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An Efficient General Method for Esterification of Aromatic Carboxylic Acids

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Abstract *: Treatment of a variety of aromatic carboxylic acids with alcohols in the presence of thionyl chloride results in excellent yields of corresponding esters. This esterification system is compatible with a wide assortment of functional groups.* Copyright © 1996 Elsevier Science Ltd

Although a plethora of experimental conditions are well known for the esterification of aromatic carboxylic acids,[1] most of these require long reaction periods and are of less use due to their limited generality and low yields. Other methods suffer from a lack of chemoselectivity when a phenolic hydroxy group or an amino group are present in aromatic carboxylic acids.

During the course of our studies on synthetic peptides, we needed (R) (-) methyl phenyl glycinate hydrochloride, which was prepared by esterification [2] of (R) (-) α-aminophenylacetic acid, using thionyl chloride and methanol without any loss of optical activity. Our interest in medicinal chemistry led us to explore the use of this reagent system for esterification of phenolic hydroxy and amino substituted aromatic carboxylic acids. We report herein an efficient method for esterification of a broad variety of aromatic carboxylic acids in reaction periods not exceeding 3 hours in the presence of thionyl chloride and commercially available methanol, ethanol or 1-butanol. The methyl esters are obtained at ambient temperatures while the ethyl and n-butyl esters require condition of reflux.

The following example is representative of a typical esterification procedure. To a stirred solution of 4-hydroxybenzoic acid (1.38 gm, 10 mmol) in 15 ml of methanol, under ice-cooling, was added thionyl chloride (1.09 ml, 15 mmol) dropwise over 10 minutes. After stirring the reaction mixture for 3 h, methanol is distilled out and 25 ml of water is added. The separated ester is extracted with ethyl acetate and washed with 10 ml of saturated sodium bicarbonate solution. Drying (Na_2SO_4) and evaporation of the ethyl acetate gave the ester in pure form. In case of ethyl and n-butyl ester preparation, the reaction mixture is refluxed for 2 h. For amino substituted aromatic esters, the reaction

mixture, after distilling out alcohol, is neutralised with saturated sodium bicarbonate solution to give the ester.

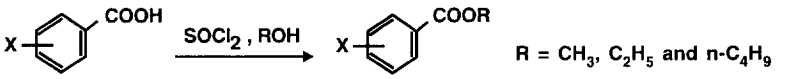


Table 1 illustrates the generality of this esterification procedure [3]. Note that phenolic hydroxy groups, amino groups and olefinic double bonds (entries 1-3, 4-6 and 7) are unaffected under these conditions.

Table 1. Esterification of Aromatic Carboxylic Acids by $SOCl_2$ and ROH

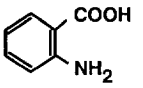
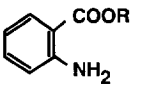
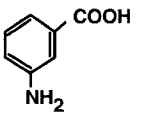
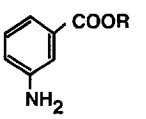
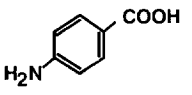
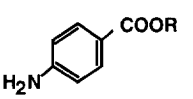
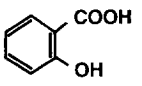
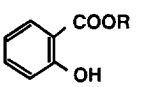
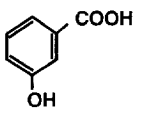
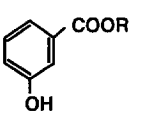
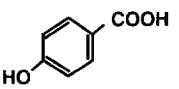
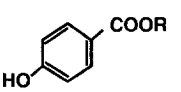
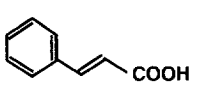
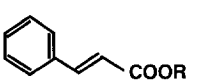
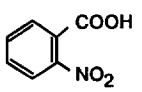
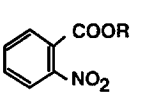
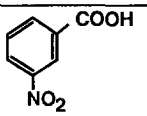
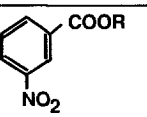
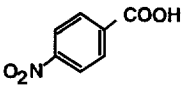
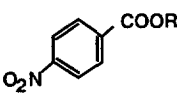
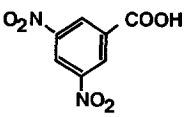
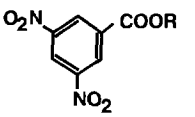
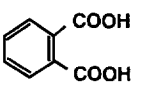
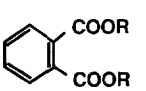
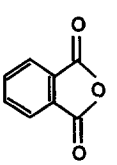
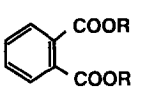
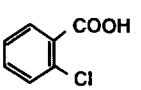
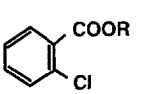
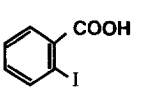
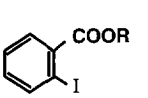
Entry	Substrate	Product	Type of Esters	% Yield[a]
1			R = CH_3 R = C_2H_5 R = n-C_4H_9	57 47 39
2			R = CH_3 R = C_2H_5 R = n-C_4H_9	96 90 90
3			R = CH_3 R = C_2H_5 R = n-C_4H_9	95 90 90
4			R = CH_3 R = C_2H_5 R = n-C_4H_9	56 46 38
5			R = CH_3 R = C_2H_5 R = n-C_4H_9	93 91 90
6			R = CH_3 R = C_2H_5 R = n-C_4H_9	94 93 90
7			R = CH_3 R = C_2H_5 R = n-C_4H_9	95 93 91
8			R = CH_3 R = C_2H_5 R = n-C_4H_9	55 47 38

