



Adenine as aminocatalyst for green synthesis of diastereoselective Mannich products in aqueous medium

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ABSTRACT

The three-component organocatalysed Mannich type reaction is carried out in a green co-solvent of ethanol and water at room temperature using adenine as catalyst and hydrogen peroxide as additive. The Mannich products are obtained in considerably good diastereoselectivity depending on the effects of substituents on aniline.

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The organocatalysis has come a long way in the field of synthetic organic chemistry, motivated by the stereoselective enzymatic processes. The secondary amine has been exploited extensively as enantioselective organocatalysts, which generally acts through either electrophilic iminium or nucleophilic enamine pathway.¹ Although the primary amine has been used by natural enzymes such as type I aldolases, decarboxylases and dehydratases, containing the catalytically active lysine residues,² very little progress has taken place in this field with chiral primary amines till date³ partly due to the unfavourable imine-secondary enamine equilibria.⁴

Amongst the innumerable synthesis of chiral compounds, the Mannich reaction has so far been exploited for the synthesis of chiral nitrogen-containing compounds, and by far the most important carbon–carbon bond-forming reactions.⁵ The vital importance of the Mannich products as important precursors of pharmaceutical and natural products⁶ has always boosted researchers to find out better process for their synthesis. The limitations⁷ associated with the classical Mannich type reaction such as drastic reaction conditions, long reaction time with low yields and formation of unwanted side products, have induced numerous modern versions⁸ of the reaction. These improved methodologies are mainly based on two-component reactions where the imine as electrophile is pre-formed and reacted with stable nucleophiles such as enolates, enol ethers and enamines.⁹ Recently, three-component approach for this reaction using organocatalyst and other catalysts, with

in situ formation of imines, has gained considerable importance as it allows structural variations.

Accordingly, several recent reports of organocatalysed asymmetric Mannich reaction in polar solvents such as DMSO and NMP are found in the literature.^{10,11} A few recent reports reveal that the reaction is carried out in aqueous medium catalysed by organic molecules.¹²

We wish to report a modified version of environmentally benign Mannich reaction with different aldehydes, ketones and amines for the synthesis of β -amino carbonyl compounds in a green solvent (ethanol–water 4:1) in presence of adenine as catalyst and 40 μ l of 30% H_2O_2 as additive as shown in Scheme 1.

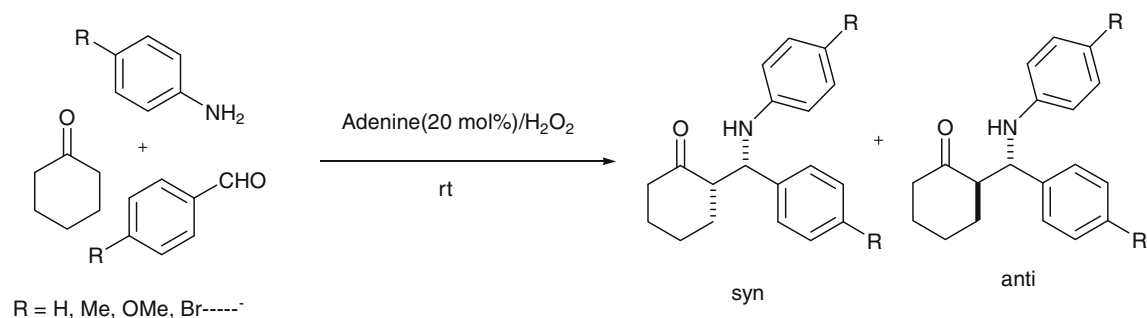
Adenine, belonging to the class of purine derivatives was chosen as the catalyst, since we envisaged that the primary amine present in adenine would take active participation in the formation of enamine intermediate with cyclohexanone. The resulting enamine can easily attack the Mannich acceptor (imine formed by aldehydes and amine), thereby assisting in the formation of Mannich products.

To start with, the reaction was screened with varying amounts of the catalyst. The model reaction of benzaldehyde, aniline and cyclohexanone was carried out with 5 mol % to 20 mol % of catalyst in ethanol and water mixture, among which 20 mol % was found to be the most effective as shown in Table 1. Consequently, ethanol and water in the ratio of 4:1 were found to be the best possible solvent to furnish the desired adduct in good yield with a comparative diastereoselective ratio.

