# CHAPTER 3

## POLYMER-SUPPORTED REAGENTS : THE USE OF ANION-EXCHANGE RESIN IN THE SYNTHESIS OF ARYLOXYACETIC ACID ESTERS

ABSTRACT

Insoluble polymer-supported nucleophilic reagent has been prepared by treatment of sodium salt of aryloxyacetic acid with Amberlite IRA-400 ($C\bar{l}$), a macroreticular anion-exchange resin containing quaternary ammonium groups. This reagent was used for the synthesis of aryloxyacetic acid esters by reaction with alkyl halides. In addition to ease and simplicity of the method and regeneration of the polymeric by-product, the polymeric reagent seems to increase the nucleophilicity of the anions. The products were obtained in higher yields and purity. In addition to this transesterification is observed when alcohol is used as solvent.

INTRODUCTION

Esterification of carboxylic acids with hydroxy compounds ($R'OH$) is usualdy effected by refluxing the acid and alcohol with a small amount of sulfuric acid, hydrogen chloride or arylsulfonic acid (8.1). The equilibrium is shifted to the right by an excess of the reactant or by removal of water either by azeotropic distillation or by means of a suitable drying agent. The necessity for continuous drying is eliminated when methylene or ethylene chlorides are used as solvents for the reaction.[1] A small amount of an acid chloride such as thionyl chloride, acetyl chloride or stearoyl chloride has proved superior to hydrogen chloride as a catalyst for certain esterifications at room temperature.[2]

Reactive halogen compounds (R'X) such as benzyl chloride,[3] 2-bromoacetylthiophene $(C_4H_3S)COCH_2Br$,[4] and 2-chloromethylthianaphthene $(C_8H_5S)CH_2Cl$[5] are readily converted to esters by treatment with sodium salt of carboxylic acids (8.2). A small amount of triethylamine has proved to be an effective catalyst.[5,6]

Reaction of alkyl chlorosulfites or alkyl sulfates on salts of carboxylic acids has been developed as a method of esterification (8.3). A vigorous exothermic reaction occurs between chlorosulfites and the acid salts. Further heating to 100-150°C results the evolution of sulfur dioxide and the formation of the esters. Aliphatic and aromatic acids including the hindered 2,4,6-trialkylbenzoic acids have been esterified.[7]

Esterification of carboxylic acids with diazomethane was discovered by Von Pechmann.[8] The fact that neutral alcohols do not react with diazomethane suggests that an acidic substance supplies a proton required for catalysis of the esterification(8.4). Dimethylformamide diethyl acetal $(CH_3)_2NCH(OC_2H_5)_2$ can be used as a reagent for esterification of carboxylic acids under mild conditions.[9,10] Thus benzoic acid (0.4 mole) reacts with 2 equivalents of the acetal to give ethyl benzoate (8.5) under the following conditions : in methylene chloride for 5 hrs at 40°C; in benzene for 1 hr at 80°C; in acetonitrile for 36 hrs at room temperature.[10]

The conversion of carboxylic acid into its t-butyl esters by acid-catalyzed addition to isobutene is illustrated by a procedure for the preparation of di-t-butyl malonate.[11] Phenyl

esters[12] are obtained by heating an acid and a phenol in polyphosphoric acid [PPA](8.6). Esters are formed when a solution of an acid (1 equivalent) and an alcohol (1 equivalent in pyridine is treated with p-toluenesulfonyl chloride (tosyl chloride; 2 equivalents).[13] The reaction is considered to involve intermediate formation of the acid anhydride (8.7). Carboxylic acids are converted into their ethyl esters when heated with an excess of triethyl orthoformate, $HC(OC_2H_5)_3$. Even hindered acids such as 2,4,6-trimethylbenzoic acid are esterified.[14] Diphenyldiazomethane, $(C_6H_5)_2CN_2$ is also used for esterification carboxylic acids. Hindered tertiary acids, react with diphenyldiazomethane to give benzhydryl esters.

t-Butyl esters of carboxylic acids[15] and sulfonic acids[16] have been prepared by reaction acid chlorides with alkoxides like Lithium t-butoxide, $LiOC(CH_3)_3$. The method is perticularly useful for preparation of highly hindered esters. The method is recommended for the preparation of t-butyl p-toluate[17] (8.8).

Carboxylic acids and phenols can be converted into methyl esters[18] and ethers in yields $>$ 90% by thermal decomposition of the trimethyl anilinium salts in an inert refluxing solvent like toluene (9.1). This method is successful even with sterically hindered acids. Trimethyl phosphate, $(CH_3)_3P=O$ can also be used for esterification[19] of hindered carboxylic acids.

