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One-Pot Three-Component Mannich Reaction Catalyzed by Iodine under Solvent-Free Conditions[1]

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Abstract—One-pot three-component Mannich reactions of ketones with aromatic aldehydes and aromatic amines are effectively catalyzed by molecular iodine at room temperature under solvent-free conditions to afford the corresponding β-amino carbonyl compounds with moderate to excellent yields. The method has the following advantages: no use of solvent, mild condition, high reaction speed and small quantity of catalyst.

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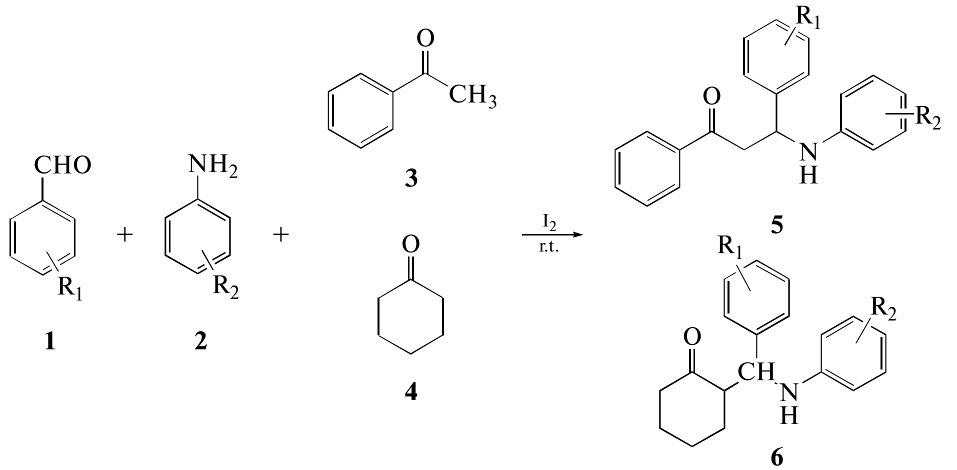
The three-component Mannich reaction is one of the most important carbon–carbon bond forming reactions in organic synthesis and one of the most fundamental and convenient methods for preparation of β-amino carbonyl compounds, which are essential synthetic intermediates for many pharmaceuticals and natural products [1, 2]. Recently, the three-component Mannich reactions have gained increasing popularity for versatile application of its products—β-amino carbonyl compounds—in drugs and natural products. Numerous versions of the Mannich reaction have been developed in the past. Generally, three-component Mannich reactions of aldehydes, ketones and amines are carried out using Brønsted acids [3–6], Lewis acids [7–10], Lewis bases [11–13] or small organic molecules as catalysts in organic solvent or water [14–17]. Moreover, most of these methods often suffer from some serious drawbacks such as long reaction time, harsh reaction condition, and difficulty in product separation, expensive reagents or catalysts, the use of large amount of catalysts, pollution of water or use of toxicity organic solvent.

Iodine as a mild and efficient catalyst has been used to promote various organic reactions [18–23]. Phukan and co-workers reported that 10 mol % iodine catalyzed Mannich reaction of benzyl carbamate with aromatic aldehyde and 1.5 equivalents of aromatic ketone in acetonitrile for 24 h. However, the method not only used noxious acetonitrile as solvent, but also needed long reaction time (24 h) [24].

In this work, we describe a mild, convenient, efficient and one-pot method for preparation of β-amino carbonyl compounds from ketones with aromatic aldehydes and aromatic amines using molecular iodine as catalyst under solvent-free conditions (Scheme).



Scheme.

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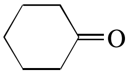
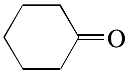
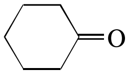
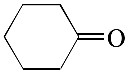
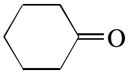
Table 1. Synthesis of β-amino ketones under different conditions*

Entry	Ketone	Aldehyde	Amine	Amount of catalyst, mol %	Time, h	Yield**, %
1	$PhCOCH_3$	PhCHO	$PhNH_2$	3	5	83
2	$PhCOCH_3$	PhCHO	$PhNH_2$	5	5	92
3	$PhCOCH_3$	PhCHO	$PhNH_2$	8	5	94
4	$PhCOCH_3$	PhCHO	$PhNH_2$	5	8	93
5	$PhCOCH_3$	PhCHO	$PhNH_2$	5	3	87
6		PhCHO	$PhNH_2$	0.5	1	90
7		PhCHO	$PhNH_2$	1	1	96
8		PhCHO	$PhNH_2$	2	1	97
9		PhCHO	$PhNH_2$	1	0.5	86
10		PhCHO	$PhNH_2$	1	2	97

* Reaction conditions: 1 equiv of ketone, 1 equiv of aldehyde, 1 equiv of amine; room temperature.

