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Graphical Abstract

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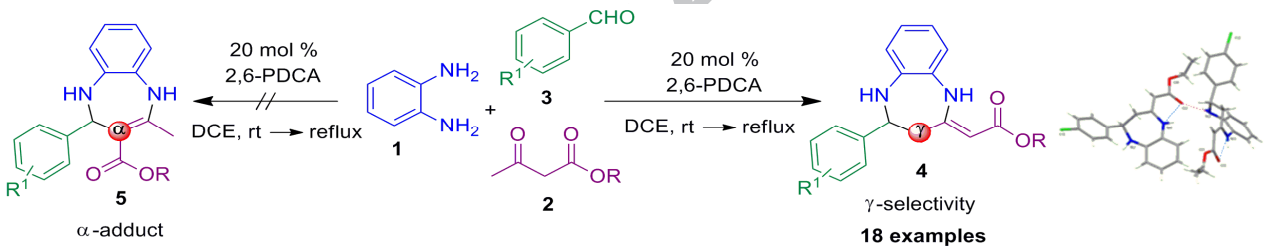

2,6-Pyridinedicarboxylic acid as organocatalyst for the synthesis of 1,5-benzodiazepines through one-pot reaction

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This work is dedicated to my mentor, Professor Goverdhan Mehta, on the occasion of his 70th anniversary.

Abstract

2,6-Pyridinedicarboxylic acid has been found to be an effective and efficient organocatalyst for the synthesis of 1,5-benzodiazepine derivatives from *o*-phenylenediamine, β-ketoesters and aromatic aldehydes by employing one-pot three-component reaction. The catalyst plays a crucial role for the regioselective *C-C* bond formation at the γ position of β-ketoesters. The salient features of this present protocol are simple reaction procedure, requirement of cost-effective catalyst, good yields and applicable to a wide range of substrates.

Keywords: 2,6-Pyridinedicarboxylic Acid, Organocatalyst, β-Ketoesters, 1,5-Benzodiazepines, Multicomponent reactions.

Organocatalyst containing acidic hydrogen(s) might interact with substrates having basic functional groups to catalyze a wide variety of reactions and they are extremely useful in organic synthesis.[1] They have the ability to transfer proton in the transition state as well as to stabilize the reactive intermediate through hydrogen-bond formation.[2] Organocatalyzed cascade reactions usually avoid costly protection/deprotection steps and less time consuming.[3] As a matter of fact,

they have been extensively utilized for the synthesis of biologically active natural products and asymmetric synthesis.[4] A few years ago, 2,6-pyridinedicarboxylic acid (2,6-PDCA) has been explored as bifunctional organocatalyst for hydrophosphonylation of aldehydes and ketone[5a] and Michael-type Friedel-Crafts reaction.[5b] We conceived that 2,6-pyridinedicarboxylic acid (2,6-PDCA) might be a useful organocatalyst for the synthesis of 1,5-benzodiazepine derivatives from β-ketoesters. Recently, various research groups have demonstrated the usefulness of β-ketoesters for the synthesis of numerous heterocyclic compounds by employing multicomponent reactions (MCRs).[6] We have also shown that β-ketoesters are valuable starting material for the synthesis of substituted pyrroles[7] and highly substituted piperidine derivatives[8] involving *C-C* bond formation either at α position[7] or both at the α and γ position[8] of β-ketoesters. However, the selective *C-C* bond formation particularly at the γ position of β-ketoesters is relatively less explored. In 2007, Kita *et al.* first reported[9a] the synthesis of seven membered 1,4-azepanes through multicomponent reaction from 1,2-ethylenediamine, β-ketoesters and aromatic aldehydes in the presence of 10 mol% *p*-toluene sulfonic acid (*p*-TSA) involving *C-C* bond formation at the γ position of β-ketoesters. They have reported only 23% yield of the product **4b** when the similar reaction was carried out with *o*-phenylenediamine instead of 1,2-ethylenediamine with methylacetoacetate and benzaldehyde using 10 mol% *p*-TSA as catalyst.[9b] However, the same research group successfully accomplished the synthesis of various 1,5-benzodiazepine using pentafluorobenzoic acid as catalyst from *o*-phenylenediamine, β-ketoesters and aromatic aldehydes.[9b] At the same time, Rodriguez and his co-workers also demonstrated[9c,9d] the synthesis of 1,4-diazepane derivatives from 1,2-ethylenediamine, β-ketoesters and aromatic aldehydes in presence of 4 Å molecular sieves in toluene under reflux conditions. They have also noticed that similar reaction was unsuccessful with *o*-phenylenediamine, acyclic β-ketoesters and

aromatic aldehydes for the synthesis of 1,5-benzodiazepine with 4 Å molecular sieves.[9d] Although these methods are quite useful,[9] still there is a further scope to devise a newer methodology for the synthesis of 1,5-benzodiazepine derivatives using other inexpensive catalyst due to their wide pharmacological activities such as anti-convulsant, anti-inflammatory, analgesic, anti-anxiety, anti-depressive, anti-biotics,[10] anti-cancer[11] and anti-viral (HIV) agents.[12]

In recent times, MCRs have been explored for the synthesis of heterocyclic compounds due to their diversity, good yields, high selectivity and atom-economy, and high bond forming efficiency.[13] Recently, our research group introduced several reagents as catalysts in multicomponent reactions for the synthesis of new heterocyclic entities.[14] In this paper, we report 2,6-PDCA catalyzed one-pot synthesis of 1,5-benzodiazepine derivatives using *o*-phenylenediamine, β-ketoesters and aromatic aldehydes as shown in Scheme 1.

