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Direct Mannich reaction mediated by Fe(Cp)₂PF₆ under solvent-free conditions

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ABSTRACT

Fe(Cp)₂PF₆ (5 mol %) efficiently catalyzed Mannich reaction of aldehydes, anilines, and ketones under solvent-free condition to give β-amino-ketones in high yield (up to 94%) within 30 min with *anti*-isomer in excess. Simple experimental conditions and product isolation procedure makes this protocol potential for the development of clean and environment-friendly strategy for the synthesis of β-amino-ketones.

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The Mannich reaction is an important carbon–carbon bond forming reaction in organic synthesis[1] for the preparation of β-amino carbonyl compounds which are vital intermediates in pharmaceuticals and natural products.[2] Attempts have been made in the past to improve methodologies based on two-component reactions, where the imine as electrophile is pre-formed and then reacted with nucleophiles such as enolates, enol ethers, and enamines.[3] However, in most cases these protocols use hazardous organic solvents[4] and suffer from long reaction time with low yields and poor selectivity. Therefore, the development of modern versions[5] of the reaction that work under mild conditions is of great importance. A more appropriate version of Mannich reaction involved the one-pot three-component approach that allowed a wide range of structural variations in the reactants—aldehydes, anilines, and ketones to give Mannich product using an appropriate catalyst such as organo-catalyst[6] and transition metal-based Lewis acid catalysts[7] in hazardous solvents such as CH₂Cl₂, CH₃CN, DMSO, NMP, and THF. Nevertheless, few recent reports have successfully used organic molecules as catalysts under aqueous medium[8] or under solvent-free conditions. However, in these cases the organo-catalysts produce colloidal dispersion or form emulsion where phase separation is often difficult.[9] The use of iron-based

catalyst is of particular interest because of its abundance in nature, less toxicity, and environmentally benign nature.[10]

Due to the attributes described above for the use of iron in catalysis and our current interest in developing solvent-free[11,12] and environmentally benign synthetic protocols for different organic transformations,[11–13] here we have demonstrated solvent-free protocol for the Mannich reaction using Fe(Cp)₂PF₆ as a catalyst in the preparation of β-amino ketones (yields up to 94%) at room temperature in short time (∼30 min). To the best of our knowledge Fe(Cp)₂PF₆ was used for the first time as a catalyst to carry out Mannich reaction.

Initially, in order to find out optimal catalyst loading the three-component Mannich reaction was carried out using benzaldehyde, aniline, and cyclohexanone as a representative reactants with 1–5 mol % of Fe(Cp)₂PF₆. The best result in terms of yield (94%) for the formation of β-amino ketone was achieved within 30 min with the catalyst loading of 5 mol % (Table 1, entry 3).

With this catalyst loading (5 mol %), the Mannich reaction of benzaldehyde and cyclohexanone with various amines viz., aniline, 2-MeO aniline, 4-Me aniline, 2-Cl aniline, and 4-Cl aniline was carried out and the data are presented in Table 2. The product yield was excellent in all the cases however the selectivity for *anti*-isomer was highest in the case of unsubstituted aniline as evident from ¹H NMR results. Barring 4-methyl aniline (entry 3) where the diastereoselectivity for the *anti* product was more, the *syn:anti* ratio was near 1 for other substituted anilines used in the present study.

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Table 1
The effect of catalyst loading on three-component Mannich reaction of benzaldehyde with aniline and cyclohexanone[a]
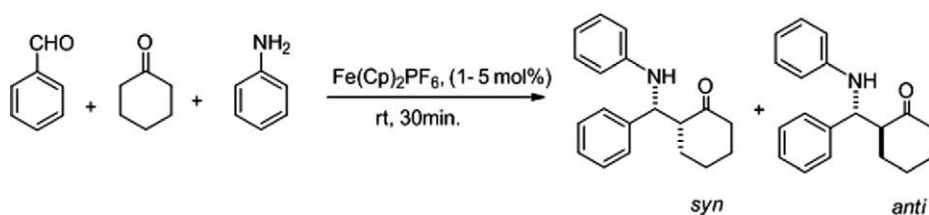
Entry	Catalyst mol (%)	Time (min)	Yield[b] (%)
1	1	30	61
2	3	30	86
3	5	30	94

[a] All reactions were carried out at room temperature using benzaldehyde (1 mmol), aniline (1 mmol), cyclohexanone (2 mmol).
[b] Isolated yield.

