Tetrahedron Vol. 36, pp. 2409 2433
Pergamon Press Ltd., 1980. Printed in Great Britain

TETRAHEDRON REPORT NUMBER 93

RECENT DEVELOPMENTS IN METHODS FOR THE ESTERIFICATION AND PROTECTION OF THE CARBOXYL GROUP

EDWIN HASLAM
Department of Chemistry, University of Sheffield, Sheffield S3 7HF, England

(*Received* 19 *February* 1980)

Abstract—The chemistry of the carboxyl group is one of the cornerstones of organic chemistry. As a consequence two very important facets of synthetic methodology are the activation of the carboxyl group to facilitate esterification and the deactivation or masking of the carboxyl group during a synthetic sequence. Some of the more recent innovations and techniques which have been developed in the past 10–15 years around these features of carboxyl group chemistry are discussed in this review.

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1. INTRODUCTION

Selectivity is crucial to organic synthesis and the use of protecting groups is an indispensable and powerful artifice at the disposal of the organic chemist to enable him to achieve this end. Protecting groups are employed to prevent or to modify reaction at a specific functional group during a synthetic sequence. Selectivity is thus made possible where none existed before. The elegant use of protecting groups in polypeptide synthesis represents for many the apotheosis of this synthetic device but the need over a much wider field to develop milder and more efficient synthetic procedures has led to rapid strides in many areas of the chemistry of protecting groups.[1] The attention devoted to the carboxyl group, its activation and protection, epitomises many of these developments and the work carried out in this sphere over the past decade or so forms the basis for this review.

Two approaches to the problem of the protection of the carboxyl group in a molecule are broadly possible. The first is to use readily available or readily prepared esters, (such as methyl and ethyl), and occasionally amides, and to devise novel, mild and if possible non-hydrolytic conditions for deprotection such that other acid or base-sensitive groups in the substrate molecule may survive. The prime advantage of this approach is the ready availability or formation of the synthetic starting materials. The second approach is to devise novel ester (and amide) protecting groups which are removable under non-hydrolytic conditions. A wide range of protecting groups (principally esters) which function on the basis of different chemical principles—oxidation, photolysis, hydrogenolysis, etc. are now available in this category. The main disadvantage of this procedure generally lies in the availability and ease of preparation of the particular ester to be used.

Parallel with this work there has been a continuing search for different means to activate the carboxyl group towards esterification and lactonisation. Many valuable ideas and techniques have been discussed and amongst these the use of thiol esters has gained particular prominence and appeal. These developments provide the starting point for this discussion and review.

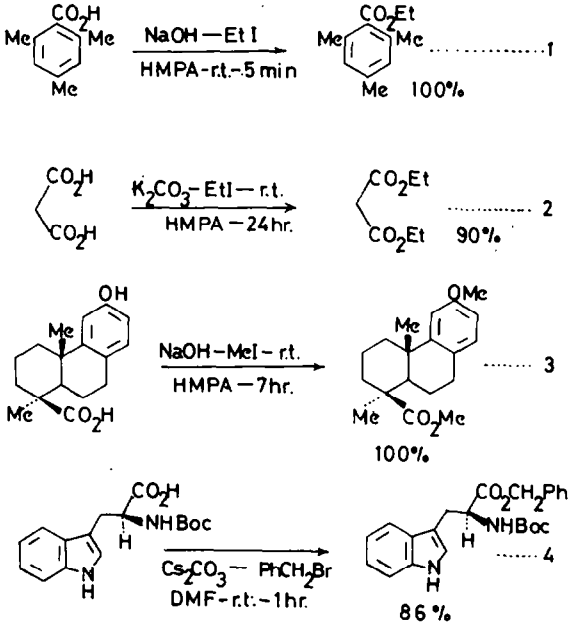
2. ESTERIFICATION OF THE CARBOXYL GROUP

Although many useful and reliable methods for the esterification of carboxylic acids have been reported in the literature[2] a great need still exists for a versatile and simple process whereby esters may

be formed under very mild conditions. Recent work has included variations and improvements of well established esterification procedures and the discovery and application of entirely new ones.

2.1 *Nucleophilic attack by the carboxyl or carboxylate group*

The well known method for the formation of carboxylic acid esters by the reaction of metal salts of carboxylic acids ($RCO_2^- M^+$, where M may be silver, lead, one of the alkali or alkaline earth metals or tertiary alkyl ammonium) and alkyl halides has not been a generally applicable synthetic procedure due principally to the poor yields brought about by the competing side reaction of dehydrohalogenation.[3] Several modifications have however increased the general utility of this method, most notable have been the improvements brought about by the use of dipolar aprotic solvents and phase transfer catalysts. Thus carboxylic acids may be converted to esters by the reaction of their sodium, potassium or calcium salts and alkyl halides in HMPA (eqns 1–3)[4,5] or DMSO.[6,7] In a related method the carboxylic acid is first converted to its caesium salt by titration with caesium carbonate or bicarbonate, the solution evaporated to dryness and then treated with the alkyl halide in DMF (eqn 4).[8]



Improvements also follow from the replacement of the metal or tertiary alkyl ammonium ion by the quaternary alkyl ammonium ion (Me_4N^+, Et_4N^+ and $^nBu_4N^+$) in dipolar aprotic media. The reaction rate and yields increase quite dramatically for n-alkyl halides in DMF, DMSO or acetonitrile,[3,9,10] (eqn 5). This amelioration has been attributed to the enhanced nucleophilicity of the carboxylate anion due to the absence of close ion-pair formation.

$$MeCO_2^- Et_4N^+ + RCH_2X \xrightarrow[r.t.]{DMF} MeCO_2CH_2R \quad \cdots\cdots 5$$

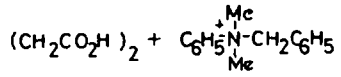
R	X	T	
^nPr	Br	0·5hr	90%
^nPr	Cl	6 hr	50%
C_6H_5	Cl	1 hr	100%

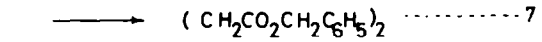
Since dichloromethane is a relatively inert compound the reaction of tetra-n-butylammonium salts of carboxylic acids and alkyl halides in dichloro-methane has also been recommended as a convenient method for the preparation of esters. Holmberg and Hanson[10] noted the formation under these conditions of small quantities of the methylene diesters of carboxylic acids and they used this observation as a basis for a synthesis of a variety of methylene diesters (eqn 6).

$$RCO_2^- {}^+N^nBu_4 + CH_2Cl_2 \longrightarrow (RCO_2)_2CH_2 \quad \cdots\cdots 6$$

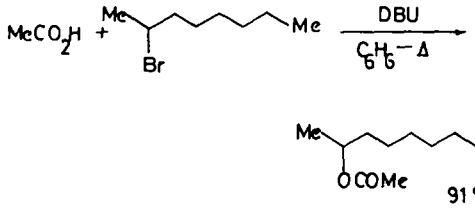
(~60–80%)

A related and mild procedure for the formation of benzyl esters and benzyl ethers of phenols is based on the thermal decomposition of the benzyldimethylanilinium salts of carboxylic acids in an inert solvent, (toluene, under reflux), eqn 7.[11,12]

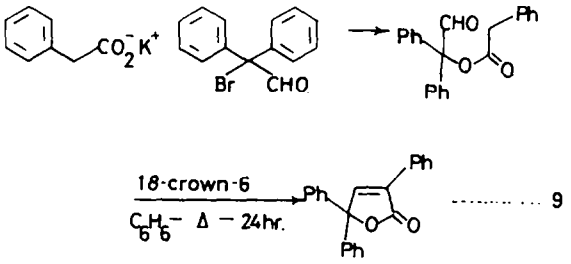




The reaction of carboxylic acids with alkyl halides in the presence of tertiary amines may often be too slow to serve as a useful esterification process. However use of the bicyclic amidine, DBU, as a base produces a considerable enhancement of rate and in benzene at room temperature or under reflux esters are formed in 70–95% yield.[13] The method has been used to form both phenacyl and methylthiomethyl esters and to esterify heterocyclic, sterically hindered, and thermally unstable carboxylic acids as well as hydroxy and amino substituted acids. The reaction conditions do not promote elimination from secondary halides (eqn 8) and these differences in reactivity between DBU and triethylamine salts has been attributed to the differences in solubility and dissociation of the salts in benzene solution.



An increasingly valuable synthetic technique utilises the ability of crown ethers to catalyse solid-liquid phase transfer reactions.[14] Thus carboxylate salts in the presence of crown ethers undergo efficient phase transfer in polar and non-polar media (acetonitrile, benzene) to give phenacyl esters in virtually quantitative fashion.[15,16] Padwa and Dehm have used this technique to synthesise the α,β-unsaturated-γ-lactone in one step (eqn 9).

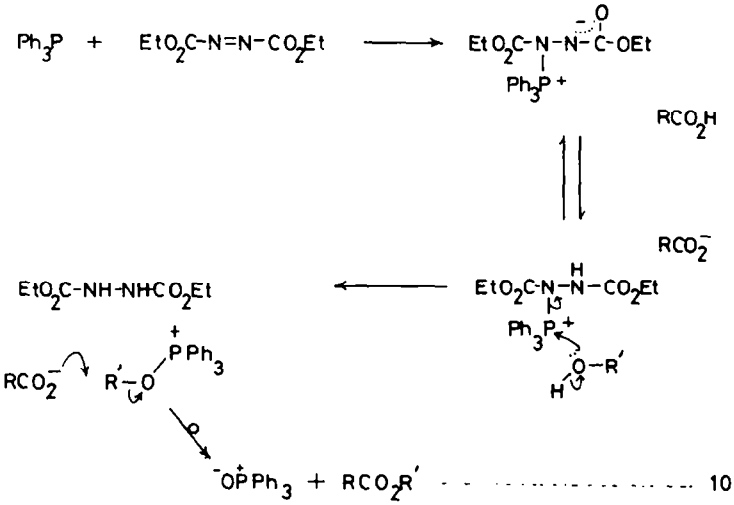


Cuprous carboxylates are believed to be key intermediates in a new method of esterification which consists in treating the carboxylic acid in refluxing benzene with the appropriate alkyl halide, cuprous oxide and pyridine, and cyclohexylisonitrile.[18]

Although alkyl halides find most frequent use in the preparation of alkyl esters utilising the carboxylate group as a nucleophile other alkylating agents may also be employed with advantage. Dimethyl sulphate has been advocated[19] as a useful reagent for the synthesis of methyl esters of sterically hindered acids and Stodola has reported the formation of methyl and ethyl esters using the corresponding dialkyl sulphates and dicyclohexylethylamine as proton acceptor in methanol or acetone solution.[20] Fairhurst and Horwell have similarly esterified thermally unstable β-keto acids (80–95% yields) in acetone at room temperature using dialkyl sulphates and DBN as base[21] and Kantlehener and Funke[22] utilised the adduct of dialkyl sulphates and dimethylformamide to esterify a range of saturated, unsaturated, halogenated aliphatic and aromatic carboxylic acids (80–98% yields). Esterification using dialkyl sulphates is well established[23,24] although relatively speaking it is a rather neglected procedure. It is a useful method to employ where acidic media must be avoided.

