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Selective Esterification of Aliphatic Nonconjugated Carboxylic Acids in the Presence of Aromatic or Conjugated Carboxylic Acids Catalysed by $NiCl_2.6H_2O$

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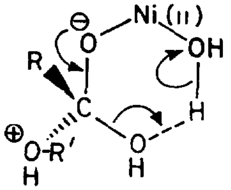
Abstract: Unhindered aliphatic nonconjugated carboxylic acids were esterified selectively in the presence of aromatic or conjugated acids on heating in the corresponding alcoholic solutions at reflux for 3-13hr with 10 mol% of $NiCl_2.6H_2O$ catalyst. © 1997 Elsevier Science Ltd.

Selective esterification of aliphatic nonconjugated carboxyl group in the presence of aromatic or conjugated carboxyl group is a synthetically important reaction. Although aliphatic nonconjugated carboxyl group is more reactive than aromatic or conjugated one in esterification with alcohols (or alkyl halides), the reaction conditions and the reactivities of most of the carboxyl-activating reagents or acid catalysts employed in the numerous reported esterification procedures are often not mild enough to allow selective esterification of aliphatic nonconjugated carboxyl group to be realised[1]. A survey of the literature revealed that this type of selective esterification of carboxylic acids with alcohols, having some degree of general applicability, has been done by catalysis with P_2O_5/anh. $CuSO_4$/anh. Na_2SO_4 [2], Ar_3Bi[3], I_2 plus H_2O[4] strongly acidic ion - exchange resin[5], PPL[6], graphite bisulphate[7], t- BuNC[8] and polymer supported-$AlCl_3$[9]. However, some of these catalysts are moisture sensitive, offensive in odour, commercially not available, and/or need to be prepared at the time of use and stored with special care. The finer details of the ion exchange resin and I_2 plus H_2O methods are accessible only through patented documents. Moreover, in the last three cases, the selectivity has not been rigorously demonstrated by either taking carboxylic acids having both the types of carboxyl groups in the same molecule or by competition experiments.

Metal ion-promoted/catalysed organic reactions have many attractive features not associated with proton-catalysed reactions, such as, wide choice for selection of the catalyst of suitable hardness (or softness), preferential multipoint interaction through chelation, if possible, with the organic substrate, easy engineering of the microenvironment around the metal ion by prior complexation with a variety of ligands, including the chiral ones, and template effect. Consequently, considerable degree of control can be exercised to realise striking reactivities and selectivities. Some of these features have been amply demonstrated by metal ion-promoted hydrolytic and other reactions[10]. However, metal ion-promoted esterification, has received relatively lesser attention. The reported metal ion-catalysed esterification reactions do not appear to exhibit selectivity between aliphatic nonconjugated and aromatic/conjugated acids and may require rather drastic conditions[11]. In the P_2O_5/anh. $CuSO_4$/anh. Na_2SO_4 method mentioned above, the main role of $CuSO_4$ is as water scavenger and indicator for the progress of the reaction and not as esterification catalyst. Moreover, they are mostly limited to the studies on only a few carboxylic acids of commercial importance with regard to their industrial implications and have appeared as patents[12].

