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A Mild and Efficient Oxalic Acid Catalysed Synthesis of 1,5-Benzodiazepines *via* Cyclocondensation of β-Amino Ketones with *o*-Phenylenediamine

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An efficient and straightforward method has been developed for the synthesis of 1,5-benzodiazepine derivatives. The methodology involves the cyclocondensation of β-amino ketones with *o*-phenylenediamine using oxalic acid (10 mol%) as a metal-free organocatalyst. The reaction is carried out in DMF at 80 ºC and affords 1,5-benzodiazepine derivatives in excellent yields (78-95%). The protocol offers operational simplicity, a broad substrate scope and employs an inexpensive, readily available catalyst. Oxalic acid efficiently promotes the cyclocondensation reaction, while β-amino ketones serve as versatile starting materials for the synthesis of a variety of 1,5-benzodiazepine derivatives.

Keywords: 1,5-Benzodiazepines, β-Amino ketones, Oxalic acid, Cyclocondensation, Organocatalysts.

INTRODUCTION

1,5-Benzodiazepines constitute an important class of nitrogen-containing heterocycles and have attracted considerable attention as privileged scaffolds in heterocyclic and medicinal chemistry owing to their broad range of biological and pharmacological properties [1-3]. Besides their biological significance, these compounds serve as valuable synthons for the synthesis of structurally diverse heterocycles and pharmaceutically relevant molecules [4-6].

Traditionally, 1,5-benzodiazepine derivatives have been synthesised through the condensation of *o*-phenylenediamine with ketones in the presence of acidic catalysts [7]. A variety of catalytic systems, such as zeolites, sulphanilic acid, metal-based catalysts, ionic liquids and carbonaceous materials, have been employed for this transformation [8-13]. Despite their effectiveness, many of these methods suffer from harsh reaction conditions, prolonged reaction times, the use of expensive or toxic catalysts and difficulties associated with catalyst recovery.

Recent efforts have focused on greener synthetic strategies, such as solvent-free protocols, microwave-assisted reactions, deep eutectic solvents, aqueous media and recyclable catalysts [14-18]. Despite their advantages, many of these methods require specialised equipment or multistep catalyst preparation. The search for simple, efficient, economical and practical catalytic systems for the synthesis of 1,5-benzodiazepine derivatives remains an important objective. Among organic acids, oxalic acid has attracted attention as an inexpensive, readily available, biodegradable and efficient organocatalyst for a variety of organic transformations [19-21], making it a suitable choice for the synthesis of heterocyclic compounds under mild, metal-free conditions.

β-Amino ketones are the versatile building blocks, which are readily prepared through multicomponent reactions and contain both nucleophilic and electrophilic reaction centres [22,23]. Their application in the synthesis of 1,5-benzodiazepine derivatives, however, remains limited. The β-amino ketones used in this study were prepared following the reported ammonium chloride-catalysed three-component Mannich reaction protocol [24]. Their synthetic utility was examined through cyclocondensation with *o*-phenylenediamine using oxalic acid as an inexpensive, readily available metal-free organocatalyst. The reaction affords a series of 1,5-benzodiazepine derivatives in good to excellent yields under mild conditions, offering a practical synthetic route while expanding the

use of β-amino ketones in the synthesis of benzodiazepine-based heterocycles.

EXPERIMENTAL

All reagents and solvents were purchased commercially and used without further purification unless otherwise stated. The reactions were followed by thin-layer chromatography (TLC) on plates coated with silica gel and detection with ultraviolet (UV) light. Column chromatography was carried out using silica gel (100-200 mesh size) as the stationary phase. Infrared (IR) spectra were taken on a Nicolet 5700 FT-IR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra were measured on the Bruker/Varian instruments using $CDCl_3$ as the solvent and TMS as the internal standard. The melting points were measured in open capillary tubes and are uncorrected.

General procedure for the synthesis of 1,5-benzodiazepines: The mixture of β-amino ketone (1 mmol), *o*-phenylenediamine (1 mmol), oxalic acid (10 mol %) and DMF (5 mL) was heated at 80 ºC for 2-3 h. The progress of the reaction was monitored by TLC. When the reaction was complete as evidenced through TLC analysis, the reaction mixture was cooled to room temperature and added to ice-cold water (20 mL). This resulted in the precipitation of the product which was filtered, washed with water to eliminate the solvents and dried under reduced pressure (**Scheme-I**). The purification of the obtained crude product by recrystallisation in ethanol gave 1,5-benzodiazepines derivatives in good to excellent yields in 78-95% range.

