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An Efficient and Green Synthesis of 1, 5-Benzodiazepines

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ABSTRACT

An efficient and green synthesis of 1, 5-Benzodiazepines is reported under neutral conditions. The ammonium chloride catalyzed condensation of o-phenylenediamine with several ketones in methanol at room temperature furnished corresponding 1, 5-benzodiazopines.

Keywords: 1, 5-Benzodiazepines, O-Phenylenediamine, Ketones, Green Chemistry, Neutral Conditions.

I. INTRODUCTION

Benzodiazepines are a class of agents that work on the central nervous system, acting selectively on gamma-aminobutyric acid-A (GABA-A) receptors in the brain. It enhances response to the inhibitory neurotransmitter GABA, by opening GABA-activated chloride channels and allowing chloride ions to enter the neuron, making the neuron negatively charged and resistant to excitation.[1] Benzodiazepines are similar in pharmacological action but have different potencies and some benzodiazepine work better in treatment of particular conditions. They are used as sedatives, hypnotics, anxiolytics, anticonvulsants, analgesic, antidepressants, hypnotic, antiinflammatory and muscle relaxant agents.[2-6] In particular, 1, 5-benzodiazepines are useful precursors for the synthesis of fused ring benzodiazepine derivatives such as triazolo, oxadiazolo, oxazino, furano benzodiazepines. More recently their use has been extended to various diseases such as cancer, viral infections (non-nucleoside inhibitors of HIV-1 reverse transcriptase) and cardiovascular diseases.[7-13]

Due to the wide range of biological activity, the benzodiazepine nucleus has attracted many investigators to synthesize and screen their analogues for all possible biological activities.[14] However, the most commonly employed methods involve the cyclocondensation of 1, 2–diamines with α, β-unsaturated ketones, β-haloketones, alkynes.[15] Literature survey reveals the various catalysts and routes for the synthesis of these compounds by condensation reaction of *o*-phenylenediamine with α, β-unsaturated carbonyl compounds in the presence of protic organic and inorganic acids catalysts.[16] However, majority of methods reported in literature have several limitations such as high temperature, long reaction time, use of expensive reagents, low yields of products, high catalyst loading, corrosive reagents, strongly acidic conditions and further purification of products. Therefore, the need of development of an efficient method for the preparation of 1, 5-benzodiazepines is of prime importance.[17]

II. Results and Discussion

In continuation with our work in development of new methods for synthesis of heterocyclic compounds,[18] herewith we are reporting an efficient and green protocol for the synthesis of 1, 5-benzodiazepines from *o*-phenylenediamine (10 mmol) and various ketones (20 mmol) in presence of NH_4Cl (20 mol%) in methanol (**Scheme 1**). Ammonium chloride has been used as green catalyst in various condensation reactions.[19] Initially, we performed the reaction between *o*-phenylenediamine (10 mmol) and acetone (20 mmol) and NH_4Cl (50 mol%) in ethanol to afford moderate to good yield. To improve the reaction condition, we performed the same reaction in different solvents (**Table 1**).

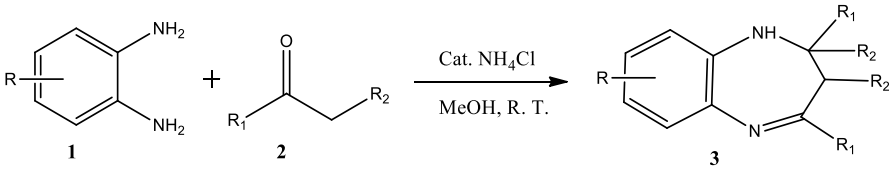
Table 1: Effect of solvent on synthesis of 1, 5-benzodiazepine.

S. N.	Solvents	Time (hr)	Yield (%)
1	Ethanol	3	95

2	THF	4	85
3	Iso-propanol	2.5	92
4	DCM	3.5	90
5	Methanol	2	98
6	Ethyl acetate	4.5	88
7	Acetonitrile	5	89
8	Toluene	6	70

It has been observed that the better solvent for the reaction is methanol. Also, we have optimized the catalyst by performing reactions at different mol%. The 20 mol % of NH_4Cl is sufficient for better results. The scope of present invention checked by performing reactions between various substituted *o*-phenylenediamines (10 mmol) and ketones (20 mmol) in presence of NH_4Cl (20 mol%) in methanol (**Scheme 1 & 2**). All the reactions furnished the corresponding 1, 5-benzodiazepines with 70-98% yields (**Table 2**). The progress of reaction was monitored by TLC. After completion of reaction, the solid product obtained was filtered and recrystallized by using ethanol. The analytical and spectral data of obtained compounds is matching with the reported in literature.