Scheme 1

To find out a suitable reaction conditions, various trial reactions were carried out using a combination of *o*-phenylenediamine, methylacetoacetate and 4-chlorobenzaldehyde using different mol % of catalyst as shown in Table 1. We have observed that 20 mol % of 2,6-PDCA catalyst is sufficient to obtain maximum yield. Subsequently, similar reaction was examined with different catalysts such as benzoic acid, 2-nitrobenzoic acid, pyridine-2-carboxylic acid, and 2,5-pyridinedicarboxylic acid. We have obtained much lower yield of 1,5-benzodiazepine derivative (**4a**) with other catalysts. To verify the role of 2,6-PDCA, we have also carried out similar reaction with isophathalic acid and it provided 32% yield of the desired product **4a**. We presume low yield of the product formation in isophathalic acid, may be due to lower acidity as compared to 2,6-pyridinedicarboxylic acid. Interestingly, 2-nitrobenzoic acid, which has almost

similar acidity like 2,6-PDCA also did not provide the desired product **4a** (Table 1, entry 7) in good yield. From this observation, we propose that both acidity and formation of intermolecular hydrogen bonding of the organocatalyst play a crucial role for the formation of desired product. In the present methodology, we did not obtain 1,5-benzodiazepine derivative **5**a, which might also be possible through α-adduct. Perhaps it is getting converted into the γ-adduct **4a** at higher temperature, which was also observed by Kita and his co-workers,[9b] due to intramolecular hydrogen bonding between NH and C=O in the product **4a**.

Table 1

After optimization of the reaction conditions, the reaction of *o*-phenylenediamine, methyl acetoacetate and benzaldehyde was performed under identical manner and it afforded the desired product **4b** in 62% yield. Encouraged by the above two successful results, a wide variety of aromatic aldehydes containing different substituents such as –Br, -NO_2, -Me, -OMe, -OH groups at various positions in the aromatic ring were conducted with *o*-phenylenediamine and methyl acetoacetate with 20 mol% 2,6-PDCA under similar conditions and the desired products **4c-i** (Table 2, entries 3-9) were isolated in good yields.

Table 2

To verify the generality and further scope of the present protocol, similar reactions were executed with various heterocyclic aldehydes, *o*-phenylenediamine and methyl acetoacetate in presence of 20 mol% of 2,6-PDCA under identical reaction conditions. The products (**4j-m**) were obtained in good yields which are mentioned in Table 2 (entries 10-13). The scope of the reaction was further examined by performing the reaction with different β-ketoesters, *o*-phenylenediamine and 4-chlorobenzaldehyde by employing 20 mol % of 2,6-PDCA under

similar reaction conditions. The desired products (**4n-r)** were obtained in good yields, which are shown in Table 3 (entries 1-5). We have not explored the reaction with other substituted *o*-phenylenediamine because it provides inseparable mixture of regio-isomers. However, we are trying to separate them, which will be disclosed later on in case we are successful.

Table 3

From ^{1}H NMR of the crude reaction mixture, it was noted that we have obtained exclusively (*Z*) configuration of the product **4n** due to intermolecular hydrogen bonding. Further, the structural assignment of compound **4n** and especially (*Z*) configuration of the double bond in the cases of acyclic β-ketoester is determined based on X-ray analysis (Figure 1)

Figure 1

Compound **4n** has both type of hydrogen bonding interaction one intra-molecular between N1–H···O1 (N1–H = 0.885 Å; N1–O1 = 2.722 Å, ∠N–H···O = 138.71°) and N4–H···O2 (N4-H =

0.884 Å; N4– O2 = 2.718 Å, ∠ N– H···O = 132.65°). Another inter-molecular hydrogen bonding interaction between O of C=O and N– H of other benzodiazepine molecule N– H···O (N3– H = 0.863 Å; N3– O2 = 2.932 Å, ∠ N– H···O = 139.77°) as shown in Figure 1.[16]

The stereochemistry between aryl group and the ring juncture in compound **4q** was also established through single XRD data as shown in Figure 2.[16]

Figure 2

We have observed from XRD structure that the benzylic proton and homobenzylic proton is in *trans-diaxial* orientation, which was also reported by Fujioka *et al*. in cases of cyclic β-ketoesters. Compound **4q** also have intra-molecular hydrogen bonding between N2– H···O3 (N2–

H = 0.860 Å; N2– O3 = 2.634 Å, ∠ N2– H···O3 = 132.46°). It was observed that torsional angle (H-21–C-21–C-20–H-20) for the solid state structure of **4q** was determined to be 171.34, which is consistent with the observed $^{3}J_{H20\text{-}H21}$ coupling constant of 11.2 Hz, which is in full agreement with the *trans* configuration. We have also noted in the compound **4r** that coupling constant value 10.4 Hz for the benzylic proton and homobenzylic proton.

The formation of the product, 1,5-benzodiazepines (**4**), can be proposed as follows: At first *o*-phenylenediamine reacts with β-ketoester to give mono enaminoester **A** (Scheme 2).