The boron trifluoride—alcohol procedure is used routinely to esterify carboxylic acids prior to glpc analysis but it is not generally considered for the preparation of esters. Marshall, Erickson and Folson[25] have however demonstrated the value of the reagent to prepare methyl, ethyl and isopropyl esters. Kabada[26] has similarly employed boron trifluoride-etherate as a catalyst to esterify *p*-amino benzoic acid and other substituted aromatic acids. Yields of 80–95% were recorded[27] of ethyl esters when carboxylic acids were treated with triethyloxonium fluoroborate[28] in dichloromethane with di-isopropylamine (24 hr, room temp).

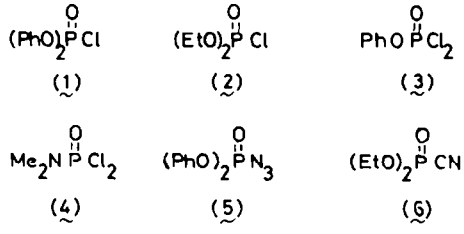
Alkoxyphosphonium salts (eqn 10) have been proposed as intermediates in esterification reactions (oxidation–reduction condensations[29,30]) promoted by triphenylphosphine and ethyl azodicarboxylate. The esterification of s-(+)-2-octanol with benzoic acid using this method gave the benzoate ester of the enantiomeric R-2-(−)-2-octanol thus supporting the suggestion that esterification occurs via initial activation of the alcohol to give the alkoxyphosphonium salt followed by an S_N2 type displacement of the alkyl group by the carboxylate anion. This reaction has also been successfully utilised for the lactonisation of ω-hydroxyacids.[31] Reactions are carried out by stirring the substrates and reagents at room temperature in a suitable solvent (e.g. ether, THF).



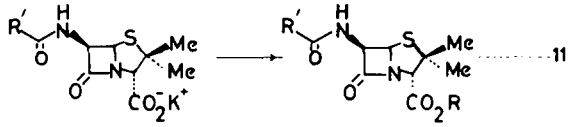
2.2 *Nucleophilic attack at the carbonyl group of the carboxylic acid*

2.2.1 *Mineral acids.* One of the oldest and still probably most widely exploited methods for esterification is the Fischer–Speier procedure and its numerous permutations. A recent interesting variation of the technique utilises[32] the distinctive properties of graphite bisulphate—prepared by electrolysis of 98% H_2SO_4 with a graphite anode. The deep blue crystals ($C_{24}^{+}HSO_4^{-}.2H_2SO_4$) are hygroscopic and must be stored in a desiccator. Esterification reactions are catalysed by the reagent which is stirred with equimolar proportions of carboxylic acid and alcohol in cyclohexane at room temperature. For primary alcohols esterification is 80–90% complete in less than 1 hr. The procedure is very efficient for the formation of acetate and formate esters but does not work for tertiary alcohols nor for benzoic and cinnamic acids. The graphite bisulphate probably plays a dual role—that of acid catalyst and dehydrating agent.

2.2.2 *Mixed anhydrides.* Various derivatives of penta-coordinate phosphorus (**1–6**) have been introduced as reagents for the condensation of carboxylic acids with thiols, amines and alcohols.[33–38] Typical is the esterification of penicillins as their readily available potassium salts[37] (eqn 11).



Esterification takes place presumably by interception of the intermediate acyl phosphate although in the case of (**5**) and (**6**) acyl azides and acyl cyanides respectively may also be formed as reactive intermediates.



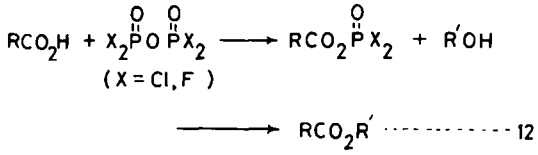
$R' = CH_2OC_6H_5$ 11

$R = C_6H_5$ ..... 85 %

$R = CH_2C_6H_5$ ..... 88 %

(4) — DME – ROH – C_5H_5N – r.t.

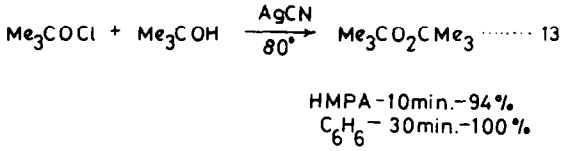
The intermediacy of mixed anhydrides $RCO_2PO(X)_2$, (X = Cl) has been postulated in the preparation of acyl chlorides from salts of carboxylic acids and phosphorus oxychloride. Compounds of this type (X = Cl, F) have now been prepared[39] from carboxylic anhydrides and dichloro- or difluoro-phosphoric anhydride ($X_2PO \cdot O \cdot POX_2$). They are highly reactive and unlike the corresponding acid chlorides they may be used to form esters with tertiary alcohols (eqn 12) in good yield and with reasonable speed.



$RCO_2H + X_2P(O)OP(O)X_2 \longrightarrow RCO_2P(O)X_2 + R'OH$ (X = Cl, F)

$\longrightarrow RCO_2R'$ 12

Hindered esters can however be formed from acid chlorides and alcohols in anhydrous benzene (at 20° or 80°) or HMPA (at 80°) by using silver cyanide as a catalyst[40] (eqn 13). Acyl cyanides are probably *not* involved as intermediates and it has been suggested that the reaction is facilitated by the electrophilic catalysis of the silver ion. This is a useful and complimentary technique to the mixed anhydride procedure[41] with trifluoracetic anhydride to employ in the esterification of hindered acids and alcohols.



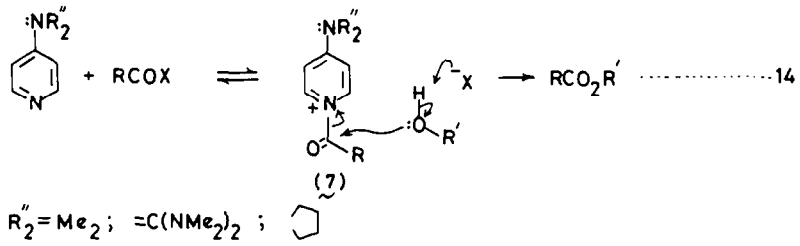
$Me_3COCl + Me_3COH \xrightarrow[80°]{AgCN} Me_3CO_2CMe_3$ 13

HMPA – 10 min. – 94 %

C_6H_6 – 30 min. – 100 %

Finally it may be noted that, in an extension of earlier work, Japanese workers[42] have shown that iodine (at reflux temp of pyridine) or bromine (at ambient temp) were able to oxidise phosphorous acid derivatives of pyridine to give N-pyridino-N-phosphonate salts capable of effecting various types of condensation reactions (esterification, amide and peptide bond formation). Mono- or di- esters of phosphorous acid may be used. With monophenylphosphite and di-isopropylphosphite n-butyl benzoate was formed in 61 and 65 % yields respectively from the component acid and alcohol. The reaction can occur by activation of the carboxylic acid or the alcohol substrate.[42]

2.2.3 4-N,N-*Dialkylaminopyridines.* Compared to pyridine itself 4-N,N-dialkylaminopyridines are approximately four powers of ten more active when used as acylation catalysts. In consequence they are used with increasing regularity for acylation reactions which proceed either incompletely or not at all in pyridine.[43–46] Generally 0.05–0.2 mole of catalyst is employed per mole of substrate with either acid anhydrides or acyl chlorides. The acid which is released may be bound with an equivalent amount of pyridine or triethylamine. Reactions may be conducted in various media—hexane, toluene, benzene, dichloromethane, ethyl acetate, THF, triethylamine or pyridine. The exceptional catalytic effect of these derivatives, even in non-polar media, is believed to be due, at least in part, to the formation of a high concentration of N-acylpyridinium salts (**7**) which are present in solution as loosely bound, highly reactive, ion-pairs. General base catalysis has been proposed for the group X^- in the reaction scheme (eqn 14) and this therefore explains why acid anhydrides ($X = RCO_2^-$) are better suited to these acylations than acyl chlorides ($X = Cl^-$).



The excellence of the method is however, in the case of the carboxylic acid component, somewhat nullified by the necessity to pre-form the acid anhydride, the requirement for an equivalent of triethylamine or pyridine in the reaction and, in the case of a valuable starting material, because half of the carboxylic acid is not converted to ester. Reports[45,47,48] from several groups have shown how these problems may be solved by the incorporation of dicyclohexyl carbodiimide into the reaction. The process is formulated as shown in Fig. 1 although it is possible that the dialkylaminopyridine may intercept the O-acylurea before formation of the postulated anhydride. Reactions are conducted in ether or dichloromethane. The reaction is based on a requirement for both the carbodiimide and the 4-N,N-dialkylaminopyridine. Its efficacy is illustrated by the following observations made in the preparation of phenyl benzoate from phenol and benzoic acid: (i) in the absence of dicyclohexylcarbodiimide the reaction does not proceed, (ii) in the absence of the aminopyridine phenyl benzoate is formed in about 10% yield and (iii) in the presence of both reagents the yield of ester is 94%. The method has been applied to the esterification of sterically hindered carboxylic acids, hydroxyacids and for the formation of t-butyl esters of acid and heat sensitive carboxylic acids.[47] It is also very useful for the formation of thiol esters.[47]

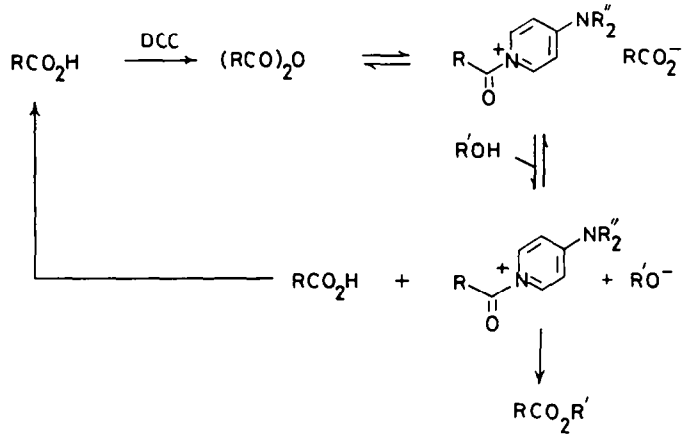
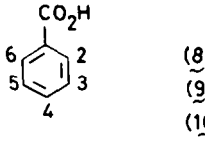
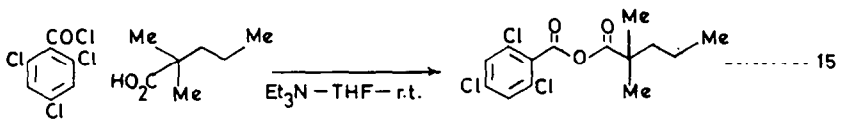


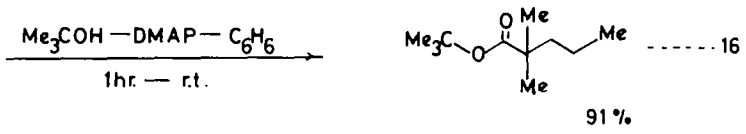
Fig. 1. Esterification of acids using 4-N,N-dialkylaminopyridines and carbodiimides.