In an attempt to obtain good diastereoselectivity of the Mannich products, we examined the reaction by adding 30% hydrogen peroxide in presence of 20 mol % of adenine. To our delight, intro-

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**Scheme 1.** Direct Mannich reaction catalysed by adenine and hydrogen peroxide.**Table 1**

Adenine catalysed three-component Mannich type reaction of benzaldehyde, cyclohexanone and aniline in the presence of varying amounts of catalyst

| Entry | Catalyst (mol %) | Time (h) | Yield ^a (%) |
|-------|------------------|----------|------------------------|
| 1 | — | 24 | 10 |
| 2 | 5 | 24 | 50 |
| 3 | 10 | 24 | 65 |
| 4 | 15 | 12 | 79 |
| 5 | 20 | 8 | 85 |

^a Isolated yield.

Table 2

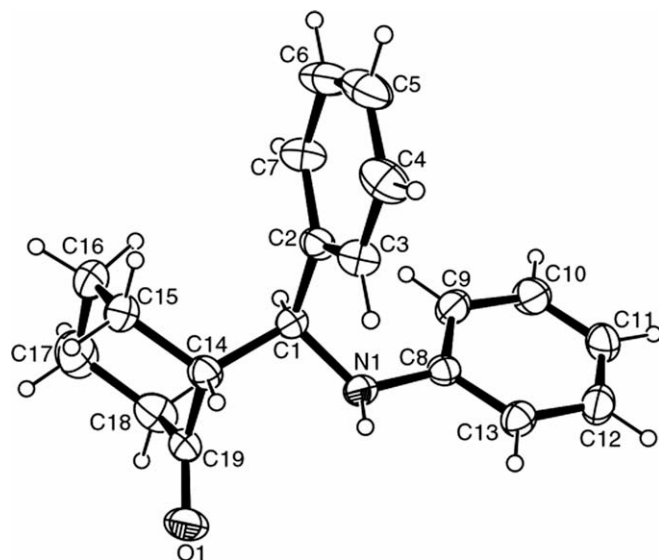
Adenine catalysed three-component Mannich type reaction of benzaldehyde, cyclohexanone and aniline in the presence of varying amounts of 30% H₂O₂

| Entry | H ₂ O ₂ (ml) | Time (h) | Yield ^a (%) | syn:anti ^b |
|-------|------------------------------------|----------|------------------------|-----------------------|
| 1 | — | 8 | 85 | 40:50 |
| 2 | .02 | 6 | 91 | 22:78 |
| 3 | .03 | 6 | 93 | 20:80 |
| 4 | .04 | 6 | 95 | 17:83 |
| 5 | .05 | 6 | 95 | 18:82 |

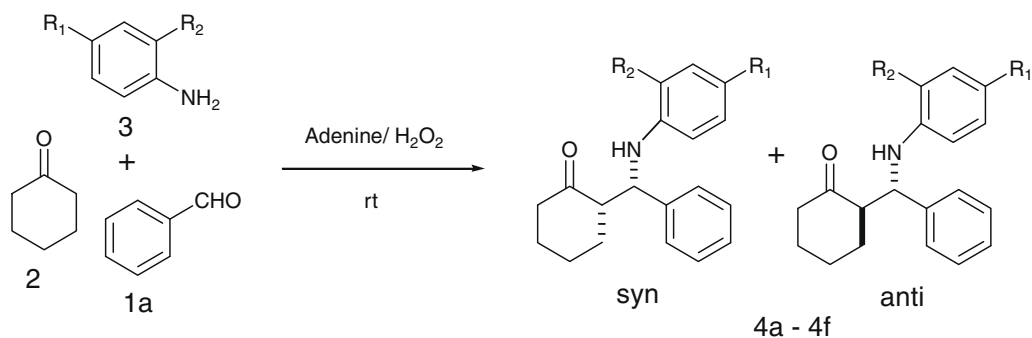
^a Yields refer to isolated yields.