Scheme 2

Then, it reacts with an aromatic aldehyde to form imine-enaminoester product **B**, which was proved unequivocally by isolation of the intermediate product **B** by Kita *et al*.[9b] It may also undergo cyclization reaction either at the α position to afford 1,5-benzodiazepine derivative **5** or at the γ position to give 1,5-benzodiazepines (**4**). However, the product **5** undergoes conversion into the compound **4** during heating, which was also noted by Kita *et al*.[9b] Then, the intermediate **B** undergoes protonation at the iminium nitrogen atom[17] in presence of organocatalyst, 2,6-pyridinedicarboxylic acid and perhaps it also stabilizes the intermediate **C** through hydrogen

bonding. Finally, the intermediate **C** undergoes concomitant cyclization to form intermediate **D** through γ-selective *C-C* bond formation and it forms 1,5-benzodiazepine derivative **4** from intermediate **D** by 1,5-hydrogen shift. We have tried to isolate the intermediate **C** by co-crystallization, but it was unsuccessful.

In summary, we have demonstrated a simple synthetic protocol for the synthesis of 1,5-benzodiazepine derivatives catalyzed by 2,6-PDCA as organocatalyst, from *o*-phenylenediamine, β-ketoesters and aromatic aldehydes through one-pot MCRs reactions. We have demonstrated the γ-selective product formation by employing organocatalyst 2,6-PDCA as catalyst with a variety of aldehydes and esters, which was earlier failure in *p*-toluene sulfonic acid (*p*-TSA) and 4 Å molecular sieves in toluene under reflux conditions. In addition, our protocol requires inexpensive catalyst as compared to pentafluorobenzoic acid. The present protocol provides good yields with different kind of aldehydes and β-ketoesters. We are currently working for proving the mechanism as well as asymmetric synthesis, which will be disclosed in full paper.

Acknowledgments

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Supporting Information

Supplementary data (X-ray crystallographic data (CIF files) of **4n** and **4q**, spectral data of all compounds and copies of ^{1}H, ^{13}C NMR and HRMS spectra of products associated with this paper can be found, in the online version, at doi:

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Lal, M.; Mir, M. H. *RSC Adv.* **2012***, 2,* 5506. (e) Khan, A. T.; Lal, M.; Basha, R. S. *Synthesis* **2013,** *45,* 406.

15. *General Procedure for the synthesis of 1,5-benzodiazepines* - Into an oven dried 25 mL round bottomed flask was taken a mixture of *o*-phenylenediamine (1.0 mmol) and β-ketoesters (1.0 mmol) in 3 mL of dichloroethane. Then, organocatalyst 2,6-pyridinedicarboxylic acid (34 mg, 0.2 mmol) was added into it and the reaction mixture was kept for stirring at room temperature. After 2 h of stirring, aromatic aldehyde (1 mmol) was added into it and the reaction mixture was refluxed in a pre-heated oil-bath. After completion of the reaction, dichloroethane was removed in rotary evaporator and the crude residue was purified through a silica gel column chromatography. The desired product **4** was obtained in good yield after eluting with ethyl acetate and hexane (1:9) mixture. ***Compound 4a*** [9b] : Yield = 0.230 g (70%), Pale yellow oily, IR (KBr) ν_{max} 1161, 1232, 1266, 1489, 1588, 1615, 1648, 2851, 2925, 3365 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.51-2.64 (m, 2H), 3.66 (brs, 3H), 4.52 (s, 1H), 4.84 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.90-7.0 (m, 3H), 7.30 (brs, 4H), 10.17 (brs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.1, 50.6, 64.7, 84.4, 121.2, 122.2, 122.7, 125.3, 127.8, 129.0, 130.4, 133.8, 138.0, 143.1, 158.3, 170.7 ppm. HRMS (ESI) calcd for $C_{18}H_{17}ClN_2O_2$ [M + H]$^+$: *m/z* = 329.1057; found: 329.1042. Anal. Calcd for $C_{18}H_{17}ClN_2O_2$: C, 65.75; H, 5.21; N, 8.52%; found C, 65.54; H, 5.06; N, 8.38%. ***Compound 4n***: Yield = 0.212 g (62%), Crystalline solid, mp 116-119^oC, IR (KBr) ν_{max} 1161, 1234, 1435, 1505, 1618, 1644, 1725, 2949, 3444 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, 3H), 2.56 (dd, *J* = 14.0 Hz, 8.0 Hz, 1H), 2.61 (dd, *J* = 14.0 Hz, 5.2 Hz, 1H), 3.64 (s, 1H), 4.11-4.18 (m, 2H), 4.54 (s, 1H), 4.83-4.87 (m, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 6.91-7.01 (m, 3H), 7.32 (s, 4H),

10.20 (brs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.7, 40.1, 59.1, 64.7, 84.8, 121.07, 122.2, 122.7, 125.2, 127.8, 129.1, 130.5, 133.8, 137.9, 143.2, 158.1, 170.4 ppm. HRMS (ESI) calcd for $C_{19}H_{19}ClN_2O_2$ $[M + H]^+$: *m/z* = 343.1213; found: 343.1196. Anal. Calcd for $C_{19}H_{19}ClN_2O_2$: C, 66.57; H, 5.59; N, 8.17%; found C, 66.46; H, 5.48; N, 8.08%.

