

Indium(III) chloride – catalyzed Michael addition of thiols to chalcones : a remarkable solvent effect

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Dedicated to Dr. A. V. Rama Rao on the occasion of his 70th birthday
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Abstract

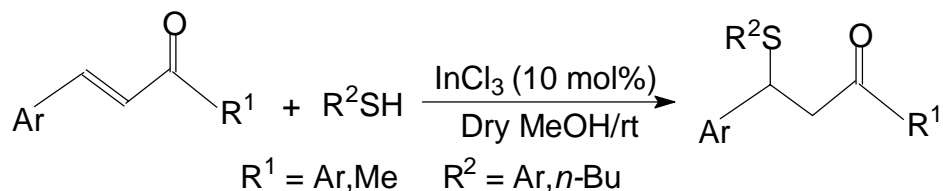
Indium(III) chloride in methanol efficiently catalyzes Michael addition of aromatic and aliphatic thiols to chalcones and related compounds. This reaction is remarkably solvent selective and it does not proceed in conventional solvents such as tetrahydrofuran, methylene chloride and water.

Keywords: Michael addition, thiol, chalcone, indium(III) chloride, solvent effect

Introduction

The Michael addition of thiols to electron deficient alkenes is a very useful process for making carbon-sulfur bond. This addition to chalcone derivatives is very interesting and challenging as it is less facile compared to the addition to aliphatic acyclic enones and thus it is not always satisfactory with the conventional reagents used for general 1,4-addition. Recently, a number of procedures involving a variety of catalysts such as synthetic diphosphate $\text{Na}_2\text{CaP}_2\text{O}_7$,^{1a} natural phosphate,^{1b} InBr_3 ,^{1c} fluorapatite,^{1d} have been reported.

Indium halides, particularly indium(III) chloride have emerged as a potent Lewis acid for various organic transformations in recent times.² As a part of our interest in indium(III) chloride catalyzed reactions³ we discovered that although InCl_3 has been used in the Michael addition of silylenol ethers,^{4a} amines,^{4b} pyrroles^{4c} and indoles^{4d} to electron-deficient alkenes no report has been found demonstrating the use of InCl_3 for addition of thiols to chalcones and related systems. This prompted us to investigate this reaction and we observed that very interestingly InCl_3 -catalyzed addition of thiol to chalcone derivatives is very much solvent dependent and it does not proceed at all in conventional solvents like CH_2Cl_2 , THF and H_2O usually chosen for indium halide mediated reactions.^{3,4} However, we discovered that the reaction goes very efficiently in dry methanol (Scheme 1).



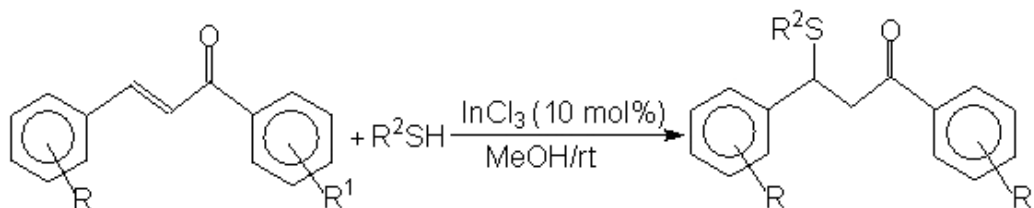
Scheme 1

Results and Discussion

The experimental procedure is very simple. A solution of chalcone and thiol in dry methanol was stirred at room temperature in the presence of a catalytic amount of indium(III) chloride. Usual work up with ether furnished the product.

Aliphatic as well as aromatic thiols underwent facile additions to a variety of chalcones by this procedure to provide the corresponding adducts in high yields. The results are summarized in Table 1. The electron withdrawing and electron donating substituents on the aromatic ring of the chalcone derivatives did not influence the progress of reaction. Additionally, additions of thiophenols with different substitutions also proceed efficiently. A vinylogous chalcone (entry 12) underwent bis-additions to provide the corresponding bis-adduct. This procedure also works well with chalcone like systems where the other ends are Me in place of Ph (entries 13-15).

The reactions are in general, considerably fast, clean and high yielding. The crude products obtained are sufficiently pure and purification by filtration through a short column of silica gel is enough to get pure samples in most of the reactions. All the products were characterized by spectroscopic data (IR, ^1H and ^{13}C NMR) together with elemental analysis for new compounds. It has been observed that the addition does not proceed at all in the absence of indium(III) chloride.

