High Yielding Methyl Esterification Catalyzed by Indium(III) Chloride

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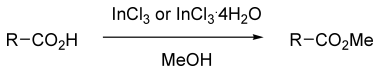
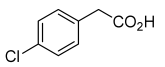
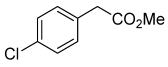
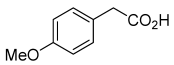
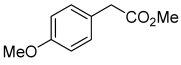
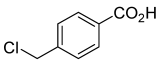
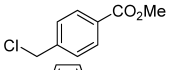
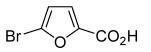
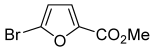
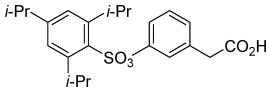
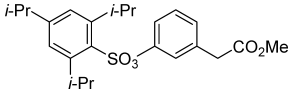
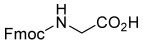
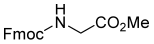
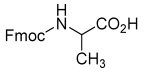
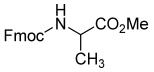
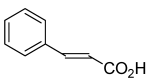
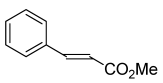
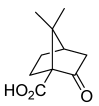
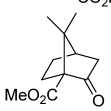
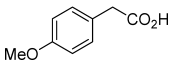
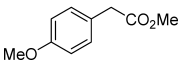
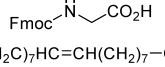
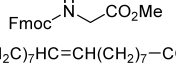
The carboxylic acids are efficiently converted into the methyl esters in methanol using indium(III) chloride as the catalyst. This method is applicable for aromatic and aliphatic carboxyl moieties as well as amino acids in high yields.

Key words indium(III) chloride; carboxylic acid; methyl ester

Methyl esterificaion of the carboxylic acids is the most fundamental reaction, and there is a variety of methods available. Among the conventional procedures, the most common is the use of *N*-methyl-*N*-nitrosourea under basic conditions,[1] which generates diazomethane *in situ*. However, due to the carcinogenic property a safer alternative, (trimethylsilyl)diazomethane,[2—5] is often preferred. Methyl esters can also be formed by the reactions[6,7] in $MeOH/H_2SO_4$ or

Table 1. Methyl Esterification Catalyzed by Indium(III) Chloride[a]



Entry	Substrate	Product	Catalyst	Temp.	Time (h)	Yield (%)
1			$InCl_3$	reflux	18	83
2			$InCl_3$	reflux	40	92
3			$InCl_3$	reflux	40	85[b]
4			$InCl_3$	reflux	12	82
5			$InCl_3$	reflux	8	85
6	$H_3C(H_2C)_7HC{=}CH(CH_2)_7{-}CO_2H$	$H_3C(H_2C)_7HC{=}CH(CH_2)_7{-}CO_2Me$	$InCl_3$	reflux	20	98
7			$InCl_3$	reflux	40	96
8			$InCl_3$	reflux	48	83
9	$HO_2CHC{=}HC{-}CH{=}CHCO_2H$	$MeO_2CHC{=}HC{-}CH{=}CHCO_2Me$	$InCl_3$[c]	reflux	48	83
10			$InCl_3$	reflux	48	93
11			$InCl_3$	reflux	96	61
12			$InCl_3$	r.t.[d]	21	91
13	$H_3C(H_2C)_7HC{=}CH(CH_2)_7{-}CO_2H$	$H_3C(H_2C)_7HC{=}CH(CH_2)_7{-}CO_2Me$	$InCl_3$	r.t.[d]	10	86
14			$InCl_3$	r.t.[d]	20	73
15	$H_3C(H_2C)_7HC{=}CH(CH_2)_7{-}CO_2H$	$H_3C(H_2C)_7HC{=}CH(CH_2)_7{-}CO_2Me$	$InCl_3\cdot 4H_2O$	reflux	21	98

a) All reactions were performed in MeOH using either 0.2 eq of indium(III) chloride or indium(III) chloride tetrahydrate as the catalyst. *b*) Side product of methyl 4-(methoxymethyl)benzoate was also formed in 12% yield. *c*) Since the starting substrate is a dicarboxylate, 0.4 eq of indium(III) chloride was used. *d*) The reaction was carried out employing sonication at room temperature.

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MeOH/TMS–Cl, and $Me_2C(OMe)_2$/HCl is utilized for amino acids.[8] These procedures still have the drawbacks of toxicity and incompatibility with the sensitive functional groups. There has been a recent report about direct condensation of carboxylic acids with alcohols using catalysts derived from the group 4 transition elements.[9]

We previously reported a promising method for tetrahydropyranylation/depyranylation of alcohols using indium(III) triflate.[10] Unlike MeOH/TMS–Cl condition that generate HCl *in situ*, indium(III) chloride, which is known to serve as an efficient and mild Lewis acid,[11] would not serve as a proton source. During the course of our continuing study on indium based chemistry, the methyl esterification of an array of carboxylic acids was found to proceed in methanol with the catalytic amount of indium(III) chloride. Thus, a solution of carboxylic acid in methanol was treated with indium(III) chloride (0.2 eq) at reflux or the sonication condition at room temperature to give a good yield of the corresponding methyl ester.