Our interest in metal ion-promoted reactions[13] prompted us to explore $NiCl_2.6H_2O$-catalysed esterification of carboxylic acids with alcohols. It was expected that Ni (II) might serve as a mild and selective catalyst owing to suitable balance between its hard and soft acid characters. Thus, a solution of carboxylic acid (0.01 mol) and alcohol (10 ml) was heated at reflux with $NiCl_2.6H_2O$ (0.001 mol, 10 mol%) for the time indicated in Table 1 to give the ester in high yields after a simple work up involving evaporation of the solvent and extraction with ether or dichloromethane. The products were characterised by IR and NMR spectroscopy and comparision with authentic samples. Under the same conditions hindered aliphatic acids were found to be less reactive. Aromatic and conjugated acids were largely recovered unchanged. The selectivity was demonstrated by competition experiments in which equimolar mixtures of the two types of acids were esterified with 10 mol% of the catalyst whereby aliphatic acids were completely esterified but aromatic/conjugated acids were mostly recovered unchanged (Table 2). The selectivity was found to be better than that observed with the same molar proportion (10 mol%) of proton as catalyst in proton catalysed reaction. The selective esterification of dicarboxylic acids having both types of carboxyl groups also illustrates the same selectivity (Table 3). With Mandelic acid as a test case, it was found that the method worked well for the preparation of methyl, ethyl and isopropyl esters but was unsatisfactory for t-butyl esters. Proton-catalysed reaction was not important under the conditions used (Entries 6 and 7, Table 1). Anhydrous $NiCl_2$ was found to be less effective than the hydrated salt. Probably, the water of coordination facilitates the removal of hydroxyl group from the tetrahedral intermediate as shown in (1). The coordination of metal ions with carboxyl oxygen is well known and was further revealed by the blue shift of Ni (II) absorption from 406 to 396 nm in the presence of lauric acid taken in the same proportion as in the reaction. Other noteworthy features of the reaction are: (a) strictly dry alcohol in the reaction is not necessarily required. (b) the configuration at the adjacent carbon is not disturbed as revealed by comparable value of specific rotation of L-dimethyl tartarate obtained from the reaction with the reported value.



(1)

In conclusion, the reaction is extremely simple to carry out and uses readily available shelf-reagent as the catalyst. It might be exploitated in enantioselective esterification of racemic acids by using chiral Ni (II) complexes as catalyst. This aspect of the reaction is currently being investigated.

Table 1

Selective esterification of monocarboxylic acids with 10 mol% of $NiCl_2.6H_2O$

$$\mathrm{RCOOH + R'OH \xrightarrow{NiCl_2.6H_2O\ (10\ mol\%),\ reflux} RCOOR' + H_2O}$$

S.No	Acid	Alcohol	Time (hr)	Isolated Yield(%)	
				Acid	Ester
1	Lauric acid	MeOH	13	-	90
2	Phenylacetic acid	MeOH	5.5	6	93
3	3-Phenylpropanoic acid	MeOH	10	-	89
4	2-Phenylpropanoic acid	MeOH	17	38	60
5	Mandelic acid	MeOH	3	-	88
6	Mandelic acid (with H^+)*	MeOH	3	71	17
7	Mandelic acid (no catalyst)	MeOH	3	76	17
8	Mandelic acid (with anhydrous $NiCl_2$)	MeOH	3	35	56
9	Mandelic acid	EtOH	5	-	74
10	Mandelic acid	i-PrOH	8.5	-	68
11	Malic acid	MeOH	12.5	-	78 (diester)
12	L (+) Tartaric acid	MeOH	11	-	87 (diester)
13	Adipic acid	MeOH	13	-	18 (mono ester) 81 (diester)
14	Cyclohexanecarboxylic acid	MeOH	20	23	67
15	Trimethylacetic acid	MeOH	11	74	-
16	Benzoic acid	MeOH	21	86	10
17	p-Toluic acid	MeOH	24	80	-
18	p-Methoxybenzoic acid	MeOH	23	84	9
19	p-Chlorobenzoic acid	MeOH	24	93	-
20	p-Nitrobenzoic acid	MeOH	23	91	-
21	Cinnamic acid	MeOH	14.5	73	20
22	Crotonic acid	MeOH	10.5	96	-
23	3-Methyl-2-butenoic acid	MeOH	20	85	-

**Proton catalysed with the same pH as shown by the same concentration of $NiCl_2.6H_2O$ in MeOH (pH 4.87) as used for the reactions*

