Esterification of Carboxylic Acids by Alcohols with 2-Chloro-1,3,5-trinitrobenzene as Condensing Agent[1)]

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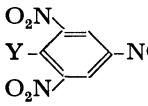
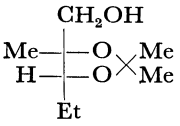
(Received November 28, 1980)

When mixtures of carboxylic acids or their sodium salts and alcohols were treated with 2-chloro-1,3,5-trinitrobenzene in the presence of pyridine under mild conditions, the corresponding carboxylic esters were formed. The yields and the rates of the ester formation depended on the types of the acids and the alcohols used.

Though the high reactivity of 2,4,6-trinitrophenyl carboxylates (**2**) in substitution reactions has been well recognized,[3)] the applications of these active esters to synthetic reactions are not many because few good methods for the general preparation of **2** under mild conditions are known.[4)] The kinetic parameters for the formation of chloride ion in the aqueous methanolic solutions of 2-chloro-1,3,5-trinitrobenzene (**1**) and sodium carboxylates,[5)] indicate that **1** reacts with carboxylates fairly rapidly and that the intermediate thus formed, in situ, may be used for the synthetic reactions. Wittmann utilized **1** in this way for the preparation of phosphoric acid esters[6)] and recently Inomate *et al.* 2-fluoro-1,3,5-trinitrobenzene (FTNB) for the preparation of *N*-phenyl amides, carboxylic esters, and thiocarboxylic *S*-esters.[7)] Several studies on the use of other polynitrohalobenzenes are also known.[8)] The present paper describes that **1** is particularly useful for the synthesis of esters of aromatic and aliphatic carboxylic acids.



1 Y=Cl
2 Y=OCOR
3 Y=OH



6

$$\mathbf{1} + 2R^1COOH(Na) \xrightarrow[\text{benzene}]{Et_3N} R^1COOCOR^1 + \mathbf{3}$$

4

$$\mathbf{1} + R^1COOH(Na) + R^2OH \xrightarrow{C_5H_5N} R^1COOR^2 + \mathbf{3}$$

5

Results and Discussion

Preliminarily, mixtures of sodium carboxylates and 2-butanol were treated with **1** at room temperature in ether, benzene, dichloromethane, acetonitrile, dimethyl sulfoxide, or hexamethylphosphoric triamide. In all cases, the formation of *s*-butyl carboxylates was observed but the esters were always contaminated with varied amounts of acid anhydrides. Alternatively, when **1**, carboxylic acids, and triethylamine were mixed in a 0.5:1:1 molar ratio under the absense of alcohols, acid anhydrides (**4**) were formed in good yields, as exemplified in Table 1.

On the other hand, however, when carboxylic acids or their sodium salts, alcohols, and **1** were mixed in pyridine used as the solvent, the corresponding esters (**5**) were formed in good yields, except for the esterification of carboxylic acids not branched at the α-carbon atom, where the use of a limited amount of pyridine in dichloromethane was preferable. Other bases such as triethylamine or 1,8-diazabicyclo[5.4.0]-undec-7-ene did not give the good yield and the products were contaminated with deep red substance. 4-Dimethylaminopyridine, known as an excellent acyl transfer reagent,[9)] was not effective and even retarded the reaction. In agreement with the trend in the nucleophilic aromatic substitution, the corresponding iodo- or bromotrinitrobenzene was less reactive than **1** and 2,4-dinitrochlorobenzene was almost useless.

The mechanism of this esterification is not clear at present. Inomata *et al.* described that the esteri-

TABLE 1. FORMATION OF ACID ANHYDRIDES

Acid	Base	Solvent	Reaction time/min	Products (Yield/%)
$(CH_3)_2CHCOOH$	Et_3N	Benzene	30	$[(CH_3)_2CHCO]_2O$[a)] (96)
$(CH_3)_3CCOOH$	Et_3N	Benzene	60	$[(CH_3)_3CCO]_2O$[a)] (98)
$CH_3CHCH_2CHCH_3$[b)] (COOH, COOH)	Et_3N	Benzene	5	$CH_3CHCH_2CHCH_3$ (CO-O-CO)[a),c)] (99)
2,3,6-$(CH_3)_3C_6H_2CO_2Na$		Pyridine	30	[2,3,6-$(CH_3)_3C_6H_2CO]_2O$[d)] (90)

a) The identity and the yield of the products were determined by GLPC by comparing with the authentic specimens. b) *meso*-2,4-Dimethylglutaric acid (1 mmol) was used per 1 mmol of **1** and 1 mmol of Et_3N. c) No *dl*-anhydride was detected. d) Isolated yield. Mp 100.5—101.5 °C. Found: C, 77.16; H, 7.08%. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14%.

