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REACTIONS OF AROMATIC ACETYLENIC COMPOUNDS WITH SULFUR HALIDES

A THESIS

PRESENTED FOR THE

DEGREE OF MASTER OF SCIENCE

in the

UNIVERSITY OF ADELAIDE

by

LOK WON NAM, B.Sc.

Department of Organic Chemistry

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CONTENTS

SUMMARY

The reactions of phenylpropiolic acid and methyl phenylpropiolate with thionyl chloride, sulfur dichloride, sulfur monochloride and sulfuryl chloride have been investigated. Formation of benzo[b]thiophene products has been observed in some cases. The procedure is not considered to be a particularly useful route to these systems due to the relatively low yield and the multiplicity of products formed in most cases. Compounds derived from the formal addition of chlorine to the triple bond are among the major products in most of these reactions.

Several routes for the synthesis of pyridylpropiolic acids and esters have been investigated. The reaction of these compounds with thionyl chloride has been studied and found to be an unattractive approach to the synthesis of the thienopyridine systems.

STATEMENT

This thesis contains no material previously submitted for a degree or diploma in any University, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

W. N. LOK

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I would like to thank my supervisor, Dr. A.D. Ward for his excellent guidance and encouragement throughout the course of the work.

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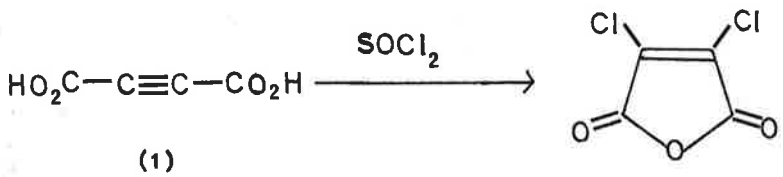
CHAPTER 1

INTRODUCTION

INTRODUCTION

The reaction of acetylenic systems with sulfur halides has received scant attention until very recently. In the past decade, however, the study of these reactions has steadily increased and particularly in the case of sulfenyl halides, a considerable amount of work has been reported.[1] In most cases, the work in this area has been concerned with simple alkynes and relatively little work has been published on the reaction of acetylenic acids or acid derivatives with sulfur halides.

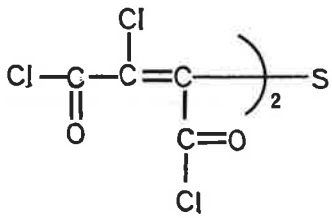
Acetylene dicarboxylic acid (1) has been shown[2] to react readily with thionyl chloride in the presence of a catalytic amount of base (dimethylformamide) to yield the dichloromaleic anhydride (2) in good yield (scheme 1). It was suggested that



(1) (2)

Scheme 1

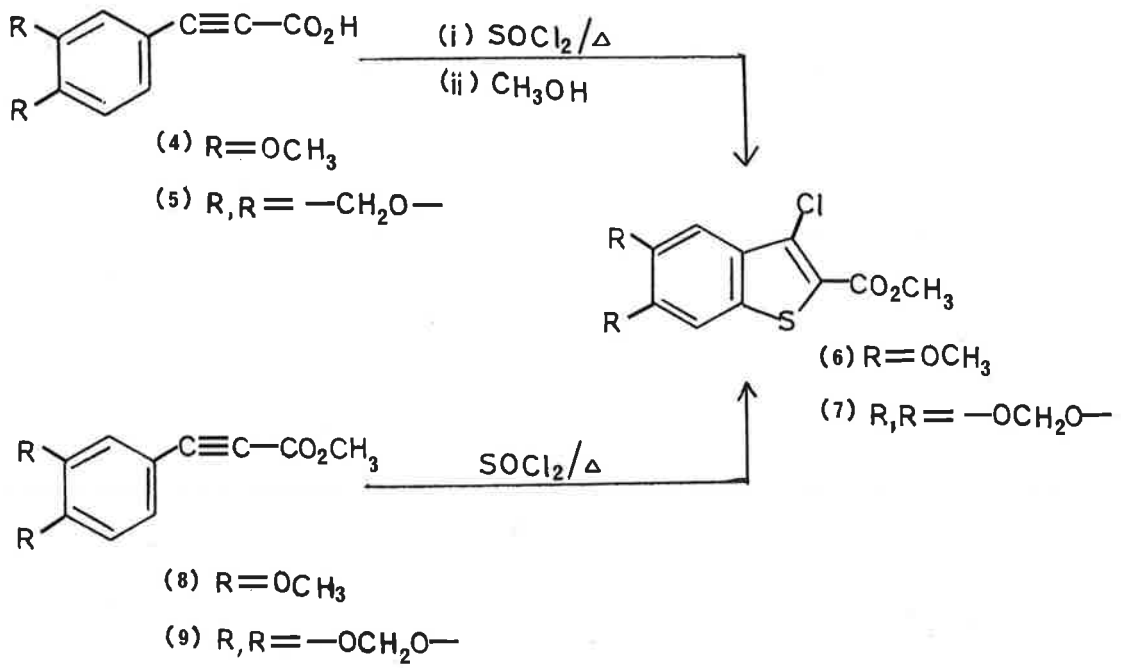
the reaction proceeded via cis addition of thionyl chloride to the triple bond with transfer of chlorine and formation of sulfur monoxide. The same product (2) was also formed, but in lower yield, when triethylamine or pyridine were used as the base. Under these conditions another product was also isolated[2] and assigned structure (3). In other cases the reaction of