** Isolated yield.

EXPERIMENTAL

Materials and Methods

All the chemicals and reagents used are of analytical grade and are used without further purification. The structure and *syn/anti* ratio of products were determined by IR, ^1H NMR, and physical data (melting points) with those reported in the literatures. IR spectra are recorded on a Bruker AM-400 spectrometer using KBr discs. ^1H NMR spectra are obtained from solution in $CDCl_3$ or acetone with TMS as internal standard using a Varian Scimitar Series 800 (400 MHz) spectrometer.

General Procedure for the Iodine-Catalyzed Mannich Reaction

Equal molecular quantities of aldehyde, amine, ketones and 5 mol % iodine were added to a 50 ml one-necked round-bottom flask. The reaction mixture was stirred vigorously with a magnetic stirrer at room temperature **(r.t.)** for the mentioned time. After reaction completion, the crude mixture was either purified by silica gel–chromatography (ethyl acetate–petroleum ether mixtures) or recrystallized from ethanol or ethanol–acetone mixture (1 : 1, v/v) to afford the corresponding compounds.

RESULTS AND DISCUSSION

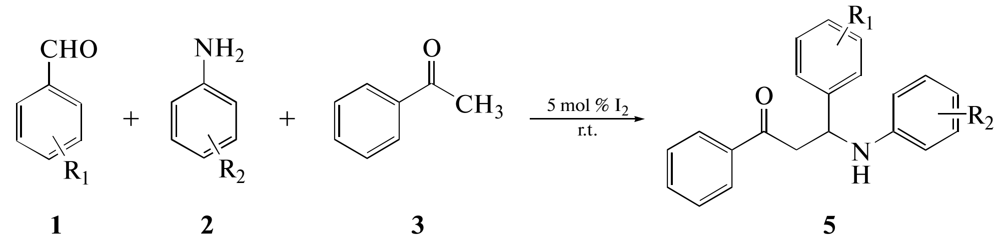
Screening of Conditions for Iodine-Catalyzed Mannich Reaction under Solvent-Free Conditions

To optimize condition of the Mannich reaction catalyzed by iodine, we examined effect of amount of iodine and time of reaction on Mannich reaction of acetophenone and cyclohexanone with benzaldehyde and aniline as typical substrates, respectively. The yields of β-amino carbonyl compounds under different reaction conditions are shown in Table 1. For Mannich reaction of acetophenone with benzaldehyde and aniline, appropriate reaction condition are 5 mol % iodine catalyst and 5 h reaction time at room temperature (entry 2). Iodine is highly efficient catalyst to Mannich reaction of acetophenone with benzaldehyde and aniline at room temperature. An excellent yield can be obtained within 1 h only using 1 mol % iodine as catalyst (entry 7). Furthermore, without making one of the reactants excess, solvent-free three-component Mannich reaction catalyzed by iodine can be smoothly carried out. Iodine should be used as a Lewis acid to catalyze Mannich reaction.

Substrate Scope of Iodine-Catalyzed Mannich Reaction

Next, to explore the generality and scope of iodine-catalyzed three-component Mannich reaction under solvent-free conditions, the Mannich reactions of acetophenone with various aromatic aldehyde and aromatic aniline were carried out under the same conditions. As shown in Table 2, these Mannich reactions of various substrates catalyzed by iodine present the following peculiarities: (1) for nitroaniline bearing strong electron-withdrawing $-NO_2$ group that deceases nucleophilicity of $-NH_2$ group, the reaction can smoothly take place and give the corresponding β-amino

Table 2. Solvent-free three-component Mannich reaction of acetophenone catalyzed by iodine*



Entry	Temperature, °C	R_1	R_2	Product **5**	Yield**, %
1	r.t.	H	H	5a	92
2	r.t.	4-Cl	H	5b	56
3	r.t.	H	4-Cl	5c	88
4	r.t.	4-CH_3O	4-Cl	5d	52
5	r.t.	4-CH_3O	H	5e	44
6	r.t.	4-CH_3O	H	5e	83***
7	r.t.	4-CH_3O	4-CH_3	5f	46
8	r.t.	H	4-CH_3	5g	86
9	r.t.	H	3-NO_2	5h	78
10	50	4-Cl	4-Cl	5i	82
11	50	4-Cl	4-CH_3	5j	90
12	50	4-Cl	4-NO_2	5k	41
13	r.t.	4-CH_3O	3-NO_2	5l	28
14	r.t.	H	4-NO_2	5m	43