A further elegant variation of the procedure has been developed by Japanese workers[49] using mixed anhydrides to esterify carboxylic acids. Mixed anhydrides with the carboxylic acids (**8**–**11**) have proved most promising. These relatively strong acids all form very good "leaving groups" and they have a sterically hindered CO group which therefore further directs attack at the alternative CO group in the mixed anhydride. Esterification consists of two stages: (i) formation of the mixed anhydride (eqn 15) followed by (ii) alcoholysis of the anhydride (eqn 16) catalysed by 4-N,N-dimethylaminopyridine. Benzene, toluene or dichloromethane proved to be the best solvents for the alcoholysis step.



(8) 2,4,6-Cl_3
(9) 2,3,6-Me_3-4,5-NO_2
(10) 2,6-Cl_2-3-NO_2
(11) 2,4,6-Br_3



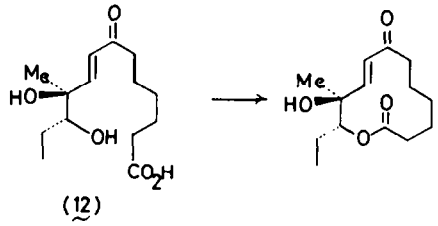


This method has been utilised for the preparation of macrocyclic lactones. The mixed anhydrides of various ω-hydroxy acids were prepared using **8** and then decomposed under high-dilution by adding to a refluxing toluene solution of 4-N,N-dimethylaminopyridine (DMAP). Typical yields of 9–13 membered lactones are shown in Table 1. When the procedure was applied to the lactonisation of the acid sensitive seco-acid (**12**) using **8** and DMAP the desired lactone was obtained in 46% yield.

Table 1. Lactonisation using 4-N,N-dimethylamino pyridine (DMAP)

	Lactone ring	Yield
$HO(CH_2)_7CO_2H$	9	36%
$HO(CH_2)_{10}CO_2H$	12	48%
$C_6H_{13}CH(OH)(CH_2)_{10}CO_2H$	13	67%

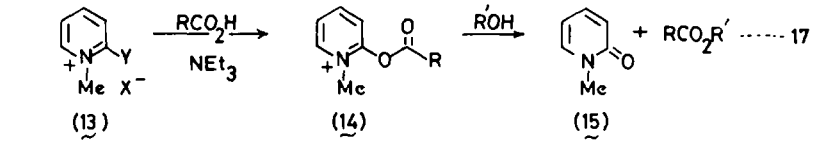
2.2.4 *Carbodiimides.* In spite of its successful use in the preparation of some esters[2] the direct condensation of acids and alcohols using dicyclohexylcarbodiimide (DCC) has serious limitations which have probably prevented its more general adoption.[47,50] Yields are variable and there is a tendency in some cases to form N-acylureas[51] as byproducts. Attempts to improve the yields of ester led first to the use of pyridine as solvent[52] and later, as noted above, of 4-dialkylaminopyridines as catalysts. It has now been found that the addition of a strong acid to the pyridine solution[50] considerably increases the yields of esters *vis à vis* the formation of the N-acylurea. Catalytic amounts of strong acids (*p*-toluene sulphonic acid, methane sulphonic acid, hydrochloric acid, sulphuric acid, perchloric acid, nitric acid) are effective but the role of the acid catalyst is itself not clear. With tertiary alcohols yields of esters still remain poor even in the presence of an acid catalyst.



(12)

2.2.5 2-*Halopyridinium salts.* These reagents have recently come into prominence as reagents for the condensation of equimolar amounts of carboxylic acids and alcohols to form esters. The work is based upon a number of considerations[53] and predictions, notably the following: (i) 2-acyloxy-1-methylpyridinium salts (**14**) are active acylating agents and would be rapidly and easily formed by nucleophilic attack of a carboxylate anion on 2-chloro- or 2-bromo-1-methylpyridinium salts (**13**) since a halogen atom at position 2 of the precursor (**13**) is readily displaced by nucleophilic attack and (ii) nucleophilic attack by an alcohol molecule at the acyl C atom of **14** would be facilitated by formation of two stable species—an ester and 1-methyl-2-pyridone (**15**) (eqn 17). Reactions are carried out in the presence of an amine as proton acceptor and the yield is generally dependent on the basicity of the amine (triethylamine > α-picoline > pyridine). The condensation may also be conducted under almost neutral conditions using the non-basic hydrogen halide acceptor (**16**).[54]

In an extension of this work designed to utilise the same principles in the lactonisation of ω-hydroxycarboxylic acids Narasaka *et al.*[55] have devised the 2-chloro-3-methoxymethylpyridium salt (**17**) as a reagent for the condensation. The ω-hydroxyacid is treated with **17** and triethylamine in dichloromethane or dichloroethane under reflux. Compared to previous results with 2-chloro-1-methylpyridinium iodide the introduction of the methoxymethyl at the 3-position in **17** enhances the degree of lactonisation which is obtained. 12-, 13- and 16-Membered lactone rings have been formed using **17** in yields of 40–71%.



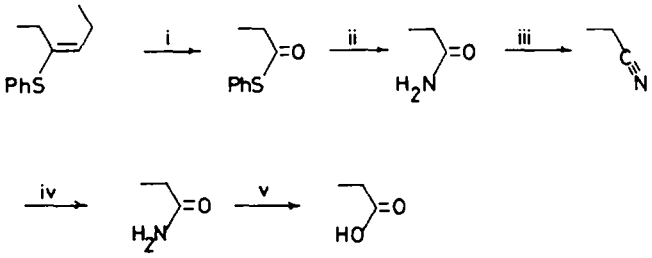
(13) (14) (15)

(Y = Cl, Br : X = OTs, I, BF_4)

(16) (17)

3. THIOL ESTER FORMATION

Each era in the history of organic chemistry has been marked by developments which because of their originality and timeliness have had a substantial influence on subsequent research. One such masterpiece in recent times was the cobyric acid synthesis of Woodward and Eschenmoser.[56] One facet of the work of some considerable interest is the generation of the carboxyl group at position "f" in the corrin nucleus. The procedure adopted by Woodward and Eschenmoser utilises at an early stage a phenyl thioester and exploits its enhanced reactivity towards ammonia when compared to oxygen esters, (Fig. 2). This work has heralded a period of unparalleled activity in which the synthetic potentialities of the thiol ester group has excited considerable interest. The use of thiol esters to selectively activate a carboxyl group towards esterification or lactonisation has engendered numerous investigations and work in this area has gained particular prominence. One outcome of these developments has been the renewed attention directed generally towards thiol ester synthesis.



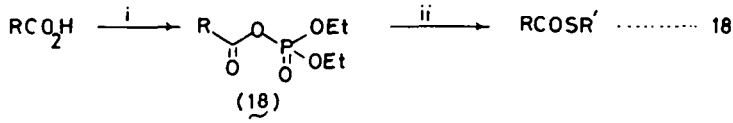
Reagents (i) O_3; (ii) NH_3; (iii) $(MeSO_2)_2O - C_5H_5N$; (iv) conc. H_2SO_4; (v) N_2O_4.

Fig. 2. Generation of the carboxyl group "f" in cobyric acid.

3.1 *From carboxylic acids*

The preparation of thiol esters has until very recently been a somewhat neglected field.[58] Their synthesis directly from carboxylic acids and thiols is unrewarding because the equilibrium constants for the reaction are so small. There has however been a proliferation of new methods for thiol ester synthesis and in these there are invariably considerable areas of overlap with many of the recent methods for O-ester preparation, noted previously. Thus mixed anhydride formation with the reagents diphenylchlorophosphate (**1**), diethylchlorophosphate (**2**),[33] phenyldichlorophosphate (**3**),[37] N,N-dimethylphosphoramidic dichloride (**4**),[37,58] diethylphosphorylcyanide (**5**),[34,38] and diphenylphosphoryl azide (**6**)[34] have all been employed as a means to activate the carboxyl group towards thiol ester formation. In a typical procedure Yamada *et al.*[34] stirred a mixture of the thiol and carboxylic acid in DMF containing triethylamine with either (**5** or **6**) at room temperature for 3 hr before isolation of the thiol ester. A penicillin derivative (as its potassium salt) was readily converted to its ethyl thiol ester using **6** and the successful conversion of N-benzyloxycarbonyl-L-threonine to its ethyl thiol ester indicates the potential selectivity of this procedure since under these conditions the OH group is unaffected. Although many of these reactions proceed best with less substituted (mainly

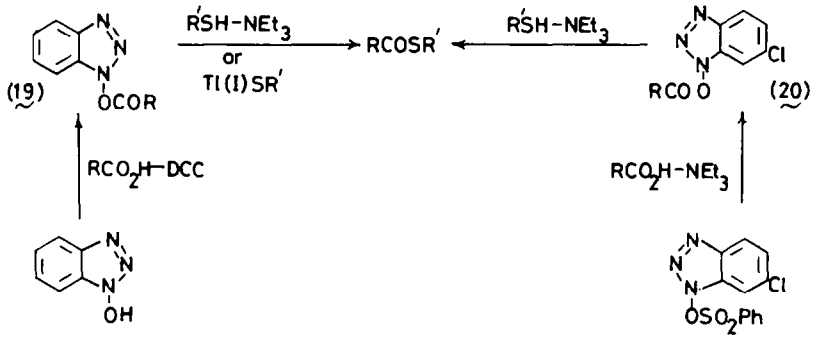
primary) alkane thiols Masamune[33] has developed an analogous but new and versatile procedure for the preparation S-t-butyl esters. The phosphochloridate (**2**) shows a high selectivity towards the carboxyl function and activates the latter towards esterification. Treatment of the mixed anhydride (**18**) with the thallium(I) thiolate brings the reaction to completion with high overall efficiency (eqn 18) and reported yields are in the range of 86–90%. This method is applicable to the preparation of activated thiol esters such as those of pyridine-2-thiol and may also be used with hydroxy-acids (e.g. cholic acid) where it permits selective activation of the carboxyl group.



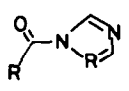
(**18**)

(i) Et_3N – THF – (**2**) – 3hr (ii) TlOEt + R'SH → Tl SR', 24hr.

