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CADMIUM NITRATE PROMOTED SYNTHESIS OF 1, 5-BENZODIAZEPINE DERIVATIVES

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ABSTRACT
An efficient and simple synthetic method for 1, 5-benzodiazepines has been developed using cyclocondensation reaction of *o*-phenylenediamine and various ketones in presence of cadmium nitrate as a catalyst in DMF at reflux temperature to yield the corresponding compound in good to excellent yield.

KEYWORDS: 1, 5-benzodiazepines, *o*-phenylenediamine, ketones, cadmium nitrate.

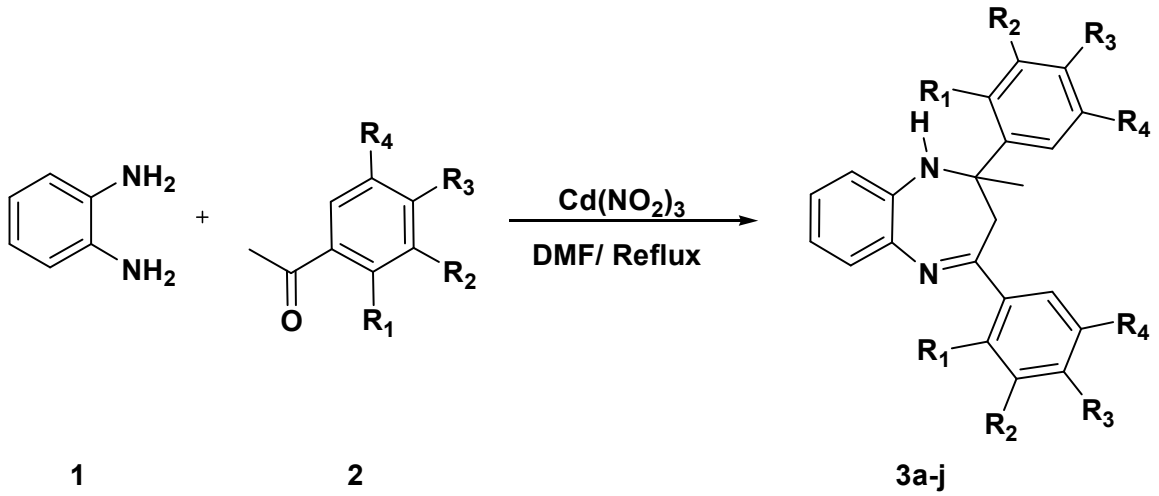
INTRODUCTION

Benzodiazepines scaffold have recently received considerable attention because of their promising biological activities and therapeutics [i-ii]. They also show antimicrobial, antioxidant, anthelmintic and antibacterial activities [iii]. In addition, benzodiazepines are used for preparation of fused ring compounds [iv].
Generaly, the method for the synthesis of 1, 5-benzodiazepines involves acid catalyzed cyclocondensation of *o*-phenelenediamine with α, β–unsaturated carbonyl compounds, ketones, β-haloketones [v-vi], have well estabilished.
The literature survey has revealed that among these, most classical and simple method is the acid catalyzed condensation of *o*-phenylenediamine with ketones. Hence, a wide range of Lewis acid catalysts [vii-ix], Solid supports acids [x-xii], Heterogeneous bifunctional catalyst [xiii] and use of solvent free and solid phase synthesis tecniques [xiv-xv] have been reported. Thus, due to wide range of biological applications of benzodiazepines, the development of an efficient and simple method for the synthesis of 1, 5-benzodiazepines is desirable. Herein we wish to report application of cadmium nitrate as catalyst for the preparation of 1, 5-benzodiazepines by reaction of *o*-phenylenediamine with ketones.

RESULT AND DISCUSSION
In the present work, a convenient method has been developed for the synthesis of 1-benzo-diazepines from the *o*-phenylenediamine and ketones respectively **(Scheme 1).** For the

optimization of reaction condition, we investigate the of model reaction of *o*-phenylenediamine (1.0 mmole), acetophenone (2.2 mmole) and cadmium nitrate as catalyst in various solvents **Table 1**. It was observed that the solvents screened for optimum conditions for the transformation, DMF was found to be most suitable along with cadmium nitrate (10 mol %) to afford the corresponding 2-methyl-2, 4-diphenyl-2, 3-dihydro-1*H*-1,5-benzodiazepine **3a** in 4 h with good yield (85%). The products of reaction were purified by recrystallization process in ethanol solvent. With these optimized reaction conditions in hand, several substituted acetophenones were treated with *o*-phenylenediamine.

Substituted acetophenones carrying either electron releasing or electron withdrawing substituents in the *ortho*, *meta* and *para*–positions afforded good yields of benzodiazepines. The structures of some the compounds were established from IR, ^{1}HNMR and mass analysis. The ^{1}HNMR spectra of **3a, 3b** showed a characteristic dd peak at δ 2.7-3.1 ppm due to benzodiazepine C-2 protons, we also noted the ^{1}HNMR spectra of **3d** upfield-shifted protons CH_2 to δ 6.7-6.8 ppm.



Scheme 1. Synthesis of 1, 5-benzodiazepines using cadmium nitrate.

