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# Direct synthesis of Cbz-protected β-amino ketones by iodine-catalyzed three-component condensation of aldehydes, ketones and benzyl carbamate

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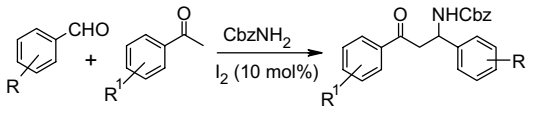
**Abstract**—Iodine has been found to be very effective catalyst for a Mannich reaction between an aryl aldehyde, an aryl ketone and benzyl carbamate, even though this is a less reactive amine, to produce Cbz-protected β-aryl β-amino carbonyl compounds in high yields.


The Mannich reaction is one of the most important multicomponent reactions in organic synthesis.[1] It provides β-amino carbonyl compounds, which are useful as building blocks for the synthesis of various pharmaceutically important compounds.[2] Traditionally, Mannich reactions have been achieved using a transition metal salt or an organic compound such as proline as catalysts.[3] However, there are limitations such as the use of toxic metal salts as catalysts, expensive reagents or catalysts, moisture sensitivity of the catalyst, use of a high amount of the catalyst, low yield, etc. Moreover, these methods use anilines or benzyl amine as nitrogen source and hence deprotection of the resulting amino-compound is difficult. Carbamates, which can be deprotected more easily,[4] are however, less reactive than amines. Recently, Xia and co-workers reported a procedure for a three-component Mannich reaction of aldehydes, ketones and carbamates using $AuCl_3$–$PPh_3$ as the catalyst,[5] but the metal salt is expensive and 5 mol equiv of the ketone and 1.5 equiv of the carbamate were required for 1 equiv of aldehyde. Iodine has emerged as a very effective catalyst for various organic transformations.[6,7] We report herein a mild, convenient and three-component method for the synthesis of Cbz-protected β-amino ketones using iodine as catalyst (Scheme 1).




**Scheme 1.**

In a systematic study (Table 1), acetophenone was added to a solution of benzaldehyde, benzyl carbamate and iodine in acetonitrile and the reaction mixture was stirred for 24 h at room temperature. Initial experiments were carried out using 1 equiv of benzaldehyde, 5 equiv of acetophenone, 1.5 equiv of benzyl carbamate and a variable amount of iodine. The use of 10 mol % of iodine (based on benzaldehyde) gave the best result and increasing the amount of iodine to 20 mol % gave a poorer result. Thereafter the reaction was carried out by varying the amount of acetophenone and benzyl carbamate. Interestingly, the results were better with less benzyl carbamate. The best result was obtained when the ratio of benzaldehyde, acetophenone, $CbzNH_2$ and iodine was 1:1.5:1.0:0.1. Dichloromethane as solvent was inferior to acetonitrile.

Next, we examined the scope of the reaction by using various aryl aldehydes and acetophenones.[8] The results are summarized in Table 2. In general, high yields of β-keto carbamates were obtained with 10 mol % of iodine at room temperature in acetonitrile for 24 h. Substrates bearing various functional groups such as $CH_3$, OMe, Cl and Br all reacted successfully to produce

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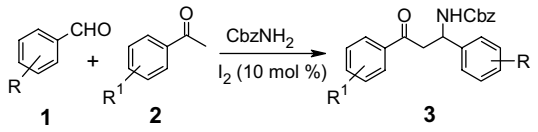
**Table 1.** Synthesis of β-amino ketones under different conditions[a]

| Entry | $PhCOCH_3$ (mmol) | $CbzNH_2$ (mmol) | Iodine (mmol) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | 5 | 1.5 | 0.05 | 64 |
| 2 | 5 | 1.5 | 0.10 | 68 |
| 3 | 5 | 1.5 | 0.20 | 50 |
| 4 | 2.5 | 1.5 | 0.10 | 47 |
| 5 | 1.5 | 1.5 | 0.10 | 54 |
| 6 | 1.5 | 1.2 | 0.10 | 65 |
| 7 | 1.5 | 1.1 | 0.10 | 71 |
| 8 | 1.5 | 1.0 | 0.10 | 78 |
| 9 | 1.0 | 1.0 | 0.10 | 38 |
| 10[c] | 1.5 | 1.0 | 0.10 | 64 |

[a] Reaction conditions: PhCHO (1 mmol), MeCN (1 ml), time (24 h), temp (25 °C).
[b] Isolated yield.
[c] DCM was used as solvent instead of MeCN.