2,4-Diphenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine (3a): Yellow solid; yield: 95%; m.p.: 130 ºC; IR (KBr, ν_{max}, cm^{-1}): 3295 (NH), 2964, 1641 (C=N), 1600, 740 (Ar-H); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.05 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.23 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.53 (br s, 1H, NH), 5.23 (dd, *J* = 4.0 Hz, 1H), 6.84 (dd, *J* = 7.1, 2.1 Hz, 1H), 6.88-7.02 (m, 1H), 7.06-7.12 (m, 1H), 7.24-7.30 (m, 1H), 7.32 (m, 2H), 7.36-7.45 (m, 5H), 7.83 (dd, *J* = 8.0, 1.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, δ ppm): 37.4, 60.1, 116.9, 120.6, 121.6, 124.5, 127.4, 128.4, 128.5, 128.9, 130.2, 131.2, 132.9, 137.9, 139.4, 143.2, 157.0.

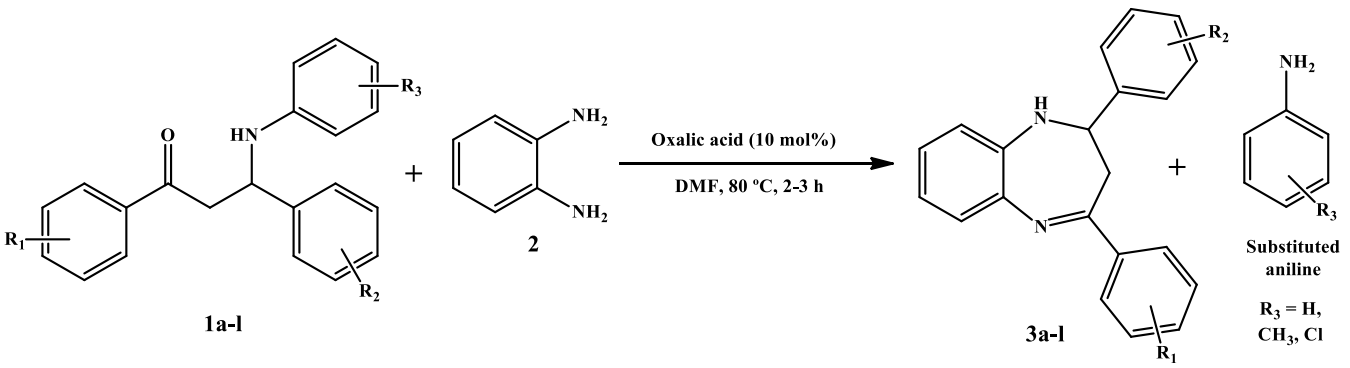
4-Phenyl-2-(*p*-tolyl)-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepine (3b): Yellow solid; yield: 90%; m.p.: 169-170 ºC; IR (KBr, ν_{max}, cm^{-1}): 3295 (NH), 2964, 1641 (C=N), 1600, 740 (Ar-H); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.3 (s, 3H, CH_3), 3.05 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.23 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.53 (br s, 1H, NH), 5.23 (dd, *J* = 4.0 Hz, 1H), 6.84 (dd, *J* = 7.1, 2.1 Hz, 1H), 6.88-7.02 (m, 1H), 7.06-7.12 (m, 1H), 7.24-7.30 (m, 1H), 7.32 (m, 2H), 7.36-7.45 (m, 4H), 7.83 (dd, *J* = 8.0, 1.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, δ ppm): 21.5, 37.4, 60.1, 116.9, 120.6, 121.6, 124.5, 127.4, 128.4, 128.5, 128.9, 130.2, 131.2, 132.9, 137.9, 139.4, 143.2, 157.0.

2-(4-Chlorophenyl)-4-phenyl-2,3-dihydro-1*H*-benzo-[*b*][1,4]diazepine (3c): Yellow solid; yield: 85%; m.p.: 136-137 ºC; IR (KBr, ν_{max}, cm^{-1}): 3295 (NH), 2964, 1641 (C=N), 1600, 740 (Ar-H); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.10 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.23 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.71 (br s, 1H, NH), 5.23 (dd, *J* = 4.0 Hz, 1H), 6.58 (dd, *J* = 7.1, 2.1 Hz, 1H), 6.88 (m, 1H), 6.88-7.02 (m, 1H), 7.24 (dd, *J* = 7.1, 2.1 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.36-7.45 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$, δ ppm): 37.4, 60.1, 116.9, 120.6, 121.6, 124.5, 127.4, 128.4, 128.5, 128.9, 130.2, 131.2, 132.9, 137.9, 139.4, 143.2, 157.0.