16. The X-ray crystal structures were determined with a diffractometer. Complete crystallographic data of **4n** (CCDC No. 827828) and **4q** (CCDC No. 930463) for the structural analysis have been deposited to the Cambridge Crystallographic Data Centre, copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

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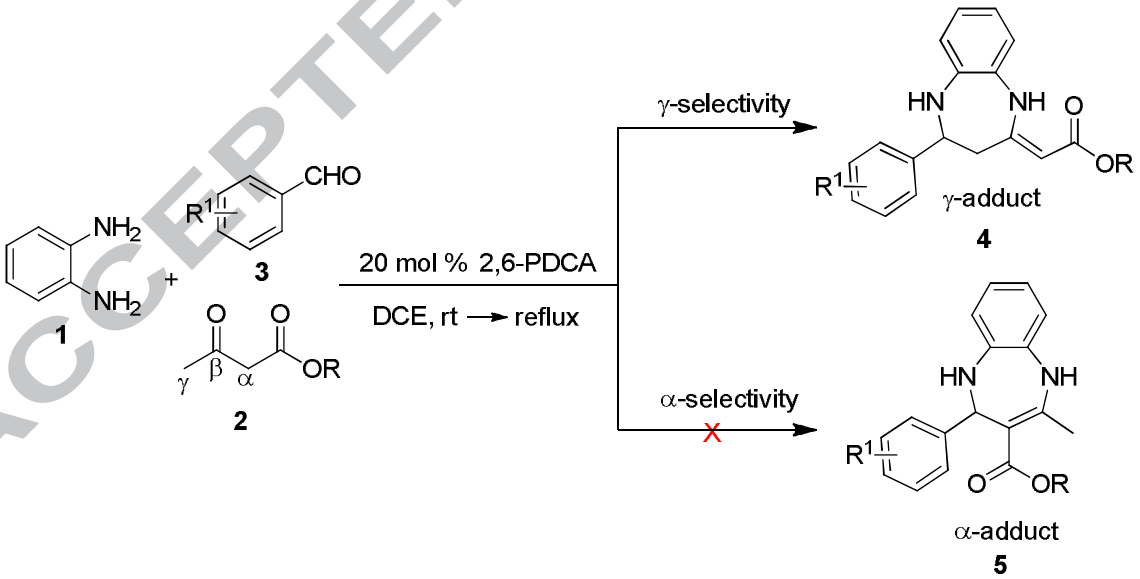
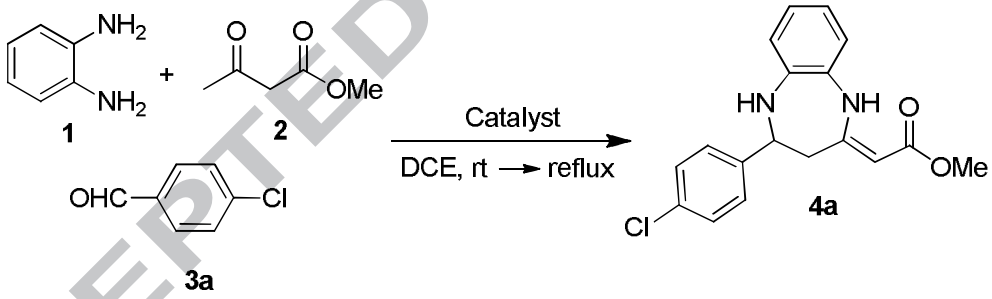


Scheme 1. 2,6-Pyridinedicarboxylic acid catalyzed synthesis of 1,5-benzodiazepine derivatives.

Table 1. Optimization of reaction condition for the synthesis of 1,5-benzodiazepine **4a**.[a]

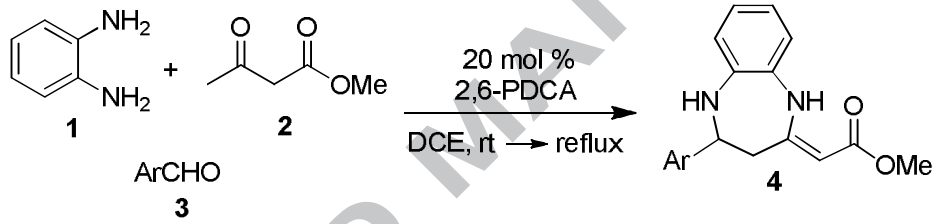


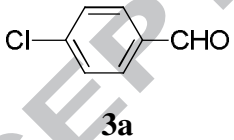
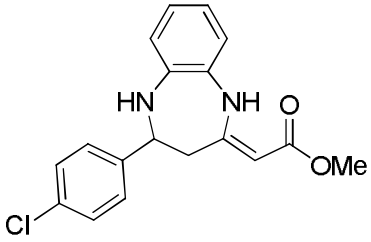
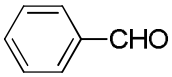
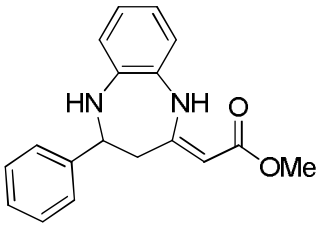
Entry	Organocatalyst used	Mol%	Time / h	% Yield[b]
1	No Catalyst	-	12	NR
2	2,6-PDCA	10	7	48
3	2,6-PDCA	15	6	55
4	2,6-PDCA	20	5	70
5	2,6-PDCA	30	5	69
6	Benzoic acid	20	8	21
7	2-Nitrobenzoic acid	20	8	26

