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ARTICLE

Hexachlorocyclotriphosphazene Catalyzed One-Pot Multicomponent Synthesis of 2,3-Dihydro-1*H*-1,5-benzodiazepines

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ABSTRACT

A hexachlorocyclotriphosphazene (HCCP) catalyzed new method has been developed for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines by cyclocondensation of *o*-phenylenediamine with aromatic aldehydes or ketones in acetonitrile at room temperature. This protocol is developed as a clean and safe method utilizing environmental-friendly and highly efficient catalyst.

KEYWORDS

2,3-Dihydro-1*H*-1,5-benzodiazepines, Hexachlorocyclotriphosphazene, *o*-Phenylenediamine, Aromatic aldehydes/ketones, Acetonitrile.

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INTRODUCTION

1,5-Benzodiazepines belong to an essential class of pharmacological vital benzodiazepines which are widely used in the various central nervous system (CNS) disorders [1]. In recent years, 1,5-benzodiazepines have received much attention because of their potential structural diversity as a privilege scaffolds towards treating various diseases such as cancer, viral infections and cardiovascular diseases and anti-inflammatory diseases [2-4]. They are also valuable synthons for the synthesis of fused ring benzodiazepines derivative such as oxadiazolo-, furano-, oxazino-, triazolo-benzodiazepines [4].

Based on the biological importance of these compounds, numerous classical synthetic methods have been described for the synthesis of 1,5-benzodiazepines using various catalyst [5]. Recently, several novel catalyst such as Gr@TiO_2 [6], MOF-235 [7], ZnS-nanoparticles [8], nano ZnS/CdS [9], $CeCl_3$ [10], nano stannic oxide [11], have been employed for the efficient synthesis of 1,5-benzodiazepines. However, methodologies involving these catalysts involve at least one of the following imperfections: expensive reagents, extended reaction times, high temperatures, low yields and requiring tedious work-up procedures.

Hexachlorocyclotriphosphazene (HCCP) is an inorganic compound having formula $(NPCl_2)_3$. The molecule has a cyclic backbone consisting of alternating phosphorus and nitrogen atoms. Catalytic activity of HCCP has recently been explored by Hu *et al.* [12,13]. In continuation of previous work for the green synthesis of pharmaceutically important medicinal compounds [14-30], herein, we report an efficient synthesis of

2,3-dihydro-1*H*-1,5-benzodiazepine *via* condensation reaction of *o*-phenylenediamine with aldehydes and ketones in the presence of catalytic amount of hexachlorocyclotriphosphazene in acetonitrile at room temperature.

EXPERIMENTAL

Hexachlorocyclotriphosphazene (HCCP) was purchased from Sigma-Aldrich. The melting points were determined on Veego-programmable melting point apparatus (microprocessor based) and are uncorrected. Proton (^{1}H) nuclear magnetic resonance spectra were obtained using Brucker AC-400 F, 400 MHz spectrometer and are reported in parts per million (ppm), downfield from tetramethylsilane (TMS) as internal standard Infrared (IR) spectra were obtained with Perkin Elmer 882 Spectrum and RXI, FT-IR model using KBr pellets (in cm^{-1}). Elemental analyses for C, H, and N were performed on Perkin-Elmer 2400 CHN elemental analyzer. Reactions were monitored and homogeneity of the products was checked by TLC which were prepared with silica gel G and activated at 110 ºC for 30 min. The plates were developed by exposure to iodine vapours. Anhydrous sodium sulphate was used as a drying agent.

General procedure for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines: Ketones (2.2 mmol), hexachlorocyclotriphosphazene (10 mol %) and acetonitrile (5 mL) were added to a beaker. The reaction mixture was stirred at room temperature for 1 h as activation time. Then nucleophile (1 mmol) (*o*-phenylenediamine) was added and the reaction mixture was stirred overnight for 24 h. After completion of reaction [monitored by TLC using $CHCl_3$ and MeOH (9.5:0.5 mL) as eluent], the reaction mass was filtered, washed thoroughly with water and dried. The residue was recrystallized from ethanol or subjected to silica gel column chromatography (15 % ethyl acetate in hexane) to get pure products (**Scheme-I**).