2-(4-Methoxyphenyl)-4-phenyl-2,3-dihydro-1*H*-benzo-[*b*][1,4]diazepine (3d): Yellow solid; yield: 89%; m.p.: 110-113 ºC; IR (KBr, ν_{max}, cm^{-1}): 3295 (NH), 2964, 1641 (C=N), 1610, 738 (Ar-H); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.10 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.23 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.71 (br s, 1H, NH), 3.80 (s, 3H, OCH_3), 5.23 (dd, *J* = 4.0 Hz, 1H), 6.58 (dd, *J* = 7.1, 2.1 Hz, 1H), 6.88 (m, 1H), 6.88-7.02 (m, 1H), 7.24 (dd, *J* = 7.1, 2.1 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.36-7.45 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$, δ ppm): 37.4, 56.2, 60.1, 113.2, 116.9, 118.8, 121.6, 124.5, 127.0, 127.4, 128.9, 131.0, 131.2, 133.5, 137.9, 143.1, 157.0, 158.2.

4-(4-Nitrophenyl)-2-phenyl-2,3-dihydro-1*H*-benzo[*b*]-[1,4]diazepine (3e): Yellow solid; yield: 78%; m.p.: 128-130 ºC; IR (KBr, ν_{max}, cm^{-1}): 3295 (NH), 2964, 1641 (C=N), 1636, 752; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.02 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.32 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.67 (br s, 1H, NH), 4.11 (dd, *J* = 8.0 Hz, 1H), 6.87 (dd, *J* = 7.1, 2.1 Hz, 1H), 6.90-7.10 (m, 1H), 7.22-7.30 (m, 1H), 7.35 (dd, *J* = 7.1, 2.1 Hz, 1H), 7.40-7.60 (m, 5H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, δ ppm): 37.4, 60.1, 116.9, 120.6, 121.6, 124.5, 125.3, 126.8, 127.4, 128.4, 128.9, 131.2, 142.5, 142.7, 142.9, 148.2, 157.0.

2,4-Di-*p*-tolyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine (3f): Yellow solid; yield: 90%; m.p.: 132-133 ºC; IR (KBr, ν_{max}, cm^{-1}): 3295 (NH), 2964, 1641 (C=N), 1630, 755; ^{1}H



Scheme-I: Synthesis of 1,5-benzodiazepine derivatives (**3a-l**) using substituted β-amino ketones (**1a-l**) and *o*-phenylenediamine (**2**)

NMR (400 MHz, $CDCl_3$, δ ppm): 2.32 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.05 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.23 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.53 (br s, 1H, NH), 5.23 (dd, *J* = 4.0 Hz, 1H), 6.60-6.68 (m, 1H), 6.73 (dd, *J* = 7.1, 2.1 Hz, 1H), 6.75-7.02 (m, 1H), 7.12 (dd, *J* = 7.1, 2.1 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, δ ppm): 21.5, 37.4, 60.1, 116.9, 120.6, 121.6, 124.5, 127.4, 128.4, 128.5, 128.9, 130.2, 131.2, 132.9, 136.6, 140.2, 143.2, 157.0.

2,4-*Bis*(4-chlorophenyl)-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepine (3g): Yellow solid; yield: 82%; m.p.: 120 ºC; IR (KBr, ν_{max}, cm^{-1}): 3295 (NH), 2964, 1641 (C=N), 1650, 748; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.10 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.25 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.53 (br s, 1H, NH), 5.25 (dd, *J* = 4.0 Hz, 1H), 6.65-6.70 (m, 1H), 6.73 (dd, *J* = 7.1, 2.1 Hz, 1H), 6.75-7.02 (m, 1H), 7.12 (dd, *J* = 7.1, 2.1 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, δ ppm): 37.5, 60.2, 116.9, 118.8, 121.6, 124.5, 128.4, 128.5, 129.2, 129.5, 131.2, 132.9, 136.4, 137.9, 139.4, 143.2, 157.0.