Scheme 1



Scheme 2

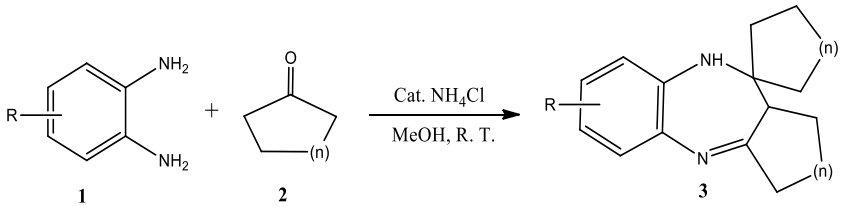
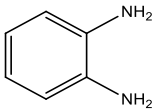
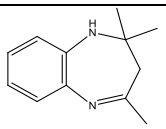
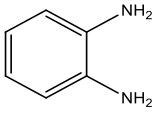
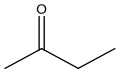
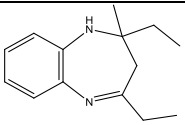
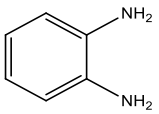
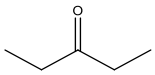
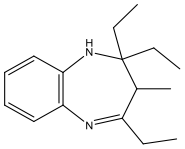
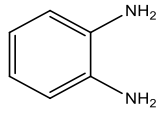
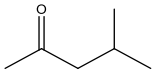
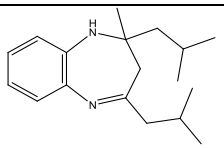
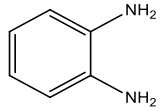
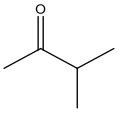
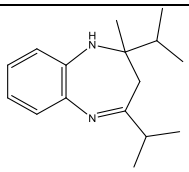
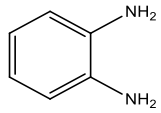
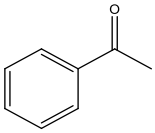
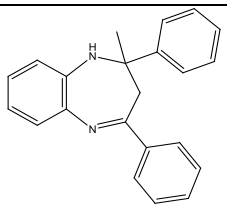
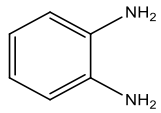
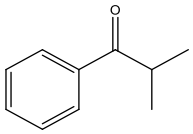
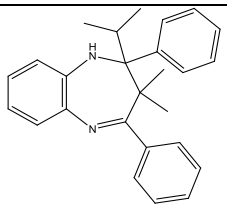
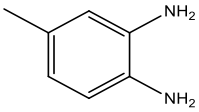
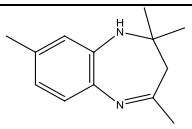
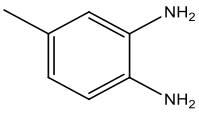
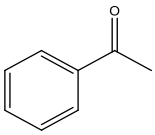
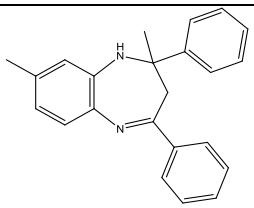
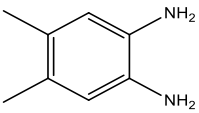
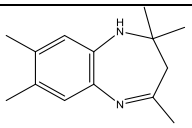
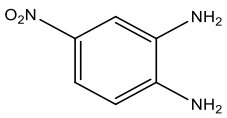
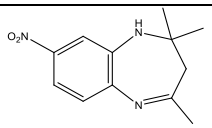
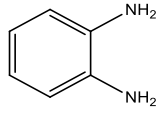
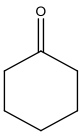
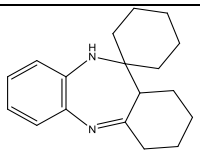
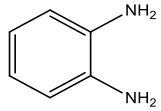
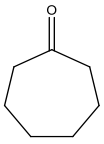
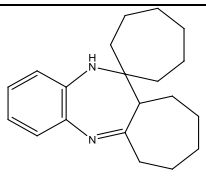
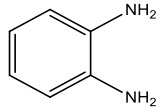
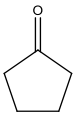
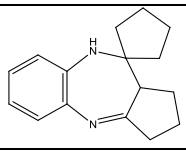
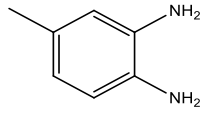
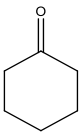
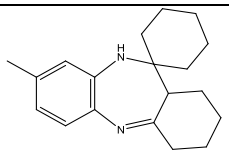
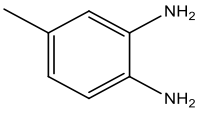
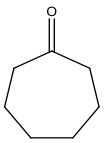
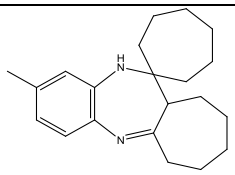


