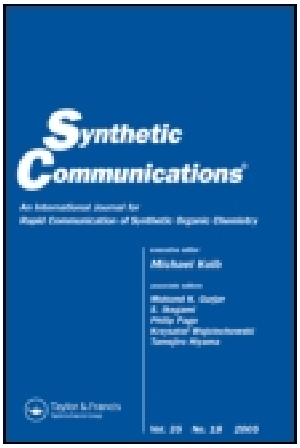

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J. S. Yadav [a] , V. Geetha [a] & B. V. Subba Reddy [a]

[a] Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad, 500 007, India

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INDIUM(III) CHLORIDE CATALYZED CONJUGATE ADDITION OF 1,3-DICARBONYL COMPOUNDS TO α,β-UNSATURATED KETONES*

J. S. Yadav,[†] **V. Geetha, and B. V. Subba Reddy**

Organic Chemistry Division-I, Indian Institute of
Chemical Technology, Hyderabad-500 007, India

ABSTRACT

Indium trichloride catalyzes efficiently the Michael reactions of 1,3-dicarbonyl compounds with α,β-unsaturated ketones to afford the corresponding Michael adducts in high yields with high selectivity.

Lewis acid promoted carbon–carbon bond forming reactions are of great interest because of their unique reactivity and selectivity. Among various Lewis acid catalyzed C–C bond forming reactions, Michael reaction is one of the most important transformations[1] in organic synthesis. Traditionally, the Michael reactions are performed, under the influence of strong bases[2] such as alkali metal alkoxides or hydroxides. However, the

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[†] Corresponding author. E-mail: yadav@iict.ap.nic.in

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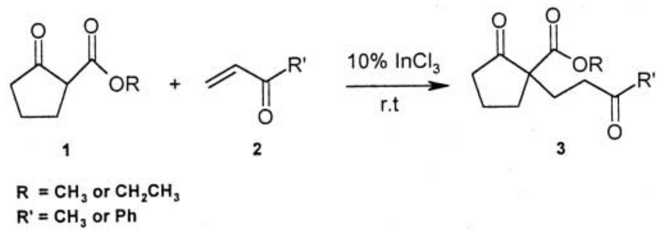
strongly basic conditions often lead to a number of undesirable side reactions such as aldol cyclizations, ester solvolysis, rearrangements such as retro-Claisen or retro-Michael reactions and polymerization reactions. Alternatively, several Lewis acids have been developed[3–7] to carry out the Michael reactions under mild conditions with high efficiency. However, most Michael reactions reported so far are performed in organic solvents, today's environmental concerns demands organic reactions in solvent free conditions or in water. Although metal triflates are found to catalyze Michael reactions in water, the reactions proceeded very slowly and required a period of three to five days for completion and also metal triflates are highly expensive. Recently, $FeCl_3{\cdot}6H_2O$ has also proved to be the most effective catalyst[8] for Michael reactions. However, the catalyst cannot be recovered and reused because it decomposes under quenching conditions. The presence of even a small amount of water causes lower yields, probably due to the rapid decomposition or deactivation of the catalyst and also the solvolysis of ester.

Recently, indium trichloride has emerged as potential Lewis acid catalyst[9] imparting high regio- and chemoselectivity in various chemical transformations in both aqueous and non-aqueous media. The reactions can be performed under mild conditions either neat or in water and the catalyst can be recovered and reused after the completion of the reactions. The unique features of indium(III) chloride prompted us to investigate the use of this catalyst for Michael reactions. Even though $InCl_3$ has been used in the conjugate addition reactions of amines to α,β-unsaturated compounds,[10] it has not been used in the Michael reaction of 1,3-dicarbonyl compounds and enones.

In this report, we describe a mild and efficient protocol for conjugate addition of 1,3-dicarbonyl compounds to α,β-unsaturated ketones using catalytic amount of indium trichloride in solvent free conditions (Sch. 1).