(3)

acetylenic acids has apparently proceeded[3,4] normally with thionyl chloride to give the expected acid chloride.

During the course of some work on alkoxysubstituted phenylpropiolic acids, Cadby[5] noticed that thionyl chloride reacted, under reflux conditions, with some disubstituted systems to yield non-acetylenic products. These products were shown by spectral data and independent synthesis to be benzo-[b]thiophene compounds (scheme 2).



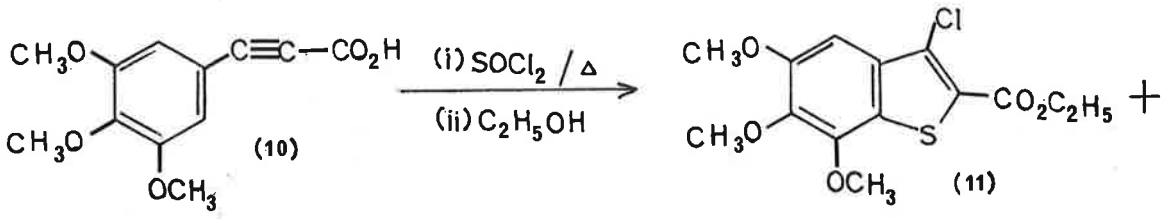
Scheme 2

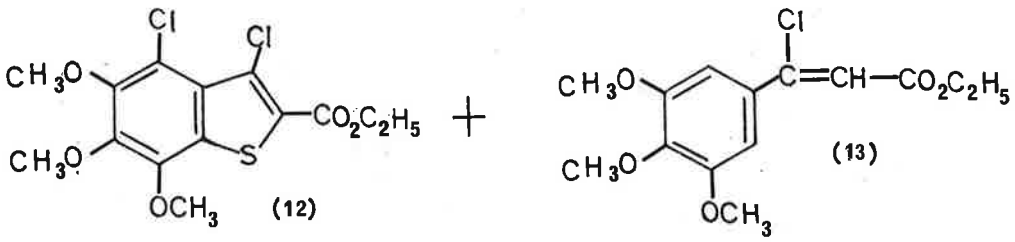
Cadby[5] further showed that the reaction proceeded equally readily on the corresponding acetylenic esters, (8) and (9) to again yield the benzo[b]thiophene system. Isolation of the benzo-[b]thiophene acid chloride after the reaction of the acetylenic acid (5) with thionyl chloride under reflux conditions established that the cyclisation occurred during the treatment with thionyl chloride. For convenience, the reactions were worked up with

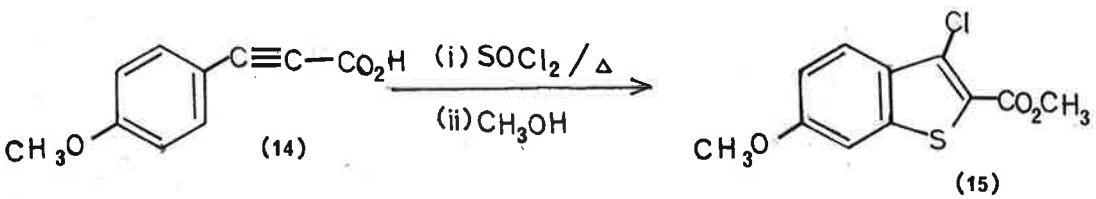
methanol, to convert the acid chloride products to the more amenable ester derivatives. However, the acid (5) gave only the corresponding acid chloride when treated with thionyl chloride at room temperature for twenty-four hours. This acid chloride was stable at room temperature. Phenylpropiolic acid reacted with thionyl chloride under the same conditions (reflux, no solvent, four hours) to give only phenylpropiolyl chloride, which was characterised as the corresponding methyl ester. Klemm and his co-workers[4] had earlier reported that the dimethoxy acid (4) reacted with thionyl chloride in benzene under reflux conditions to yield the acetylenic acid chloride, although they did not isolate the product but used it in situ to form an ester.