Table 1. Michael addition of thiols to chalcone derivatives and related systems

Entry	R	R ¹	R ²	Time(h)	Yield(%) ^a	Ref
1	H	H	<i>n</i> -Bu	1.0	92	
2	H	H	Ph	1.0	95	1a
3	H	H	(<i>o</i> -NH ₂)C ₆ H ₄	2.0	72	1a
4	H	Me	Ph	2.5	72	6
5	H	Me	<i>n</i> -Bu	3.0	61	
6	(<i>p</i> -Cl)	H	<i>n</i> -Bu	1.5	86	
7	(<i>p</i> -Cl)	H	(<i>p</i> -Cl)C ₆ H ₄	2.0	90	
8	(<i>p</i> -NO ₂)	H	<i>n</i> -Bu	2.5	74	
9	(<i>p</i> -NO ₂)	H	(<i>p</i> -Cl)C ₆ H ₄	1.5	86	
10	(<i>p</i> -OMe)	H	<i>n</i> -Bu	2.5	75	
11	(<i>p</i> -OMe)	H	Ph	2.5	69	1d
12			<i>n</i> -Bu	2.0	72 ^b	7
13			<i>n</i> -Bu	1.75	84	
14			Ph	2.0	80	8
15			(<i>o</i> -NH ₂)C ₆ H ₄	2.0	72	

^a The yields refer to those of pure isolated products characterized by spectroscopic (IR, ¹H and ¹³C NMR) data. ^b The yield refers to bis - addition product.

The reactions are accomplished most efficiently with 10 mol% of InCl_3 with respect to chalcone; however with the lower amount than that the reactions are found to be slow. The influence of methanol as solvent towards progress of this InCl_3 catalyzed reaction, though interesting is not unprecedented.⁵

In conclusion, the present procedure catalyzed by indium(III) chloride provides an efficient methodology for the Michael addition of thiols to chalcone derivatives and related systems. The mild reaction conditions (room temperature), simple operation, high yields of adducts, relatively low catalyst loading and much lower cost of indium(III) chloride compared to indium(III) bromide that has been used earlier for this conjugate addition^{1c} make this procedure an attractive alternative to the existing procedures. Moreover, this work demonstrates the potential of indium(III) chloride as a Lewis acid and the remarkable effect of solvent in promoting catalytic activity.

Experimental Section

General Procedures. NMR spectra were recorded on a Bruker DPX 300 instrument at 300 MHz for ^1H and at 75 MHz for ^{13}C NMR in CDCl_3 solutions. IR spectra were measured on a FT-8300 Shimadzu spectrometer in neat for liquids and in KBr pellet for solids. Methanol was distilled over sodium metal. Chalcones were prepared by standard procedure.⁹ Thiols were distilled before use. Indium(III) chloride (98%) was purchased from Aldrich and was used as such.

Representative experimental procedure for Michael addition (entry 1, Table 1)

A mixture of chalcone (208 mg, 1 mmol), butanethiol (117 mg, 1.3 mmol) in dry methanol (1.5 mL) was stirred at room temperature in the presence of a catalytic amount of indium(III) chloride (10 mol% with respect to chalcone, 22 mg) for 1 hr. The reaction mixture was then extracted with ether and the ether extract was washed with H_2O , brine and dried (Na_2SO_4). Evaporation of solvent furnished the crude product that was purified by column chromatography over silica gel (hexane/ether 96:4) to give pure adduct, 1,3-diphenyl-3-(thiobutyl)propan-1-one (274 mg, 92%) as a colourless oil, IR 3028, 2952, 1675, 1603 cm^{-1} ; ^1H NMR δ 0.82 (t, $J = 7.2$ Hz, 3H), 1.26-1.34 (m, 2H), 1.39-1.56 (m, 2H), 2.27-2.37 (m, 2H), 3.52 (d, $J = 7.0$ Hz, 2H), 4.55 (t, $J = 7.0$ Hz, 1H), 7.17-7.54 (m, 8H), 7.88-7.91 (m, 2H); ^{13}C NMR δ 14.0, 22.4, 31.5, 31.7, 44.7, 45.9, 127.6, 128.3 (2C), 128.5 (2C), 128.8 (2C), 128.9, 129.0, 133.6, 137.3, 142.7, 197.4. Anal. calcd for $\text{C}_{19}\text{H}_{22}\text{OS}$: C, 76.47; H, 7.43. Found: C, 76.31; H, 7.28.