2-(2-(4-Methoxyphenyl)-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepin-4-yl)phenol (3h): Yellow solid; yield: 86%, m.p.: 108-110 ºC; IR (KBr, ν_{max}, cm^{-1}): 3385, 1650, 1610, 755; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.07 (dd, *J* = 12, 8 Hz, 1H). 3.31 (dd, *J* = 12, 8 Hz, 1H), 3.80 (s, 3H, OCH_3), 3.95 (br s, 1H, NH), 5.25 (dd, *J* = 8 Hz, 1H), 6.74 (t, *J* = 7.6 Hz, 1H), 6.86 (t, *J* = 7.8 Hz, 2H), 6.97-6.91 (m, 2H), 7.09-6.98 (m, 4H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.30-7.21 (m, 2H), 11.3 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, δ ppm): 36.4, 56.5, 60.1, 113.2, 116.9, 117.8, 118.2, 120.3, 120.8, 121.4, 121.6, 124.5, 127.5, 129.6, 131.2, 133.5, 133.8, 142.5, 157.0, 160.4.

2-(2-(4-Chlorophenyl)-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepin-4-yl) phenol (3i): Yellow solid; yield: 85%, m.p.: 111-112 ºC; IR (KBr, ν_{max}, cm^{-1}): 3380, 3295, 2964, 1641, 1600, 742; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.07 (dd, *J* = 12, 8 Hz, 1H). 3.31 (dd, *J* = 12, 8 Hz, 1H), 3.95 (br s, 1H, NH), 5.25 (dd, *J* = 8 Hz, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 2H), 6.95-7.01 (m, 2H), 6.98-7.09 (m, 4H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.21-7.30 (m, 2H), 11.2 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, δ ppm): 36.4, 60.1, 113.2, 116.9, 117.8, 118.2, 120.3, 120.8, 121.4,121.6, 124.5, 127.5, 129.6, 131.2, 133.5, 133.8, 142.5, 157.0, 160.4.

2-(2-(2,4-Dichlorophenyl)-2,3-dihydro-1*H*-benzo[*b*]-[1,4]diazepin-4-yl)phenol (3j): Yellow solid; yield: 86%, m.p.: 115 ºC; IR (KBr, ν_{max}, cm^{-1}): 3380, 3295, 2964, 1641, 1600, 740; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.07 (dd, *J* = 12, 8 Hz, 1H). 3.31 (dd, *J* = 12, 8 Hz,1H), 3.95 (br s, 1H, NH), 5.25 (dd, *J* = 8 Hz, 1H), 6.61 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.69-6.80 (m, 1H), 7.01-7.10 (m, 1H), 7.12-7.18 (m, 1H), 7.21(dd, *J* = 7.8, 1.2 Hz, 1H), 7.25 -7.30 (m, 2H), 7.35 (dd, *J* = 7.8,1.2 Hz, 2H), 7.40 (dd, *J* = 7.8, 1.2 Hz, 2H), 11.2 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, δ ppm): 36.4, 60.1, 116.9, 117.8, 118.2, 120.6, 120.8, 121.4, 124.5, 127.5, 129.6, 130.0, 130.6,131.0, 131.9, 133.1, 134.2, 138.4, 142.5, 157.0, 160.4.

8-Methyl-2,4-di-*p*-tolyl-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepine (3k): Yellow solid; yield: 90%, m.p.: 140-142 ºC; IR (KBr, ν_{max}, cm^{-1}): 3295, 2964, 1641, 1600, 735; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.32 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.05 (dd, *J* = 12, 8Hz, 1H); 3.23 (dd, *J* = 12, 8 Hz, 1H), 3.53 (br s, 1H, NH), 5.23 (dd, *J* = 4 Hz, 1H), 6.60-6.68 (m, 1H), 6.73 (dd, *J* = 7.1, 2.1 Hz, 1H), 6.75-7.02 (m, 1H), 7.12 (dd, *J* = 7.1, 2.1 Hz, 1H), 7.16 (d, *J* = 8.0, Hz, 2H); 7.19 (d, *J* = 8.0, Hz, 2H), 7.24 (d, *J* = 8.0, Hz, 2H), 7.26 (d, *J* = 8.0, Hz, 1H), ^{13}C NMR (101 MHz, $CDCl_3$, δ ppm): 21.2, 21.5, 37.4, 60.1, 116.9, 120.6, 121.6, 126.8, 127.4, 128.4, 128.5, 128.9,129.5, 130.2, 134.4, 135.5, 136.6, 140.2, 141.2, 146.2, 157.0.