In all the cases the reaction proceeded smoothly at room temperature and the products (Michael adducts) were obtained in high yields. In the



Scheme 1.

absence of catalyst, the reactions did not yield any product even after a long reaction time at room temperature. It should be noted that no *bis*-Michael adduct was obtained in the reaction of cyclic β-ketoesters with enones. The Michael acceptors such as ethyl acrylate and acrylonitrile failed to react with enones under the similar reaction conditions. The reaction of ethyl 2-oxo-cyclopentanecarboxylate with methyl vinyl ketone in the presence of 10 mol% indium chloride under neat conditions resulted in the formation of corresponding Michael adduct in 90% yield. Similarly various β-keto esters were reacted with enones to afford respective Michael adducts in high yields. The best results were obtained by carrying out the reactions at room temperature in the presence of 10 mol% $InCl_3$ without any solvent. Reactions in dry media or under solvent free conditions are especially appealing, as they provide an opportunity to work with an open vessel, thus avoiding the risk of high internal pressure development and with the possibility of upscaling the reactions to large scale. Several examples illustrating this novel procedure for the conjugate addition of β-keto esters to α,β-unsaturated compounds are summarized in Table 1. Among various Lewis acids such as YCl_3, $BiCl_3$ and $YbCl_3$ used for this transformation $InCl_3$ was found to be effective in terms of yields and reaction times.

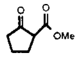
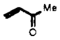
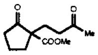
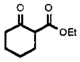
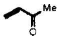
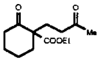
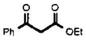
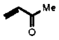
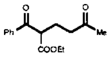
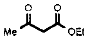
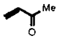
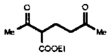
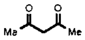
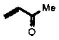
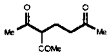
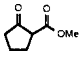
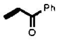
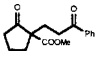
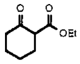
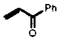
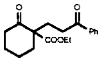
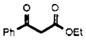
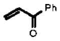
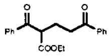
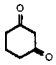
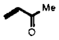
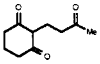
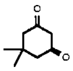
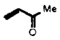
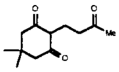
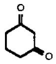
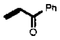
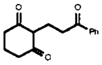
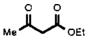
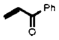
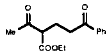
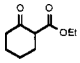
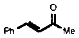
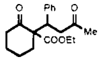
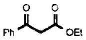
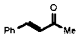
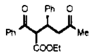
In conclusion, we have demonstrated that indium trichloride is a superior and water-tolerant Lewis acid in the conjugate addition of β-keto esters to α,β-unsaturated ketones under neat conditions. In addition to its simplicity and milder reaction conditions, this method works well even with acid sensitive substrates such as methyl vinyl ketone. Improved yields, greater selectivity, experimental simplicity, stability and recoverability of the catalyst are the notable features of this procedure.

EXPERIMENTAL

General Procedure for the Conjugate Addition of β-Keto Esters to α,β-Unsaturated Ketones

A mixture of β-keto ester (5 mmol), α,β-unsaturated ketone (5 mmol) and indium trichloride (10 mol%) was stirred at room temperature under neat conditions for an appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched by water (10 mL) and extracted with ether (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh,

Table 1. $InCl_3$ Catalyzed Conjugate Addition of 1,3-Diketones to Enones

Entry	β-Keto Ester **1**	Enone **2**	Product[a] **3**	Reaction Time (h)	Yield[b] (%)
a)				6.0	90
b)				8.0	87
c)				7.0	82
d)				8.5	89
e)				6.0	87
f)				8.5	90
g)				9.0	88
h)				7.0	85
i)				6.5	81
j)				7.0	78
k)				8.5	84
l)				9.0	80
m)				7.5	85
n)				8.0	80

[a]All products were characterized by ^1H NMR, IR and Mass spectra.
[b]Isolated and unoptimized yields.

ethyl acetate : hexane, 1 : 9) to afford Michael adduct in pure form. The aqueous layer was concentrated in vacuo to recover the catalyst.

Spectral data of compounds:

3a: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.80–2.05 (m, 4H), 2.05–2.15 (m, 1H), 2.20 (s, 3H), 2.25–2.52 (m, 4H), 2.72 (ddd, $J = 17.5$, 9.5 and 5.6 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR ($CDCl_3$, 200 MHz, proton decoupled): 19.42, 27.01, 29.58, 33.81, 37.62, 39.21, 58.79, 61.41, 172.42, 208.47, 215.31. IR (cm^{-1}): 2959, 1714, 1436, 1368, 1260, 1165, 1022, 817. EI MS: *m/z* 212.