This procedure is followed for all the reactions listed in Table 1. Several products are known compounds and were identified by spectroscopic data (IR, ^1H and ^{13}C NMR) which are in good agreement with those reported (references in Table 1). The spectroscopic and analytical data of a few products whose spectroscopic data are not readily available are provided here in order of their entries in Table 1.

1-(4-Methylphenyl)-3-phenyl-3-thiobutylpropan-1-one (entry 5). White crystal; m.p. 58 °C (hexane-ether 4:1); IR 3028, 2952, 1674, 1606 cm^{-1} ; ^1H NMR δ 0.83 (t, $J = 7.3$ Hz, 3H), 1.26-1.37 (m, 2H), 1.42-1.50 (m, 2H), 2.27-2.36 (m, 2H), 2.37 (s, 3H), 3.47 (d, $J = 7.1$ Hz, 2H), 4.54 (t, $J = 7.1$ Hz, 1H), 7.20-7.32 (m, 5H), 7.41 (d, $J = 8.2$ Hz, 2H), 7.81 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR δ 14.0, 22.0, 22.3, 31.6, 31.7, 44.8, 45.7, 127.5, 128.2 (2C), 128.6 (2C), 128.9 (2C), 129.7 (2C), 134.8, 142.8, 144.4, 197.0. Anal. calcd for $\text{C}_{20}\text{H}_{24}\text{OS}$: C, 76.88; H, 7.74. Found: C, 77.09; H, 7.69.

3-(4-Chlorophenyl)-1-phenyl-3-thiobutylpropan-1-one (entry 6). Colorless liquid; IR 2956, 2869, 1687, 1596 cm^{-1} ; ^1H NMR δ 0.84 (t, $J = 7.2$ Hz, 3H), 1.20-1.57 (m, 4H), 2.26-2.40 (m, 2H), 3.49 (d, $J = 7.0$ Hz, 2H), 4.52 (t, $J = 7.0$ Hz, 1H), 7.24-7.57 (m, 7H), 7.89 (d, $J = 7.8$ Hz, 2H); ^{13}C NMR δ 14.0, 22.3, 31.5, 31.6, 43.9, 45.7, 122.9 (2C), 128.9, 129.0, 129.1 (2C), 129.7 (2C), 133.8, 137.0, 141.3, 143.7, 197.1. Anal. calcd for $\text{C}_{19}\text{H}_{21}\text{OSCl}$: C, 68.55; H, 6.36. Found: C, 68.38; H, 6.30.

3-(4-Chlorophenyl)-3-(4-chlorothiophenyl)-1-phenylpropan-1-one (entry 7). White crystal; m.p. 84-86 °C (hexane-ether 4:1); IR 3061, 1685, 1473, 688 cm^{-1} ; ^1H NMR δ 3.58 (d, $J = 7.1$ Hz, 2H), 4.88 (t, $J = 7.1$ Hz, 1H), 7.16-7.58 (m, 11H), 7.88 (d, $J = 7.8$ Hz, 2H); ^{13}C NMR δ 44.8, 48.3, 128.4 (2C), 128.9 (2C), 129.0, 129.1 (2C), 129.4 (2C), 129.5 (2C), 130.8, 133.9, 134.5, 134.8 (2C), 137.5, 140.1, 196.8. Anal. calcd for $\text{C}_{21}\text{H}_{16}\text{OSCl}_2$: C, 65.12; H, 4.16. Found: C, 64.94; H, 4.04.

3-(4-Nitrophenyl)-1-phenyl-3-thiobutylpropan-1-one (entry 8). Colorless oil; IR 2956, 2871, 1687, 1519, 1346 cm^{-1} ; ^1H NMR δ 0.84 (t, $J = 7.2$ Hz, 3H), 1.27-1.36 (m, 2H), 1.44-1.52 (m, 2H), 2.25-2.39 (m, 2H), 3.57 (d, $J = 7.1$ Hz, 2H), 4.62 (t, $J = 7.1$ Hz, 1H), 7.41-7.62 (m, 5H), 7.88-7.91 (m, 2H), 8.14-8.17 (m, 2H); ^{13}C NMR δ 13.9, 22.3, 31.5, 31.7, 44.1, 45.4, 123.9 (2C), 128.2 (2C), 129.1 (2C), 129.2 (2C), 133.9, 136.7, 147.3, 150.7, 196.6. Anal. calcd for $\text{C}_{19}\text{H}_{21}\text{O}_3\text{SN}$: C, 66.45; H, 6.16; N, 4.08. Found: C, 66.51; H, 6.03; N, 3.92.

