SHORT PAPER

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A simple method for the preparation of monomethyl esters of dicarboxylic acids by selective esterification of the nonconjugated carboxyl group in the presence of an aromatic or conjugated carboxyl group[†]

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Various dicarboxylic acids have been converted selectively into monomethyl esters in which the nonconjugated carboxyl group is selectively esterified in the presence of an aromatic or conjugated carboxyl group at room temperature (~ 25–27°C) in methanol using a catalytic amount of thionyl chloride.

The esterification of carboxylic acids is an important reaction in organic synthesis, and numerous methods have been reported in the literature for this transformation.[1] In contrast, reports on selective esterification of a nonconjugated carboxyl group in the presence of an aromatic or conjugated carboxyl group under simple and mild conditions are limited in number[2] notwithstanding its importance in multistep synthesis. Therefore, there is still a need for a simple, mild, efficient and faster method for this reaction. A method using a catalytic amount of anhydrous HCl, generated *in situ* from trimethylsily chloride or acid chlorides in a mixture of 2,2-dimethoxypropane and methanol has been reported recently for the selective esterification of aliphatic over aromatic carboxylic acids.[2b] However, this method generally requires a long reaction time and the selectivity in the presence of conjugated carboxyl group was not investigated. Moreover, *para*-substituted aromatic diacids have not been examined for selective esterification. The Amberlyst-15 method[2c] looks promising for selective esterification in the presence of a conjugated carboxyl group. However, the selectivity has not been thoroughly explored in the presence of an aromatic carboxyl group.

While carrying out esterification of dicarboxylic acids with $SOCl_2$ in methanol[3], we observed that a nonconjugated carboxyl group was selectively esterified in the presence of an aromatic or conjugated carboxyl group at room temperature (~ 25–27 ºC) in the presence of 3–5 mol% of $SOCl_2$ within a reasonable time. Workup procedure involves simple evaporation and chemical separation of the monoester from the small amount of diester formed in the reaction by treatment with $NaHCO_3$ solution. The results are shown in Table 1. All the compounds have been characterised by IR and NMR spectral studies. Under similar conditions, ethyl esters are not formed with $SOCl_2$ in ethanol. Considering the mild reaction conditions and easy availability of the reagent, the present method appears to be a useful addition to the existing methods.

Experimental

Melting points are uncorrected and recorded in a glass capillary with electrical heating. The IR spectra have been recorded on a Nicolet 5DX FTIR Spectrometer on samples taken as KBr discs. The ^1H and ^{13}C NMR spectra were recorded on Bruker Spectrospin DX-300MHZ NMR spectrometer in $CDCl_3$ with TMS as the internal standard. The mass spectra were recorded on KRATOS MS80 RFA Mass Spectrometer at the R&D Center, IOC, Faridabad, India. The microanalysis was carried out using Perkin-Elmer 240C rapid elemental analyser.

All the diacids were prepared by reported methods as mentioned below except itaconic acid which, was obtained from CDH, Mumbai, India. The diacids (**1**) and (**2**) (Table 1) were prepared by oxidation of indene[6] and α-tetralone[7] with $K_2Cr_2O_7/H_2SO_4$ and conc. HNO_3 respectively; (**3**)[8] and (**4**)[9] from the corresponding methyl toluate by NBS-bromination followed by substitution with NaCN and alkaline hydrolysis; (**5**) from salicylaldehyde by treatment with chloroacetic acid followed by oxidation with alkaline $KMnO_4$;[4] (**6**) by the reaction of methyl *p*-hydroxy benzoate with ethyl chloroacetate followed by alkaline hydrolysis;[10] (**8**) by the reaction of methyl levulinate with phosphonoacetate followed by alkaline hydrolysis;[11] (**9**) by the Stobbe condensation.[12]

General procedure for selective esterification: To a solution of diacid (5mmol) in methanol (10 ml) (in the case of Sr. No. 6, 40 ml) was added 3–5 mol% of thionyl chloride and the solution was stirred at room temperature (~ 25–27 ºC) for the time indicated in the Table 1. The progress of the reaction was monitored by TLC. After the completion of the reaction, the solvent was evaporated under reduced pressure, and the residual material was taken up in ether (75 ml) and washed successively with saturated $NaHCO_3$ solution (3×10 ml) and water (10 ml). The combined bicarbonate and aqueous extract was acidified with HCl to get the nonconjugated monomethyl ester by filtration or extraction with ether followed by recrystallisation. The ether layer was dried (anh. Na_2SO_4) and evaporated to obtain the diester.