2-(2-(3,4-Dimethoxyphenyl)-2,3-dihydro-1*H*-benzo[*b*]-[1,4]diazepin-4-yl)phenol (3l): Yellow solid; yield: 88%, m.p.: 96-98 ºC; IR (KBr, ν_{max}, cm^{-1}): 3380, 3295, 2964, 1641, 1600, 732; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.07 (dd, *J* = 12, 8 Hz, 1H), 3.31(dd, *J* = 12, 8 Hz, 1H), 3.76 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.95 (br s, 1H, NH), 5.25 (dd, *J* = 8 Hz, 1H), 6.74 (t, *J* = 7.6 Hz,1H), 6.86 (t, *J* = 7.8 Hz, 2H), 6.97-6.91 (m, 2H), 7.09-6.98 (m, 4H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.30-7.21 (m,1H), 11.3 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, δ ppm): 36.4,56.5, 60.1, 111.2, 114.5, 116.9, 117.8, 118.2, 120.6, 120.8, 121.2, 121.6, 124.5, 129.6,131.2, 133.5, 135.2, 142.5, 148.2, 149.3, 157.0, 160.4.

RESULTS AND DISCUSSION

This study explores a practical approach for the synthesis of 1,5-benzodiazepine derivatives through the cyclocondensation of β-amino ketones with *o*-phenylenediamine. In contrast to conventional methods that employ ketones as starting materials, the present protocol uses readily accessible β-amino ketones in the presence of oxalic acid as a metal-free organocatalyst. The reaction proceeds under mild conditions and provides a simple and efficient route to the target compounds. The effects of solvent, temperature, catalyst and catalyst loading were evaluated to optimise the reaction conditions.

Model reaction: As representative, 1,3-diphenyl-3-(phenylamino)propan-1-one (β-aminoketone, **1**) and *o*-phenylenediamine (**2**, 1 mmol each) were selected as model substrates. The reaction was evaluated under various conditions to optimise the reaction parameters (**Scheme-I**).

Effect of solvent: The influence of solvent on the cyclocondensation reaction was examined using solvents of varying polarity and protic character and the results are shown in Table-1. Protic solvents such as methanol and ethanol (entries 1 and 2) afforded good yields, although lower than that obtained with DMF. Acetonitrile and toluene (entries 3 and 4) gave poor yields, which may be attributed to the limited solubility of the reactants. Water (entry 5) was likewise ineffective, furnishing a low yield, possibly due to its poor substrate solubility and competing side reactions. Among the solvents investigated, DMF (entry 6) provided the highest yield (95%) with a reaction time of 2 h. Its superior performance can be attributed to its polar aprotic nature, which facilitates substrate dissolution and stabilises the reaction intermediates. On the basis of these results, DMF was selected as the reaction solvent. Although DMF poses environmental concerns, the evaluation of greener solvent systems capable of delivering comparable efficiency remains a subject for future investigation.

Effect of temperature: Reaction temperature also had a marked effect on the cyclocondensation and the results are

TABLE-1
EFFECT OF SOLVENT ON THE SYNTHESIS OF 1,5-BENZODIAZEPINE

Entry	Solvent	Time (h)	Isolated yield (%)
1	Ethanol	5	68
2	Methanol	4.5	72
3	Acetonitrile	4	75
4	Toluene	6	60
5	Water	7	50
6	DMF	2	95

shown in Table-2. At room temperature, the reaction afforded only 40% yield, indicating incomplete conversion. Increasing the temperature from 50 to 80 ºC resulted in a steady improvement in product yield, which can be attributed to faster imine formation and cyclisation. The highest yield (95%) was obtained at 80 ºC with complete conversion within 2 h. Raising the temperature to 90 ºC did not improve the yield, indicating that 80 ºC is optimum for efficient completion of the reaction. Accordingly, 80 ºC was selected as the optimum reaction temperature.

TABLE-2
EFFECT OF TEMPERATURE ON THE SYNTHESIS OF 1,5-BENZODIAZEPINE

Entry	Temperature	Time (h)	Isolated yield (%)
1	Room temperature	10	40
2	50	6	65
3	60	5	75
4	70	4	85
5	80	2	95
6	90	2	91

Effect of catalyst: The effect of catalyst on the cyclocondensation reaction was evaluated under identical reaction conditions and the results are shown in Table-3. In the absence of a catalyst (entry 1), the reaction afforded only a low yield, confirming the requirement for acid catalysis. Acetic acid and *p*-toluenesulfonic acid (*p*-TSA) (entries 2 and 3) promoted the reaction with moderate efficiency. Among the catalysts examined, oxalic acid (entry 5) afforded the highest yield (95%) with the shortest reaction time. Its superior catalytic performance may be attributed to the presence of two carboxylic acid groups, which facilitate carbonyl activation and promote nucleophilic attack by *o*-phenylenediamine. These results identify oxalic acid as an efficient, inexpensive and metal-free catalyst for the synthesis of 1,5-benzodiazepine derivatives.