3b: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.25 (t, $J = 7.8$ Hz, 3H), 1.36–1.46 (m, 1H), 1.55–1.66 (m, 2H), 1.68–1.75 (m, 1H), 1.85 (ddd, $J = 13.5$, 9.8 and 5.4 Hz, 1H), 1.90–2.0 (m, 1H), 2.05 (ddd, $J = 13.5$, 9.8 and 5.2, 1H), 2.12 (s, 3H), 2.35 (m, 1H), 2.42–2.55 (m, 3H), 2.60 (m, 1H), 4.10–4.25 (q, $J = 7.8$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 200 MHz, proton decoupled): 14.52, 22.57, 28.01, 29.42, 31.30, 35.86, 39.01, 41.05, 61.21, 62.72, 173.41, 208.71, 209.12. IR (cm^{-1}): 2989, 2871, 2357, 1736, 1514, 1195, 1135, 1092, 1020, 861. EI MS: *m/z* 240, 212, 194, 170, 151, 124.

3c: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.25 (t, $J = 7.8$ Hz, 3H), 2.15 (s, 3H), 2.18–2.30 (m, 2H), 2.55–2.70 (m, 2H), 4.12–4.25 (q, $J = 7.8$ Hz, 2H), 4.50 (m, 1H), 7.50–7.55 (m, 2H), 7.62–7.73 (m, 1H), 8.0 (m, 2H). ^{13}C NMR ($CDCl_3$, 200 MHz, proton decoupled): 14.01, 23.14, 30.22, 41.71, 52.51, 61.07, 128.37, 129.12, 134.17, 135.89, 170.41, 194.94, 207.76. IR (cm^{-1}): 3063, 2982, 2940, 2905, 1735, 1715, 1685, 1597, 1448, 1369, 1286, 1246, 1180, 1157, 1025, 691. EI MS: *m/z* 262, 105, 77, 43.

3d: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.24 (t, $J = 7.8$ Hz, 3H), 1.96–2.12 (m, 2H), 2.12 (s, 3H), 2.21 (s, 3H), 2.45–2.50 (m, 2H), 3.15 (t, $J = 7.8$ Hz, 1H), 4.15–4.22 (q, $J = 7.8$ Hz, 2H). IR (cm^{-1}): 2983, 2940, 1738, 1713, 1445, 1419, 1359, 1244, 1217, 1151, 1097, 1023, 957, 858. EI MS: *m/z* 200, 158, 112.

3e: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.05 (m, 2H), 2.18 (s, 9H), 2.50 (dd, $J = 11.0$ and 6.0 Hz, 2H), 3.6 (t, $J = 6.8$ Hz, 1H). IR (cm^{-1}): 2970, 2941, 1699, 1569, 1420, 1358, 1154. EI MS: *m/z* 170, 102, 92, 71, 55.

3g: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.30 (t, $J = 6.8$ Hz, 3H), 1.60–1.80 (m, 6H), 2.0–2.30 (m, 2H), 2.45–2.60 (m, 2H), 2.80–3.0 (m, 1H), 3.05–3.25 (m, 1H), 4.25 (q, $J = 6.8$ Hz, 2H), 7.45–7.50 (m, 3H), 8.0 (d, $J = 8.0$ Hz, 2H). EI MS: *m/z* 302.

3h: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.20 (t, $J = 7.0$ Hz, 3H), 2.40 (m, 2H), 3.05–3.20 (m, 2H), 4.20 (q, $J = 7.0$ Hz, 2H), 4.58 (t, $J = 6.8$ Hz, 1H), 7.45–7.60 (m, 6H), 7.95 (d, $J = 8.0$ Hz, 2H), 8.10 (d, $J = 8.0$ Hz, 2H). EI MS: *m/z* 324.

3n: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.85 (t, $J = 6.8$ Hz, 3H), 2.01 (s, 3H), 2.81–2.84 (m, 2H), 3.75–3.85 (m, 2H), 4.15–4.24 (m, 1H), 8.05–8.07 (m, 2H). EI MS: *m/z* 338, 292, 247, 233, 187, 147, 105, 77.

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