Analogous reactions with 3,4,5-trimethoxy-phenylpropiolic acid (10) and p-methoxyphenylpropiolic acid (14) gave considerably reduced yields of benzo[b]thiophene products and several other compounds were also obtained (scheme 3).

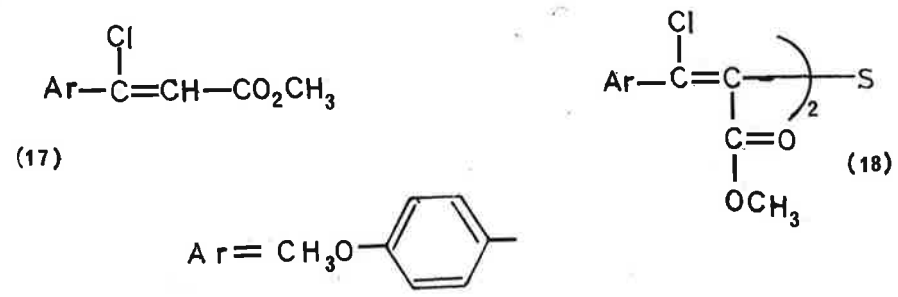
Bonnin[6] continued the work of Cadby and was particularly concerned with obtaining information on the reaction mechanism(s). She observed[6] that 3,4-methylenedioxycinnamic acid formed only


CH3O
CH3O
OCH3
C≡C—CO2H
(10)
(i) SOCl2 / Δ
(ii) C2H5OH
Cl
CO2C2H5
S
(11)

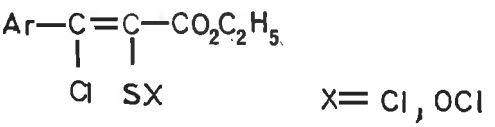

Cl
Cl
CH3O
CH3O
OCH3
CO2C2H5
S
(12)
Cl
C=CH—CO2C2H5
(13)


C≡C—CO2H
CH3O
(14)
(i) SOCl2 / Δ
(ii) CH3OH
Cl
CO2CH3
S
(15)

Scheme 3


Cl
Ar—C=CH—CO2CH3
(17)
Ar= CH3O
Cl
Ar—C=C
S
2
C=O
OCH3
(18)

the corresponding acid chloride under these conditions, although the β-chlorocinnamate (13) was slowly converted to benzo[b]thiophene products by refluxing in thionyl chloride. She further showed that the β-chlorocinnamate (13) was not formed to any appreciable extent during the reflux period with thionyl chloride but was obtained during the work-up of the reaction with an alcohol. It is known[7] that HCl adds quite readily to the triplet bond of alkoxysubstituted phenylpropiolic systems. Thus although it is possible that HCl, formed during the alcoholysis of residual thionyl chloride and the acid chloride, may well be adding to the triple bond of unreacted starting material, it is also possible that the alcohol is converting an addition product of type (16) to the observed β-chlorocinnamate (13). Addition of HCl to phenyl-



(16)

propiolic acid is known[8,9] to add in the Markownikoff sense to form a mixture of the cis- and trans-β-chlorocinnamic acid systems.