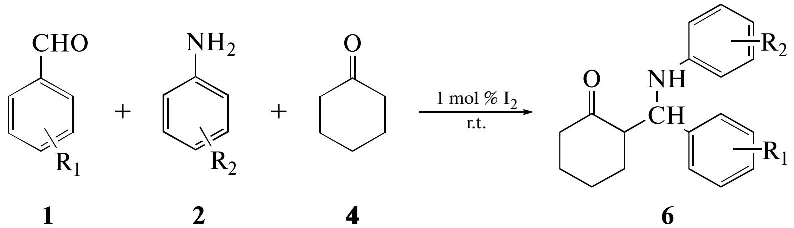
Notes: * Reaction conditions: 1 equiv of ketone, 1 equiv of aldehyde, 1 equiv of amine, 5 h.
** Isolated yield.
*** 24 h.

ketones compounds in good yields (entries 9, 12–14); (2) activity of anisaldehyde bearing strong electron-donating CH_3O^- group is lower than that of benzaldehyde, but a good yield of corresponding product can be obtained by prolonging reaction time from 5 to 24 h (entries 4–7, 13); (3) amines and aldehydes with $-CH_3$ and –Cl groups gave the corresponding amino ketones in good yields (entries 2, 3, 8, 10, 11).

Further, iodine-catalyzed three-component Mannich reactions of cyclohexanone with various aromatic aldehydes and aromatic anilines are also researched under solvent-free conditions as shown in Table 3. We find out that activity of cyclohexanone is evidently better than that of acetophenone in the Mannich reaction catalyzed by iodine. By comparison with that of acetophenone, the Mannich reaction of cyclohexanone can give the desired product in a good to excellent yield only using 1 mol % iodine as catalyst within 3 h. To our surprise, the Mannich reaction of cyclohexanone with benzaldehyde and aniline is very rapid, and a 96% yield can be obtained within 1 h (entry 1). We consider that the reason why reactivity of cyclohexanone is better than that of acetophenone is electron-withdrawing inductive effect of alkylcarbonyl which is stronger than that of benzoyl. For aldehydes and amines with substitution group, even nitroaniline with strong electron-withdrawing groups and 4-methoxybenzaldehyde with strong electron-donating groups, the desired product was also obtained in a good yield within 3 h (entries 5, 7–10).

This study demonstrates that molecule iodine is a convenient, efficient catalyst for the solvent-free one-pot three-component Mannich reactions of ketones with aromatic aldehydes and aromatic amines under mild conditions. It is worth mentioning that iodine can highly efficiently catalyze Mannich reaction of cyclohexanone with benzaldehyde and aniline, and a 96% yield can be obtained in the present of only 1 mol % iodine within 1 h. The solvent-free Mannich reactions catalyzed by iodine have the following advantages: (1) no need any solvent, (2) a low amount of catalyst used, (3) a short reaction time.

Table 3. Solvent-free three-component Mannich reaction of cyclohexanone catalyzed by iodine*



1 **2** **4** **6**

Entry	R_1	R_2	Time, h	Temperature, °C	Product **6**	Yield**, %
1	H	H	1	r.t.	6a	96
2	H	4-Cl	3	r.t.	6b	92
3	H	$4\text{-}CH_3$	3	r.t.	6c	80
4	4-Cl	4-Cl	3	50	6d	85
5	$4\text{-}CH_3O$	4-Cl	3	r.t.	6e	78
6	4-Cl	H	3	r.t.	6f	84
7	$4\text{-}CH_3O$	$4\text{-}CH_3$	3	r.t.	6g	80
8	$4\text{-}CH_3O$	H	3	r.t.	6h	79
9	$4\text{-}CH_3O$	$3\text{-}NO_2$	3	r.t.	6i	74
10	4-Cl	$3\text{-}NO_2$	3	50	6j	81

* Reaction conditions: 1 equiv of ketone, 1 equiv of aldehyde, 1 equiv of amine, room temperature.

** Isolated yield.

ACKNOWLEDGMENTS

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