Although dicyclohexylcarbodiimide (DCC) has been investigated as a condensing agent for carboxylic acids and thiols to prepare thiol esters there are certain limitations to its use. Baig and Owen[59] found purification of the products troublesome and Grunwell and Forest[60] found that thiophenols are more effective in the condensation than alkane thiols and that primary alkane thiols were more reactive than secondary and tertiary thiols. Lloyd and Young[61] have however successfully employed the reagent to prepare various 2-pyridylthiol esters of amino-acids and an efficient thiol ester synthesis has been reported by Horika[62] using the analogous active esters of 1-hydroxybenztriazole (**19**) and 1-hydroxy-6-chlorobenztriazole (**20**). Although thiophenol and toluene-α-thiol are sufficiently reactive to interact with (**19**) and (**20**) in the presence of triethylamine to give thiol esters, alkane thiols are generally not. In these cases excellent yields of thiol esters are obtained by treatment with thallium(I) thiolate. This method is however inapplicable to hydroxy-acids.



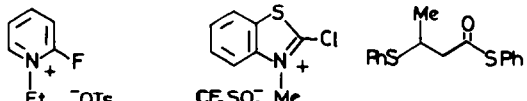
Where other considerations permit acid chlorides may well provide the most direct and conventional route to thiol esters.[63] Masamune[64] has used the reaction of thallous 2-methylpropane-2-thiolate to prepare S-t-butyl esters in almost quantitative yields from the corresponding acid chlorides. Carboxylic acid imidazolides (**21**) or 1,2,4-triazolides (**22**) are accessible in good yields from carboxylic acids and carbonyl di-imidazole (CDI) or carbonyl 1,2,4-triazole (CDT) respectively. Gais[65] has shown that the derivatives (**21** and **22**) react with alkane and aryl thiols (or selenols) to give thiol esters (or their selenium analogues) in excellent yields (71–97%). The selective activation of the carboxyl group with CDI was demonstrated by the formation of thiol esters from 11-hydroxy-*trans*-8-heptadecenyl carboxylic acid (ricinelaidic acid).



(**21** R=CH)
(**22** R=N)

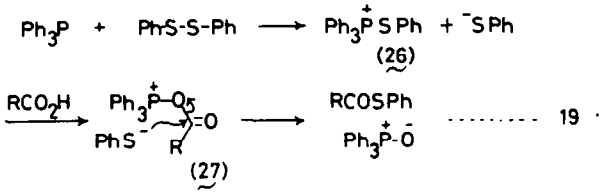
2-Halopyridinium salts and related compounds have similarly found applications in the preparation of thiol esters from carboxylic acids. Yields of thiol esters (75–96%) were reported by Mukaiyama[66] using a range of carboxylic acids and thiols with different structural characteristics and

the condensing agent (**23**) and Masamune[67,68] has employed the analogous benzothiazolium salt (**24**) to similarly prepare thiol esters from acids and thiols. The intermediacy of the acid chloride and anhydride was however suggested in the latter process, and in order to avoid side reactions due to activation of the thiol it is recommended that the thiol (or alcohol) is *added to* a mixture of the carboxylic acid, triethylamine and (**24**).



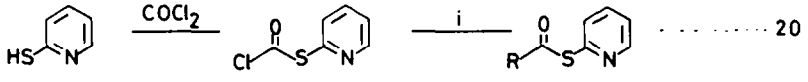
(23) (24) (25)

Particular importance has recently become attached to 2-pyridylthiol esters because of their application in macrolide synthesis. Attention has in consequence been focussed on the preparation of these esters. Mukaiyama[69] first noted that carboxylic acids reacted readily with diphenyl disulphide and triphenyl phosphine in refluxing acetonitrile to give thiol esters, benzene thiol and triphenyl phosphine oxide. Thiol esters were generally obtained in high yield although crotonic acid formed the adduct (**25**) by addition of the benzene thiol to the α,β-unsaturated system of the crotonate ester. The reaction pathway was formulated by assuming the initial formation of the phosphonium salt (**26**) which in turn is transformed by attack of the carboxylic acid to give (**27**). This then undergoes decomposition to give the thiol ester (eqn 19). No reaction took place with diethyl disulphide and



(26) (27) 19

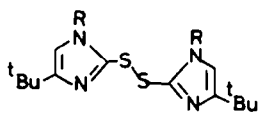
Mukaiyama suggested that the reactivity of the disulphide in this reaction is dependent on its oxidising power which in turn decreases with the decreasing stability of the thiolate anion. Corey and Nicolau[70] have used this reaction to form the 2-pyridylthiol esters of a series of ω-hydroxy-acids and these were then subsequently employed to promote lactonisation. A major difficulty associated with the 2,2′-pyridyldisulphide—triphenylphosphine method is the necessity for chromatographic separation of the 2-pyridyl thiol esters, co-products and excess reagents. This has proved difficult on a large scale (>0.1 M) and Corey and Clark[71] have recently circumvented this problem by using 2-thiopyridyl chloroformate to form the active ester in essentially quantitative yields (eqn 20). The products are sufficiently pure for most synthetic operations after more rigorous drying.



..... 20

(i) $RCO_2H - NEt_3 - 0° - 0.5hr$

In related work Corey and Brunelle[72] have exemplified the potential of the 4-t-butylimidazole reagents (**28**) to form active esters which, analogously to the 2-pyridyl thiol esters, may be used to promote lactonisation of hydroxy-acids.



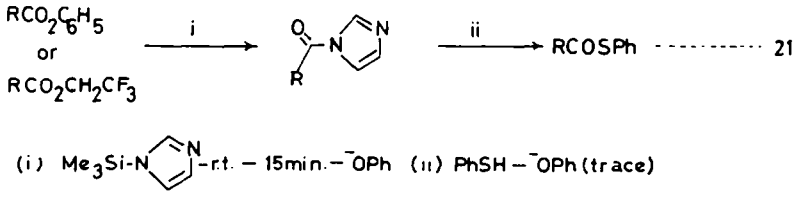
(R=Me or ^{t}Bu)

(28)

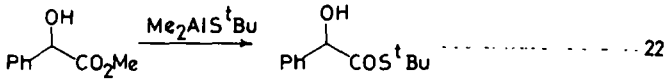
Miscellaneous thiol ester preparations include those of ethyl thiol esters by treatment of the carboxylic acid with triethyl thioboranes[73] (in refluxing ether, benzene, or diglyme for 2–8 hr, yields ~ 80%) and phenyl thiol esters[74] by the reaction of carboxylic acids with phenylisothiocyanate and tri-n-butyl phosphine (0.5–3 hr in dichloromethane at room temperature under nitrogen, yields 43–96%). This latter reaction does not proceed in the analogous 2-pyridyl thiol series.

3.2 *From O-esters*

Parallel with the work on the synthesis of thiol esters from carboxylic acids there have been some interesting reports of thiol ester synthesis from O-esters. Masamune *et al.* have devised an intriguing procedure of fairly wide application which permits one to distinguish between two oxygen ester functions in the same molecule if one of these ester groups is derived from a weakly acidic alcohol such as phenol or 2,2′,2″-trifluoroethanol.[75] These workers showed that both phenyl and 2,2′,2″-trifluoroethyl esters are readily converted to the corresponding acyl imidazoles when treated with N-trimethylsilyl imidazole at room temperature in the presence of a catalytic amount of sodium phenoxide (eqn 21). The acylimidazole may then be manipulated as required but treatment with benzene thiol gives for example the phenyl thiol ester (eqn. 21).



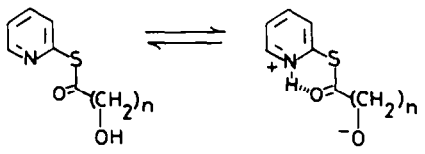
Phenylthiol esters have also been prepared from O-esters by reaction with boron thiophenoxide and its aluminium analogue.[76] The former reagent is capable of converting O-esters, including α,β-unsaturated esters, to phenylthiol esters in good yield at the temperature of refluxing xylene. Aluminium thiophenoxide brings about the same conversion to a phenylthiol ester in benzene but under much milder conditions (1 hr at 25°, 4 hr at 5°). In the case of α,β-unsaturated esters however the products, using the aluminium reagent, are contaminated with 3-(phenylthio)-thiolesters and in two other examples quoted a β-ketoester was recovered unchanged and a γ-ketoester was transformed to its diphenylthioacetal thiol ester. Corey and Beames[77] have also reported the formation of phenyl thiol esters and toluene-α-thiol esters of phenylacetic acid by reagents derived from trimethylaluminium and the corresponding thiol (1:1 ratio) in methylene dichloride at 25°. Analogously t-butyl thiol esters have been derived from Me and Et esters by reaction with dimethyl aluminium t-butyl thiolate in methylene chloride at room temperature (eqn 22). Correspondingly α,β-unsaturated esters give rise to products from conjugate addition with this reagent as with the aluminium thiophenoxide.



4. LACTONISATION

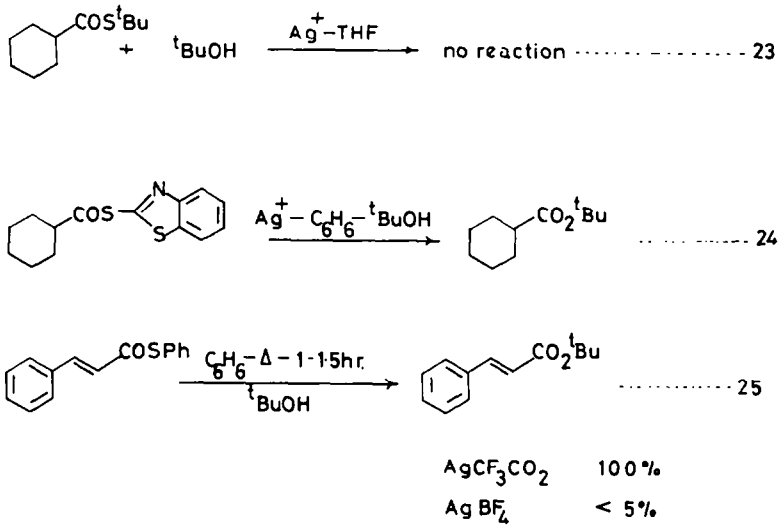
The presence of a macrocyclic lactone is common to a range of natural products and many of these have interesting biological properties. This association has prompted in recent years a more than passing interest in lactone forming reactions which might lead to the eventual synthesis of these macrolides. Until comparatively recently successful syntheses have been rare and this was principally due to the limited utility of most existing methods for the cyclisation of ω-hydroxycarboxylic acids to form medium-large ring lactones. Several examples have been noted in the discussion (*vide supra*) and two excellent and comprehensive reviews of macrolide synthesis have recently appeared[79,80] which discuss in detail some of the recent work in this area of natural product synthesis. An abbreviated discussion is therefore given here.