To evaluate the general applicability of this transformation, various compounds having diverse substituents or protecting groups were subjected to the methyl esterifying reactions. The reaction conditions were mild, not containing inorganic acids, and gave the corresponding methyl esters in excellent yields (Table 1). It worked not only for aliphatic carboxylic acids but also for aromatic ones (entries 3, 4). Protecting groups such as the 2,4,6-triisopropylbenzenesulfonoyl group (entry 5) and the 9-fluorenylmethoxycarbonyl (Fmoc) group (entries 7, 8) are stable to these reaction conditions. The substrates bearing the olefin units were able to be converted to the desired methyl eaters, including a C-7 long aliphatic carboxylate (entry 6) and α,β-unsaturated carboxylates (entries 9, 10). The reaction with ketopinic acid required 96 h to complete and ended up with 61% yield, presumably due to the steric hindrance (entry 11). A couple of esterification employing sonication was attempted, and we revealed that the reaction could proceed at room temperature, shortening the reaction time in half (entries 12—14). We also revealed that it was possible to carry out the esterification in the presence of the water molecules, using the catalytic amount of indium(III) chloride tetrahydrate instead of indium(III) chloride, without affecting the completion of the esterification (entry 15).

In conclusion, the indium(III) chloride-catalyzed esterification described here is a high yielding method and can serve as an alternative to the previously known procedures.

Experimental

General Methods NMR spectra were recorded on a JEOL JNM-ECA-500. The chemical shifts (δ) are reported in parts per million (ppm) and J values in Hz, using $CDCl_3$ for ^{1}H-NMR (7.26 ppm) and ^{13}C-NMR (77.0 ppm) as an internal standard. High resolution mass spectra were measured on JEOL AccuTOF LC-plus JMS-T100LP. All commercially available chemicals were used without purification.

General Experimental Procedure In a typical experimental procedure, the substrate of the carboxylic acid (1 mmol) was dissolved in methanol (10 ml) and indium(III) chloride (0.2 mmol, 44 mg) was added to the solution at room temperature. The mixture was heated at reflux and monitored for completion by TLC. The solvent was removed by rotary evaporation under vacuum, and water (20 ml) was pored to the residue. This solution was extracted with ethyl acetate (3×15 ml), washed with brine (30 ml), and dried over Na_2SO_4. After evaporation of the organic solvent, column chromatography on silica gel was applied to obtain the methyl ester, which was then confirmed by the spectral data. Products of entries 1—4, 6, 10, 12, 13, and 15 could be compared with the commercially available sources, and the product of entries 8, 9, and 11 was identical with those of the previously reported spectroscopic data.[12—14]

3-(2,4,6-Triisopropylphenylsulfonyloxy)phenylacetic Acid Methyl Ester ^{1}H-NMR (500 MHz, $CDCl_3$): δ: 7.24 (dd, 1H, J=8.6, 8.1 Hz), 7.20 (s, 2H), 7.16 (d, 1H, J=7.5 Hz), 6.96 (s, 1H), 6.90 (d, 1H, J=8.0 Hz), 4.06 (sep, 2H, J=6.9 Hz), 3.65 (s, 3H) 3.55 (s, 2H), 2.93 (sep, 1H, J=6.9 Hz), 1.27 (d, 6H, J=6.9 Hz), 1.18 (d, 12H, J=6.9 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ: 171.09, 154.26, 151.22, 149.50, 135.77, 129.63, 129.59, 127.91, 123.85, 123.43, 121.11, 52.11, 40.72, 34.25, 29.76, 24.54, 23.53; HR-MS (ESI$^+$): $[M+Na]^+$ Calcd for $C_{24}H_{32}O_5S$ 455.1868, Found 455.1893.

***N*-9-Fluorenylmethoxycarbonylglycine Methyl Ester** ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.77 (d, 2H, J=7.4 Hz), 7.61 (d, 2H, J=7.5 Hz), 7.40 (t, 2H, J=7.5 Hz), 7.32 (dt, 2H, J=7.5, 1.2 Hz), 5.36 (br s, 1H), 4.42 (d, 2H, J=7.5 Hz), 4.24 (t, 1H, J=7.5 Hz), 4.00 (d, 2H, J=5.8 Hz), 3.76 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 170.44, 156.23, 143.73, 141.23, 127.68, 127.02, 125.03, 119.94, 67.13, 52.35, 47.02, 42.58; HR-MS (ESI$^+$): $[M+Na]^+$ Calcd for $C_{18}H_{17}NO_4$ 334.1055, Found 334.1048.

Acknowledgement The authors thank Professor Mitchell A. Avery (University of Mississippi) for his generous support.

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