TABLE-3
EFFECT OF CATALYST ON THE SYNTHESIS OF 1,5-BENZODIAZEPINE

Entry	Catalyst	Time (h)	Isolated yield (%)
1	No catalyst	8	30
2	Acetic acid	5	70
3	*p*-TSA	4	82
4	Sulfanilic acid	4	80
5	Oxalic acid	2	95

Effect of catalyst loading: The effect of catalyst loading on the cyclocondensation reaction was evaluated to determine the optimum amount of oxalic acid. Increasing the catalyst loading from 5 to 10 mol% markedly improved the product yield, with the highest yield (95%) obtained at 10 mol%. No appreciable increase in yield was observed at higher catalyst loadings (15-20 mol%) confirmed that 10 mol% is sufficient for efficient conversion (Table-4). Thus, 10 mol% was selected as the optimum catalyst loading.

TABLE-4
EFFECT OF CATALYST LOADING ON THE SYNTHESIS OF 1,5-BENZODIAZEPINE

Entry	Catalyst loading (mol %)	Time (h)	Isolated yield (%)
1	0	8	30
2	5	5	75
3	10	2	95
4	15	3	93
5	20	3	93

Substrate scope: The substrate scope of the developed protocol was examined under the optimised reaction conditions (Table-5). A series of β-amino ketones bearing electron-donating and electron-withdrawing substituents on the aromatic ring underwent smooth cyclocondensation with *o*-phenylenediamine to afford the corresponding 1,5-benzodiazepine derivatives (**3a-l**) in good to excellent yields. The results indicate

TABLE-5
EFFECT OF SUBSTRATE SUBSTITUTION ON REACTION TIME AND YIELD IN THE SYNTHESIS OF 1,5-BENZODIAZEPINES[a]

Entry	R_1	R_2	Product	Time (h)	Yield[b] (%)	m.p. (ºC)	Literature m.p. (ºC)	Ref.
1	H	H	**3a**	2.0	95	130	128-132	[24]
2	H	*p*-CH_3	**3b**	2.0	90	169	168-171	[28]
3	H	*p*-OCH_3	**3c**	2.5	85	112	110-113	[28]
4	H	*p*-Cl	**3d**	3.0	89	136	135-138	[28]
5	H	*p*-NO_2	**3e**	3.0	78	128	126-129	[29]
6	*p*-CH_3	*p*-CH_3	**3f**	2.0	90	132	130-134	[30]
7	*p*-Cl	*p*-Cl	**3g**	3.0	82	120	–	–
8	OH	OCH_3	**3h**	2.5	86	108	–	–
9	OH	-Cl	**3i**	3.0	85	111	112	[26]
10	H	2,4 di-Cl	**3j**	3.0	86	115	115-118	[27]
11	H	tri-CH_3	**3k**	2.0	90	140	140-142	[29]
12	H	di-OCH_3	**3l**	2.0	88	96	–	–

[a]Reaction condition: Substrate (1 mmol), *o*-phenylenediamine (1 mmol), oxalic acid (10 mol%), DMF, 80 ºC, 2-3 h; [b]Isolated yield.

broad substrate compatibility, irrespective of the electronic nature of the substituents.