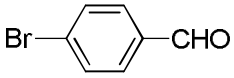
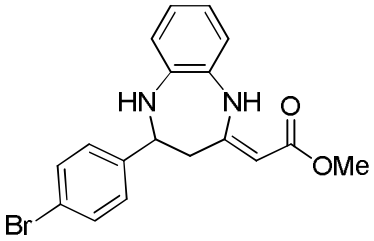
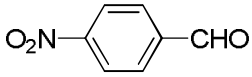
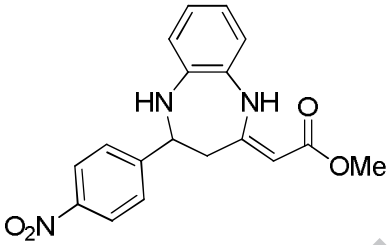
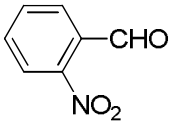
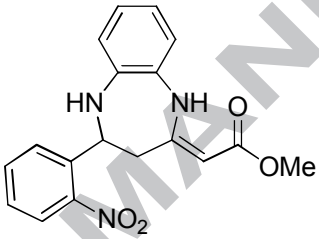
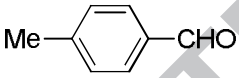
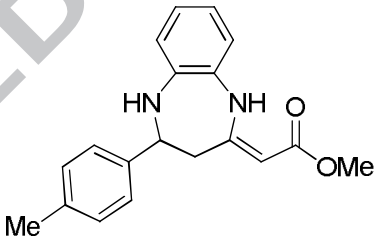
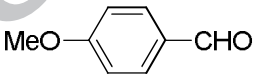
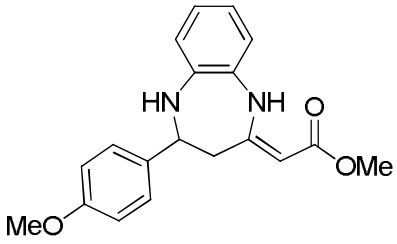
8	Pyridine-2-carboxylic acid	20	8	25
9	2,5-PDCA	20	7	35
10	Isophathalic acid	20	8	32

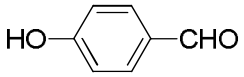
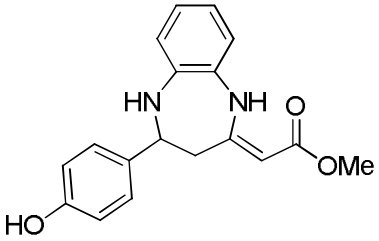
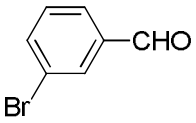
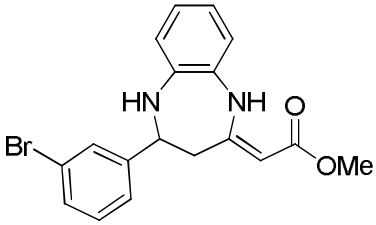
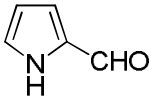
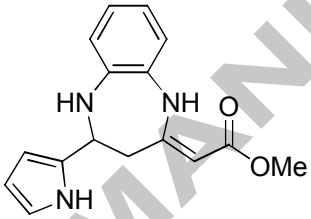
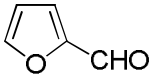
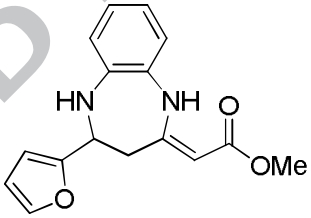
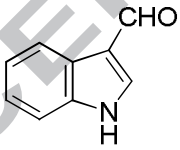
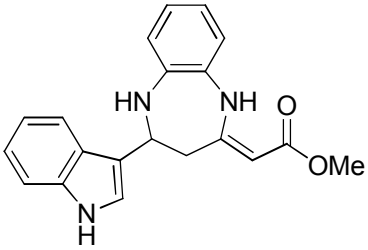
[a]The reactions were performed using 1 mmol scale of *o*-phenylenediamine (**1**), methyl acetoacetate (**2**), and 4-chlorobenzaldehyde (**3a**) in DCE from room temperature to reflux condition. [b]Isolated yield.

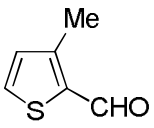
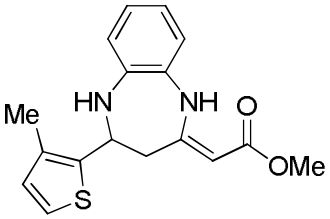
Table 2. Synthesis of 1,5-benzodiazepines using a combination of *o*-phenylenediamine, methyl acetoacetate and aromatic aldehydes in presence of 20 mol % 2,6-PDCA.[15]



Entry	Aldehyde (**3**)	Compound (**4**)[a]	Time (h)	%Yield[b]
1	 **3a**	 **4a**	5	70
2	 **3b**	 **4b**	4.5	62