Carboxylic acids react with 6-chloro-1-p-chlorobenzenesulfonyloxybenzotriazole (9.2) in $CHCl_3$ or acetonitrile in the presence of 1 equivalent triethylamine to form an active ester(9.3),

# CHART-8

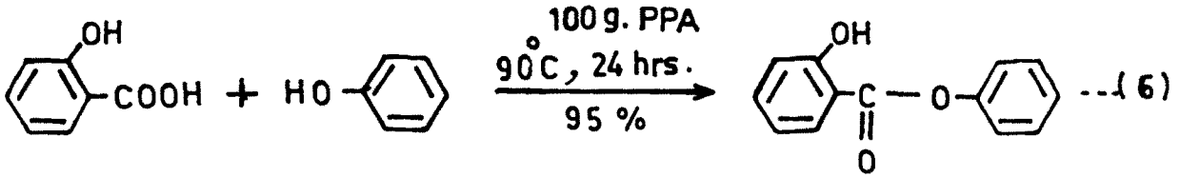
$$RCOOH + R'OH \rightleftharpoons RCOOR' + H_2O \quad \text{-------(1)}$$

$$RCOONa + RX \longrightarrow RCOOR' + NaX \quad \text{-------(2)}$$

$$RCOONa + ROSOCl \longrightarrow RCOOR' + SO_2 + NaCl \quad \text{---(3)}$$

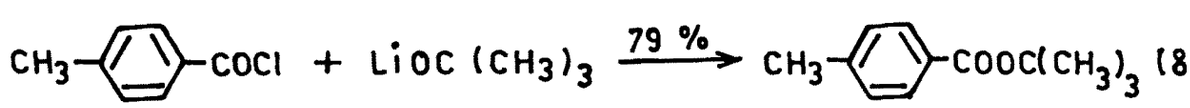
$$RCOOH \xrightarrow{H^+} R-\overset{HO^+}{\overset{\|}{C}}-OH \xrightarrow[-N_2]{CH_2\overset{-}{N}\equiv\overset{+}{N}} R-\overset{+OCH_3}{\overset{\|}{C}}-OH \longrightarrow R-\overset{OCH_3}{\overset{|}{C}}=O \xrightarrow{-H^+} \quad \text{----------(4)}$$

$$C_6H_5COOH + (CH_3)_2NCH(OC_2H_5)_2 \xrightarrow[90\%]{} C_6H_5COOC_2H_5 + C_2H_5OH + (CH_3)_2NCHO \quad \text{----------(5)}$$



(6)

$$RCOOH \xrightarrow[Py]{TsCl} (RCO)_2O \xrightarrow{R^1OH} RCOOR^1 + RCOOH \quad \text{-----(7)}$$



(8)

which can be isolated if desired. The esters (9.3) react with an alcohol, again in the presence of 1 equivalent of base, to form an ester of carboxylic acid (9.4). The esterification[20] can be carried out in one step by mixing the acid, the alcohol, the coupling reagent and 2 equivalent of base in ether. In either case, the reaction takes place at 20°.

Shaw and Kunerth[21] have reported the esterification of sodium salts of carboxylic acids with alkyl halides in hexamethylphosphoric triamide (HMPT) at room temperature. The method is applicable to the preparation of ethyl esters of hindered acids. In esterification of acids that undergo ready decarboxylation, anhydrous potassium carbonate rather than NaOH is used as base (9.5). Diesters[21] can be obtained by reaction of sodium salt of acids with dibromomethane (9.6).

The reaction of carboxylic acids and alcohols in presence of 1.2 equivalent of 1-methyl-2-bromopyridinium iodide (9.7) and 2.4 equivalent of tri-n-butyl amine affords esters[22] (9.8) in 60-90% yield. Optimum yields are obtained in refluxing toluene or $CH_2Cl_2$. The method is useful for synthesis of sterically hindered esters. Esters of protected amino acids and peptides can be prepared by treatment of cesium salt of acids with an alkyl halide in DMF (9.9). The reaction proceeds without observable racemization.[23]

Carboxylic acids can be esterified[24] by reaction with alkyl halides and 1,5-diazobicyclo [5.4.0] undecene-5 (DBU) in benzene at 25 or 80° (9.10). The reaction is widely applicable to hindered or unstable acids. Presumably the hydrogen bonded

complex of DBU and the acid plays a significant role in the reaction. The DBU can be recovered by treatment of the hydrochloride with sodium hydroxide.[25]

Esters[26] can be prepared by the reaction of an acid and an alcohol in the presence of pyridine (3 equivalents) and N,N-dimethylphosphoramidic dichloride, $(CH_3)_2NPOCl_2$ (1.5 equivalents) at room temperature. Phenyl dichlorophosphate, $C_6H_5OPOCl_2$, can also be used as the activating agent, often with somewhat improved yields. This esterification is applicable even to tertiary alcohols.