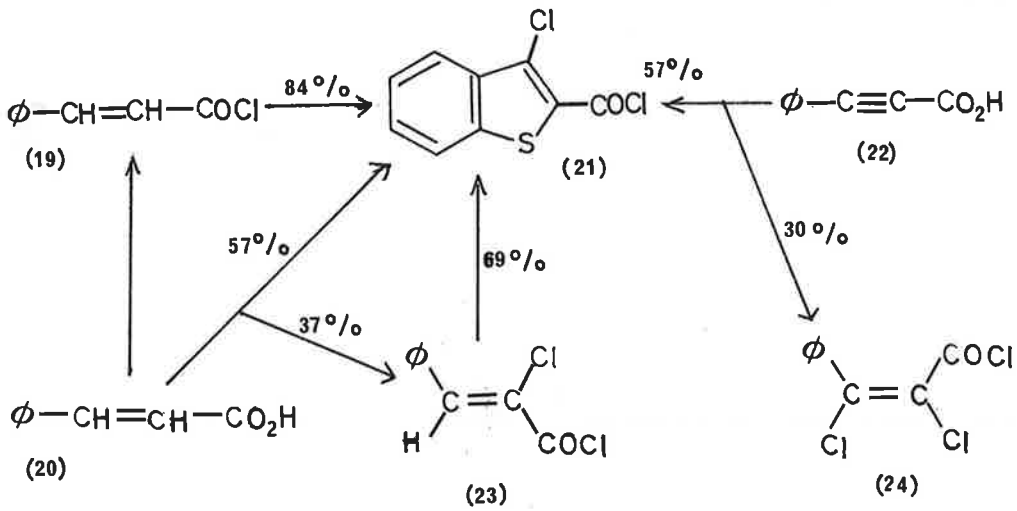
Bonnin[6] repeated the reaction on p-methoxy-phenylpropiolic acid and obtained, in addition to the benzo[b]thiophene (15)

reported by Cadby,[5] two non-cyclised products (17) and (18). In addition other products were obtained in unsufficient amounts or purity to enable them to be characterised. However it is clear from the data reported[6] that two of these products can be tentatively identified, as a result of the work (see page 29) presented in this thesis. In contrast to the result reported by Cadby, Bonnin was unable to obtain cyclised products when m-methoxyphenylpropiolic acid or the corresponding ester was refluxed with thionyl chloride.

It was noted[6] that the ester (8) was stable to reflux with thionyl chloride in a variety of solvents with boiling points similar to that of thionyl chloride. It was therefore suggested that the formation of the benzo[b]thiophene (6) from (8) involved ionic species, since it is known[10] that neat thionyl chloride is ionized to some extent and addition of an inert solvent would suppress this ionization.

Shortly after the completion of Bonnin's work, a preliminary communication[11] appeared which outlined the results of an investigation of the reaction of phenylpropiolic acid and cinnamic acid with thionyl chloride in the presence of a catalytic amount of pyridine. These results are summarised in

scheme 4. It was noted that cinnamic acid (20) reacted with

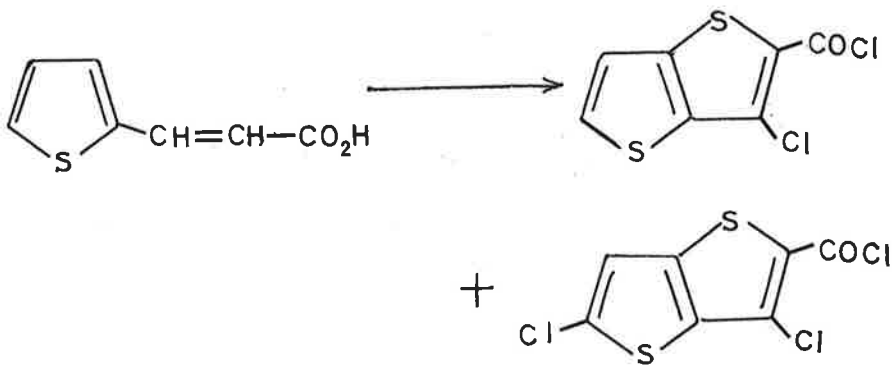


Scheme 4

thionyl chloride to give only cinnamoyl chloride (19), whereas the reaction of (20) in the presence of pyridine afforded (21) and (23). A similar reaction of (20) with sulfur monochloride did not give any identifiable product. Compound (23) was converted to the benzo[b]thiophene (21) with both sulfur monochloride and thionyl chloride in the presence of pyridine. The benzo[b]thiophene (21) was also obtained from acetylenic acid (22) with thionyl chloride and pyridine. Unfortunately the experimental details of this work have not yet been pub-

lished and it is thus not possible to clarify the somewhat ambiguous statements in the preliminary communication.

It had already been noted,[12] though only as a footnote to another preliminary communication, that cinnamic acid reacted with thionyl chloride in the presence of pyridine to form the benzo[b]thiophene product (21) in 61% yield and (23) in 13% yield. Further examples of benzo[b]thiophene formation under these conditions from substituted cinnamic acids were provided in a later communication.[13] The reaction has been somewhat improved by Wright and Brabander[14] but the yields are still not good and the reaction conditions (reflux for 3 days in chlorobenzene) are rather extreme. By-products formed in these reactions were identified[15] as thiazolo[3,2-a]pyridinium chlorides. Both Wright[16] and Gronowitz[17] have extended the reaction to prepare thieno[3,2-b]thiophene systems from the corresponding thiophene-2-acrylic acid (scheme 5).