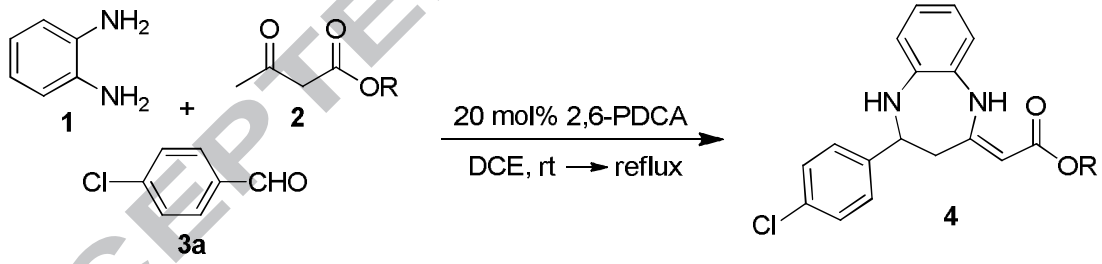
3	 **3c**	 **4c**	4	68
4	 **3d**	 **4d**	4.5	68
5	 **3e**	 **4e**	4	62
6	 **3f**	 **4f**	2.5	71
7	 **3g**	 **4g**	3.5	70

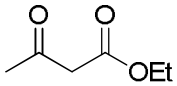
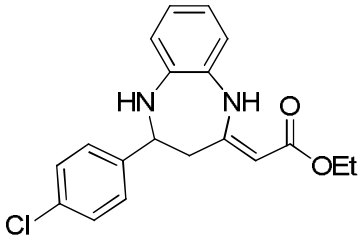
8	 **3h**	 **4h**	4	66
9	 **3i**	 **4i**	3.5	72
10	 **3j**	 **4j**	4	55
11	 **3k**	 **4k**	3	61
12	 **3l**	 **4l**	3.5	55

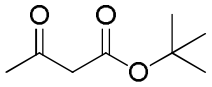
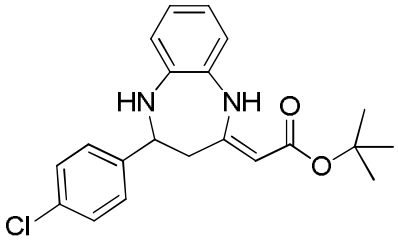
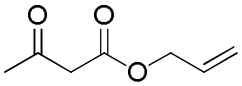
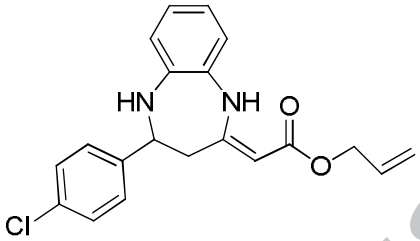
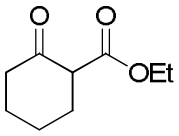
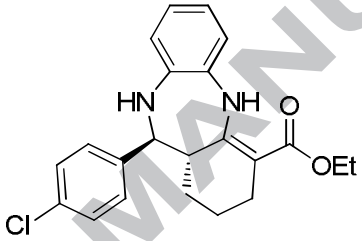
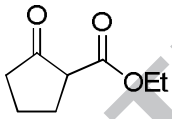
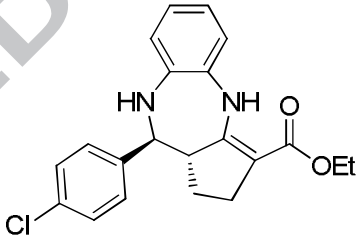
13	 **3m**	 **4m**	4	74

[a] The reactions were performed in 1 mmol scale involving β-ketoesters, *o*-phenylenediamine and aromatic aldehyde.
[b] Isolated yield.

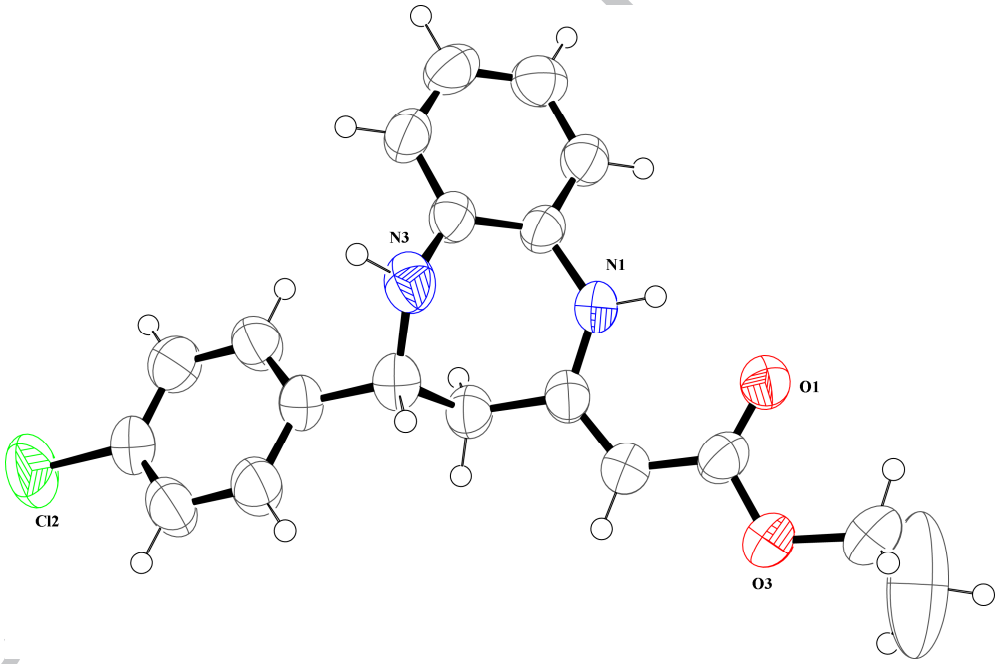
Table 3. Formation of 1,5-benzodiazepines by employing *o*-phenylenediamine, 4-chlorobenzaldehyde with different β-ketoesters.[15]