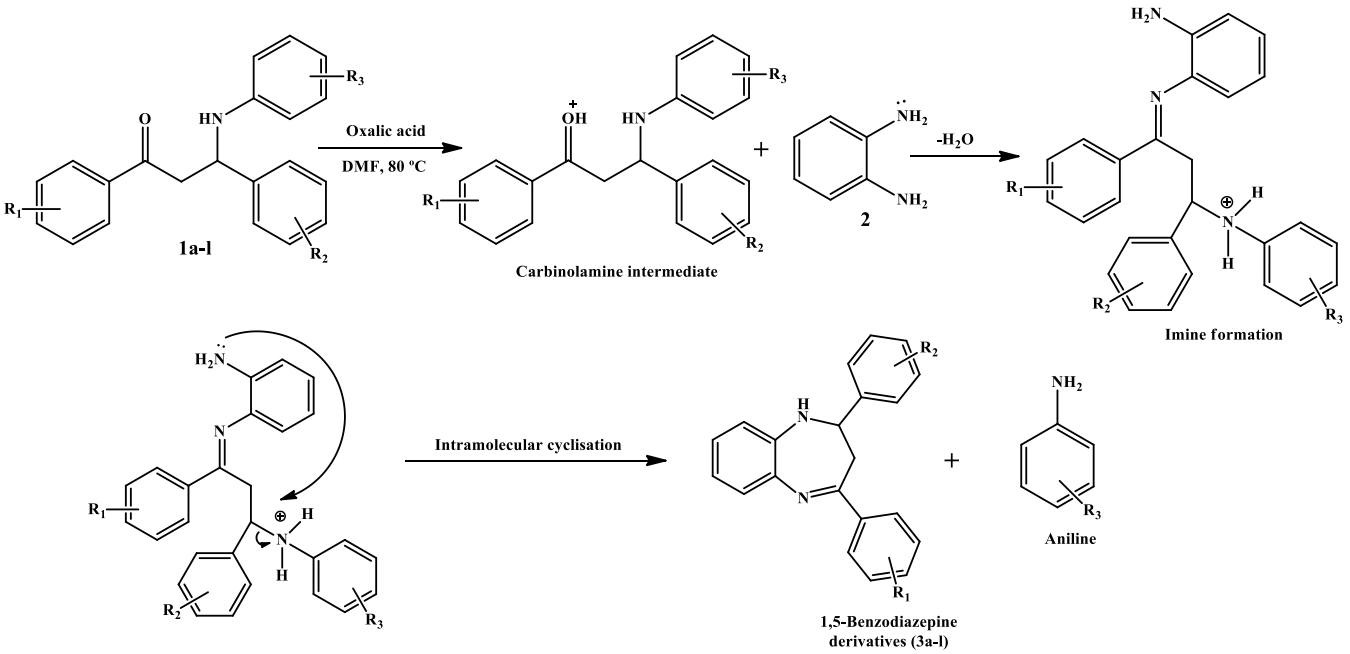
The identities of the synthesised compounds (**3a-l**) were confirmed by comparing their melting points with the reported literature values. The observed melting points were in close agreement with the reported data, with deviations of only ±2-3 ºC, supporting the identity and purity of the products. Variations in melting points were influenced by the nature of the substituents on the aromatic ring. Derivatives bearing electron-donating groups, such as methyl (**3b**, **3f**, **3k**) and methoxy (**3c**, **3l**), generally exhibited lower melting points, whereas compounds containing electron-withdrawing substituents, such as chloro (**3d**, **3g**) and nitro (**3e**), showed comparatively higher melting points. These differences may arise from changes in the molecular polarity and intermolecular interactions and are consistent with previously reported studies on benzodiazepine derivatives [25].

The electronic nature of the substituents also affected the reaction rate and product yield. β-Amino ketones containing electron-donating groups afforded the desired products in higher yields with shorter reaction times, whereas substrates bearing electron-withdrawing substituents required slightly longer reaction times and furnished moderately lower yields. Even so, both classes of substrates were well tolerated under the optimised reaction conditions. The optimisation studies establish oxalic acid as the most effective catalyst among those examined. The reaction proceeds efficiently under mild conditions with broad substrate scope, providing a practical and metal-free route for the synthesis of 1,5-benzodiazepine derivatives from β-amino ketones.

Characterization: The formation of the product **3a** was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral analysis. IR spectrum showed the absorption peaks at 3295 cm^{-1} is attributed to the N-H stretching vibration, while the band at 1633 cm^{-1} corresponds to the C=N stretching vibration of the diazepine ring. The ^{1}H NMR spectrum showed the signals at δ 3.05 and 3.23 ppm (dd, 1H each) were assigned to the methylene protons (CH_2) at C-3 of the diazepine ring, while the signal at δ 5.23 ppm (dd, 1H) corresponds to the methine proton (CH) at C-2. The broad singlet at δ 3.53 ppm was assigned to the NH proton. Aromatic protons appeared in the range δ 6.84-7.84 ppm confirm the presence of aromatic protons. The ^{13}C NMR spectrum exhibited signals at δ 37.29 ppm for the C-3 carbon atom of the benzodiazepine ring, δ 157.87 ppm for the imine carbon (>C=NH), and δ 58.00 ppm for the methine carbon adjacent to the nitrogen atom in the diazepine ring.

