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Note

Three-component Mannich-type reaction catalyzed by iodine

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Iodine catalyzes Mannich-type reaction of aldehydes, benzyl carbamate and silyl ketene acetal in a three component condensation to afford the corresponding Cbz protected β-amino esters in high yields.

Keywords: Iodine, Mannich reaction, aldehydes, benzyl carbamate, silyl ketene acetal, β-amino ester

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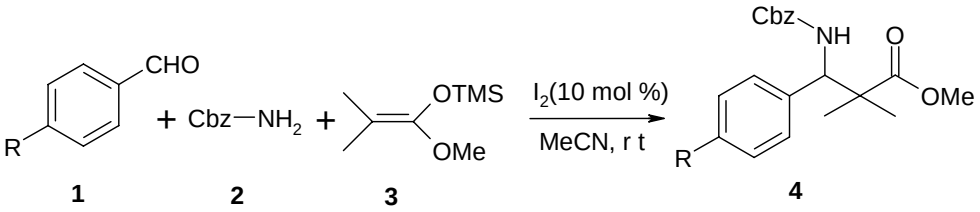
Multicomponent coupling reactions (MCRs) are emerging as useful tools for the carbon-carbon and carbon-heteroatom bond-forming reactions in organic synthesis[1]. The Mannich reaction is one of such MCRs and is the most widely utilized chemical transformation for constructing β-amino carbonyl compounds[2]. Bioactivity of β-Amino carbonyl compounds as well as their use as synthetic intermediates for various pharmaceuticals, natural products are well known in the literature[3]. In past decades, the Mannich reaction has gained importance and recently, direct Mannich reactions of aldehydes, ketones, and aryl amines have been achieved via transition metal salt catalysis and organocatalytic approaches[2, 4]. However, many of these procedures are fraught with limitations such as the use of metal salts as catalyst, expensive reagents or catalyst, long reaction time etc. These drawbacks are eliminated by the use of metal triflates but these are very expensive and some are moisture sensitive. Moreover, these strategies use anilines or benzyl amine as nitrogen source and hence deprotection of the resulting amino-compound is difficult. Therefore, attempt to extend the applicability of catalytic protocols to less-reactive compounds, such as amide or carbamate is one of the challenges. Recently, iodine is emerging as a very effective catalyst for various organic transformations[5]. The advantages in the use of iodine are (i) mild neutral condition (ii) inexpensive reagent (iii) no stringent dry conditions required. We also reported recently, few organic synthetic methodologies using iodine as very effective catalyst[6]. In continuation of our interest in catalytic applications of iodine for organic transformations[6], we report herein the preliminary results of a mild, convenient and three-component method for the synthesis Cbz protected β-amino esters using iodine as catalyst (**Scheme I**).

Initially a systematic study was carried out for catalytic evaluation of iodine for benzaldehyde. The reaction was performed by adding 1-methoxy-2-methyl-1-(trimethylsilyloxy)-1-propene (1.2 mmole) to a solution of benzaldehyde (1 mmole), benzyl carbamate (1.05 mmole) and iodine (0.1 mmole) in acetonitrile at room temperature. Reaction goes into completion in 2 hr when 10 mol % of iodine was used as catalyst. Rate enhancement was observed when 20 mol % of iodine was used but resulted in relatively lower yield. Moreover, use of dichloromethane as solvent instead of acetonitrile led to weaker results.

Encouraged by these results, we have extended the process to a variety of aldehydes, which are summarized in **Table I.** In general, good yields of β-amino esters were obtained with 10 mol % of iodine at room temperature in acetonitrile. No traces of the corresponding mukaiyama product[6b] resulting from direct addition of silyl ketene acetal to the aldehyde were observed. Although most of the substrate having electron donating substituent produced good yield, substrate bearing electron withdrawing group gave weaker result (**Table I**, entry-g). This may be because of the poor nucleophilicity of benzyl carbamate, which in combination with the electron withdrawing effect of the substituent led to a weaker result.

In conclusion, iodine acts as an efficient catalyst for the Mannich-type reaction of *in situ* prepared imines to produce Cbz protected β-aminoesters. The merits of this method are: (a) very simple, one-pot process; (b) Less reactive substances such as carbamate react successfully to give the Cbz-protected β-aminoesters; (c) unlike other protected amines, this method offers easy deprotection of the amine functionality. Moreover, this method does not require prior isolation of the imine. Study in this area in detail is in progress.

