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A Selective Method for the Preparation of Aliphatic Methyl Esters in the Presence of Aromatic Carboxylic Acids

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Abstract: 2,2-Dimethoxypropane, methanol and a catalytic amount of HCl selectively esterify aliphatic carboxylic acids, in the presence of aromatic carboxylic acids, at room temperature and in high yields.

Selective esterification of aliphatic carboxyl groups in the presence of aromatic carboxyl groups is a synthetically useful reaction. Although many effective and reliable methods for the preparation of methyl esters have been reported in the literature there is still a great need for a simple, mild and selective process.[1,2] $NiCl_2.6H_2O$ at reflux temperature has been recently introduced as a catalyst for the selective esterification of aliphatic carboxylic acids.[3] However, sterically hindered acids did not react under those conditions. Other published methods require moisture sensitive reagents or are incompatible with additional functionality in the molecule.[4-6]

In the present communication we describe a mild, practical and efficient method for the preparation of aliphatic methyl esters from the corresponding carboxylic acids even in the presence of aromatic carboxylic acids.

2,2-Dimethoxypropane in the presence of a catalytic amount of HCl has been used for the formation of methyl esters.[2] TMSCl and other chlorosilanes in alcohols are a convenient source of anh. HCl and have been described to facilitate the formation of esters.[7,8] We wish to report that a mixture of 2,2-dimethoxypropane/ methanol in the presence of a catalytic amount of anh. HCl, generated in situ from TMSCl or acid chlorides, selectively esterified aliphatic over aromatic carboxylic acids (Table 1).[9] All by-products are volatile and can be removed in vacuum leaving the pure monoester in almost quantitative yield. The amount of diester observed was generally less than 2.2% (Table 1, entry 1-6), only in one case 4.2% was obtained (Table 1, entry 7).

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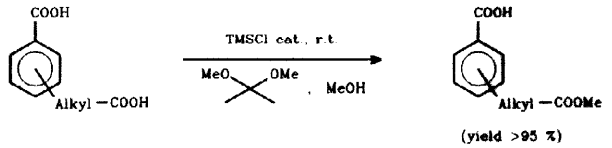
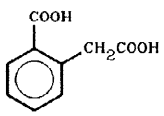
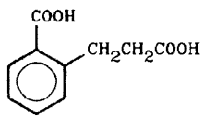
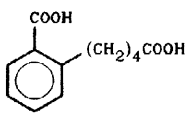
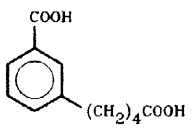
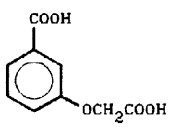
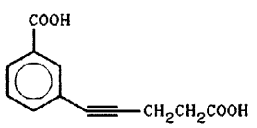
PII: S0040-4039(98)01958-3

Table 1. Selective Esterification of Aliphatic over Aromatic Carboxylic Acids.[10]

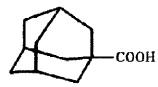
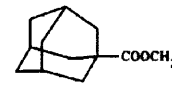
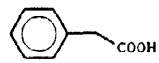
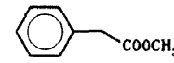
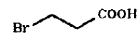
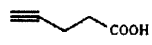
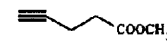
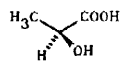
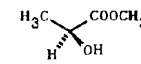
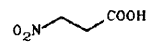
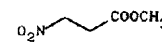
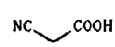
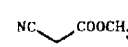
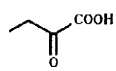
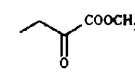
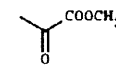
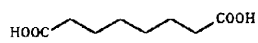
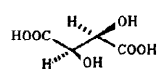
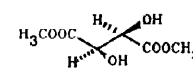
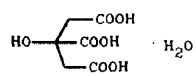
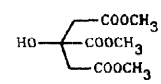
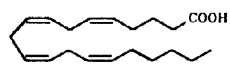
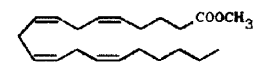
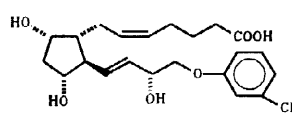
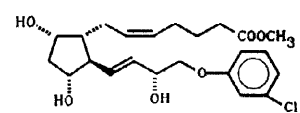
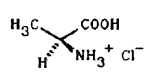
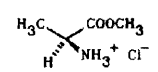
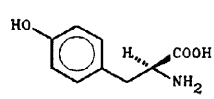
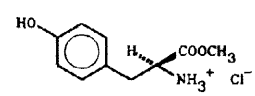