Table 1. Contd.

Entry	Substrate	Product	Type of Esters	% Yield[a]
9			R = CH_3 R = C_2H_5 R = n-C_4H_9	94 92 90
10			R = CH_3 R = C_2H_5 R = n-C_4H_9	94 93 90
11			R = CH_3 R = C_2H_5 R = n-C_4H_9	94 92 90
12			R = CH_3 R = C_2H_5 R = n-C_4H_9	90 84 72
13			R = CH_3 R = C_2H_5 R = n-C_4H_9	81 74 61
14			R = CH_3 R = C_2H_5 R = n-C_4H_9	91 86 81
15			R = CH_3 R = C_2H_5 R = n-C_4H_9	84 79 69

[a]Yields refer to pure isolated materials.

The method is equally convenient for esterification of a dicarboxylic acid [4], its anhydride, and chloro, iodo and nitro substituted aromatic carboxylic acids. Lower yields in the case of ortho-substituted aromatic carboxylic acids (entries 1, 4 and 8) can be attributed to intramolecular hydrogen bonding. However, no efforts were made to optimize the yield of these esters. The method works equally well with aliphatic carboxylic acids.

The standard method [5] of the preparation of dialkyl sulphite is also by reaction of thionyl chloride with alcohol. The possibility that dialkyl sulphite was the esterifying agent could not be ruled out. High yield of p-nitro phenyl esters [6] of N-acyl amino acids using di-p-nitrophenyl sulphite in the presence of pyridine, as well as esterification of salicylic acid [7] with diaryl sulphite in presence of N-heterocyles have been reported. The esterification of 3, 5-dinitrobenzoic acid with dimethyl sulphite,

under neutral conditions in benzene (refluxing) failed. However, esterification could be achieved with anhydrous p-toluenesulphonic acid and pyridine in 94% and 84% yield respectively. However, this experimental protocol is cumbersome besides needing freshly prepared alkyl sulphite.

In conclusion, this esterification reaction is an attractive and efficient route to synthesise methyl, ethyl and n-butyl esters of substituted aromatic carboxylic acids.

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References and Notes :

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2. (a) Chang, Z.-Y. ; Coates, R.M. *J. Org. Chem.* **1990**, 55, 3475-3483. (b) Brenner, M. ; Huber, W. *Helv. Chim. Acta* **1953**, 36, 1109-1115.
3. Most of the products are commercially available and the identity of reaction products was determined by direct comparison of TLC, 1H NMR, IR, and melting point.
4. For 10 mmole phthalic acid, we used 30 mmole of thionyl chloride.
5. Vogel, A.I. ; Cowan, D.M. *J. Chem. Soc.* **1943**, 16-24.
6. Iselin, B. ; Rittel, W. ; Sieber, P. ; Schwyzer, R. *Helv. Chim. Acta* **1957**, 40, 373-387.
7. Boellert, V. ; Schnell, H. *Ger. Pat.* 1, 288, 094, **1969**.

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