Although the internal esterification of long chain ω-hydroxy-acids as a route to macrocyclic lactones is not favoured on the basis of entropy factors it is in many cases the most direct route and recent work in this area has sought to improve this particular approach. Successful procedures have been developed using mixed anhydrides,[49] N-acyl imidazoles[81] and various types of thiol ester to activate the carboxyl function in the hydroxy-acid. The Corey–Nicolau procedure using the "double activation" afforded by the 2-pyridylthiol ester has been applied successfully in a number of syntheses of natural products[79,80] and its efficacy has been rationalised on the basis of the facilitation of proton-transfer from the OH group to the CO group oxygen in the intermediate (**29**).[82,83]



(29)

Almost simultaneously Gerlach and Thalmann *et al.* announced a modification of the use of 2-pyridylthiol esters to promote lactonisation.[84,85] Silver ion (as the perchlorate or tetrafluoroborate salt) is used to activate the 2-pyridylthiol esters by complexation. Esters of hydroxy-acids undergo cyclisation at room temperature in benzene solution and simple alkyl esters (including secondary alcohols) are similarly formed in high yield by addition of the appropriate alcohol to the 2-pyridyl thiol ester. In contrast the procedure developed by Masamune[86,87] uses S-t-butyl esters as intermediates for esterification and to form large ring lactones. The "soft" thiophilic mercury(II) ion (as its trifluoroacetate or methane sulphonate) is used to catalyse the S → O conversion. Other thiophilic cations have been examined by Masamune[87] and some general trends were noted. The more acidic the reacting thiol then the less thiophilic the metal cation, which is required to effect the reaction, needs to be (eqns 23, 24). In several cases Cu(I), Cu(II) and Ag(I) are superior to Hg(II) and a remarkable difference was noted in one case between silver trifluoroacetate and tetrafluoroborate (eqn 25).



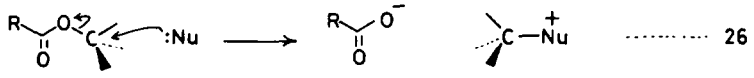
The formation of macrocyclic lactones by the use of 2-halopyridinium salts was developed by Mukaiyama[55] *et al.* and some examples have been noted above. Finally mention should be made once more of the "oxidation-reduction" method for lactonisation employed by Mitsunobu.[31]

5. PROTECTION OF THE CARBOXYL GROUP BY ESTER OR AMIDE GROUPS

The needs of the synthetic chemist demand that the search for milder and more specific methods to bring about familiar and well known transformations is a never ending one. For a great many years protection of the carboxyl group has relied on a relatively small number of well known procedures.[2] Comparatively recently however there has been unparalleled activity in this field which has brought a rich harvest of new techniques and ideas to bear on the problem.[1] The majority of the new methods involve an ester as protecting group; each has a given range of applicability and usefulness. Many use ester groups which may be removed under non-hydrolytic conditions (e.g. hydrogenolysis, photolysis, oxidation). Their major limitation often proves to be the availability and ease of formation of the particular protecting group. The alternative *modus operandi* is to employ readily available—methyl and ethyl—ester groups and to devise novel, mild and if possible non-hydrolytic conditions for their removal. Clearly the prime advantage here is the ready formation and availability of the starting material. Developments using these two distinct approaches are delineated below.

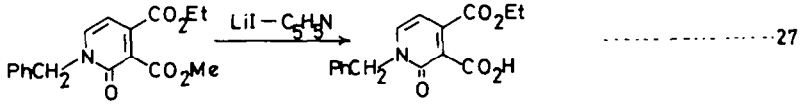
5.1 *Ester deprotection by S_N2 dealkylation and related methods*

The principle underlying this method of generation of the carboxyl group from an ester function is shown in eqn 26 where displacement of the carboxylate anion is achieved by attack of an external (usually) nucleophile. Various anions (iodide, chloride, t-butoxide, cyanide, thiocyanate and thiolate) or neutral molecules (thiols, amines, DBN and DBU), usually in dipolar aprotic media, have been utilised as nucleophilic species to bring about the displacement reaction.



26

The general synthetic utility of this approach to ester deprotection[88] was first established by Taschner and Liberek[89] although perhaps because of the inaccessibility of their published work it was not until 1960 that the advent of the work of Eschenmoser *et al.*[90] gave the idea sufficient momentum to establish its present popularity. As is normal in S_N2 attack the ease of substitution at the C atom to which the carboxylate group is attached frequently determines the ease with which the procedure works. This may often permit a nice selectivity between different ester groups in a molecule (eqns 27, 28). Ester cleavage works best when the alcohol carbon atom is primary (Me) or relatively unhindered (Et) but appropriate choice of reagents and conditions allows these two ester groups to be distinguished. Of the halide ions which have been employed iodide ion (as its Li salt) is probably the



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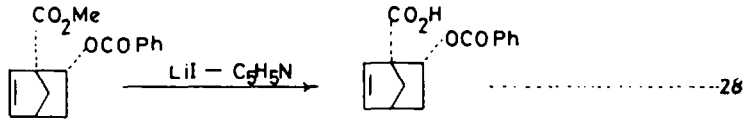
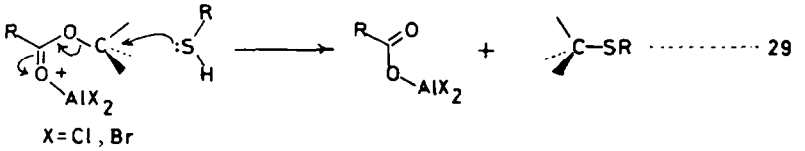


28

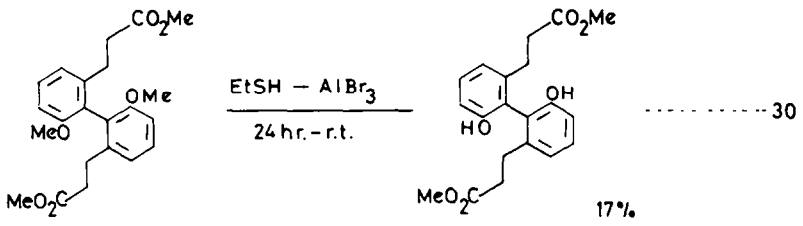
ion of choice for S_N2 dealkylation of esters. Thiols and thiolate anions have been rather less widely employed[91-94]. Bartlett and Johnson[91] have discussed the especial advantages of lithium n-propylmercaptide in HMPA at room temperature to effect S_N2 dealkylation of esters. The reagent thus cleaves methyl mesitoate—a classic example of a hindered ester—to give mesitoic acid (100%, 1.25 hr, 25°) and under similar mild conditions methyl-O-methylpodocarpate gave O-methylpodocarpic acid (100%, 1.5 hr, 25°) without demethylation of the phenolic group (Fig. 3). Under more vigorous conditions (100°, DMF) ethyl mercaptide brings about both demethylation of the phenolic and ester groups in the same molecule. Lithium thiomethoxide has also been employed in analogous dealkylations of esters.[94] Its use has been recommended as an alternative to the thiopropoxide because of its relative ease of preparation and its stability. Japanese workers[93] have approached the problem of the dealkylation of esters with thiols in an alternative manner. The carboxylate ester is activated to form a better leaving group by coordination of the oxygen to a Lewis acid—aluminium trichloride or tribromide—and the thiol group is used as a nucleophile (eqn 29). Reactions are carried out at room temperature and bring about the dealkylation of benzyl, methyl and ethyl esters. Boron trichloride has also been used to bring about the dealkylation of esters[95] and it presumably functions in a similar way but with nucleophilic attack on the alkyl group occurring via the displaced halide anion.



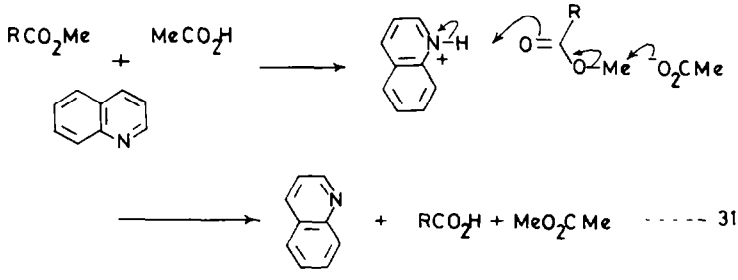
X = Cl, Br

29

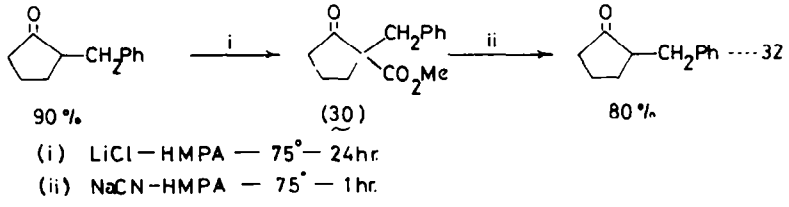
The reagent (ethane thiol—aluminium trihalide) is a powerful demethylating reagent for aromatic methyl ethers and this suggests its possible use as a reagent to bring about demethylation of an aryl methyl ether in the presence of an ester function (eqn 30).[93] In related work Liotta[96] has successfully used the uncomplexed phenyl selenide anion to bring about S_N2 dealkylation of esters.

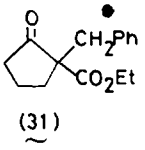


A new and unusual method for the dealkylation of hindered esters and which probably involves the acetate anion as the attacking nucleophile (eqn 29) consists in refluxing the ester in quinoline containing acetic acid under a slow stream of nitrogen. The procedure is of general applicability and has been formulated[97] as shown in eqn (31). The reaction is relatively slow but under these conditions methyl-O-methylpodocarpate gave an 84% yield of the acid in 40 hr (Fig. 3).



There are several clear instances where cyanide anion acts as a nucleophile in promoting S_N2 ester cleavages and there is good evidence to indicate that the reactions proceed by the $B_{Al}2$ mechanism for ester hydrolysis since the substrate (**30**) is approximately 70 times more reactive than the corresponding ethyl ester (**31**)[98] and in a competitive reaction with sodium cyanide in HMPA at 75° for 24 hr methyl mesitoate was converted to mesitoic acid (85%) but ethyl benzoate was recovered virtually unchanged (93%). Muller and Siegfried[99] suggested a reactivity order $CN^- \gg Cl^- > Br^-$ in HMPA, with compound **30** as substrate, of anions for nucleophilic attack at the ester alkyl group (eqn 32).

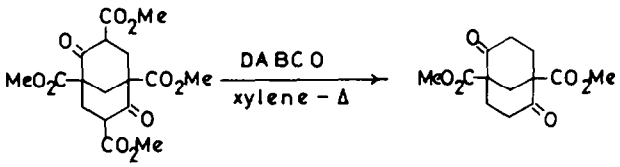




(31)

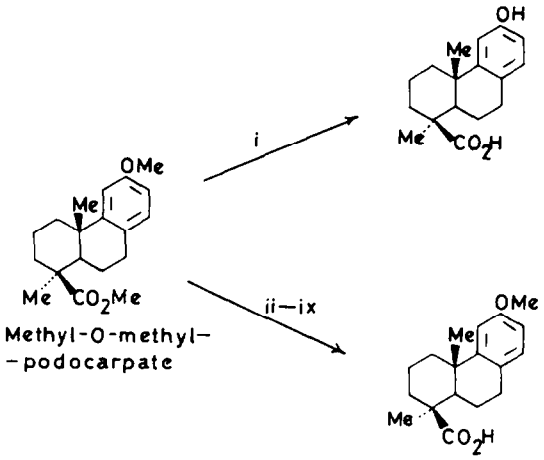
Although cyanide anion has been used for S_N2 ester dealkylation it has gained particular prominence for the simultaneous non-hydrolytic deprotection and decarboxylation of β-ketoesters and malonic ester derivatives.[88] However in these particular cases the mechanism of reaction may involve initial attack at the ester *carbonyl* group. It has for example been suggested that this pathway contributes up to 20% of the total reaction pathway in the reaction of sodium cyanide with (**31**), and the analogous isopropyl and t-butyl esters, in HMPA.