Table 1. Optimization of reaction condition in different solvents using cadmium nitrate [a]

Entry	**Solvent**	**Time (h)**	**Yields (%)**[b]
1	EtOH	12	0
2	MeOH	12	0
3	CH3CN	6	79
4	DMF	4	85

[a] Reaction condition: *o*-phenylenediamine (1.0 mmol), ketone (2.2 mmol) and cadmium nitrate (10 mol %)

[b] Isolated yields

Table 2: Cadmium nitrate catalyzed synthesis of 1, 5-benzodiazepines

Entry	R_1	R_2	R_3	R_4	Product (3)	Yields (%) [a]	M.P. (^{0}C)
1	H	H	H	H	**3a**	85	152-153
2	H	H	Cl	H	**3b**	86	110-111
3	H	Br	OH	Br	**3c**	87	160-161
4	OH	I	H	Cl	**3d**	80	112-113
5	OH	I	CH_3	Cl	**3e**	85	114-115
6	OH	Br	CH_3	Cl	**3f**	83	140-141
7	OH	I	H	CH_3	**3g**	88	113-114
8	OH	Br	H	CH_3	**3h**	79	108-109
9	OH	I	H	I	**3i**	84	104-105
10	OH	Br	H	Cl	**3j**	84	110-112

[a] Isolated yields

EXPERIMENTAL

Melting points of the compounds were determined in open capillary tubes and are uncorrected, IR Spectra were recorded on Shimadzu FT-IR Spectrometer using potassium bromide pellets, ^{1}H NMR was determined on a Bruker Avance II 400 Spectrometer against TMS as internal standard. Mass spectra were recorded on waters Micromass Q-Tof Micro spectrometry. The purity of the compounds was checked by thin layer chromatography (TLC).

General procedure for the preparation of 1, 5-benzodiazepines (3a-j):

A mixture of *o*-phenylenediamine (1.0 mmole), ketones (2.2 mmole) and cadmium nitrate (10 mol %) in DMF (15 mL) was refluxed for a reaction time 4 h. After completion of the reaction (monitored on TLC, eluent: ethyl acetate: pet ether (3:7), the solvent was removed by distillation under reduce pressure. The crude product was recrystallised from ethanol to afforded the corresponding 1,5-benzodiazepines in good to excellent yields.

2,3-Dihydro-2-methyl-2,4-diphenyl-1*H*-benzodiazepine (3a): Yield 85 %; m.p. 152-153 ^{0}C; IR (KBr, cm^{-1}): 3320 (-NH stretching), 1612 (-C=N stretching), 1500 (-C=C stretching of aromatic ring); ^{1}H NMR (400 MHz, $CDCl_3$ δ / ppm): 1.79 (3H, s, CH_3); 2.99-3.01 (1H, dd, Ha); 3.15-3.18 (1H, dd, Hb); 6.86 (1H, m, aromatic); 7.05-7.11 (2H, m, aromatic); 7.2-7.3 (7H, m, aromatic); 7.62-7.64 (4H, m , aromatic); Mass: m/z 313 (M+1).

2,4-Bis(4-chlorophenyl)-2,3-dihydro-2-methyl-1*H*-benzodiazepine (3b): Yield 86 %; m.p. 110-111 ^{0}C; IR (KBr, cm^{-1}) : 3348 (-NH stretching), 1647 (-C=N stretching), 1589 (-C=C stretching of aromatic ring); ^{1}HNMR (400 MHz, $CDCl_3$ δ / ppm): .63 (3H, s, CH_3); 2.77-2.80 (1H, dd, Ha); 2.95-2.98 (dd, 1H, Hb); 3.33 (1H, s, NH); 6.72-6.74 (1H, m, aromatic); 6.94-7.01 (2H, m, aromatic); 7.09-7.16 (4H, m, aromatic); 7.19-7.22(1H, m, aromatic); 7.36-7.44 (4H, m, aromatic); Mass: m/z 381 (M+), 383 (M+2).

2,4-Bis(2-hydrohy-5-chlorophenyl)2,3-dihydro-2-methyl-1*H*-benzodiazepine (3d): Yield 80 %; m.p. 112-113^{0}C; IR (KBr, cm^{-1}) : 3348 (-NH stretching), 1647 (-C=N stretching), 1597 (-C=C stretching of aromatic ring); ^{1}HNMR: (400 MHz, $CDCl_3$□δ / ppm): 2.40 (3H, s, CH_3); 2.67 (s, 1H, NH) 6.72-6.6.74 (1H, dd, Ha); 6.80-6.82 (dd, 1H, Hb); 7.04-7.11 (4H, m,

aromatic); 7.62-7.63 (1H, d, aromatic); 7.73-7.74 (1H, d, aromatic); 7.84-7.85 (1H, d, aromatic); 7.94-7.95 (1H, d, aromatic), 13.0 (2H, s, OH).

CONCLUSION

In conclusion, we have successfully carried out an efficient and simple process for the synthesis of 1, 5-benzodiazepines using different substituted acetophenones and *o*-phenylenediamine in presence of cadmium nitrate catalyst at reflux temperature.

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