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# CONVENIENT PROCEDURES FOR ESTERIFICATION OF CARBOXYLIC ACIDS

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Methods available for the conversion of carboxylic acids into esters are abundant, but few are direct, general, and economically viable for large scale preparation while employing sufficiently mild conditions to be widely applicable to acid and/or base sensitive compounds[1]. We wish to report two closely related methods for the condensation of carboxylic acids with alcohols of a wide variety of structural types. The reaction proceeds smoothly at room temperature under virtually neutral conditions. The procedure is operationally simple and can be applied generally.

The methods differ from each other only in the reagent involved for the activation of carboxylic acids. In one case, N,N-dimethylphosphoramidic dichloride $[(CH_3)_2NPOCl_2]$[2] is used, and in the other, phenyl dichlorophosphate $(C_6H_5OPOCl_2)$[3]. The common procedure is illustrated below by a typical example.

To a solution of phenoxyacetic acid (304 mg, 2 mmol) in 1,2-dimethoxyethane (10 ml) at 0°C, were added sequentially pyridine (0.485 ml, 6 mmol), N,N-dimethylphosphoramidic dichloride (486 mg, 3 mmol), and 2-phenoxyethanol (552 mg, 4 mmol). The resulting solution was stirred at room temperature under an atmosphere of argon for 16 hr. The solution was poured into ice-cold 1 N

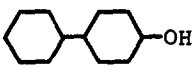
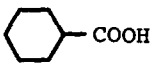
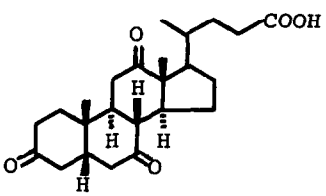
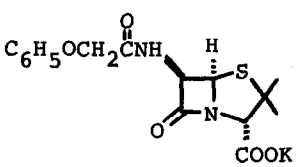
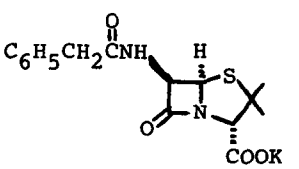
hydrochloric acid (40 ml) and extracted with chloroform (4 x 30 ml). The combined extracts were dried ($MgSO_4$), filtered and concentrated. Column chromatography of the residue on silica gel with benzene elution gave 2-phenoxyethyl phenoxyacetate (445 mg; 82% yield): mp 83-84°C (chloroform-ether); ir ($CHCl_3$) 1755 (ester), 1595 and 1585 $cm^{-1}$ (aromatic); nmr ($CDCl_3$) δ 4.09 (t, 2H, J = 5 Hz, $-COOCH_2\underline{CH_2}-$), 4.49 (t, 2H, J = 5 Hz, $-COOCH_2-$), 4.60 (s, 2H, $-CH_2COO-$), and 6.82-7.38 (complex, 10H, aromatic); ms $M^+$ 272.1057 (calcd. for $C_{16}H_{16}O_4$: 272.1049). Anal. calcd. for $C_{16}H_{16}O_4$: C 70.58, H 5.92; found: C 70.22, H 5.88. When the reaction was repeated with phenyl dichlorophosphate in place of N,N-dimethylphosphoramidic dichloride, 445 mg (88% yield) of the pure product was isolated.

Under similar conditions, the condensation of several functionally diverse carboxylic acids with alcohols of various types were examined. The generality of the methods is apparent from the results outlined in Table 1. Comparison of Entries 1-4 and of Entries 6-9 further reveals that the reaction is independent of the steric environment of alcohols. Even in the case of a tertiary alcohol (Entries 2 and 9), the yields of products are compatible with those involving sterically less hindered ones. An especially noteworthy feature of the method is the application of mild and near-neutral conditions throughout the reaction, whereby the acid and/or base sensitive functional groups are expected to be unaffected. The experimental results obtained for the esterification of penicillins V (Entry 13) and G (Entry 14) with benzyl alcohol and phenol respectively agree with the expectation. In these two reactions, the readily available potassium salts were used and the amount of pyridine was reduced to two equivalents[4].