Scheme 5

CHAPTER 2

REACTIONS OF PHENYLPROPIOLIC ACID AND ITS METHYL ESTER

2.1. REACTION OF PHENYLPROPIOLIC ACID AND ITS METHYL ESTER WITH THIONYL CHLORIDE AND PYRIDINE

At the commencement of this investigation no experimental details for the reaction of phenylpropiolic acid (PPA) with thionyl chloride, in the presence of pyridine, had been published (indeed some three years later this is still the case). It was thus decided that the investigation should concentrate initially on the reaction and its potential as a general route to benzo[b]thiophenes. In particular answers were sought to the following questions:

(1) Does the reaction occur with other related systems e.g. esters of arylpropiolic acids?

(2) What is the optimum amount of pyridine relative to both thionyl chloride and the acetylenic system for maximum yield of the benzo[b]thiophene product?

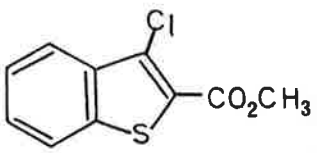
(3) What other products are formed in these reactions?

It was soon established, qualitatively, that PPA reacted more readily than methyl phenylpropiolate (MPP) with thionyl chloride and pyridine, under similar conditions as judged by t.l.c. data. In addition, no acetylenic bond could be detected in the total crude product from the reaction of PPA after six hours reflux, whereas

some acetylene absorption was still present in the corresponding reaction of MPP after twenty-four hours.

It can be inferred from the preliminary communication concerned[11] that the conditions used for the cyclisation of PPA involved a small amount only of pyridine in excess thionyl chloride. These are the conditions used for similar cyclisation involving cinnamic acid related systems.[12,14-17] However, rather than assume these conditions it was considered that it was worthwhile to determine the variation, if any, of the benzo[b]thiophene yield according to the variation in relative amounts of pyridine and thionyl chloride.

The data obtained are summarised in Table 1, and it is clear from these figures that the maximum yield of the cyclised product (25) is obtained when small amounts only of pyridine are used



(25)

$C_6H_5-CH=CCl-CO_2CH_3$

(26)

$C_6H_5-CCl=CCl-CO_2CH_3$

(27)

Table 1

Variation in the yield of benzo[b]thiophene (25) with the relative ratio of pyridine and thionyl chloride

pyridine (ml)	thionyl chloride (ml)	% yield (25)[a]
2	1	14
0.062	2	18[b]
1.78	2[c]	21
1.78	2[d]	24
1	4	26

a. ca. 500 mg of MPP was refluxed in the thionyl chloride/pyridine system for two days. The benzo[b]thiophene (25) was separated by preparative plate chromatography and purified by crystallisation.

b. 61 mg of pyridine was used. Some starting material was detected in the total crude product.

c. 1:1 mole ratio.

d. toluene (5 ml) was used as the solvent and the solution refluxed as described above.

relative to thionyl chloride concentration. The yields given in Table 1 are isolated yields and are undoubtedly lower than the actual yield, due to losses in the work-up procedure. However, it is felt that the trend in these figures is meaningful. It was also noticed that increasing the amount of pyridine relative to thionyl chloride gave increased amounts of tarry material, which made the separation and purification of (25) more difficult.

Preparative t.l.c. did not enable any of the other products of these reactions to be separated and characterised. Accordingly, the total reaction product was analysed by vapour phase chromatography and the peaks identified by use of a coupled mass spectrometer. Table 2, gives the results obtained after MPP was refluxed with thionyl chloride and pyridine (4 ml : 1 ml) for six hours. As expected a considerable amount of starting material was present. The yield of (25) was ca. 36% of the total volatile material, assuming an equal response ratio for each of the products. The other products identified were the cis and trans isomers of methyl β-chlorocinnamate (26) and the cis and trans isomers of methyl αβ-dichlorocinnamate (27). It is not possible, with certainty, to identify which isomer is which in both these cases. However, the n.m.r. spectrum of the crude reaction product has singlets at δ 6.38 and 6.57. These peak positions are consistent with those expected[18] and found[19] for the β-chlorocinnamate system and rule

Table 2

Products and relative yields[a] from the reaction of PPA and MPP with thionyl chloride and pyridine[b]