Spectral data of monomethyl esters

Methyl 3-(2-carboxyphenyl) propanoate (**2**) : IR (ν/cm^{-1}): 3446 (w, free OH), 3217-2450 (s, CH and H-bonded OH), 1729 (ester C=O), 1693(acid C=O); δ_H 2.69-2.74 (t, 2H, ^3J=7.65Hz, $\underline{CH_2}COOCH_3$), 3.33-3.38 (t, 2H, ^3J=7.65Hz, $\underline{CH_2}Ar$), 3.67 (s, 3H, $COO\underline{CH_3}$), 7.30–7.34 (m, 2H, aromatic), 7.47–7.52 (m, 1H, aromatic), 8.06–8.09 (m, 1H, aromatic) ; δ_C 29.7, 34.2, 50.59, 126.39, 127.98, 131.14, 131.70, 132.95, 143.2,172.47, 173.99; *m/z*: 208 (M^+) (Calc. 208.21)

(Found : C, 63.77; H, 5.79 $C_{11}H_{12}O_4$ requires C, 63.45; H, 5.81%).
3-Methyl-5-methoxycarbonylpent-2-enoic acid (**8**): IR (ν/cm^{-1}): 3461 (w, free OH), 3300–2483 (s, CH and H-bonded OH), 1740 (ester C=O), 1708 (acid C=O), 1634 (C=C); δ_H 1.96 (s, 3H, $\underline{CH_3}$), 2.51 (s, 4H, $\underline{CH_2CH_2}$), 3.69 (s, 3H, $COO\underline{CH_3}$), 5.69) (s, 1H, ethylenic $\underline{CH}$ 10.5 (bs, 1H, $O\underline{H}$) ; δ_C 18.74, 31.61, 35.52, 51.58, 115.56, 160.36, 171.68, 172.71; *m/z:* 172 (M^+) (Calc. 172.18)(Found : C, 55.40; H, 7.36, $C_8H_{12}O_4$ requires C, 55.81; H, 7.02%).

2-Methoxycarbonylmethyl-3-phenylpropenoic acid (**9**): IR (ν/cm^{-1}): 3483 (w, free OH), 2725-2401 (m, H-bonded OH), 1725 (ester C=O), 1712 (acid C=O), 1636 (C=C); δ_H 3.56 (s, 2H, $\underline{CH_2}$), 3.75 (s, 3H, $COO\underline{CH_3}$), 7.35-7.44 (m, 5H, aromatic), 8.03 (s, 1H, ethylenic $\underline{CH}$), 8.59 (bs, 1H, $O\underline{H}$) ; δ_C 33.13, 52.23, 125.19, 128.67, 129.14, 129.27, 134.59, 144.26, 144.55, 171.46, 172.98; *m/z:* 220 (M^+) (Calc. 220.22) (Found : C, 65.98; H, 5.04 $C_{12}H_{12}O_4$ requires C, 65.44; H, 5.49%).

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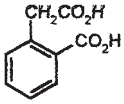
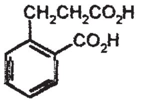
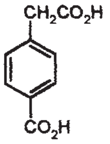
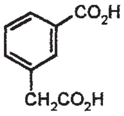
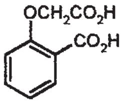
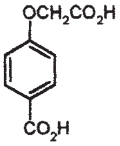
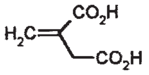
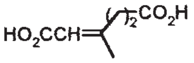
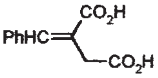
[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Selective monoesterification of dicarboxylic acids

Sr. No.	Dicarboxylic acid	SOCl$_2$ mol%	Time (h)	Yield (%)		m.p of monomethyl ester (Lit. m.p.)$^{ref.}$ (°C)
				Nonconjugated Monomethyl	Di-methyl ester	
1		5	10	96	1	96–97 (98)^4
2		5	23	86	5	79–80
3		5	7	90	5	136–137 (136)^4
4		3	9	89	4	66^a (92–93)^4
5		3	9	74	20	102–103 (100–101)^4
6		3	30.5	90	7	169–171 (174)^4
7		3	19	90	4	70–71 (67–70)^5
8		3	7	91	6	56
9		5	36	85	10	95–96

[a]The disparity between the observed and literature melting points for **4** has been examined but the values could not be reconciled (for **4**; found C, 61.61; H, 5.13 requires C, 61.85; H, 5.19%).

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