3-(4-Chlorothiophenyl)-3-(4-nitrophenyl)-1-phenylpropan-1-one (entry 9). White crystal; m.p. 95-97 °C (hexane-ether 4:1); IR 3058, 1681, 1519, 1346, 688 cm^{-1} ; ^1H NMR δ 3.65 (d, $J = 7.1$ Hz, 2H), 4.94 (t, $J = 7.1$ Hz, 1H), 7.15-7.61 (m, 9H), 7.88-7.91 (m, 2H), 8.09-8.12 (m, 2H); ^{13}C NMR δ 44.3, 48.5, 124.2 (2C), 128.2 (2C), 128.4, 128.8 (2C), 128.9 (2C), 129.4 (2C), 131.6, 132.2, 134.1, 135.1 (2C), 136.6, 149.3, 196.2. Anal. calcd for $\text{C}_{21}\text{H}_{16}\text{O}_3\text{SN}$: C, 69.60; H, 4.45; N, 3.86. Found: C, 69.80; H, 4.26; N, 4.09.

3-(4-Methoxyphenyl)-1-phenyl-3-thiobutylpropan-1-one (entry 10). Colorless oil; IR 3057, 2835, 1683, 1608 cm^{-1} ; ^1H NMR δ 0.84 (t, $J = 7.2$ Hz, 3H), 1.26-1.35 (m, 2H), 1.43-1.54 (m, 2H), 2.24-2.38 (m, 2H), 3.50 (d, $J = 7.1$ Hz, 2H), 3.77 (s, 3H), 4.52 (t, $J = 7.1$ Hz, 1H), 6.84 (d, $J = 7.4$ Hz, 2H), 7.26-7.56 (m, 5H), 7.90 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR δ 14.1, 22.4, 31.5, 31.7, 44.1, 45.9, 55.6, 114.2, 114.3, 128.5 (2C), 129.0 (2C), 129.2, 129.3, 133.6, 134.6, 137.2, 158.9, 197.6. Anal. calcd for $\text{C}_{20}\text{H}_{24}\text{O}_2\text{S}$: C, 73.13; H, 7.36. Found: C, 73.01; H, 7.21.

1-Phenyl-3-(thiobutyl)butan-1-one (entry 13). Colorless oil; IR 3032, 2929, 1685, 1596 cm^{-1} ; ^1H NMR δ 0.91 (t, $J = 7.4$ Hz, 3H), 1.35 (d, $J = 6.7$ Hz, 3H), 1.36-1.46 (m, 2H), 1.53-1.64 (m, 2H), 2.57 (t, $J = 7.3$ Hz, 2H), 3.05-3.33 (m, 2H), 3.42-3.52 (m, 1H), 7.26-7.59 (m, 3H), 7.90-7.97

(m, 2H); ^{13}C NMR δ 14.1, 22.2, 22.5, 31.0, 32.2, 35.9, 46.6, 128.5 (2C), 129.1 (2C), 133.3, 137.4, 198.7. Anal. calcd for $\text{C}_{14}\text{H}_{20}\text{OS}$: C, 71.14; H, 8.53. Found: C, 70.96; H, 8.45.

1-Phenyl-3-(2-aminothiophenyl)butan-1-one (entry 15). Colorless oil; IR 3460, 3361, 2927, 1683, 1452, 692 cm^{-1} ; ^1H NMR δ 1.36 (d, $J = 6.7$ Hz, 3H), 2.55 (dd, $J_1 = 10.6$ Hz, $J_2 = 12.8$ Hz, 1H), 3.06 (dd, $J_1 = 5.3$, $J_2 = 12.8$ Hz, 1H), 4.00-4.12 (m, 1H), 7.03-7.59 (m, 7H), 8.04-8.07 (m, 2H); ^{13}C NMR δ 22.3, 38.1, 53.0, 124.9, 125.3, 127.8 (2C), 128.5 (2C), 129.1, 131.4, 135.7, 138.7, 153.1, 170.7, 198.7. Anal. calcd for $\text{C}_{16}\text{H}_{17}\text{NOS}$: C, 70.82; H, 6.31; N, 5.16. Found: C, 70.69; H, 6.23; N, 5.01.

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