2,3-Dihydro-2-methyl-2,4-diphenyl-1*H*-1,5-benzodiazepine (Entry 1): IR (KBr, ν_{max}, cm^{-1}): 3277 (*sec*. N-H), 3061 (arom. C-H), 2972 (aliph. C-H), 1559 (arom. C=C); ^{1}H NMR ($CDCl_3$): δ 1.8 (s, 3H, $-CH_3$), 3.1 (d, 1H, -CH), 3.2 (d,1H, -CH), 6.8-7.7 (m, 14H, ArH). Anal. calcd. (found) % for $C_{22}H_{20}N_2$: C, 84.58 (84.60); H, 6.45 (6.42); N, 8.97 (8.94).

11-Spirocyclocyclohexane-2,3,4,10,11,11a-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepine (Entry 4): IR (KBr, ν_{max}, cm^{-1}): 3279 (*sec*. NH), 3059 (arom. CH), 2859 (alkane CH), 1635 (imine C=N), 1481 (arom. C=C), 751 (*o*-substituted oop); ^{1}H NMR ($CDCl_3$): δ 1.2-1.9 (m, 16H, $-CH_2$), 2.3-2.6 (m, 3H, -CH), 4.5 (1H, br, NH), 6.8-7.9 (m, 4H, ArH). Anal. calcd. (found) % for $C_{18}H_{24}N_2$: C, 80.55 (80.62); H, 9.01 (9.05); N, 10.44 (10.54).

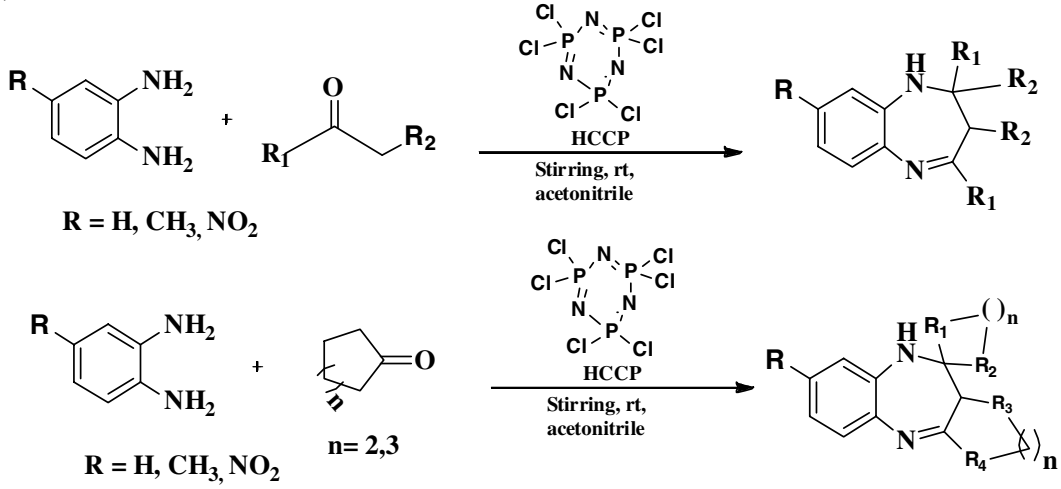
2,3-Dihydro-2,8-dimethyl-2,4-diphenyl-1*H*-1,5-benzodiazepine (Entry 7): IR (KBr, ν_{max}, cm^{-1}): 3335 (*sec*. NH), 3058 (arom. CH), 2970 (alkene CH), 2858 (alkane CH), 1613 (imine C=N), 1493 (arom. C=C), 1328 (C-N), 759 (*ortho* substituted oop); ^{1}H NMR ($CDCl_3$): δ 1.75 (s, 3H, $-CH_3$), 2.6 (br, 4H,$-CH_3$, -NH), 2.9 (d, 1H, -CH), 3.1 (d, 1H, -CH), 7.2-7.9 (m, 14H, ArH). Anal. calcd. (found) % for $C_{23}H_{22}N_2$: C, 84.63 (84.68); H, 6.79 (6.84); N, 8.58 (8.45).

10-Spirocycloheptan-6,7,8,9,10,10a,11,12-octahydro-8-methylbenzo[*b*]cyclohepta[*e*][1,4]diazepine (Entry 9): IR (KBr, ν_{max}, cm^{-1}): 3266 (NH), 2916 (arom. CH), 1633 (imine C=N), 1484 (arom. C=C). ^{1}H NMR ($CDCl_3$): δ 1.6 (m, 22H, $-CH_2$), 2.2 (s, 3H, $-CH_3$), 3.1 (br, 2H, -NH, -CH), 6.5 (s, 1H, -CH), 6.76 (d, 1H, J = 7.8, -CH), 7.1 (d, 1H, J = 7.9, -CH). Anal. calcd. (found) % for $C_{21}H_{30}N_2$: C, 81.24 (81.29); H, 9.74 (9.79); N, 9.02 (9.15).