Compound	Starting material (reaction time)		
	MPP (6 hours)	MPP (2 days)	PPA (6 hours)
MPP	2	-	-
(26)[c]	3	1	1
(27)[c]	2	2	7
(25)	4	4	17
% yield (25)[d] of total volatile material	36	57	68
% yield (25), isolated.		26	37

a. ratio of peak areas of the v.p.c. spectra, assuming an equal response ratio for the products.

b. compound refluxed thionyl chloride (4 ml) and pyridine (1 ml) for the specified time.

c. *cis* and *trans* isomers combined.

d. amount of (25) expressed as a percentage of the total amount of material recorded by the v.p.c. instrument.

out the alternate α-chlorocinnamate structure for the HCl addition product. If it is assumed that the higher field signal of the two singlets is due to the cis isomer as seems reasonable,[18-19] then the trans isomer is the one obtained in greater amount.

A crystalline dichloro acid obtained from some later work (page 33) is tentatively assigned the cis structure. If this assignment is correct then the dichloro ester obtained in greater amount in these reactions has the cis structure also by comparison of the v.p.c. data. The Japanese work[11] also assigned the cis geometry to the dichloro acid (24), they obtained from their reaction (scheme 4, page 8) on the basis of melting point data. It is not clear whether the isomer ratio for (26) and (27) has any significance in mechanistic terms. In both cases it appears that the thermodynamically more stable isomer[9] is present in greater amount and the isomer ratio may simply reflect the order of stability of the respective systems.

When the MPP was refluxed with thionyl chloride and

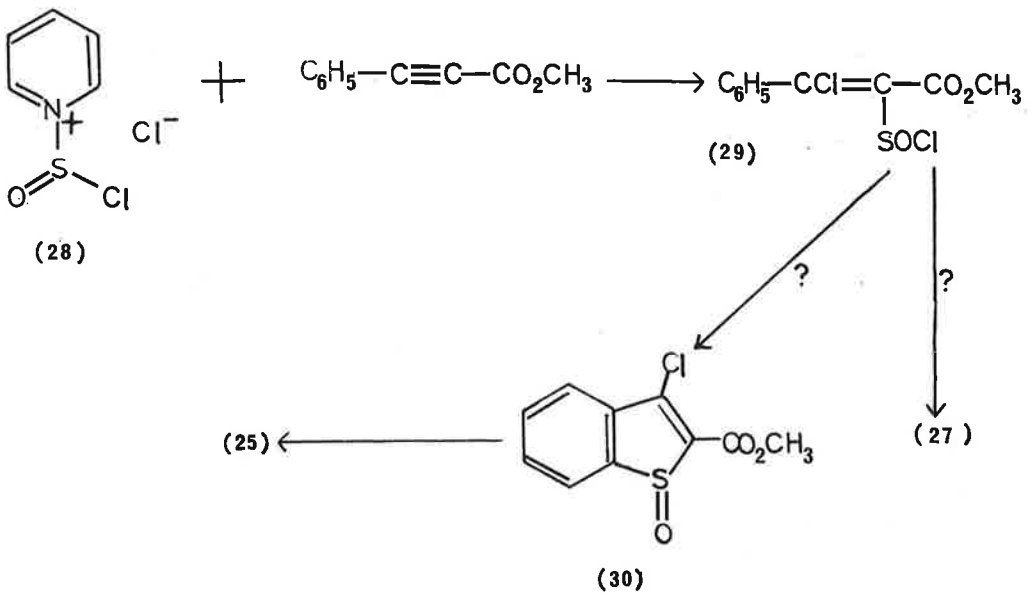
pyridine for a longer period (two days) the starting material could no longer be detected in the products, as analysed by v.p.c. and the relative yield of (25) had increased. After six hours refluxing under similar conditions, PPA had formed the same products but in a different ratio (Table 2). The higher yield of (25) from the acid, when compared to the ester, was determined by v.p.c. was reflected in the greater yield (37%) of this material, when a similar reaction was worked up as described for the reactions in Table 1. It should be emphasised that percentage yield of (25) as determined by v.p.c. is likely to be greater than the actual yield since some polymeric material is also formed in these reactions, which would make the actual yield somewhat lower than that indicated by v.p.c.