Mechanism: Oxalic acid initially protonates the carbonyl oxygen of the β-amino ketone, increasing the electrophilicity of the carbonyl carbon and facilitating nucleophilic attack by one amino group of *o*-phenylenediamine to form a carbinolamine intermediate. Subsequent acid-catalysed dehydration generates an imine intermediate, while protonation of the β-amino group enhances its leaving-group ability. The remaining amino group of *o*-phenylenediamine then undergoes intramolecular nucleophilic attack on the imine carbon, resulting in cyclisation and formation of the seven-membered diazepine ring. Cleavage of the C–N bond, accompanied by the elimination of aniline, affords the corresponding 1,5-benzodiazepine derivatives (**3a-l**) (**Scheme-II**). Throughout the reaction, oxalic acid functions as a Brønsted acid catalyst by activating the carbonyl group and promoting imine formation and cyclisation, whereas DMF provides a polar aprotic medium that enhances substrate solubility and stabilises reactive intermediates. The reaction temperature of 80 ºC supplies sufficient energy for the condensation, dehydration and ring-closure steps, while β-amino ketones and *o*-phenylenediamine serve as the carbon and nitrogen sources required for construction of the 1,5-benzodiazepine framework.

Comparison with literature: The present protocol offers several advantages over previously reported methods for the



Scheme-II: Synthetic mechanism of oxalic acid catalysed synthesis of 1,5-benzodiazepines *via* cyclocondensation

TABLE-6
COMPARISON OF CATALYTIC SYSTEMS FOR THE SYNTHESIS OF 1,5-BENZODIAZEPINES.

Entry	Catalyst/system	Solvent	Temp. (ºC)	Time (h)	Yield (%)	Remarks	Ref.
1	Acetic acid	Ethanol	Reflux	6-8	60-70	Longer reaction time	[26]
2	*p*-TSA	Ethanol	Room temp.	4-6	65-80	Strong acid required	[27]
3	Silica sulphuric acid	Solvent-free	90-100	3-5	70-85	Heterogeneous catalyst	[28]
4	$ZnCl_2$	Ethanol	Reflux	0.33	60-75	Metal catalyst	[29]
5	H-MCM-22	Acetonitrile	Room temp.	1-3	65-87	Rapid coke formation	[30]
6	Ionic liquid ([bmim]BF_3)	Ionic liquid	80-100	2-3	80-90	Expensive medium	[31]
7	Oxalic acid (10 mol%)	DMF	80	2-3	78-95	Metal-free catalyst, simple procedure, broad substrate scope and good to excellent yields	Present work

synthesis of 1,5-benzodiazepines. Many reported procedures rely on mineral acids, metal-based catalysts, ionic liquids, or stringent reaction conditions, whereas the present method employs oxalic acid as an inexpensive, readily available and metal-free organocatalyst. Unlike conventional methods that employ ketones as starting materials, the present protocol uses β-amino ketones as versatile precursors for the synthesis of 1,5-benzodiazepine derivatives. The reaction proceeds under mild conditions with broad substrate scope and affords good to excellent yields. Although DMF was used as the reaction medium, the protocol offers operational simplicity and employs an inexpensive, metal-free catalyst. Compared with reported green methodologies based on solvent-free conditions, microwave irradiation, deep eutectic solvents, aqueous media and recyclable catalysts (Table-6), the present method avoids specific equipments and complex catalyst preparation while maintaining high synthetic efficiency.

Conclusion

A straightforward and efficient method has been developed for the synthesis of 1,5-benzodiazepine derivatives (**3a-l**) through the cyclocondensation of β-amino ketones with *o*-phenylenediamine using oxalic acid as a metal-free organocatalyst. Under the optimized reaction conditions (10 mol% oxalic acid in DMF at 80 ºC), the desired products were obtained in good to excellent yields (78-95%). The study also establishes the utility of previously prepared β-amino ketones as valuable synthetic precursors for the construction of diverse 1,5-benzodiazepine frameworks. The protocol is characterised by operational simplicity, broad substrate scope, metal-free reaction conditions and the use of an inexpensive, readily available organocatalyst, providing a practical and efficient approach for the synthesis of 1,5-benzodiazepine derivatives.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

DECLARATION OF AI-ASSISTED TECHNOLOGIES

During the preparation of this manuscript, the authors used an AI-assisted tool(s) to improve the language and no data, results or scientific conclusions were generated by AI. All analyses, interpretations and conclusions are the authors' own. The authors reviewed and edited the content and take full responsibility for the published work.

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