2,2,4-Trimethyl-2,3-dihydro-8-nitro-1*H*-1,5-benzodiazepine (Entry 12): IR (KBr, ν_{max}, cm^{-1}): 3280 (NH), 1645, 1600 (imine C=N). ^{1}H NMR ($CDCl_3$): δ 1.90 (s, 6H), 2.95 (s, 3H), 3.20 (s, 2H), 7.18 (s, 1H), 8.0-8.10 (m, 1H), 8.5-8.9 (m, 1H). Anal. calcd. (found) % for $C_{12}H_{15}N_3O_2$: C, 61.78 (61.85); H, 6.48 (6.66); N, 18.01 (18.12).

RESULTS AND DISCUSSION

In preliminary experiments, we investigated the influence of hexachlorocyclophosphazene (HCCP) for the synthesis of 1,5-benzodiazepines using the model reaction between *o*-phenylenediamine and acetophenone and varying the amount of HCCP by simple optimization study. The results of optimization experiments are summarized in Table-1. The catalyst quantity was optimized to 10 mol % and excellent result (88 %) were achieved. Similarly, other 1,5-benzodiazepines derivatives have been synthesized in 80-88 % yield (Table-2). Upon solvent screening, acetonitrile was found to be the most effective solvent for the generation of the desired product with no side products at all. The use of other solvents such as THF, DMF and CH_2Cl_2 did



Scheme-I: Hexachlorocyclotriphosphazene-catalyzed the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines

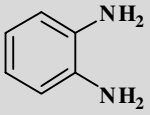
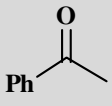
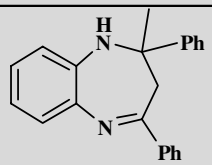
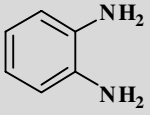
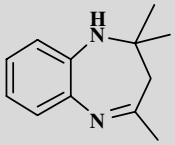
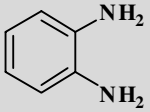
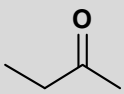
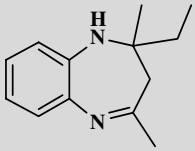
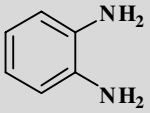
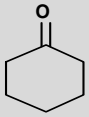
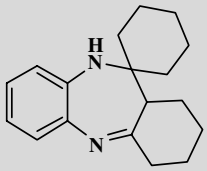
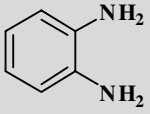
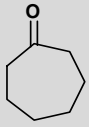
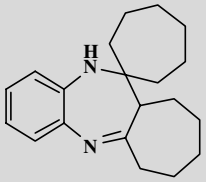
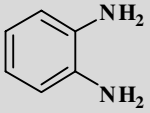
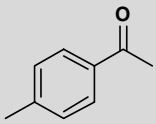
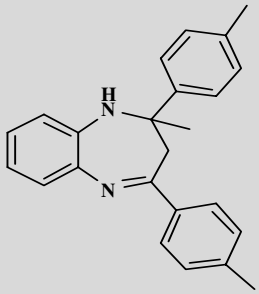
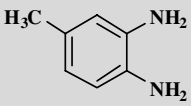
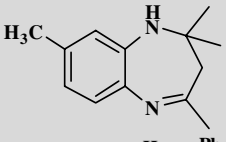
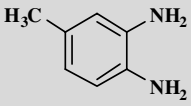
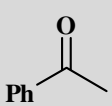
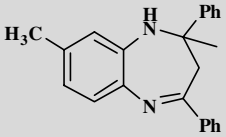
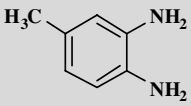
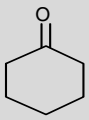
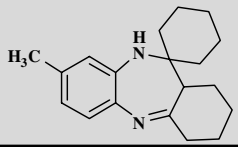
TABLE-1
OPTIMIZATION STUDY OF
HEXACHLOROCYCLOTRIPHOSPHAZENE (HCCP)