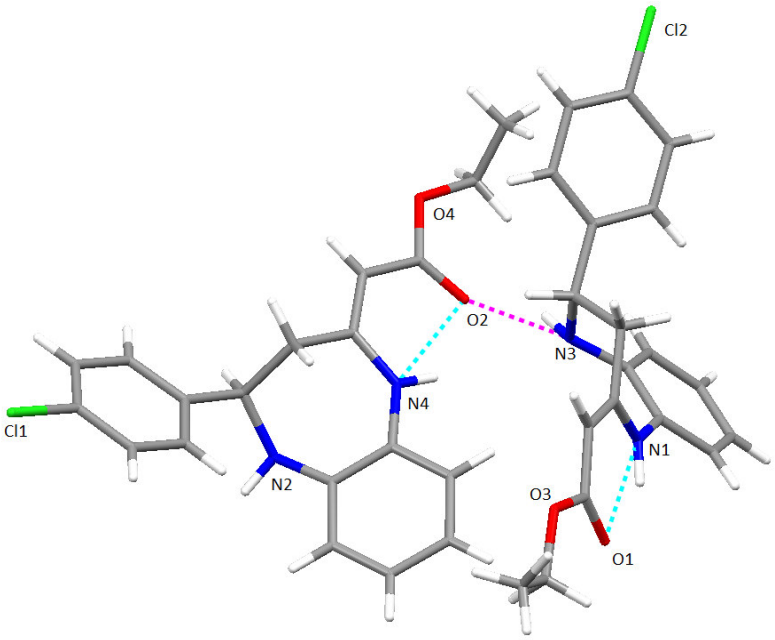
S.No	β-ketoester (**2**)	Compound (**4**)[a]	Time (h)	% Yield[b]
1	 **2b**	 **4n**	4.5	62

2	 **2c**	 **4o**	4	66
3	 **2d**	 **4p**	5	64
4	 **2e**	 **4q**	5.5	64
5	 **2f**	 **4r**	4	64

[a]The reactions were carried out in 1 mmol scale of β-ketoesters, *o*-phenylenediamine and 4-chlorobezaldehyde.
[b]Isolated yield.

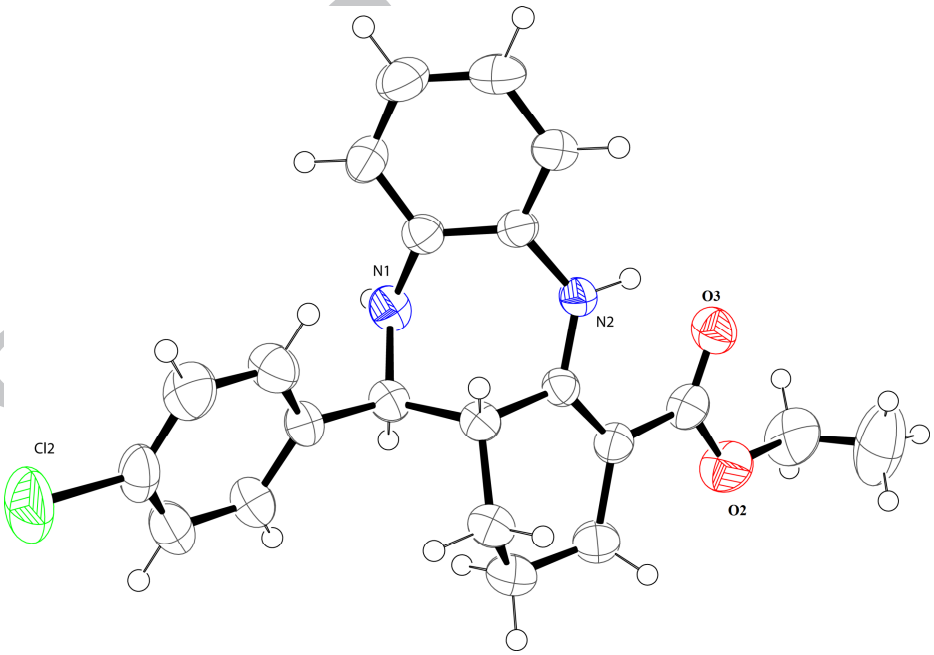


(a)