fication using FTNB proceeds through the acyl fluorides as the intermediates which undergo the nucleophilic attack.[7b] On the other hand, in the esterification using **1** the main reaction seems to proceed through the acid anhydrides presumably formed from the other more reactive intermediates, the active esters (**2**) and/or acyl chlorides, by the attack of carboxylate anions remaining in the mixture. However, the direct attack of alcohols on **2** or on acyl chlorides are also considered to participate to a varied extent. For example, the formation of *t*-butyl pivalate (entry 7, Table 3) can not be explained by the anhydride route alone because the reaction between 2-methyl-2-propanol and pivalic anhydride in pyridine is extremely slow.[10] The difference between the two reagents, **1** and FTNB, in the esterification reaction can be easily understood when we consider the fact that fluorine atom attached to aromatic nucleous is much more reactive than chlorine atom in nucleophilic aromatic substitution, but that the acyl fluorides are, in turn, comparatively sluggish in nucleophilic displacements. In fact, the esterifications with FTNB are much slower than those with **1**.[11]

Aromatic Acids. Common aromatic acids were smoothly esterified in pyridine by the procedure exemplified in experimental part (Method A). They are summarized in Table 2. The esterification of 2,3,6-trimethylbenzoic acid by secondary or tertiary alcohol was difficult and a considerable amount of the acid anhydride was formed (entry 14 and 15, Table 2). An alcohol (**6**)[12] having an acid-sensitive acetal group could also be benzoylated in good yield.

Aliphatic Acids Branched at the α-Carbon Atom. The esters of primary, secondary, and tertiary alcohols were prepared by the same procedure as used in the above aromatic acid esters. The results are summarized in Table 3. Sterically crowded *t*-butyl pivalate was formed only in poor yield and a large amount of pivalic anhydride was detected. In order to examine the stability of the epimerizable α-carbon atom during the reaction, methyl hydrogen *meso*-2,4-dimethylglutarate was esterified with 2-methyl-2-propanol (entry 9, Table 3). The ester was obtained in good yield but the product was partly epimerized (*dl*:*meso*=1:10). On the other hand, the ester of secondary alcohol was obtained without any epimerization (entry 8, Table 3), presumably because of the rapidness of the reaction.

Aliphatic Acid Not Branched at the α-Carbon Atom. When aliphatic carboxylic acids which do not bear alkyl substituents on the carbon atom α to the carboxyl group, were esterified by the same procedure as described above (Method A), the products were contaminated by reddish brown substance and by some unchanged **1**. The yield of the esters was accordingly not satisfactory (50—60%). Various modifications were made to improve the yield, and the best result was obtained by conducting the reaction in dichloromethane using a limited amount of pyridine as catalyst (2—3 mole equiv. per 1 mole of **1**; Method B).[13] This procedure required much longer reaction time and the rate of esterification decreased in the order of primary alcohols>secondary alcohols>tertiary alcohols. They are summarized in Table 4.

Phenol Esters. The present method was not suitable for the preparation of phenol esters because of the concomitant formation of phenyl 2,4,6-trinitrophenyl ether (Table 5). Alternatively, the same ether