^b Diastereomeric ratio was determined by ¹H NMR analysis at 400 MHz.

duction of 30% hydrogen peroxide induced a relatively better diastereoselectivity along with increased yield. The reaction was final-

**Figure 1.** ORTEP plot of compound 4a.**Table 3**

Adenine catalysed three-component Mannich type reaction of benzaldehyde, cyclohexanone and various amines



| Entry | Amine (3) | Time (h) | Yield ^{a,b} (%) | syn:anti ^c |
|-------|---|----------|--------------------------|-----------------------|
| a | R ₁ = R ₂ = H | 6 | 95 | 17:83 |
| b | R ₁ = Br, R ₂ = H | 4 | 90 | 71:29 |
| c | R ₁ = Me, R ₂ = H | 8 | 80 | 26:73 |
| d | R ₁ = OMe, R ₂ = H | 10 | 82 | 23:77 |
| e | R ₁ = I, R ₂ = H | 4 | 92 | 70:30 |
| f | R ₁ = NO ₂ , R ₂ = H | 5 | 84 | 82:18 ^d |

^a Yields refer to isolated yields.

^b Compounds were analysed by ¹H NMR, ¹³C NMR and elemental analysis.

^c Diastereomeric ratio was determined by ¹H NMR analysis at 400 MHz.

^d Compounds were purified by column chromatography.

ly optimised with 40 μ l of 30% H_2O_2 which gave excellent yield and better diastereoselectivity as presented in Table 2. The Mannich product is precipitated out after the completion of the reaction. The reaction mixture was added to water and the product was isolated by simple filtration and further purified by recrystallisation from chloroform.

These significant results encouraged us to examine the generality and scope of our protocol with a variety of anilines and aldehydes substituted by both electron-withdrawing and electron-donating groups. Thus a variety of amines **3a–f** were examined by the reaction with benzaldehyde **1a** and cyclohexanone **2**.¹³ Table 3 points out to the fact that the substituents play a vital role in directing the diastereoselectivity of the β -amino ketones. The presence of electron-withdrawing substituents on amine leads to the major formation of *syn* products while the electron-donating sub-

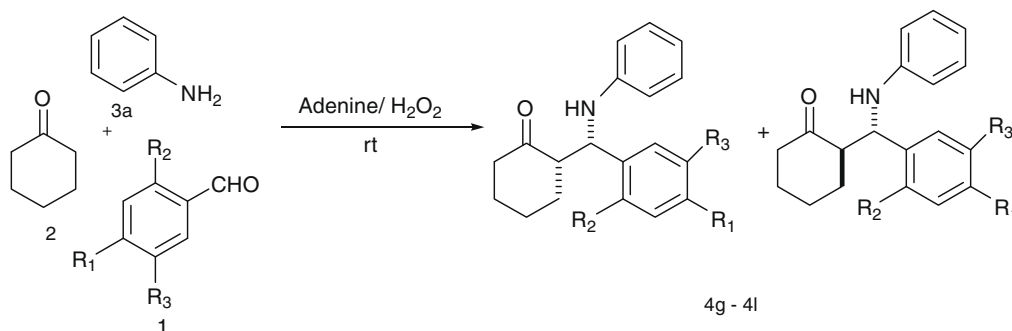
stituents gave *anti*-form as the chief products as evident from ^1H NMR results. These observations indicate that diastereoselectivity of the Mannich products is governed by the nature of substituents in aniline with our protocol.

Secondly, we tried to examine our protocol with a diverse range of aldehydes **1g–l**. The annotations indicate that both electron-donating and electron-withdrawing substituents on aldehydes undergo the reaction with good to excellent yields. In contrast to aniline, the *anti*-products were invariably formed in a major scale, independent of the nature of substituents on the aldehyde as depicted in Table 4. It is worth mentioning that the aliphatic aldehydes were inactive and failed to furnish the desired products with this protocol.

The structure of **4a** was further confirmed by recording a single-crystal XRD and the ORTEP plot is shown in Figure 1.