The two reagents were shown to be complementary. Whereas the commercially available phenyl dichlorophosphate was generally more effective, better results were obtained for certain cases such as the esterification of penicillins (Entries 13 and 14) by using N,N-dimethylphosphoramidic dichloride[5]. It is also noted that both reagents were found to be superior to chlorophosphates $(PhO)_2POCl$ and $(EtO)_2POCl$ which along with closely related compounds [e.g. $(PhO)_2PON_3$ and $(EtO)_2POCN$], have been successfully used as activating agents for the transforma-

Table 1. Esterification of Carboxylic Acids

$$RCOOH + R'OH \xrightarrow[\text{or } C_6H_5OPOCl_2\ (\underline{B})]{C_5H_5N;\ (CH_3)_2NPOCl_2\ (\underline{A})} RCOOR'$$

| Entry | RCOOH | R'OH | Isolated Yield (%) A | B |
|---|---|---|---|---|
| 1 | $C_6H_5OCH_2COOH$ | $C_6H_5OCH_2CH_2OH$ | 82 | 88 |
| 2 | | $(CH_3)_3COH$ | 89 | 94 |
| 3 | |  | 76 | 84 |
| 4 | | $CH_3CH_2OH$ | 84 | 97 |
| 5 |  | $C_6H_5CH_2CH_2CH_2OH$ | 70 | 81 |
| 6 | $C_6H_5OCH(CH_3)COOH$ | $CH_3CH_2OH$ | 83 | 92 |
| 7 | | $CH_3OH$ | 84 | 85 |
| 8 | | $C_6H_5CH_2OH$ | 96 | 95 |
| 9 | | $(CH_3)_3COH$ | 84 | 90 |
| 10 | $CH_2=CH(CH_2)_8COOH$ | $CH_2=CHCH_2OH$ | 73 | 77 |
| 11 | $CH_3CH_2OCH_2COOH$ | $C_6H_5OH$ | 96 | 98 |
| 12 |  | $C_6H_5OH$ | 78 | 88 |
| 13 |  | $C_6H_5CH_2OH$ | 88 | 65 |
| 14 |  | $C_6H_5OH$ | 84 | 60 |

tion of carboxylic acids to thiol esters, acyl azides and amides.[7-13] For example, when the condensation of cyclohexanecarboxylic acid and 3-phenyl-1-propanol was carried out under the aforementioned conditions using $(PhO)_2POCl$ or $(EtO)_2POCl$, substantially lower (<25%) yields[14] of the corresponding ester were obtained (see Entry 5).

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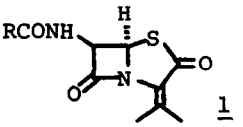
References and Notes

1. For reviews, see S.R. Sandler and W. Karo, "Organic Functional Group Preparations," Vol. I, Academic Press, New York, N.Y. 1968, Chapter 10; C.A. Buchler and D.E. Pearson, "Survey of Organic Syntheses," Wiley-Interscience, New York, N.Y. 1970, Chapter 14.
2. E.N. Walsh and A.D.F. Toy, Inorg. Synth., 7, 69 (1963).
3. Phenyl dichlorophosphate obtained from Aldrich was used without purification
4. These reactions were worked up by the addition of ice-cold water and extraction with chloroform.
5. The relatively poor yields obtained for the esterification of the penicillines using phenyl dichlorophosphate was partly due to the concomitant formation of the corresponding anhydropenicillins (1) in varying amounts via a competing rearrangement process[6].



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6. For an analogous rearrangement, see S. Wolfe, J.C. Godfrey, C.T. Holdrege, and Y.G. Perron, Can. J. Chem., 46, 2549 (1968).
7. M.A. Insalaco and D.S. Tarbell, Org. Synth., 50 (1970) and references cited therein.
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12. S. Masamune, S. Kamata, J. Diakur, Y. Sugihara, and G.S. Bates, Can. J. Chem., 53, 3693 (1975).
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14. The low yields are probably due to the preferential attack on the mixed anhydrides $C_6H_{11}COOPO(OR)_2$ at the phosphorus center by the alcohol anticipated on the basis of the observation made on carboxylic-phosphinic anhydrides (cf. ref. 13).

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