It is of interest to note that the relative amount of the HCl addition product (26) decreases with increasing reaction time. It was considered that this product may arise from an addition of HCl, formed during the alcoholysis of the reaction mixture to unreacted acetylene and that this would explain the decrease in relative amount. However, in a separate experiment, MPP was found to give only trace amounts of the HCl addition product when refluxed in methanol containing anhydrous hydrogen chloride. When MPP was refluxed with thionyl chloride and pyridine for twenty-four hours

and worked up by addition of water rather than methanol, (26) could be detected by v.p.c. When the same reaction solution, prior to the addition of water, was injected directly onto the v.p.c. column no HCl addition product (26) could be detected. Instead a new major peak was evident with a longer retention time. After the usual work-up involving addition of a proton source, this peak was essentially absent. However, since it had a very similar retention time on the column to one of the isomers of (27), it was not possible to be absolutely certain that it was no longer present. This data suggests that the HCl addition product (26) arises by protonolysis of a reaction intermediate and the decrease in yield of (26) with longer reaction times, in turn indicates the consumption of intermediate. Bonnin[6] had previously found that the HCl addition product (13) formed in the analogous reaction of p-methoxyphenylpropiolate was not present in the reaction solution until the mixture was worked up.

It does not appear to be profitable to speculate at length on the mechanism (or mechanisms) for the formation of these products. It would be expected[10] that the pyridine would coordinate with the thionyl chloride to form a complex that is more activated toward electrophilic attack than thionyl chloride itself and hence this would explain the catalytic effect of pyridine. However, the mechanisms for the formation of (26) and (27) from such an inter-

mediate are not clear and indeed it is not possible to distinguish between an ionic or a radical mechanism. It is reasonable to suggest that addition to the triple bond by thionyl chloride (or the pyridine complex, 28) could lead to an intermediate (29) that could either cyclise (via 30) to the benzo[b]thiophene (25) or collapse to the dichloro-product (27). Conversion of (30) to (25)



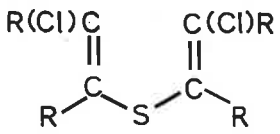
seems reasonable since a fully aromatic compound is obtained and it is known[10] that thionyl chloride can function as an "oxygen transfer" reagent. It is known[20] that thionyl chloride begins to dissociate at its boiling point to chlorine and other products. This process is facilitated by strong light and is detectable at

ambient light strength. It is thus possible that the dichloro products (27) may arise by direct chlorination of the triple bond, particularly if the pyridine present can facilitate the dissociation process.

Thionyl chloride is known[10] to be weakly ionised as a pure liquid, this ionisation would be suppressed in a non-polar solvent. It is thus not surprising that conducting the reaction in toluene makes no appreciable difference to the yield of (25) for the effect of the higher reaction temperature would be offset by the decreased reactivity of the thionyl chloride in the non-polar solvent. A carboxylic acid could facilitate the ionisation of thionyl chloride and hence increased its reactivity; this effect would not be expected to the same extent with an ester and this may explain the decreased reactivity of MPP when compared to PPA.

2.2. REACTION OF METHYL PHENYLPROPIOLATE WITH SULFUR DICHLORIDE

Barton and Zika[21] have studied the reaction of acetylenes with sulfur dichloride and found that dialkylacetylenes afford the corresponding divinyl disulfides (31) in quantitative yield. In contrast diphenylacetylene and sulfur dichloride in equimolar quantities formed the benzo[b]thiophene (32) or the divinyl disulfide (31, R = C_6H_5) depending on the reaction solvent. In ether as solvent (32) was obtained in 90% yield,but in other solvents, e.g. dichloromethane hexane and acetonitrite, only the divinyl disulfide (31, R = C_6H_5) was formed. The authors were



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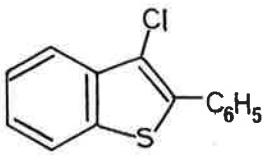

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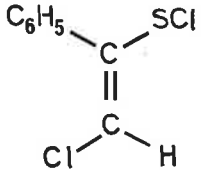


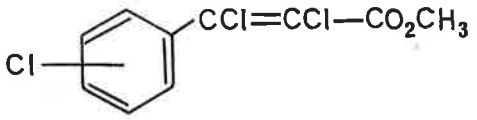
(33)

unable to offer an adequate explanation for this surprising solvent difference. When two equivalents of diphenylacetylene

were used (31) was the only product. Reactions involving unsymmetrical alkynes showed that the reaction was largely anti-Markownikoff and that the stereochemistry of the addition was trans. In some cases the initial adduct (e.g. 33) could be isolated.