Amines, in contrast, have been little used to effect S_N2 ester dealkylation but two recent reports have drawn attention to the application of the bicyclic amines DBN and DBU for this purpose.[100,101] Although 1,4-diazabicyclo[2,2,2]-octane (DABCO) does not attack saturated esters it readily (refluxing xylene, 4 hr) and selectively cleaves β-ketoesters, with one or more α-H atoms, to the corresponding ketone.[102] The selectivity which may be achieved is typified by the reaction of the tetramethyl ester (**32**).



(32)

A measure of the efficacy of any new method for ester deprotection or hydrolysis is often taken to be the time and conditions required to effect the transformation of methyl-O-methylpodocarpate. It is clearly a virility symbol in this area of chemistry and Fig. 3 shows some comparisons of the effectiveness of the various reagents discussed above which bring about S_N2 ester dealkylation.



(i) $AlBr_3$-EtSH ····· CH_2Cl_2-r.t. — 5-5hr. ····· 98% ref. 93

(ii) $^-O^tBu$ ····· DMSO-56°— 2hr. ····· 97% ref. 91

(iii) $^-S^nPr$ ····· HMPA - r.t. — 1-5hr. ····· 100% ref. 91

(iv) BCl_3 ····· CH_2Cl_2- -25°→0°— 5-6hr. ····· 90% ref. 95

(v) LiI ····· collidine-reflux — 4hr. ····· 92% ref 103

(vi) DBN ····· o-xylene-165°— 6hr. ····· 96% ref. 100
DBU ····· o-xylene-165° — 48hr. ····· 97% ref. 101

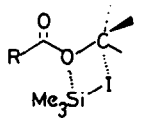
(vii) quinoline-acetic acid ····· reflux — 40hr. ····· 85% ref. 97

(viii) ^-SePh ····· THF-HMPA-reflux - 10hr. ····· 100% ref. 96

(ix) aq. KOH (25%) ····· EtOH-H_2O — 150°— 4hr.

Figure 3 —S_N2 Dealkylation of methyl-O-methylpodocarpate

Nucleophilic substitition and displacement of the carboxyl group from esters is facilitated not only by a powerful nucleophile but also by coordination of the O atom of the carboxyl group in such a way as to create a better leaving group (*cf* aluminium trihalide–ethane thiol,[93] boron trichloride,[95] above). Both of these features are embodied in a single reagent which has recently come to the fore, iodotrimethylsilane. According to Saville's rules[104] relating to "hard and soft" acids and bases it has the ideal combination of qualities to interact in the correct manner with an ester to bring about particularly facile dealkylation; the "soft" iodide and carbon atoms interacting and similarly the "hard" silicon centre with the oxygen of the ester. Olah and Ho[105] (eqn 33) have interpreted its mode of action on this basis but Jung *et al.*[106] favour a two stage mechanism (eqn 34). Phenyl esters as expected are stable to this reagent but a measure of S_N1 character in the mechanism may be detected from the order of reactivity of esters, t-Bu, $PhCH_2$ > Me, Et, i-Pr.



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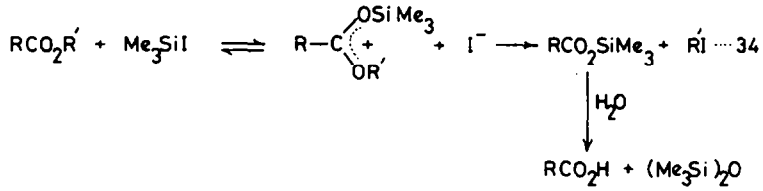

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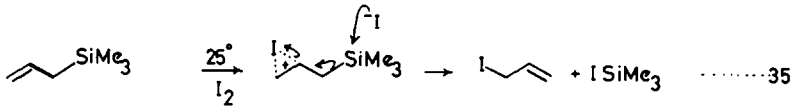
In the original reports of the use of iodotrimethylsilane the reagent was utilised neat or in carbon tetrachloride or deuteriochloroform solution. Under these latter conditions[106] ethyl benzoate took 48 hr to complete hydrolysis at 50° but the t-butyl ester was hydrolysed in 0.5 hr at 25°. Using the reagent neat at 100° Ho and Olah[105] reported 70–90% yields of various acids from the corresponding methyl, ethyl and benzyl esters under reaction times varying from 2 to 18 hr. Isolated acetylenic and olefinic bonds, amide, amine, furan and thiophene groups are stable to the reagent but alkyl ethers are dealkylated, alcohols are converted to alkyl iodides and dimethyl acetals are transformed to the parent ketone.[107-109] One difficulty relating to the use of this reagent concerns its preparation and storage (it is decomposed by light and by moisture) and there have been various developments for the *in situ* generation of iodotrimethylsilane—*or its equivalent.* Procedures involving the use of phenyltrimethylsilane and iodine,[105] allyltrimethylsilane and iodine[110] (eqn 35), 3,4-bis-(trimethylsilyl)-1,4-cyclohexadiene and iodine[110] (eqn 36) and chlorotrimethylsilane and sodium cyanide in acetonitrile[108] have been recommended for this purpose.



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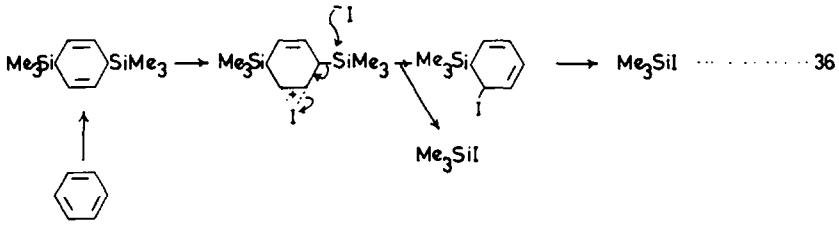

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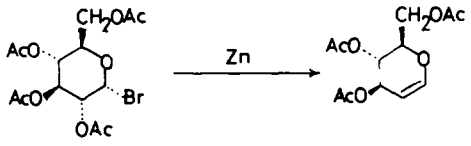
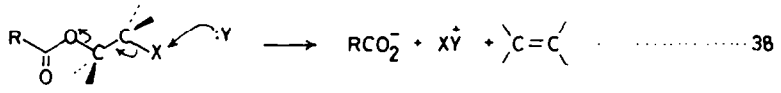
A very simple and effective method to generate the reagent has been introduced by Olah.[109] This consists of mixing hexamethyldisilane and iodine in chloroform solution and to this is then added the substrate under nitrogen. The mixture is then stirred at room temperature or heated under reflux, as appropriate, to bring about reaction.

5.2 *Ester deprotection by elimination from β-substituted ethyl groups*

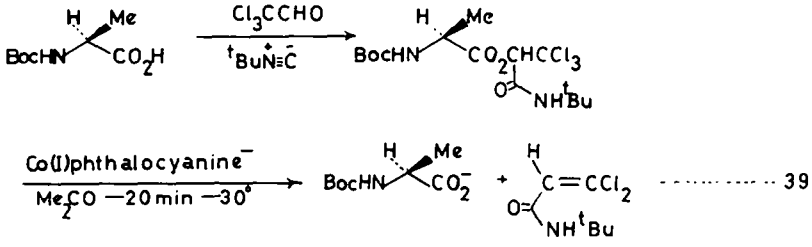
The alternative to carboxyl protection by means of the simple and readily available methyl, ethyl and related ester groups is to devise novel and occasionally esoteric ester protecting groups which are removable under mild non-hydrolytic conditions. Numerous procedures have been developed which fall under the umbrella of this particular approach to carboxyl protection and these are considered here. The first is ester cleavage by elimination from β-substituted Et groups. Woodward[111] was the first to highlight the elegance of this method using the 2,2′,2″-trichloroethyl ester group in his cephalosporin synthesis of 1966. The theory behind the method had however been exploited previously in olefin synthesis. Emil Fischer[112] first utilised reductive elimination from bromohydrin acetates as a means of generation of olefins and his preparation of tri-O-acetyl-D-glucal (eqn 34) is typical. The same ideas were extended and developed by Cornforth[113] in the late 1950s in an olefin synthesis from epoxides. It was however left to Woodward to employ the essentially complementary

feature implicit in these synthetic reactions as a basis for the design of an ester group which could be used to protect a carboxyl group during synthesis. Hence came his utilisation of the trichloroethyl group in the cephalosporin synthesis.[111] The trichloroethyl ester group continues to enjoy enormous popularity in organic synthesis but since Woodward's original publication a wide variety of methods have been introduced for carboxyl protection based essentially on this β-elimination idea (eqn 38).

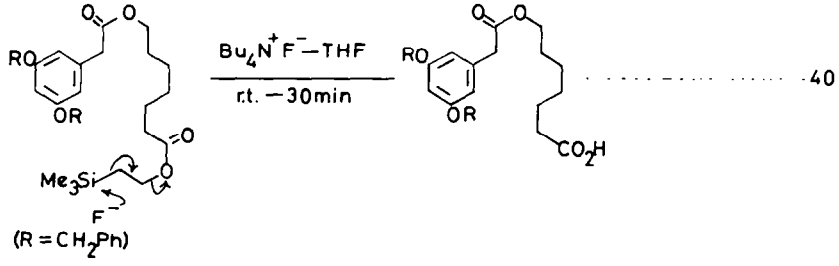




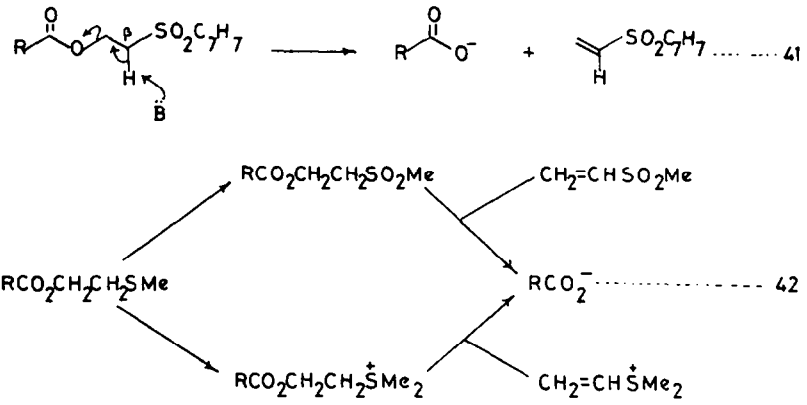
Numerous variations upon the 2-haloethyl ester theme have been introduced. The Woodward 2,2′,2″-trichloroethyl ester has been widely used and several modifications (zinc-methanol, zinc-acetic acid, zinc-phosphate buffer solution pH 4.5–6.0, zinc-ammonium acetate buffer solution pH 7.2 or electrolytic reduction) have been advocated in the deprotection sequence.[114] Ho has exploited the remarkably high nucleophilicity of the HSe^- and Se^{2-} ions to unmask β-haloethyl esters[115] and Eckert has made interesting use of the supernucleophile lithium or sodium cobalt(I) phthalocyanine to deprotect β-haloethyl esters and β-chloroethyl esters of α-amino-acids—prepared by the Passerini reaction[116,117] (eqn 39). This latter reagent has also been employed more generally to deprotect 2,2′,2″-trichloroethyl esters.