Table 2
Competition experiments with mixtures of two carboxylic acids

S.No.	Acid 1 + Acid 2	Time (hr)	* Yield (%)			
			Acid 1	Acid 2	Methyl ester 1	Methyl ester 2
1	Phenylacetic acid + Toluic acid	6	-	93	85	5
2	Lauric acid + Crotonic acid	13	-	87	96	-
3	3-Phenyl propanoic acid + Cinnamic acid	10	-	86	72	9
4	Lauric acid + Benzoic acid	13	-	89	88	-
5	Lauric acid + Benzoic acid (with 10 mol% H$^+$)	1.75	-	68	96	20

**The Yields have been calculated by NMR of isolated acid and ester fractions.*

Table 3
Esterification of dicarboxylic acids

S.No.	Dicarboxylic acid	Time (hr)	Yield %		
			Nonconjugated monomethyl ester	Conjugated monomethyl ester	Dimethyl ester
1	Itaconic acid	10.5	86	-	6
2	Homophthalic acid	6	95	-	-
3	Homoterephthalic acid	10	85	-	6

Experimental

The NMR and IR spectra were recorded on Jeol JNM-FX-100 FT-NMR and 5-DX-Nicolet FT-IR spectrometers respectively. UV spectra were recorded on a Perkin-Elmer Lambda 3B UV/VIS spectrophotometer. The optical rotation was determined on a Rudolph Autopol II, automatic polarimeter. Homophthalic[14] and Homoterephthalic[15] acids were prepared according to the reported procedures. Other carboxylic acids are available commercially and were used as such.

General Procedure for Esterification : A solution of carboxylic acid (0.01 mol) and $NiCl_2.6H_2O$ (0.001 mol, 10 mol%) in alcohol (10 ml) was heated at reflux. The solvent was evaporated under reduced pressure. The residual mass was taken up in ether (75 ml) and washed successivley with water (2x10 ml) and saturated solution of $NaHCO_3$ (3x10 ml) to remove the nickel salt and the unreacted carboxylic acid. The ether layer was dried (anh. Na_2SO_4) and evaporated to get the ester. The bicarbonate extract gave the unreacted acid on acidification.

In the case of dicarboxylic acid, the diester and monoester were separated by treatment with bicarbonate solution as described above and characterised by spectral analysis.

Methyl 3-carboxybut-3-enoate : mp. 69° (Lit.[16] mp. 67-70°); NMR ($CDCl_3$, TMS): δ 3.36 (s, 2H, allylic $C\underline{H}_2$), 3.71 (s, 3H, $COOCH_3$), 5.84 (d, 1H, J=0.7 Hz, ethylenic CH), 6.48 (s, 1H, ethylenic CH), 10.89 (br s, 1H, $O\underline{H}$).

Methyl 2-carboxyphenylacetate : mp. 97° (Lit.[2h] mp. 98°); NMR (TFA-d, TMS): δ 3.88 (s, 3H, $COOC\underline{H}_3$), 4.19 (s, 2H, - $C\underline{H}_2$), 7.38-7.72 (m, 3H, aromatic), 8.20-8.29 (m, 1H, aromatic).

Methyl 4-carboxyphenylacetate : mp. 137° (Lit.[2h] mp. 136°); NMR (TFA-d, TMS): δ 3.90 (s, 5H, $C\underline{H}_2$, CO_2 $C\underline{H}_3$), 7.79 (q, 4H, J=8, 70 Hz, aromatic).

For water soluble esters : The reactions were performed at 0.05 mol scale of the acid. After the reaction was complete, the solvent was evaporated. The residue was taken up in $CHCl_3$ or CH_2Cl_2 (100 ml), and washed with brine (5 ml). The organic layer was dried (anh. Na_2SO_4) and evaporated. The liquid thus obtained was distilled under reduced pressure to get the ester.

Competition Experiments : A mixture of aromatic/α, β-unsaturated acid (0.01 mol), nonconjugated aliphatic acid (0.01 mol) and $NiCl_2.6H_2O$ (0.001 mol, 10 mol%) in methanol (10 ml) was heated at reflux. The reaction mixture was worked up as usual to get the ester and acid fractions which were analysed by NMR to determine the yields.

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