Methyl and ethyl esters[27] of carboxylic acids can be prepared by the reaction of carboxylic acids with trialkyloxonium tetrafluoroborate. The reaction is rapid even with hindered acids.

Dimethylchloroformiminium chloride, generated <u>in situ</u> from DMF and oxalyl chloride, converts carboxylic acids into an activated derivative, which reacts with alcohols or phenols in presence of pyridine to form esters[28] in 70-90% yield. The method is also useful for preparation of active esters for N-protected amino acids, since no racemization is observed.

Chemiabsorption of dicarboxylic acid on alumina or silica can be used to effect selective esterification[29] of one acid group with diazomethane. The method was demonstrated by conversion of terephthalic acid, $C_5H_4$-1,4-$(COOH)_2$, into the monomethyl ester in quantitative yield.

Acids can be esterified at 25° and in yields of 85-95% by treatment with 2-fluoro-1,3,5-trinitrobenzene (1 equivalent), 4-dimethylaminopyridine (DMAP; 2 equivalents) and an alcohol in acetonitrile for 2-24 hrs. The method is successful with hindered acids but t-butyl esters can not be prepared under these mild conditions. Presumably a trinitrophenyl ester is an intermediate.[30]

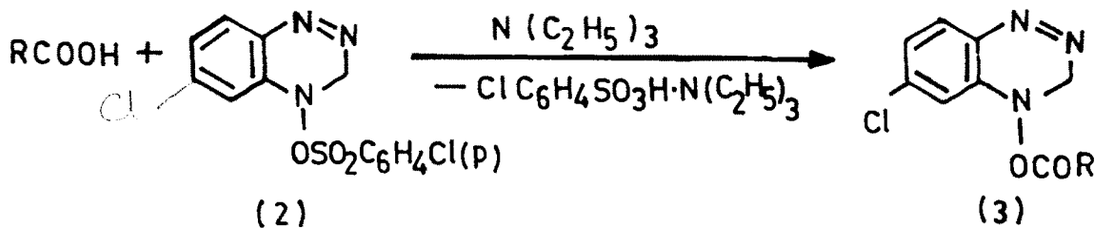
PRESENT WORK

Polystyrene-Aluminium chloride,[31] Ⓟ-$AlCl_3$ is a mild catalyst for esterification. It has the advantage of being both a Lewis acid and a dehydrating agent. Insoluble polymer-bound nucleophilic reagent derived from poly (vinyl benzyltriphenyl-phosphonium chloride) has been prepared by treatment with the sodium salt of carboxylic acids. This reagent was used for the synthesis of carboxylic acid esters.[32] In continuation of our work on polymer-supported reactions[33] and in view of the importance of aryloxyacetic acid esters is flavouring agents,[34] a simple and efficient method is now reported for esterification of aryloxyacetic acids.

Reaction of sodium salt of aryloxyacetic acid with Amberlite IRA-400 ($C\bar{l}$) forms the polymer-supported aryloxyacetate ion (9.12) which can be alkylated by treatment with alkyl halide in a suitable solvent (9.11). The products were obtained in higher yields and purity. The results are summarised in Table 1. The esterifications proceed in nonpolar solvents as well as in polar solvents, showing that the reactions involving the polymeric reagents are independent of the nature of the solvent. Hydrophilic and hydrophobic solvents are equally effective indicating that the microenvironment of the resin, in which the reaction site is made, is almost independent of the medium. Thus, less expensive and less poisonous solvents may often be employed. Runs with catalytic amount of the resin do not give satisfactory results in the esterification. Thus, the nucleophilicity of polymer-bound aryloxyacetate ion is increased sufficiently to allow esterification with alkyl halides in a manner which is related to the principles of phase transfer technique with low molecular catalysts. In addition to this transesterification is observed when alcohol is used as solvent. The results are summarised in Table 2.