Replacement of the β-halogen atom by a trimethylsilyl[119,120] or trimethylstannyl[118] group provides a β-substituted Et group in which elimination is then facilitated by the attack of a fluoride anion at the Si or Sn atom in the β-position. Gerlach has used this facile elimination process with a 2-trimethylsilyl ester group in a neat synthesis of the bacterial macrocylic lactone-curvularin.[120] The key step in which the β-substituted ester is deprotected in presence of another ester group is shown in eqn (40).

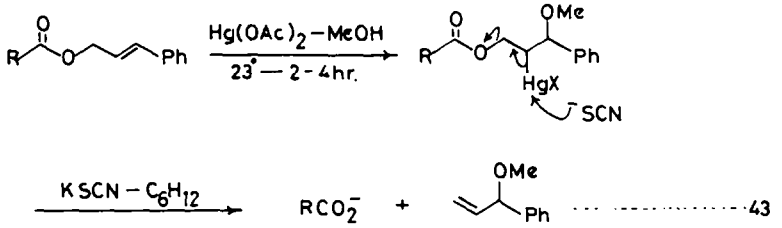


Two protecting groups the 2-*p*-toluenesulphonyl ethyl[81,121] and the 2-thiomethyl ethyl,[122] are further variations on the 2-haloethyl theme. Both utilise the incipient acidity of the 2 β-hydrogen atoms of the Et group to initiate elimination of the carboxylate group from the ester (eqns 41, 42). In the case of the 2-thiomethyl ethyl ester this is brought about either by oxidation to the sulphone or by conversion with methyl iodide to the sulphonium salt. The respective elimination reactions are facile

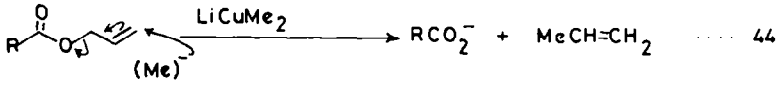


although in aqueous media the pH required may be quite high (pH 10–11) and therefore not compatible with other functional groups in the molecule. Alternative procedures employ organic bases (e.g. DBN) in benzene to initiate the fragmentation reaction.[81]

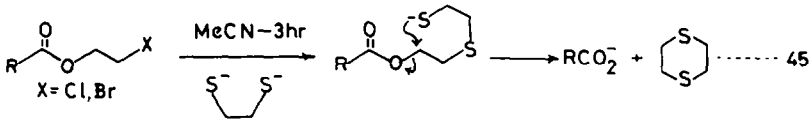
Corey has devised a novel method for the cleavage of cinnamyl esters under nearly neutral conditions which is based on the principles of the β-elimination (eqn(43).[123] The process is based on the highly regiospecific methoxymercuration of cinnamyl esters which is then followed by the fragmentation of the organomercury intermediates catalysed by attack of the thiocyanate anion at the thiophilic Hg atom (eqn 43).



The same procedure cannot be utilised for allyl esters since methoxymercuration does not proceed with the correct regioselectivity. However deprotection of these esters may be accomplished by treatment with dimethyl lithium cuprate (eqn 44).[124]

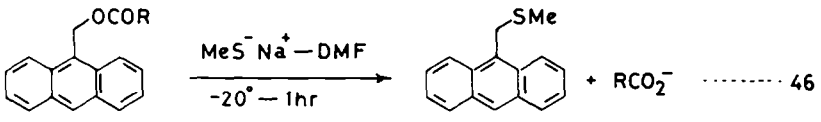


Finally in this section the elegant work of Ho which has led to the formulation of a procedure for the deprotection of any ω-haloalkyl ester should be noted.[125-127] Reaction of the ω-haloalkyl ester with a bidentate nucleophile (trithiocarbonate dianion, sulphide anion or the dianion of ethane dithiolate) results in the formation of an intermediate ω-substituted ester which is now capable of intramolecular S_N2 displacement of the ester carboxylate function. The process is illustrated by the example shown in eqn (45).



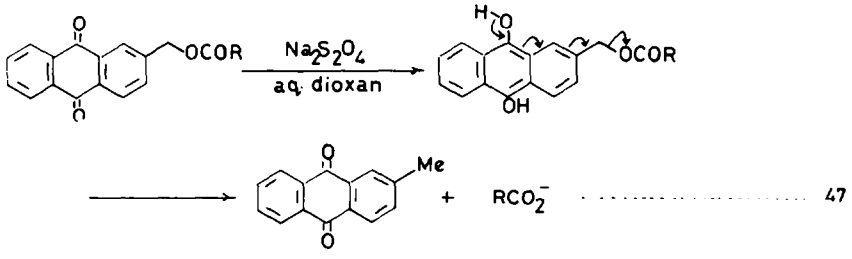
5.3 *Miscellaneous methods of carboxyl group protection and deprotection*

5.3.1 *9-anthrylmethyl.* Jaeger and Kornblum have discussed[128,129] the potential use and applicability of 9-anthrylmethyl esters for carboxyl group protection. Esters are prepared by standard means from 9-anthrylmethyl chloride or 9-anthrylmethanol. Cleavage of the ester is generally achieved by treatment with the sodium salt of methane thiol in DMF at $-20°$ for 1 hr, (eqn 46). Quoted yields of the product carboxylic acid were in the range 86–99%. Reduction of the nitro group in *m*-nitrobenzoate esters did not compete with de-esterification and in the case of cinnamate esters

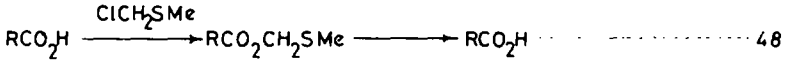


Michael addition of the thiolate to the α,β-unsaturated system was avoided by using just one equivalent of the thiolate salt. The behaviour of 9-anthryl-methyl mesitoate towards several different reagents and conditions was investigated so as to provide some insight into the properties of these esters. This ester was stable to acid in oxygen containing solvents such as dioxan or aqueous dioxan (0.14N H_2SO_4 in aqueous dioxan at 25°; dioxan–CF_3CO_2H at 25°) however in oxygen free solvents (dichloromethane) the ester was rapidly cleaved by the addition of CF_3CO_2H (10 min at 0°)–presumably by alkyl oxygen cleavage. The ester is similarly completely stable to anhydrous $EtNH_2$ in DMF at 25° and to lithium hydroxide in aqueous dioxan at 25° but at the same temperature the ester is deprotected in 93% yield in 30 seconds by sodium methane thiolate in HMPA.

5.3.2 *Esters of 2-oxymethylene anthraquinone* (maq). Esters of 2-oxymethylene anthraquinone have been exploited most extensively in connection with peptide synthesis.[130] They are formed from the corresponding alcohol and carboxylic acids by a DCC–hydroxybenztriazole promoted condensation and once formed are stable to trifluoracetic acid (1 hr at 20°), hydrochloric acid in CH_2Cl_2 (1 hr at 20°) and triethylamine in aqueous dioxan. Deprotection may be achieved in a number of ways; (i) by reaction with sodium dithionite in aqueous dioxan (pH 7–8, 5 equivs, 8 hr–100% yield–eqn 47), (ii) by photolysis at 340 nm in iso-propanol containing N-methyl morpholine–99% yield (iii) by reaction with 9-hydroxyanthrone in DMF containing triethylamine—99% yield or (iv) by stirring with excess polystyrene resin functionalised with 9,10-dihydroxyanthracene—100% yield.

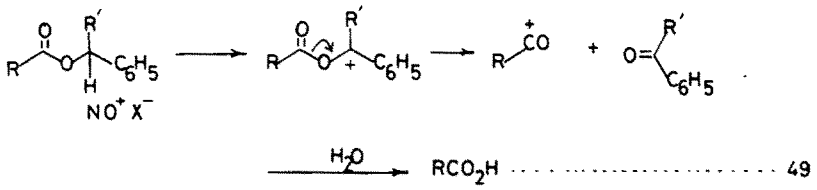


5.3.3 *Methylthiomethyl esters.* A further ester group whose potentialities as a carboxyl protecting group are clear but which has similarly been little exploited to date is the methylthiomethyl ester.[131–133] Esters are formed from the potassium salt of the carboxylic acid or the carboxylic acid plus triethylamine and chloromethyl thiomethyl ether. The protecting group may be removed by treatment with trifluoroacetic acid (15 min r.t.), refluxing in aqueous acetone with methyl iodide (17 hr) or treatment with mercuric chloride in refluxing aqueous acetonitrile followed by hydrogen sulphide to remove all traces of mercuric compounds (eqn 48).

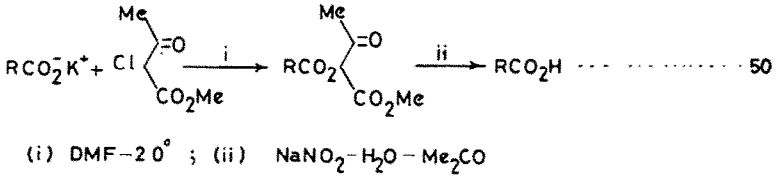


Deprotection (i) H_3O^+ ; or (ii) MeI – H_2O – Δ; or (iii) $HgCl_2$–H_2O , H_2S

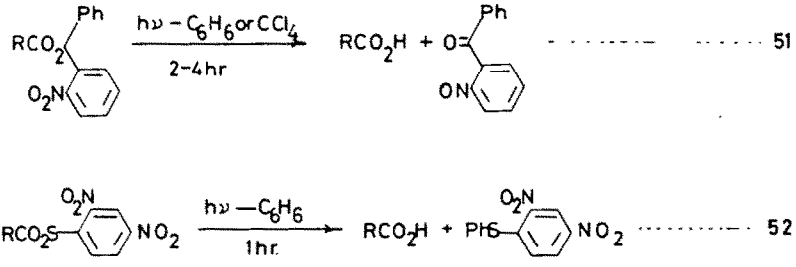
5.3.4 *Benzyl and benzhydryl esters.* The particular attraction of these ester groups to date has lain no doubt in the fact that they are both removed by hydrogenolysis or, after suitable substitution in the case of the benzyl group, by mild acid treatment. Ho and Olah[134] reasoned that the benzylic hydrogen of benzyl esters could be abstracted by the nitrosonium ion (NO^+) and that creation of the cationic centre should then induce spontaneous fragmentation into an acylium ion and a carbonyl compound. A precedent for this type of fragmentation is apparent in the case of the methylthiomethyl esters (5.3.3). Benzylic esters with one α hydrogen atom on the alcohol group are cleaved by treatment with nitrosonium hexafluoro-phosphate in nitromethane (50°, 0.5 hr) followed by quenching with water. Yields of acids are in the range 80–98%.