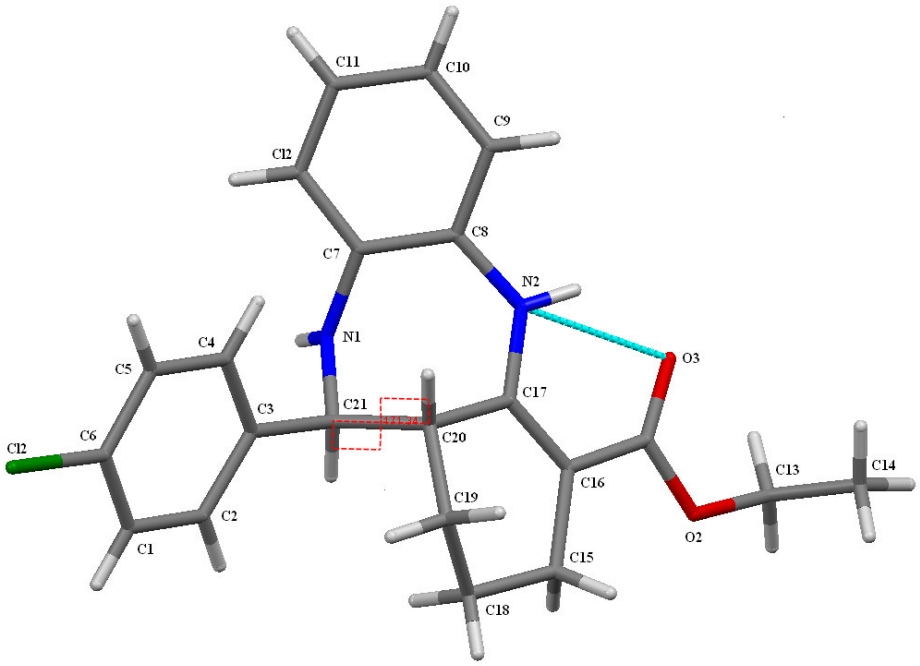


(b)

Figure 1. (a) ORTEP molecular structure of **4n** and (b) Intra (light blue color) and inter (pink color) hydrogen bonding interactions between two molecules of **4n** (CCDC 827828).[16]

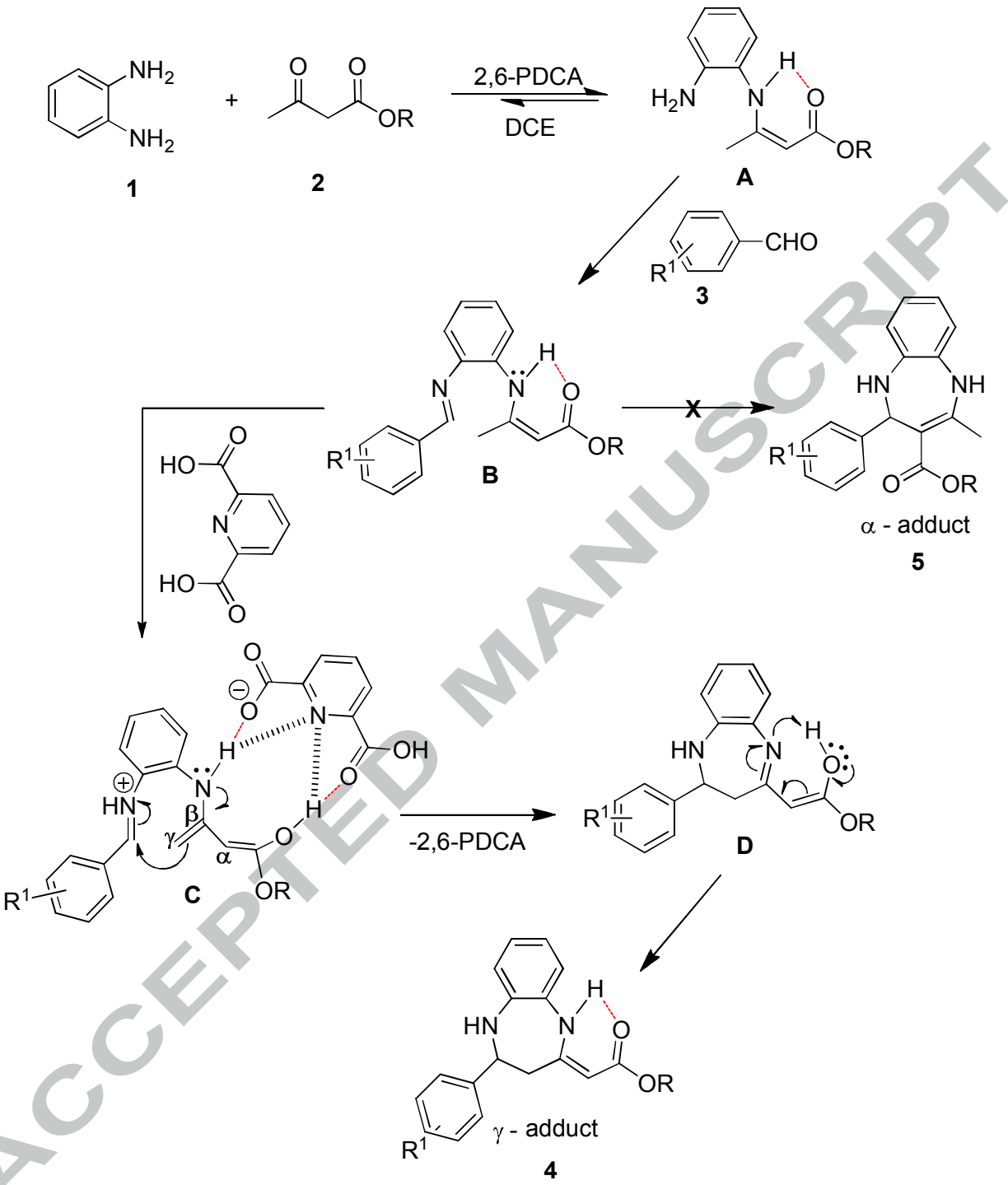


(a)



(b)

Figure 2. (a) ORTEP molecular structure of **4q** and (b) Shows Intra molecular hydrogen bond (light green color) between NH and ester CO group in the compound **4q** and exhibits *trans* configuration between aryl group and the ring juncture of the product **4q** (CCDC No. 930463).[16]



Scheme 2. Mechanism for the formation of 1,5-benzodiazepines **4**