Table 4

Adenine catalysed three-component Mannich type reaction of cyclohexanone, aniline and various aldehydes in the presence of 30% H_2O_2



| Entry | Aldehyde (1) | Time (h) | Yield ^{a,b} (%) | <i>syn:anti</i> ^c |
|-------|--|----------|--------------------------|------------------------------|
| g | $\text{R}_1 = \text{OMe}, \text{R}_2 = \text{R}_3 = \text{H}$ | 8 | 88 | 29:71 ^d |
| h | $\text{R}_1 = \text{Cl}, \text{R}_2 = \text{R}_3 = \text{H}$ | 6 | 93 | 41:59 |
| i | $\text{R}_1 = \text{Br}, \text{R}_2 = \text{R}_3 = \text{H}$ | 6 | 89 | 35:65 |
| j | $\text{R}_1 = \text{OH}, \text{R}_2 = \text{R}_3 = \text{H}$ | 7 | 91 | 31:69 |
| k | $\text{R}_1 = \text{R}_3 = \text{H}, \text{R}_2 = \text{NO}_2$ | 10 | 75 | 39:61 ^d |
| l | $\text{R}_1 = \text{R}_2 = \text{H}, \text{R}_3 = \text{Br}$ | 9 | 78 | 34:76 |

^a Yields refer to isolated yields.

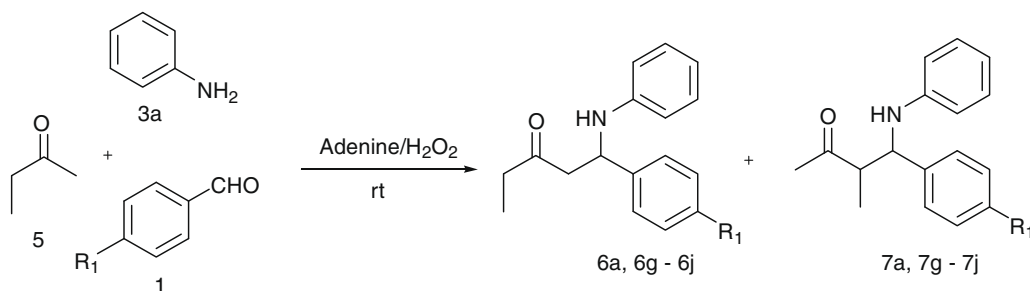
^b Compounds were analysed by ^1H NMR, ^{13}C NMR and elemental analysis.

^c Diastereomeric ratio was determined by ^1H NMR analysis at 400 MHz.

^d Compounds were purified by column chromatography.

Table 5

Adenine catalysed three-component Mannich type reaction of amines, 2-butanone and various aldehydes



| Entry | Aldehyde (1) | Time (h) | Yield ^{a,b} (%) | Regioisomer (6:7) ^c | <i>syn:anti</i> (7) ^d |
|-------|---------------------------|----------|--------------------------|---|---|
| a | $\text{R}_1 = \text{H}$ | 6 | 95 | 56:44 | 17:83 |
| g | $\text{R}_1 = \text{OMe}$ | 4 | 90 | 70:30 | 29:71 |
| h | $\text{R}_1 = \text{Cl}$ | 8 | 79 | 53:47 | 26:74 |
| i | $\text{R}_1 = \text{Br}$ | 4 | 91 | 72:27 | 31:69 |
| j | $\text{R}_1 = \text{OH}$ | 7 | 75 | 75:25 | 49:51 |

^a Yields refer to isolated yields.

^b Compounds were analysed by ^1H NMR, ^{13}C NMR and elemental analysis.

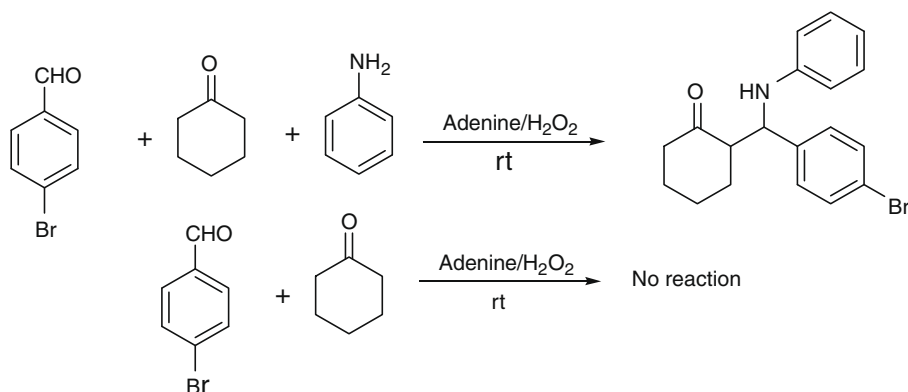
^{c,d} Diastereomeric and regioisomeric ratios were determined by ^1H NMR analysis at 400 MHz.

