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Silicotungstic Acid in Organic Synthesis: Synthesis of 1, 5-Benzodiazepines and β-Amino Carbonyl Compounds

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Abstract

An efficient methodology, employing silicotungstic acid (STA) as catalyst leads to synthesis of 1, 5-benzodiazepines and β-amino carbonyl compounds, employing condensation reaction of o-phenylenediamine with ketones and one pot three component Mannich reaction at room temperature under solvent free conditions in good to excellent yields. The synthetic protocol offers a novel and improved modification for the synthesis of 1, 5-benzodiazepines and β-amino carbonyl compounds in terms of mild reaction conditions and clean reaction profiles, high yields and a simple workup procedure. They are characterised by IR and ^{1}H NMR spectroscopy.

Keywords: Silicotungstic acid (STA), 1, 5-benzodiazepines, β-amino carbonyl compounds, solvent free conditions, room temperature.

Introduction

Nitrogen containing molecules are significant synthetic targets owing to their wide range of application as pharmaceutical and bioactive compounds. 1, 5-benzodiazepines and β-amino carbonyl compounds have been one of important nitrogenous compounds. Benzodiazepines are important pharmaceutical compounds that are frequently used as prescribed drugs for combating central nervous system (CNS) related diseases mainly because of their anticonvulsant, hypnotic and other properties[1,2]. In addition, 1, 5-benzodiazepines are valuable synthons for the preparation of other fused ring compounds s uch as triazolo[3,4,5] oxadiazolo[6,7] and furano-benzodiazepines[8]. Despite their importance from pharmacogical, industrial and synthetic point of view, comparatively large number of processes for the preparation of 1, 5-benzodiazepines reported in the literature. These include a condensation reaction of o-phenylenediamine with α, β-unsaturated carbonyl compounds[9], β-haloketones[10], chalcones[11] or ketones using different types of catalysts such as $BF_3.OEt_2$[12], $NaBH_4$[13], $FeCl_3$[14], PPA-SiO_2[15], MgO-$POCl_3$[16], NBS[17], HOAc microwave[18], $InBr_3$[19], $Sc(OTf)_3$[20], kaolin[21]. Mannich reaction is important in carbon-carbon bond forming reaction in organic synthesis[22, 23], because it affords synthetically and biologically important β-amino carbonyl compounds which are important intermediate for construction of various nitrogen containing natural products and pharmaceutical[24, 25]. Recently a more desirable version of the Mannich reaction involves the use of catalyst assisted one-pot, three-component strategy that allows for the simplicity and atom economy of the reaction[26,27].

However, many of these methods in both the synthesis are associated with several drawbacks such as application of expensive reagents, drastic reaction conditions, extended reaction time, unsatisfactory yields, occurrence of side products, and complex experimental procedure. Hence there is need to develop an efficient and practically convenient process for the synthesis of 1, 5-benzodiazepines and β-amino carbonyl compounds. In continuation of our interest in heterocyclic synthesis[28], the present paper reports the results of condensation reaction leads to the synthesis of 1, 5-benzodiazepines and one pot three component Mannich reaction which leads to synthesis of β-amino carbonyl compounds catalysed by silicotungstic heteropoly acid under the solvent free conditions.

Heteropolyacids (HPAs) are well defined molecular clusters that have importance for their molecular and electronic structural diversity and their significance in many areas, e.g., catalysis, medicine, and materials science[29]. The applications of HPAs in the field of catalysis are growing continuously as they possess unique properties such as Bronsted acidity, possibility to modify their acid-base and redox properties by changing their chemical composition, high proton mobility, ability to accept and release electrons, easy work- up procedures, easy filtration, and minimization of cost[30]. Among them, the compounds of keggin structure are known for their very strong acidity redox properties and have attracted much attention as catalysts in both academic and industrial applications[31].

Material and Methods

Experimental: Melting points were recorded on gallen kamp apparatus and are uncorrected. ^{1}H NMR (400MHz) spectra were determined with a Brucker Advance 400 spectrometer ($CDCl_3$) using tetramethylsilane (TMS) as internal standard. Infrared (IR) spectra (cm^{-1}) were measured with Perkin Elmer

spectrometer. All reactions were carried out using reagent-grade solvents, and the reagents were purchased from local suppliers.