**Table 2.** Iodine-catalyzed direct Mannich reaction with $CbzNH_2$[a]

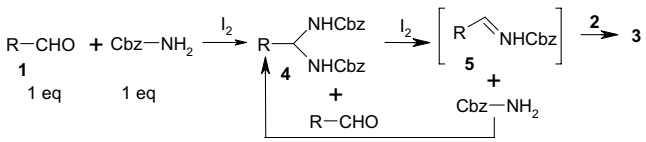



| Entry | R | $R^1$ | % Yield (product)[b] |
|---|---|---|---|
| 1 | H | H | 78 (**3a**) |
| 2 | 4-Cl | H | 78 (**3b**) |
| 3 | 4-$CH_3$ | H | 82 (**3c**) |
| 4 | 4-$OCH_3$ | H | 81 (**3d**) |
| 5 | 2-$OCH_3$ | H | 78 (**3e**) |
| 6 | 3-$OCH_3$ | H | 0 (**3f**) |
| 7 | 2,4-Dichloro | H | 48 (**3g**) |
| 8 | H | 4-$CH_3$ | 75 (**3h**) |
| 9 | 4-Cl | 4-$CH_3$ | 86 (**3i**) |
| 10 | 4-$CH_3$ | 4-$CH_3$ | 68 (**3j**) |
| 11 | 4-$OCH_3$ | 4-$CH_3$ | 75 (**3k**) |
| 12 | H | 4-Cl | 65 (**3l**) |
| 13 | 4-Cl | 4-Cl | 75 (**3m**) |
| 14 | 4-$CH_3$ | 4-Cl | 66 (**3n**) |
| 15 | H | 4-Br | 70 (**3o**) |
| 16 | 4-Cl | 4-Br | 42 (**3p**) |
| 17 | 4-$CH_3$ | 4-Br | 68 (**3q**) |

[a] Reaction conditions: aldehyde (1 mmol), ketone (1.5 mmol), $CbzNH_2$ (1.01 mmol), iodine (0.1 mmol), MeCN (1 mL), room temp 24 h.
[b] Isolated yield; products were characterized by IR, NMR, mass and elemental analysis.

the corresponding β-amino carbonyl compounds. Although, *ortho* and *para* substituted aldehydes gave good results, *meta*-substituted aldehydes such as 3-methoxybenzaldehyde (Table 2, entry 6) failed to yield any product.

The merits of this method are (a) a very simple, one-pot and high yielding process; (b) iodine is very cheap and easily available; (c) a low amount of catalyst (10%) is employed; (d) the absence of toxic catalysts; (e) iodine is not moisture sensitive and reactions are carried out in air; (f) unlike other protected amines, this method offers easy deprotection of the amine functionality.




**Scheme 2.**

Presumably, the reaction may proceed through the iodine catalyzed formation of bisurethane **4** by reaction of the carbamate with the aldehyde (Scheme 2).[7a,9] Bisurethane derivatives of aldehydes have been used as precursors for in situ generation of acylimines for reactions such as cycloadditions, amidoalkylations, etc.[10] The active acylimine species **5** is next formed, which undergoes attack by ketone **2** to produce the β-keto carbamate **3**.

In summary, we have demonstrated that iodine shows good catalytic activity for direct three-component condensation of an aryl aldehyde, an aryl ketone and benzyl carbamate to produce N-protected β-aryl-β-amino ketones under mild conditions.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.05.136.

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8. Typical procedure: To a solution of iodine (10 mol %) in acetonitrile (1 mL), benzyl carbamate (1.01 mmol), aldehyde (1 mmol) and ketone (1.5 mmol) were added successively at room temperature. After stirring the reaction mixture for 24 h, iodine was destroyed by adding solid sodium thiosulfate. Water was added to dissolve the thiosulfate and the mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried (sodium sulfate), filtered and evaporated. The crude product was purified by column chromatography over silica gel (60–120 mesh) using ethyl acetate–petroleum ether as eluent. Typical spectral data: **3a**: Mp 110–111 °C; IR (KBr, $cm^{-1}$): 3421, 3058, 2932, 2862, 1723, 1524, 1347, 1266, 1081, 739, 699; $^1H$ NMR (300 MHz, $CDCl_3$): 7.88 (d, $J = 7.5$ Hz, 2H), 7.57–7.22 (m, 13H), 5.89 (br s, 1H), 5.36–5.30 (m, 1H), 5.09 (s, 2H), 3.69 (d, $J = 15.3$ Hz, 1H), 3.44 (dd, $J = 5.7$ Hz, $J = 16.8$ Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$): 198.0, 155.7, 136.6, 136.4, 133.4, 128.6, 128.4, 128.0, 127.4, 126.3, 66.8, 51.8, 44.0. Analysis: $C_{23}H_{21}NO_3$ requires C 76.86, H 5.89, N 3.90%. Found: C 76.80, H 5.95, N 3.73%.
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