In order to broaden the generality of our protocol further, we tried to extend our application to an acyclic ketone which was chosen to be 2-butanone **5**. A set of reactions were carried out with different aldehydes **1a** and **1g–j** with compounds **5** and **3a** as shown in Table 5. Although the reaction proceeded smoothly, it was not selective on the direction of attack on the α -position of the carbonyl group giving two products **6** and **7**, respectively. Subsequently, we observed two different diastereomers of **7** as indicated from the ^1H NMR spectra. However compound **5** was found to be much less reactive than cyclohexanone and required 40 mol % of catalyst for completion. The *anti*-form was the major product in these reactions.

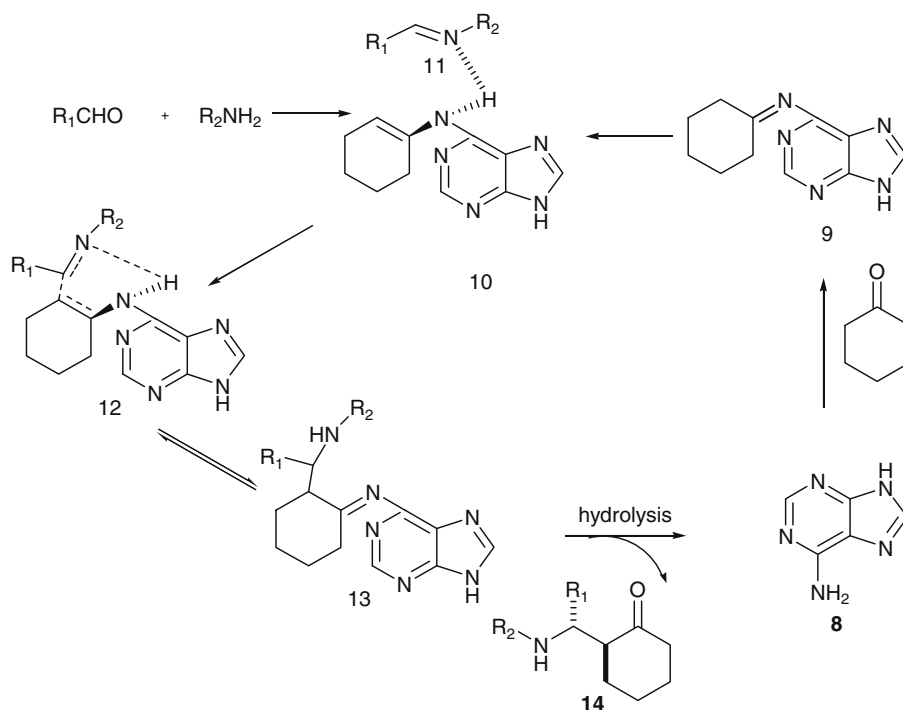
In order to observe the chemoselectivity of cyclohexanone towards the in situ-formed aldimines with the present protocol, another set of reactions were accomplished as shown in Scheme 2. The results highlight the fact that there is no aldol type of reaction between aldehyde and cyclohexanone moiety. The chemoselectiv-

ity is due to the more basic nature of nitrogen as compared to that of oxygen.

Taking mechanism into consideration, the reaction proceeds through the initial formation of imine **11** between the aldehyde and the amine. Simultaneously, the catalyst **8** forms an imine **9** with the cyclohexanone moiety which tautomerises to form enamine intermediate **10**. Although both the *E* and *Z* enamines can be formed, the formation of *E* enamine is thermodynamically more favourable, leading to the formation of the diastereoselective Mannich products.¹⁴ Consequently the imine **11** comes in close proximity to **10** due to the hydrogen bonding and forms a six-membered transition state **12** in due course. The proton transfer takes place to form **13** which is further hydrolysed to **14** and the catalyst **8** is regenerated which takes part in the cycle of reaction again. The presence of water probably accelerates the reaction by helping in hydrolysis and regeneration of the catalyst. The proposed reaction mechanism is depicted in Scheme 3.