Table 2. Esterification of aromatic carboxylic acids

	Acid (2 mmol)	Alcohol (2.4 mmol)	Reaction time/h	Yield of esters/%
1	$C_6H_5CO_2H$	2-Butanol	3	93[a]
2	$C_6H_5CO_2Na$	2-Butanol	3	98[b]
3	$C_6H_5CO_2Na$	2-Methyl-2-propanol	18	85[a]
4	$4\text{-}NO_2C_6H_4CO_2H$	Ethanol	2	91[c]
5	$4\text{-}NO_2C_6H_4CO_2H$	Benzyl alcohol	2	97[c]
6	$4\text{-}NO_2C_6H_4CO_2H$	2-Propanol	3	93[c]
7	$4\text{-}NO_2C_6H_4CO_2H$	2-Methyl-2-propanol	3	88[c]
8	$4\text{-}NO_2C_6H_4CO_2Na$	2-Methyl-2-propanol	3	93[c]
9	$3,5\text{-}(NO_2)_2C_6H_3CO_2H$	2-Propanol	3	98[c]
10	$3,5\text{-}(NO_2)_2C_6H_3CO_2H$	2-Methyl-2-propanol	3	97[c]
11	$3,5\text{-}(NO_2)_2C_6H_3CO_2Na$	2-Methyl-2-propanol	3	90[c]
12	$2,3,6\text{-}(CH_3)_3C_6H_2CO_2H$	Benzyl alcohol	6	92[a]
13	$2,3,6\text{-}(CH_3)_3C_6H_2CO_2Na$	Methanol	1	96[b,d]
14	$2,3,6\text{-}(CH_3)_3C_6H_2CO_2Na$	2-Propanol	24	30[e,f] (37% Anhydride)
15	$2,3,6\text{-}(CH_3)_3C_6H_2CO_2Na$	2-Methyl-2-propanol	24	6[f] (44% Anhydride)

a) Isolated yield of once distilled product. b) Yield was determined by GLPC by comparison with authentic sample. c) Yield of crude ester. All these crude crystals melted within one degrees of melting points reported in the literature. d) A new compound. Bp 90 °C (bath)/2666 Pa. Found: C, 73.84; H, 7.85%. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92%. e) The authentic sample was prepared from the sodium salt of the acid and isopropyl bromide in HMPA. f) A mixture of ester and anhydride was obtained after preparative TLC. Yield was calculated from NMR data.

Table 3. Esterification of aliphatic acids branched at α-carbon atom

Acid (2 mmol)	Alcohol (2.4 mmol)	Reaction time/h	Isolated yield of esters/%
$CH_3(CH_2)_2CHCO_2H$ (CH₃ branch)	Benzyl alcohol	2	95[a]
	Cyclohexanol	3	95
	2-Methyl-2-propanol	3	74
$CH_3(CH_2)_2CHCO_2Na$ (CH₃ branch)	2-Methyl-2-propanol	3	69
$(CH_3)_3CCO_2H$	Benzyl alcohol	3	95
	Cyclohexanol	3	73(85[b])
	2-Methyl-2-propanol	32	30[b] (60% Anhydride)
$CH_3CHCH_2CHCH_3$[c] (COOH, $COOCH_3$)	2-Propanol	10 min	83[d]
	2-Methyl-2-propanol	3	79[e]

a) A new compound. Bp 85 °C (bath)/5599 Pa. Found: C, 75.56; H, 8.80%. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80%. b) Yield was determined by GLPC. c) Methyl hydrogen *meso*-2,4-dimethylglutarate. d) No *dl*-ester was detected. e) The ratio of *meso*-: *dl*-ester was 10 : 1 (GLPC).

Table 4. Esterification of aliphatic acids not branched at α-carbon atom

Acid (1 mmol)	Alcohol (1.1 mmol)	Pyridine (mmol)	Reaction time/h	Isolated yield of esters/%
Propionic acid	Benzyl alcohol	2.1	20	96[a]
	Cyclohexanol	2.1	30	97[a]
	2-Methyl-2-propanol[b]	2.1	60	83
Valeric acid	Benzyl alcohol	3.5	15	87
	Cyclohexanol	3.5	25	94[a]
	2-Methyl-2-propanol[b]	3.5	50	84
Hexanoic acid	Benzyl alcohol	3.5	15	88
	Cyclohexanol	3.5	25	93

a) Yield was determined by GLPC. b) Two mmol of 2-methyl-2-propanol was added.