Entry	DICARBOXYLIC ACID	TMSCl (mol%)	Time (h)	Ratio (%) *		
				DIACID	ALKYL MONOMETHYL ESTER	DIMETHYL ESTER
1		5	20	28.2	71.2	0.6
		5	48	-	**99.1**	**0.9**
2		10	18	-	**98.3**	**1.7**
3		10	4	78.0	22.0	-
		10	24	23.7	76.0	0.3
		10	48	-	**99.5**	**0.5**
4		7	17	-	**99.3**	**0.7**
5		5	17	34.9	63.5	1.6
		5	24	16.1	82.0	1.9
		5	41	-	**97.8**	**2.2**
6		5	5	45.2	53.9	0.9
		5	24	-	**98.0**	**2.0**
7		10	24	43.2	54.0	2.8
		10	45	-	**95.8**	**4.2**

* Determined by 300 MHz ^{1}H NMR analysis

A variety of aliphatic carboxylic acids are quantitatively converted to their methyl esters at room temperature (Table 2). Double and triple bonds, amino, cyano, halo, hydroxy, α-keto and nitro groups are tolerated (Table 2, entries 3-9, 11-16). Di- and tri-carboxylic acids are converted to the di- and tri-carboxylic acid methyl esters respectively (Table 2, entries 10-12).

Table 2. Esterification of Aliphatic Carboxylic Acids with 2,2-Dimethoxypropane/Methanol/cat. TMSCl at r.t. (24 h).[10]

Entry	CARBOXYLIC ACID	METHYL ESTER	Yield [a]
1			quant.
2			quant.
3			quant.
4			quant.
5			quant.[b]
6			quant.
7			quant.
8			quant.
9			71% [c]
10			quant.
11			90% [d]
12			quant.
13			quant.
14			>95% [e]
15			quant.
16			quant.[f]

a) Yield refers to isolated materials that were homogeneous by TLC and NMR.
b) Lactic acid was used as an 85% aqueous solution.
c) 29% of dimethyl ketal ester was observed.
d) 10% of isopropylidene diester was observed. The crude product was purified by recrystallisation.
e) After chromatographic purification.
f) Free amino acids require 1.05 equiv. of TMSCl.

Free carboxylic acids in the presence of 2,2-dimethoxypropane and methanol were not transformed into the methyl ester even after prolonged exposure. Other catalysts such as pyridinium *p*-toluenesulfonate, *p*-toluenesulfonic acid or Amberlite® (IR-120, RSO_3H) did not induce esterification under these conditions.[2]

Aromatic and heteroaromatic carboxylic acids were mainly recovered unchanged (Table 3), even under the exposure to higher contents of HCl (20% TMSCl), explaining the selectivity observed in Table 1.

Table 3. Reaction of Aromatic Carboxylic Acids with 2,2-Dimethoxypropane/Methanol/TMSCl (20%) at r.t.[10]

Entry	ACID	Time (h)	Yield (%)	
			ACID	ESTER
1	Benzoic Acid	28	99.9	0.1
2	2-Bromobenzoic acid	22	99.3	0.7
3	2-Iodobenzoic acid	23	98.1	1.9
4	2-Iodobenzoic acid	96	96.9	3.1
5	2-Chlorobenzoic acid	22	99.6	0.4
6	3-Methoxybenzoic acid	5	99.6	0.4
7	3-Methoxybenzoic acid	72	94.2	5.8
8	3-Fluorobenzoic acid	48	99.4	0.6
9	4-Fluorobenzoic acid	24	96.6	3.4
10	2-Furoic Acid	24	98.9	1.1
11	2-Furoic Acid	720	97.0	3.0
12	3-Furoic Acid	48	98.6	1.4

In conclusion, an extremely simple and selective method for the preparation of aliphatic methyl esters in the presence of aromatic carboxylic acids has been developed. High yields combined with simple work-up makes it an attractive alternative to already existing methods.

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9. A representative experimental procedure is as follows: 0.38 ml (3.0 mmol) of trimethylsilyl chloride were added to a stirred suspension of 5.4 g (30.0 mmol) of homophthalic acid (Aldrich Chemical Company, Inc.) in 48 ml of 2,2-dimethoxypropane and 12 ml of methanol. The mixture was stirred for 18 hours at room temperature. Concentration under reduced pressure afforded crude monoester. Analysis by NMR showed the presence of 1.7% of diester. The crude product was purified by recrystallisation from ethyl acetate mp= 96-97 °C (Lit.[4] mp 98 °C) (95% yield).
10. Satisfactory spectroscopical data, ^{1}H-NMR, ^{13}C-NMR, FT-IR, were obtained for all compounds.