Table 2
Data for the Mannich reaction of various aniline with benzaldehyde and cyclohexanone[a]
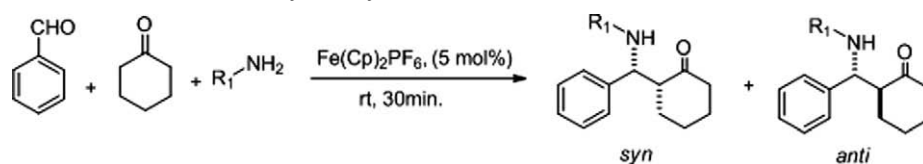
Entry	Amine	Product	Yield[b,c] [syn:anti]
1			94 (24:76)
2			89 (44:56)
3			90 (37:63)
4		(Fig. 1)	85 (49:51)
5			88 (48:52)

[a] All reactions were carried out at room temperature using, benzaldehyde (1 mmol), amine (1 mmol) cyclohexanone (2 mmol), and Fe(Cp)$_2$PF$_6$ (5 mol %).
[b] Isolated yield.
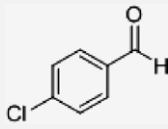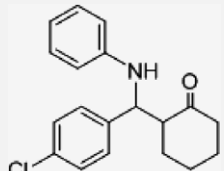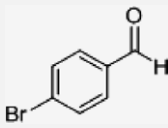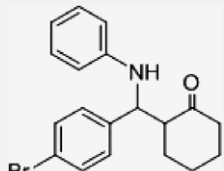[c] Syn/anti ratio has been calculated by ^{1}H NMR spectroscopy.
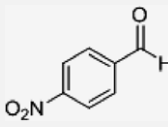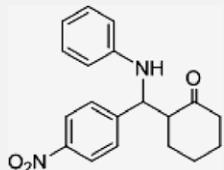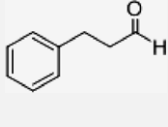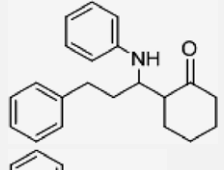
Table 3
Data for the Mannich reaction of various aldehydes with aniline and cyclohexanone[a]
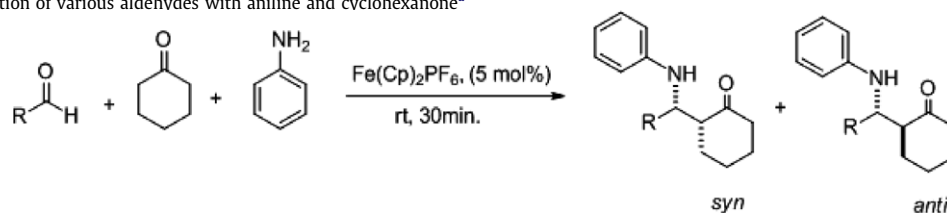
Entry	Aldehydes (R)	Product	Yield[b,c] [syn:anti]
1			94 (24:76)
2			88 (33:67)
3			90 (32:68)
4			93(30:63)
5			92 (35:65)
6			89 (44:56)
7		(Fig. 2)	90 (24:76)
8			79(33:67)

Table 3 (continued)

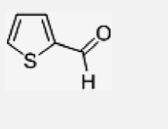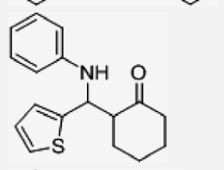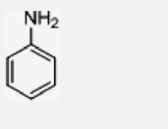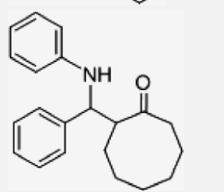| Entry	Aldehydes (R)	Product	Yield[b,c] [syn:anti]
9			76 (39:61)
10			80 (34:66)
11			77(34:66)
12			89 (34:66)
13			85 (55:45)
14[*]			81 (48:52)

[*] The reaction was conducted with benzaldehyde, aniline, and cyclooctanone under the present reaction conditions.