Table 5. Formation of phenol esters

Acid	Reaction[a] time/h	Yield/%[b] Ester	Yield/%[b] $2,4,6\text{-}(NO_2)_3\text{-}C_6H_2OC_6H_5$
$4\text{-}NO_2C_6H_4CO_2Na$	3	66	27
$CH_3(CH_2)_3CO_2H$	40	54	36

a) The salt or acid (1 mmol), phenol (1 mmol), and **1** (1 mmol) were mixed by method B. b) Yields were calculated from the NMR data of the mixture of two products obtained.

was obtained in 73% yield by mixing **1** and phenol in the presence of pyridine. Similar preparation of unsymmetrical diphenyl ethers has already been reported.[14]

Experimental

All reagents employed were dried by appropriate methods. Commercial 2-chloro-1,3,5-trinitrobenzene (**1**) was recrystallized from chloroform to a constant mp 81—82 °C. The whole procedures were carried out under the exclusion of moisture. The progresses of the reactions were followed by GLPC and the esters formed were identified by comparing their NMR spectra with those of the authentic specimens.

Acid Anhydrides (Table 1). A mixture of **1** (1 mmol, 245 mg), carboxylic acid (2 mmol), and triethylamine (2 mmol, 276 μl) in benzene (3 ml) was stirred at room temperature. The products were identified by the comparison of the retention time in GLPC with the authentic specimens, and the yields were determined by comparison with appropriate internal standards.

Esters of Aromatic Acids and Esters of Aliphatic Acids Branched at the α-Carbon Atom (Method A) (Tables 2 and 3). The typical example is as follows. **1** (2 mmol, 490 mg) was added to a stirred mixture of benzoic acid (2 mmol, 244 mg) and 2-butanol (2.4 mmol, 220 μl) in pyridine (2 ml). After stirring for 3 h, an 8% aqueous sodium hydrogencarbonate solution (20 ml), water (10 ml), and ether (20 ml) were added and the whole mixture was stirred until the precipitate of pyridine picrate dissolved in the aqueous layer. The ether layer was separated and combined with the second extract (ether, 20 ml). The ether extract was washed with water until the yellow color of the solution was removed, then twice with 2% aqueous hydrochloric acid (20 ml) and water, and dried with sodium sulfate. Distillation of the residue gave *s*-butyl benzoate in 93% yield.

Crystalline esters (entries 4—13, Table 2) were filtered after treating with sodium hydrogencarbonate solution and washed well with water. All these crude crystalline esters showed correct mp and NMR spectra without further purification.

dl-erythro-*2,3-Isopropylidenedioxy-2-methylpentyl Benzoate.* It was prepared by the method A by stirring the corresponding isopropylidenedioxy alcohol (**6**)[12] (1.05 mmol, 186 mg), sodium benzoate (1.05 mmol, 152 mg), and **1** (1.05 mmol,

260 mg) in pyridine (1 ml) at room temperature for 3 h in 86% yield. Mp 70.5—71 °C. Found: C, 69.05; H, 7.97%. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97%.

Esters of Aliphatic Acids Not Branched at the α-Carbon Atom (Method B) (Table 4). A typical example is as follows. Pyridine (2.1 mmol, 170 μl) was slowly added over a period of five minutes to a stirred mixture of propionic acid (1 mmol, 75.5 μl), benzyl alcohol (1.1 mmol, 114.4 μl), and **1** (1 mmol, 245 mg) in dichloromethane (2 ml). The mixture was stirred for 20 h at room temperature. The reaction mixture was worked up as described in method A, giving benzyl propionate in 96% yield.

Phenol Esters. Carboxylic acid, phenol, and **1** (1 mmol each) reacted according to the method B (3.5 mmol of pyridine). Results were shown in Table 5. In an experiment without the carboxylic acid (40 h), 2,4,6-trinitrophenyl phenyl ether was obtained in 73% yield.

This work was partially supported by a Grant-in-Aid for Scientific Research No. 443008 from the Ministry of Education, Science and Culture.

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10) For example, a mixture of pivalic anhydride (1 mmol) and 2-methyl-2-propanol (1 mmol) in pyridine (2 ml) gave the ester only in 10% yield at room temperature after 10 d.

11) For example, FTNB method gave benzyl pivalate in 27—42% yield by refluxing in acetonitrile for 92 h,[7b] while the present method gave the same ester in 95% yield in 3 h at room temperature (entry 5, Table 3).

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