# CHART—9

$$RCOOH + (CH_3)_3\overset{+}{N}\,C_6H_5\bar{O}H \xrightarrow{\Delta} RCOOCH_3 + (CH_3)_2NC_6H_5 \quad ---(1)$$

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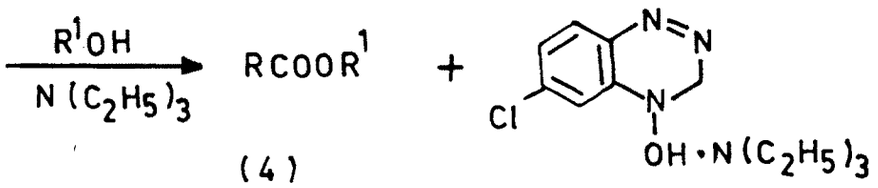
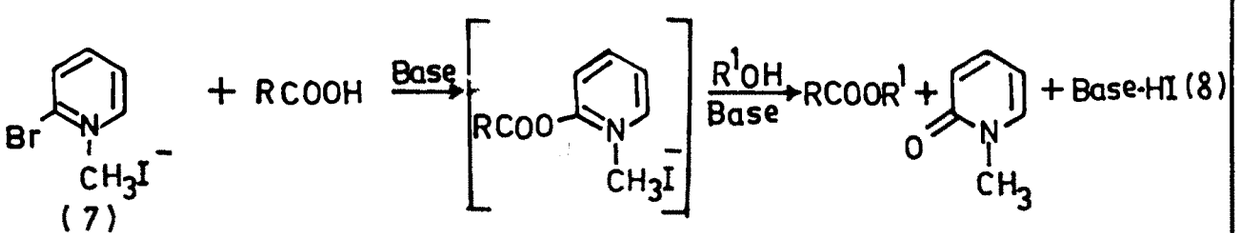



(4)

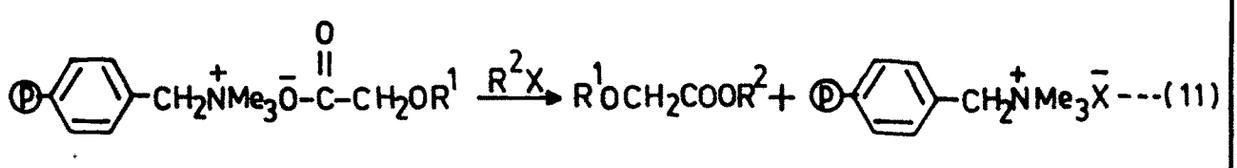
$$CH_2(COOH)_2 + C_2H_5Cl \xrightarrow[91\ \%]{K_2CO_3,\ HMPT} CH_2(COOC_2H_5)_2 \quad ------(5)$$

$$C_6H_5COOH + CH_2Br_2 \xrightarrow[86\ \%]{NaOH,\ HMPT} (C_6H_5COO)_2CH_2 \quad ------(6)$$




$$RX + R^1COOCs \xrightarrow[70-90\ \%]{DMF} R^1COOR + CsX \quad -------(9)$$

$$RCOOH + R^1X + DBU \xrightarrow{C_6H_6} RCOOR^1 + DBU\cdot HX \quad -----(10)$$




(12) (13)

Table 1. Alkylation of Polymer-supported Aryloxyacetate Ion to give Esters at 25°C

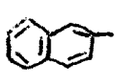
| $R^1$ | $R^2X$ | Solvent | Reaction time (hrs.) | Yield (%) |
|---|---|---|---|---|
| $C_6H_5$- | $CH_3I$ | Benzene | 4 | 92 |
| | $C_2H_5I$ | Benzene | 5 | 90 |
| | $CH_3I$ | 1,2-Dimethoxyethane | 4 | 90 |
| | $C_2H_5I$ | 1,2-Dimethoxyethane | 5 | 91 |
| | $CH_3I$ | Methanol | 5 | 94 |
| | $C_2H_5I$ | Ethanol | 5 | 93 |
| | $CH_2=CHCH_2Br$ | Benzene | 12 | 60 |
| | n-$C_4HgBr$ | Benezne | 15 | 65 |
| o-$CH_3$-$C_6H_4$- | $CH_3I$ | Benzene | 6 | 87 |
| | $C_2H_5I$ | Benzene | 6 | 85 |
| m-$CH_3$-$C_6H_4$- | $CH_3I$ | Benzene | 6 | 90 |
| | $C_2H_5I$ | Benzene | 6 | 85 |
| p-$CH_3$-$C_6H_4$- | $CH_3I$ | Benzene | 5 | 85 |
| | $C_2H_5I$ | Benzene | 5 | 83 |
|  | $CH_3I$ | Benzene | 4 | 90 |
| | $C_2H_5I$ | Benzene | 4 | 97 |

Table 2. Transesterification : Alkylation of Polymer-supported Aryloxy acetate Ion at 25°C

| $R^1$ | $R^2X$ | Solvent | Product | Reaction time (hrs) | Yield (%) |
|---|---|---|---|---|---|
| $C_6H_5$ - | $CH_3I$ | $C_2H_5OH$ | $C_6H_5OCH_2COOC_2H_5$ | 12 | 86 |
| $C_6H_5$- | $C_2H_5I$ | $CH_3OH$ | $C_6H_5OCH_2COOCH_3$ | 12 | 87 |