Table 2. Ammonium chloride catalyzed synthesis of 1, 5-benzodiazepines

S. N.	O-Phenylenediamine (1)	Ketones (2)	1, 5-Benzodiazepines (3)	Time (h)	Yield (%)	MP (^oC, Obs.)	MP (^oC, Lit.)
1				2	98	119-121	120-122
2				2.5	85	138-140	138-139
3				3	82	141-143	142-144

4				4	78	119-121	118-120
5				5	75	117-119	118-120
6				3.5	85	148-150	150-152
7				5.5	82	119-121	121-122
8				3	84	125-127	127-128
9				4.5	79	90-92	92-93
10				6	87	110-112	112-114
11				5.5	82	111-113	113-114
12				4.5	72	135-137	136-137
13				5.5	70	134-136	135-136
14				6	80	135-137	136-138

15				6.5	72	122-124	124-125
16				3.5	75	136-136	138-139

III. Experimental

All chemicals were purchased from commercial suppliers and used without further purification. All solvents were treated according to the standard procedure. The progress of the reactions was monitored by TLC. ^{1}H NMR (400 MHz) and ^{13}C(100 MHz) spectra were recorded with tetramethylsilane as the internal standard.

General procedure for 1, 5-benzodiazepines.

A mixture of *o*-phenylenediamine (10 mmol), Ketone (20 mmol) and ammonium chloride (20 mol%) in methanol (10 ml) was taken in a round bottom flask. The reaction mixture was stirred at room temperature for an appropriate time as mentioned in Table 2. After completion of reaction (monitored by TLC) solvent was evaporated under reduced pressure. The reaction mixture was extracted by ethyl acetate. The organic layer was dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure. The crude product was purified by recrystallization by using ethanol to furnish the corresponding 1, 5-benzodiazepines with 70-98% yields.

2, 2, 4-Trimethyl-2, 3-dihydro-1H-benzo[b][1, 4]diazepine (Entry 1): Pale yellow solid; **MP**: 119-121^{o}C [lit. 120-122^{o}C]; **IR** ($CHCl_3$) ν_{max}: 3345, 2109, 1630, 1456, 1246, 1051, 945, 713 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.35 (s, 6H), 2.23 (s, 2H), 2.37 (s, 3H), 2.99 (bs, 1H), 6.73-6.75 (m, 1H), 6.98-7.01 (m, 2H), 7.13-7.15 (m, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 29.9, 30.5, 45.1, 68.4, 121.8, 122.1, 125.5, 126.9, 137.9, 140.8, 172.4.

IV. Conclusion

In conclusion, we have reported an efficient and green protocol for synthesis of various substituted 1, 5 benzodiazepines from *o*-phenylenediamine and ketones in presence of catalytic amount of NH_4Cl in methanol under neutral conditions. The present protocol has several advantages over earlier reported. This will be alternative and highly useful method for preparation of substituted 1, 5 benzodiazepines.

V. Conflicts of interest

There are no conflicts of interest to declare.

VI. Acknowledgements

PSP gratefully acknowledge the financial support of CSIR New Delhi.

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