Scheme 2. Chemoselectivity of the present protocol.



Scheme 3. Probable reaction mechanism towards the synthesis of Mannich products.

In conclusion, we have reported an environmentally green and benign protocol for the synthesis of diastereoselective Mannich products using adenine as the aminocatalyst. The lack of column chromatography for majority of the compounds partially overcomes the major problem of epimerisation of the Mannich products¹⁵ faced during their purification through column chromatography. Additionally, the non-requirement of work-up procedure with organic solvents provides a greener edge to our protocol. In a nutshell, our *modus operandi* should find a significant place in the sphere of green synthetic organic chemistry.

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- Experimental procedure:** To a mixture of aldehyde (1 mmol), cyclohexanone (1 mmol) and amine (1 mmol) in ethanol–water 4:1 was added catalyst (20–40 mol %) followed by 40 μ L of 30% H₂O₂. The reaction mixture was allowed to stir at room temperature until the completion of the reaction as indicated by thin layer chromatography (TLC). On completion, the reaction mixture was poured in water upon which the product precipitates out. The product was separated out by filtration and washed with water. The crude product was recrystallised from chloroform and directly analysed for certain compounds without further purification. Some compounds required purification by column chromatography (hexane–ethyl acetate 9:1) and were later analysed.
Compound 4a: Dirty white solid; ¹H NMR (400 MHz, CDCl₃, A (syn)/B (anti)) = 17/83; δ 1.51–1.66 (m, 4H), 1.68–1.73 (m, 1H), 1.81–1.91 (m, 1H), 2.01–2.04 (m, 1H), 2.29–2.43 (m, 1H), 2.72–2.79 (m, 1H), 4.61 (d, 0.83H, *J* = 6.8 Hz for B), 4.79 (d, 0.17H, *J* = 4.0 Hz for A), 6.52 (t, 2H, *J* = 8.4 Hz), 6.60–6.64 (m, 1H), 7.03–7.08 (m, 2H), 7.19 (t, 2H, *J* = 7.6), 7.27–7.31 (m, 2H), 7.35 (t, 2H, *J* = 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃, A/B = 17/83): δ for A 25.09, 27.29, 28.90, 42.67, 56.89, 57.45, 114.34, 117.82, 127.29, 127.45, 128.79, 129.36, 142.24, 147.53, 212.47; for B 23.89, 28.19, 31.56, 42.03, 57.75, 58.19, 113.88, 117.76, 127.55, 127.79, 128.75, 129.35, 142.00, 147.53, 213.26. Anal. Calcd for C₁₉H₂₁NO: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.51; H, 7.61; N, 5.21.
Compound 4b: ¹H NMR (400 MHz, CDCl₃, A (syn)/B (anti)) = 71/29; δ 1.65–1.69 (m, 4H), 1.84–1.93 (m, 1H), 1.98–2.23 (m, 1H), 2.28–2.35 (m, 1H), 2.38–2.42 (m, 1H), 2.63–2.77 (m, 1H), 4.53 (d, 0.29H, *J* = 6.8 Hz for B), 4.72 (d, 0.71H, *J* = 4.4 Hz for A), 6.39 (t, 2H, *J* = 5.6 Hz), 7.11 (d, 1H, *J* = 8.0 Hz), 7.12 (d, 1H, *J* = 8.0 Hz), 7.19 (t, 1H, *J* = 6.0 Hz), 7.27–7.32 (m, 4H); ¹³C NMR (100 MHz, CDCl₃, A/B = 71/29) for A: δ 23.95, 28.06, 31.65, 42.07, 57.45, 58.29, 109.25, 115.39, 127.32, 127.57, 128.59, 131.81, 141.07, 146.45, 211.42; for B 24.94, 27.03, 28.61, 42.48, 56.49, 58.31, 109.45, 115.80, 127.45, 128.59, 131.81, 141.31, 146.65, 212.87. Anal. Calcd for C₁₉H₂₀BrNO: C, 63.70; H, 5.63; N, 3.91. Found: C, 63.89; H, 5.75; N, 3.83.
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