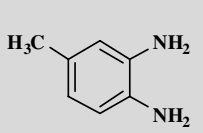
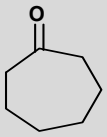
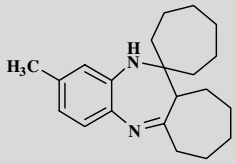
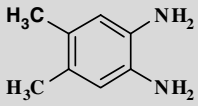
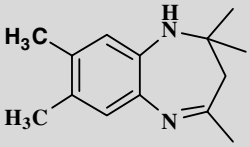
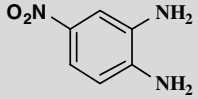
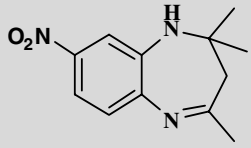
HCCP (mol %)	Time (h)	Yield (%)
0	24	46
5	24	75
10	24	88
15	24	88

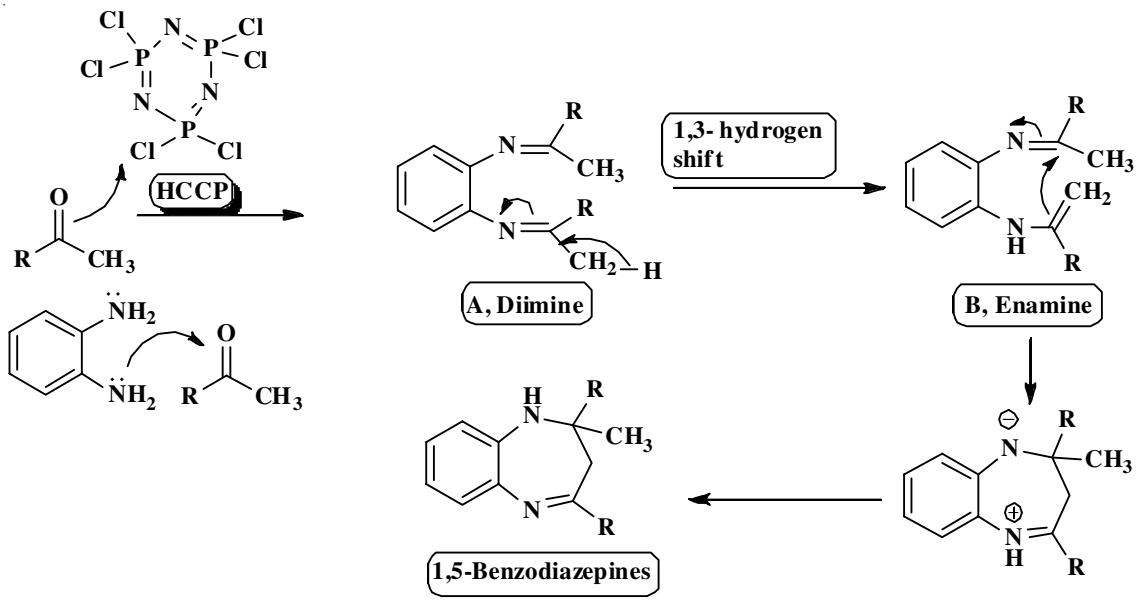
not improve the product yield instead some unidentified by-products were observed by TLC.

The proposed mechanism involves an intramolecular imine enamine cyclization promoted by HCCP. The role of HCCP has been proposed to activate *in situ* the oxygen atom of carbonyl group which ultimately enhances the electrophilicity of ketone. Then nucleophilic attack *o*-phenylenediamine on activated ketone

TABLE-2
CONDENSATION OF *o*-PHENYLENEDIAMINE WITH VARIOUS KETONES
CATALYZED BY HEXACHLOROCYCLOTRIPHOSPHAZENE (HCCP)

Entry	Diamine	Ketone	Product	Yield (%)	Time (h)	m.p. (°C)
1				88	24	149-150
2				85	24	138-139
3				84	24	138-139
4				85	24	137-138
5				88	24	133-134
6				87	24	97-100
7				84	24	126-128
8				85	24	91-92
9				82	24	140-142

10				85	24	121-122
11				80	24	111-114
12				84	24	113-115



Scheme-II: Proposed mechanism for hexachlorocyclotriphosphazene catalyzed reaction

gives the intermediate diimine A. A 1,3-hydrogen shift of the attached methyl groups to form isomeric enamine B, which cyclize to afford seven membered ring with the generation of catalyst. Same reactions can be performed for the synthesis of 1,5-benzodiazepines (**Scheme-II**).

Conclusion

In summary, a new catalytic and efficient protocol to the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines have been developed. This method using this catalyst has several advantages such as high yields of products, short reaction time, mild reaction condition, simple work-up procedures, inexpensive, non-toxic and environmental friendly catalyst.

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