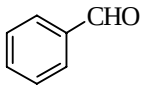
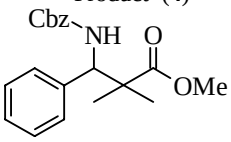
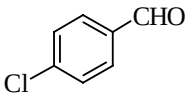
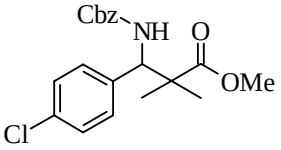
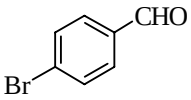
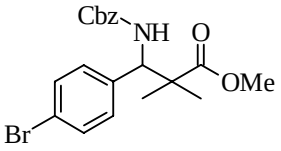
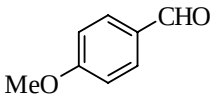
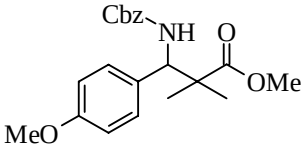
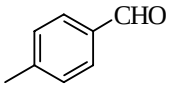
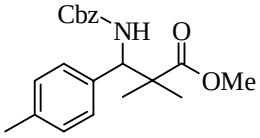
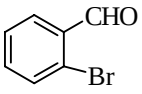
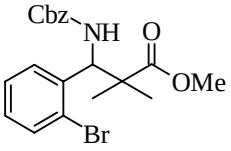
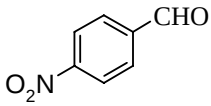
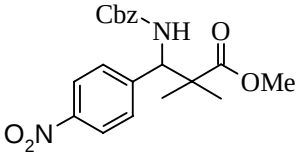


1 **2** **3** **4**

R = H, Me, Cl, Br, OMe, NO_2 etc.

Scheme I

Table I—Synthesis of Cbz protected β-amino esters

Entry	Aldehyde(**1**)	Time (h)	Product[a] (**4**)	Yield[b](%)
a.		2.5		67
b.		2.5		67
c.		2		70
d.		3		66
e.		3.2		73
f.		2.5		64
g.		5		32

[a]: Products are characterized by IR, NMR and elemental analysis. [b] isolated yield after chromatographic purifications

Experimental Section

Iodine was purified by sublimation before use. ^{1}H NMR and ^{13}C NMR spectra were recorded in Bruker 400 MHz instrument. Chemical shifts are given in δ units relative to the tetramethylsilane (TMS) signal as an internal reference in $CDCl_3$. Coupling constants (*J*) are reported in hertz. IR spectra were recorded in Perkin-Elmer Spectrum RXI FT-IR spectrometer. Elemental analyses were carried out in Perkin-Elmer 2400 Series II elemental analyser.

General procedure for the synthesis of β-amino esters

To a solution of aldehyde (1 mmole) and iodine (0.1 mmole) in acetonitrile (1 mL), benzyl carbamate (1.05 mmole) was added followed by the addition of 1-methoxy-2-methyl-1-(trimethylsilyloxy)-1-propene (1.2 mmole). After completion of reaction (monitored by TLC), sodium thiosulfate (20 mg approx.) was added and the reaction mixture was stirred for 20 min. It was then extracted with ether, washed with brine, dried (Na_2SO_4) and concentrated. Purification of the crude product by chromatography on silica gel (60-120 mesh) with pet. ether - EtOAc (10-15%) as eluent gave the pure product (32-82 %).

Spectral data of representative compounds

Methyl 3-{[(benzyloxy)carbonyl]amino}-3-(4-bromophenyl)-2,2-dimethylpropanoate, 4c. Colourless gum IR (Neat): 3430, 3048, 2929, 2848, 1723, 1643, 1537, 1450, 1265 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 1.09 (s, 3H), 1.32 (s, 3H) 3.64 (s, 3H), 4.64 (d, *J* = 6.8 Hz 1H), 4.95-5.15 (m, 2H), 6.34 (d, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 7.1-7.45 (m, 7H); $C_{20}H_{22}BrNO_4$ requires C, 57.15; H, 5.28; N, 3.33 %; Found: 57.63; H, 5.37; N, 3.39.

Methyl 3-{[(benzyloxy)carbonyl]amino}-3-(4-methoxyphenyl)-2,2 dimethylpropanoate 4d. Colourless gum IR (Neat): 3469, 3057, 2972, 2944, 1726, 1611, 1513, 1464, 1263 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 1.09 (s, 3H), 1.14 (s, 3H) 3.72 (s, 3H), 3.80 (s, 3H) 4.85 (s, 1H), 4.95-5.15 (m, 2H), 6.25 (d, *J* = 7.8 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.15-7.40 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): 19.0, 23.1, 47.8, 52.1, 54.4, 55.2, 78.4, 113.2, 128.5, 128.7, 128.8, 132.1, 154.0, 159.1, 178.3; $C_{21}H_{25}NO_5$ requires C, 67.91; H, 6.78; N, 3.77 %; Found: C, 67.86; H, 6.67; N, 3.73.

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