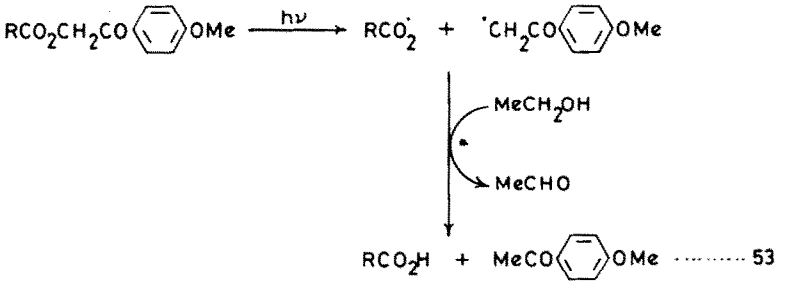
Analogous, in some respects, to this oxidative removal of benzyl and benzhydryl ester groups is the use by Japanese workers of α-halo-β-dicarbonyl compounds to protect the carboxylic acid function. The ester group is removed subsequently by treatment with sodium nitrite in aqueous acetone[135] (eqn 50).



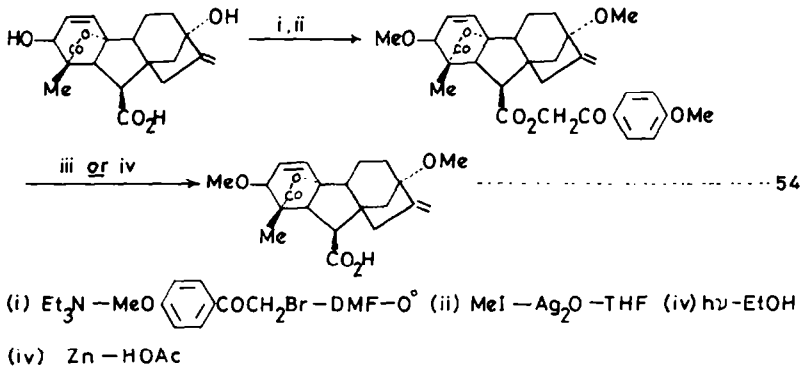
5.3.5 *Photosensitive ester groups.* *o*-Nitrobenzhydryl[136] and 2,4-dinitrobenzene sulphenyl esters[137] have been used as protecting groups for the carboxyl function.[2,138] They are removed by photolysis under neutral conditions and the quoted yields of carboxylic acids are high (85–98%), eqns (51, 52). Analogous to the *o*-nitrobenzhydryl ester is the 2,2′-dinitrodiphenyl methyl ester which has been advocated by Patchornik *et al.*[139] as a photosensitive ester group. Yields of carboxylic acid following its removal are quantitative.



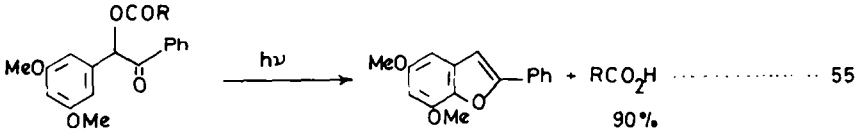
Phenacyl esters are cleaved photochemically and the mechanism is considered to be a simple radical scission of the carbon oxygen bond of the ester (eqn 53). The other product of the photolysis is an acetophenone. Sheehan has examined both the *p*-methoxyphenacyl and α-methylphenacyl functions as photolabile ester protecting groups.[140] Both types of ester are cleaved in ethanol or dioxan at 20° by UV irradiation. A recent application illustrates the general utility of this type of



carboxyl protecting group. The sensitivity of the gibberillins to acid and base was until very recently an obstacle to their recovery from alkyl ester derivatives. Alkyl esters can be cleaved with lithium mercaptide[141] and phenacyl esters can be successively deprotected by reduction with zinc and acetic acid.[2,142,143] Russian workers have now illustrated how the photolabile *p*-methoxyphenacyl ester group may be used in the transformation of gibberillin A-3[144] (eqn 54). Sheehan has also drawn attention[145] to the possible use of dimethoxy benzoin as a photosensitive carboxyl protecting group



although it has yet to receive sufficient interest to outline the scope of its applicability (eqn 55). Similarly the use of "maq" esters (5.3.2) as photolabile carboxyl protecting groups remains to be examined in detail.[130]



5.3.6 *Amides, hydrazides and related compounds.* Amides are not regularly encountered as protecting groups for the carboxyl function. That they can be used to considerable advantage in this role was amply demonstrated in the Woodward–Eschenmoser synthesis of cobyric acid.[56] The protection of the carboxyl group (f) in the cobyric acid as an amide in the synthesis did nevertheless present difficulties in the final transformation from the amide to the free carboxyl group. These were caused principally by the susceptibility of the corrin nucleus to nitrosate, at position 10, with nitrous acid. Woodward[56] finally resolved the problem using nitrogen dioxide in carbon tetrachloride but it is interesting to note how this conversion was achieved by Eschenmoser[146] to provide a method of general applicability (but of diabolical cleverness) for the amide to carboxyl group transformation. In the Eschenmoser procedure (Fig. 4) the extremely reactive N-alkyl-N-vinylnitrosium ion–derived from the α-chloronitrone by treatment with silver ion—is generated in presence of the amide which it attacks at oxygen. Subsequent mild acid hydrolysis gives the aldehydo ester. When this is treated with dimethylamine in iso-propanol the "f" acid is smoothly formed.

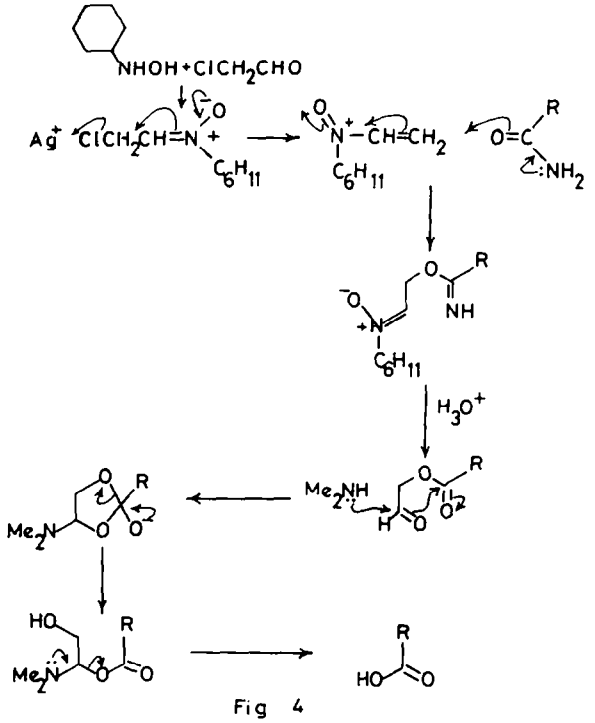
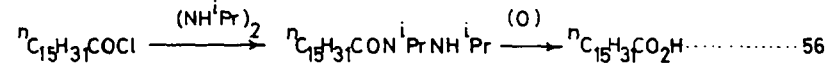


Fig 4

Barton *et al.*[147] have reported the use of acyl hydrazides as carboxyl protecting groups in penicillin chemistry. N,N′-Di-isopropylhydrazine reacts with either acyl chlorides or mixed anhydrides to give the corresponding monoacyl hydrazides. The carboxylic acid group was regenerated from the hydrazide by selective mild oxidation (lead tetra-acetate and pyridine in benzene at r.t.) (eqn 56). Although lead tetra-acetate was the preferred oxidant other agents were examined and found suitable ($NaIO_4$, NBS and CrO_3 in AcOH). Japanese workers[148] have similarly used molecular oxygen and cupric acetate to release the carboxyl group from the corresponding hydrazide.



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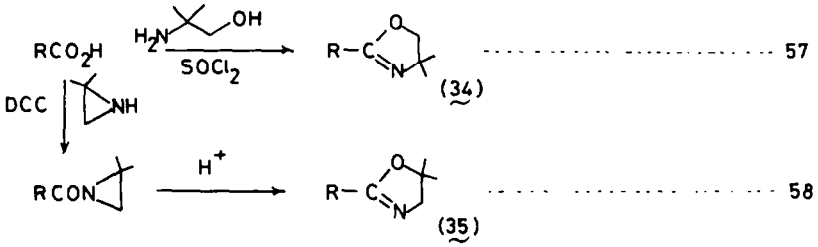
Oxazolines have been recommended by Meyers *et al.* as useful protecting groups for the carboxyl function.[2,149,150] They are inert to both Grignard reagents and metal hydrides. Oxazolines (**34**, **35**) may be formed from carboxylic acids by two alternative procedures as shown (eqns, 57, 58). The



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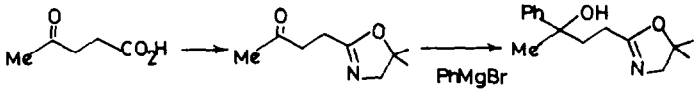
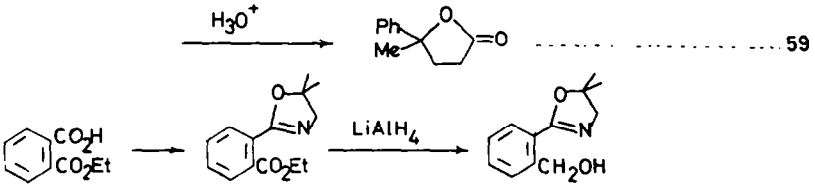
carboxyl group may be released from the oxazoline either by acid-catalysed hydrolysis or its ester formed by acid-catalysed alcoholysis. Some examples of its use as a protecting group are shown in eqns (59, 60). Certain limitations to the use of oxazolines as protecting groups have also been noted by Meyers. In particular the instability of the oxazolines derived from halocarboxylic acids such as **36** and **37** clearly precludes their use with these and analogous substrates.





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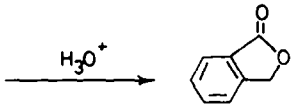

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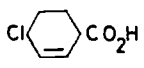

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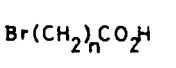

(37, n=3,4,5)

Postcript. There is very little need to testify to the health and vigour of this area of the chemistry of protecting groups. In the future the search for new functionalities and ideas will doubtless be prosecuted with the same interest, originality and enthusiasm. However the events of the past decade amply justify those words of Robert Louis Stevenson in *El Dorado* "*to travel hopefully is a better thing than to arrive, and the true success is to labour*".

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