[a] All reactions were carried out at room temperature using aldehyde (1 mmol), aniline (1 mmol) cyclohexanole (2 mmol), and $Fe(Cp)_2PF_6$ (5 mol %).

[b] Isolated yield.

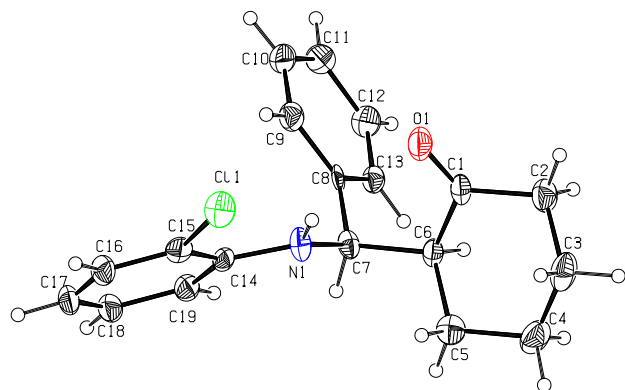[c] Syn/anti ratio has been calculated by ^1H NMR spectroscopy.

Figure 1. ORTEP diagram of the compound (Table 2, entry 4) with atom numbering scheme (30% probability factor for the thermal ellipsoids).
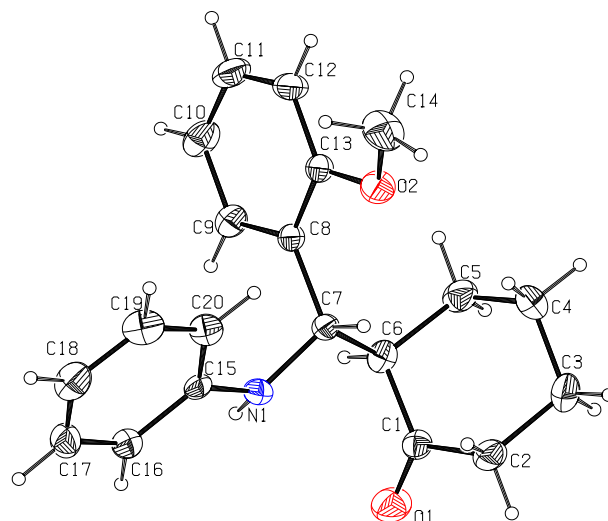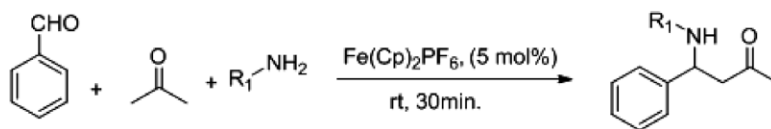

Figure 2. ORTEP diagram of the compound (Table 3, entry7) with atom numbering scheme (30% probability factor for the thermal ellipsoids).

Table 4
Data for the Mannich reaction of various aniline with benzaldehyde and acetone[a]

Entry	Amine	Product	Yield[b]
1			89
2			86
3			82
4			88

[a] All reactions were carried out at room temperature using, aldehyde (1 mmol), aniline (1 mmol) acetone (2 mmol), and Fe(Cp)$_2$PF$_6$ (5 mol %).
[b] Isolated yield.