General procedure for the synthesis of 1, 5-benzodiazepines: A mixture of o-phenylenediamine (1mmol), ketone (2.2mmol) and STA (10 mol%) was stirred at room temperature. The progress of the reaction was monitored by TLC. After the completion of reaction, the reaction mixture was extracted with ethyl acetate and then washed with water. Then the combined extracted layers were dried over sodium sulphate and concentrated under reduced pressure to obtain the crude product which was purified by silica gel columm chromatography using hexane:ethyl acetate (7:3) as eluent to afford the desired compound in pure form.

General procedure for the synthesis of β-amino carbonyl compounds: To the mixture of acetophenone (1mmol), benzaldehyde (1mmol), and aniline (1mmol) STA (10 mol%) was added and the mixture was stirred at room temperature until the reaction was completed as indicated by TLC. The resulting mixture was washed with water and the crude product was obtained which was purified by recrystallization from ethanol to give corresponding pure compound.

Results and Discussion

In this paper we reported a facile method for the synthesis of 1, 5-benzodiazepines by condensation of o-phenylenediamine with ketones and synthesis of β-amino carbonyl compounds via reaction of aromatic ketones, aromatic aldehydes and aromatic amines using STA as a catalyst (scheme 1and scheme 2).

Initially the reaction of o-phenylenediamine and acetone was carried out using catalytic amount of STA at room temperature under solvent free conditions. Further to find the optimum reaction conditions, effect of amount of catalyst and solvent effect was studied. The reaction was started with 1mol % of catalyst. Further we observed that the yield of the product gradually increased on increasing the amount of catalyst. The maximum yield was obtained using 10mol% of catalyst. No improvement in yield was observed with further increase in amount of catalyst figure-1.

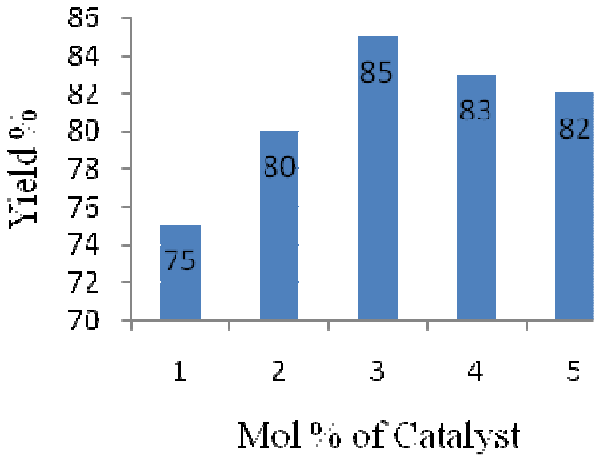
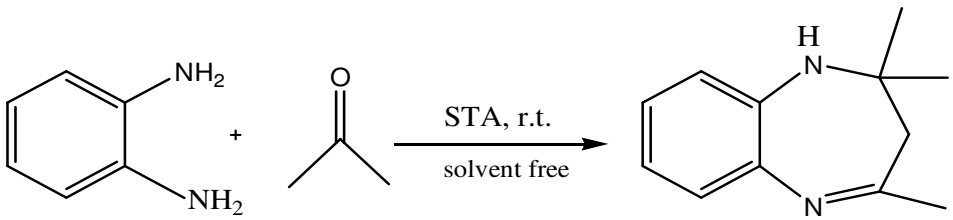
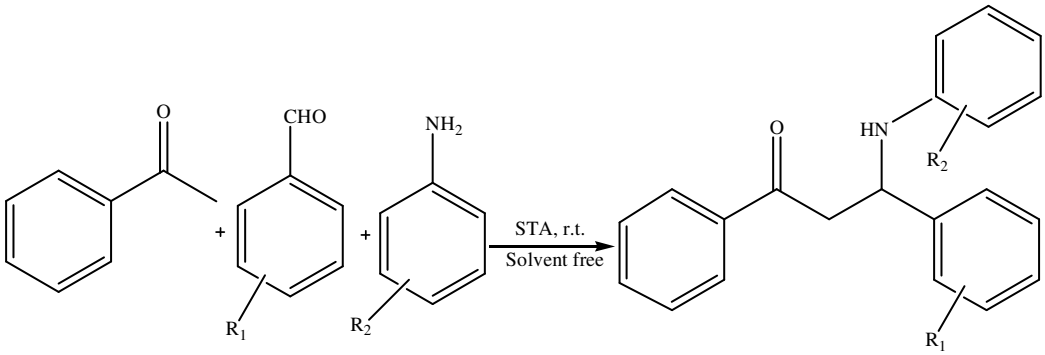


