, high yield.

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of IR Spectra, ¹H NMR for characterization of synthesized compounds.

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