Based on the above observations we varied aldehydes namely, 4-Me benzaldehyde, 3-Me benzaldehyde, 2-Me benzaldehyde, 4-MeO benzaldehyde, 3-MeO benzaldehyde, 2-MeO benzaldehyde, 4-F benzaldehyde, 4-Cl benzaldehyde, 4-Br benzaldehyde, 4-NO$_2$ benzaldehyde, 2-thiophene-carboxaldehyde, and hydrocinnamaldehyde while retaining other reactant (aniline and cyclohexanone) (Table 3). The electronic effect of substituents present on benzene ring of aldehyde moiety had significant effect on overall yield of the product β-amino ketone. The aldehydes with electron-donating groups (–OMe, –Me) gave higher yield of β-amino ketone (entries 2–7) than the aldehydes having electron-withdrawing groups (entries 8–11). Relatively, the aldehydes with electron-withdrawing groups favored the formation of anti-isomer as against respective aldehydes with electron-withdrawing groups, nevertheless
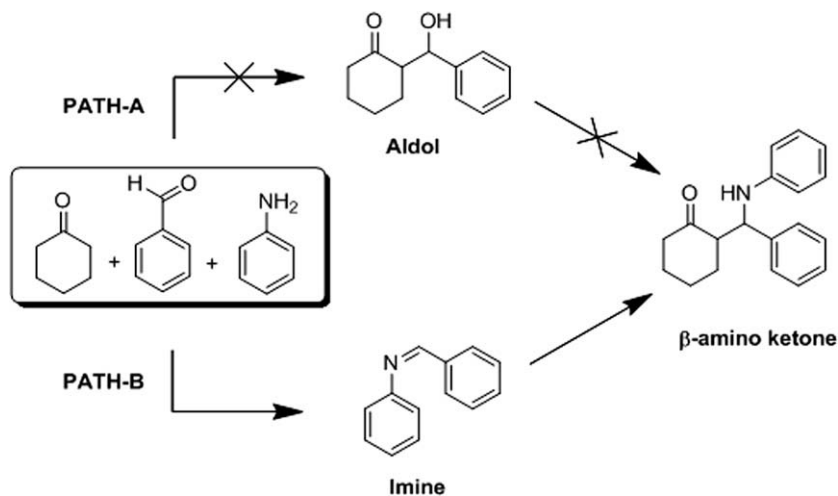
Scheme 1. Probable path for the product formation in three-component Mannich reaction.

anti-isomer was in excess than their respective *syn* isomer. In the case of hydrocinnamaldehyde 89% product yield was obtained with *syn:anti* ratio of 34:66 whereas in the case of 2-thiophene-carboxaldehyde 85% yield of β-amino ketone was achieved with marginally higher *syn* diastereoselectivity. On conducting the Mannich reaction with benzaldehyde and cyclooctanone with aniline under the identical reaction conditions the Mannich product was obtained in 81%, however in this case the *syn:anti* ratio was near 1 (entry 14).

The present Mannich protocol worked well under the identical reaction condition even with less reactive ketone such as acetone to give the Mannich product in 82–89% isolated yield with various anilines and benzaldehyde (Table 4).

Scheme 1 depicts a probable route for the formation of β-amino ketone. To understand this we conducted a series of experiments with benzaldehyde, aniline, and cyclohexanone in the presence and absence of $Fe(Cp)_2PF_6$ as catalyst. The reaction mixture when stirred for 6 h in the absence of the catalyst showed no sign of the product formation on TLC at room temperature. In an another experiment, a mixture of benzaldehyde and cyclohexanone was stirred in the presence of $Fe(Cp)_2PF_6$ for 6 h which failed to give any aldol condensation product. This rules out the path-A for the product formation. However, when pre-formed imine (a condensation product of benzaldehyde and aniline) was allowed to react with cyclohexanone in the presence of $Fe(Cp)_2PF_6$ at room temperature the product β-amino-ketone formed in a similar manner with similar *syn:anti* ratio as in the case of reaction conducted as per the condition given in Table 2 (entry 1). Based on these observations it can be concluded that path-B is operative in the present catalytic protocol.

In conclusion we have developed a very simple, efficient, and eco-friendly protocol for the synthesis of β-amino ketone using easily commercially available $Fe(Cp)_2PF_6$ as a catalyst under solvent-free conditions. The excellent yield of β-amino ketone was achieved up to 94% within 30 min.

Acknowledgements

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