Figure-1
Effect of the amount of the catalyst on 1, 5-benzodiazepines



1 2 3

Scheme-1



Scheme-2

To explore the versatility of the catalysed process, various ketones were used to afford the synthesis of 1, 5-benzodiazepines at room temperature under solvent free conditions in 78-89 % yields table-1. The reactions were clean and the products were obtained within 5-40 minutes. No reaction was observed when o-phenylenediamine was reacted with acetone under similar conditions in the absence of STA even after 24h, thus STA is used as promoter. The reactions of alkyl ketones i.e. 2-butanone and 4-methylpentan-2-one produced 1, 5-benzodiazepines in 78% to 79% yield (table 2 and entry b, c) but the cyclisation occurs from less sterically hindered carbon atom having α-hydrogen. The cyclic ketones such as cyclopentanone and cyclohexanone (entry d, e) condense with o-phenylenediamine in the presence of STA to afford the cyclic/fused 1, 5-benzodiazepines in good yields. The products were purified by column chromatography and characterised by IR and ^{1}H NMR spectroscopy.

Initially the reaction of acetophenone, benzaldehyde and aniline were performed in the presence of various amounts of catalyst figure-2. The maximum yield of the product was obtained 10mol%. By lowering the amount of catalyst from 10mol% decreases the yield and increasing the amount of catalyst did not affect the yield.

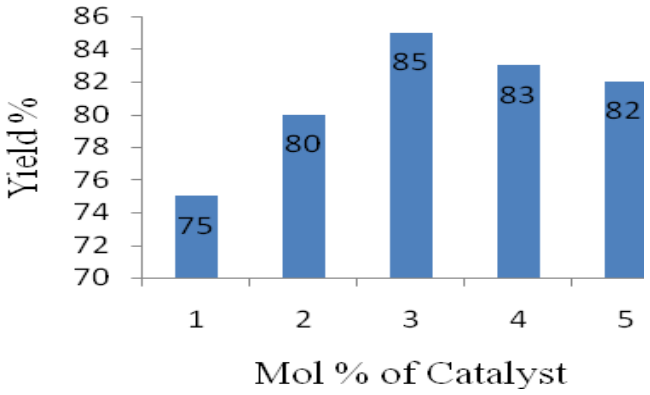


Figure-2
Effect of the amount of the catalyst on synthesis of β-amino carbonyl compounds

Table-1
STA catalysed synthesis of 1, 5-benzodiazepines at room temperature

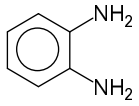
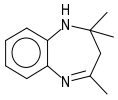
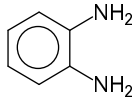
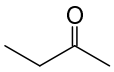
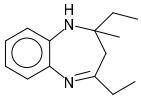
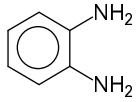
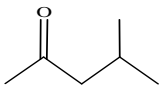
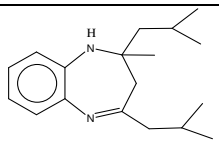
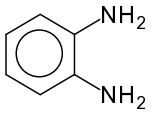
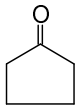
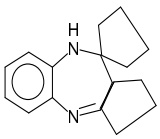
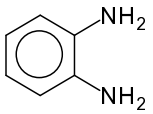
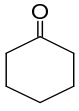
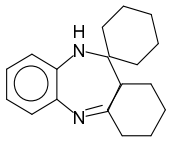
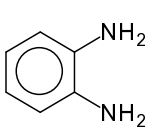
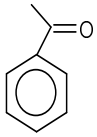
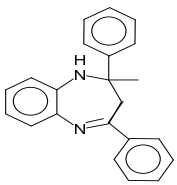
Sr. No.	Diamine	Ketone	Product	Time (min.)	Yield (%)	Mp(^{0}C) observed	Mp (^{0}C) Reported
a				20	89	135-137	137-139
b				25	78	135-138	137-139
c				30	79	117-118	118-120
d				20	80	136-138	137-139
e				7	88	136-137	138-139
f				35	87	109-110	107-109

Table-2
STA catalysed synthesis of β-amino carbonyl compounds at room temperature

Entry	R_1	R_2	Product	Time (min)	Yield	Mp(^{0}C) (observed)	Ref. Mp (^{0}C) (reported)
1	H	H	4a	20	85	142-144	143-144
2	H	4-NO_2	4b	60	65	181-184	184-186
3	H	4-Cl	4c	40	79	169-171	170-171
4	H	4-OCH_3	4d	90	73	120-123	124-125
5	H	4-F	4e	25	68	160-162	162-163
6	H	2-CH_3	4f	360	Trace	-	-
7	H	3-CH_3	4g	30	75	129-130	131-132
8	H	2-OCH_3	4h	300	Trace	-	-
9	H	2-Cl	4i	120	59	112-114	113-115
10	H	2-NO_2	4j	180	67	103-106	-
11	4-OCH_3	H	4k	100	72	142-145	147-149
12	4-OCH_3	4-Cl	4l	30	68	155-156	158-160
13	4-OCH_3	4-OCH_3	4m	20	62	145-147	-
15	4-OCH_3	2-Cl	4o	360	Trace	-	-
16	4-OCH_3	2-NO_2	4p	420	Trace	-	-
17	4-OCH_3	2-CH_3	4q	450	Trace	-	-
18	4-Cl	H	4r	60	64	110-111	114-115
19	4-Cl	4-Cl	4s	80	69	115-116	118-119

The feasibility of the catalysed process was observed with different substrates (table-2). It was noted that anilines carrying different electron-donating or electron-withdrawing substituents at the meta and para positions all reacted well. The ortho substituted anilines with electron-withdrawing gave comparatively low yields but with electron-donating gave very low yield. In the absence of catalyst only trace amount of yield of product was obtained under similar conditions. The products were purified by recrystallization and characterised by IR and ^{1}H NMR spectroscopy.

Spectroscopic data: 2,2,4- Trimethyl -2,3-dihydro-1*H*-1,5-benzodiazepines (3a), m.p. 135-137^{0}C. **IR** (KBr) υ, cm^{-1}: 3293.3, 1632.3. **^{1}H NMR** (400 MHz, $CDCl_3$) δ, ppm (J, Hz): 1.34 (6H, s); 2.25 (2H, s); 2.36 (3H, s); 2.95 (1H, NH, br, s); 6.71-7.14 (4H, m). **1, 3-Diphenyl-3-(phenylamino) propan-1-one (4a): m.p**. 142-143^{0}C. **IR** (KBr) υ, cm^{-1} : 3384.8, 2917.8, 1671, 1291.5. **^{1}H NMR** (400 MHz, $CDCl_3$) δ, ppm (J, Hz): 357-3.58 (d, 2H), δ 5.01- 5.042 (m, 1H), δ 6.64-6.66 (d, 2H), δ 6.74 (t, 1H), δ 7.10-7.60 (m, 10H), δ 7.91-7.92 (d, 2H).

Conclusion

In conclusion, STA was found to be an effective, an efficient catalyst for an efficient and simple method for the synthesis of 1, 5-benzodiazepines and β-amino carbonyl compounds at room temperature under solvent free conditions. Simple experimental work up, shorter reaction time, solvent free process, no inert reaction conditions, eco-friendly (green chemistry) and easily available STA as catalyst and excellent yields are the attractive features of the proposed method, which made it important addition to existing synthetic protocols.

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