Bonnin[6] had shown that methyl 3,4-dimethoxy-phenylpropiolate with a large excess of sulfur dichloride gave a good yield of the benzo[b]thiophene (6). In contrast, however, methyl m-methoxyphenylpropiolate gave intractable material under the same conditions.

It was thus of interest to examine the reaction of MPP with sulfur dichloride. If the results of Barton and Zika[21] apply to acetylenic esters the anti-Markownikoff addition of the reagent would give a product that is not suitably orientated for cyclisation to a benzo[b]thiophene system. When MPP was treated with excess sulfur dichloride in dichloromethane the starting material could not be detected by t.l.c. after three hours at room temperature. Analysis of the product by v.p.c. coupled to a mass spectrometer showed that the following compounds had been formed in addition to the benzo[b]thiophene (25). When the reaction was repeated, but using ether as the solvent, some starting material was still present after three hours and the overall yield of (25)



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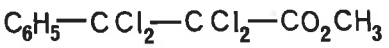


(35)

was lower. The ratios of the peak areas for these products in each reaction are shown in Table 3. Although the reaction using ether as a solvent had not gone to completion, it is clear that sulfur dichloride does not form the benzo[b]thiophene in a synthetically useful yield in either case. The major product in both cases was the dichloroaddition product (27). The cis and trans ratio for (27) was 6:1 when dichloromethane was used as solvent and 4:1 in the other case.

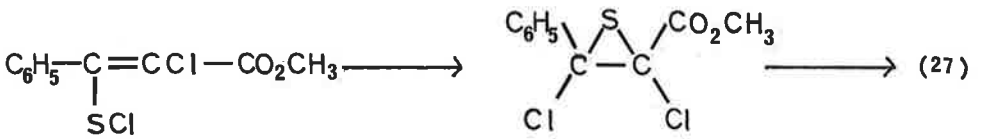
The mechanism for the formation of these products is not clear. An episulfonium intermediate is considered to be involved[22-24] in the reaction of sulfur dichloride with olefins

Table 3

Relative yields of products from MPP and sulfur dichloride

solvent	MPP	(27)	(34)	(35)	(25)
CH_2Cl_2	-	8	1	trace	2
ether	5	13	5	1	1

and it is possible that a similar intermediate (e.g.(36) may also form in this case. Loss of sulfur could then provide the dichloro compound (27). Alternatively a disproportionation of the sulfur



(36)

dichloride to either chlorine atoms or chlorine molecules could

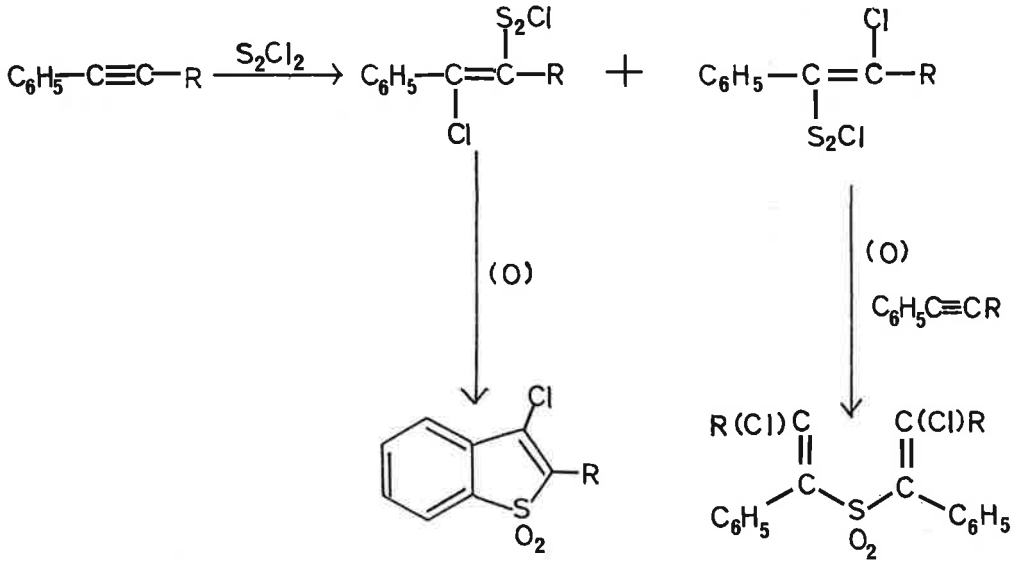
also be involved in the formation of (27). A radical mechanism would seem a more likely possibility for the formation of the ring chlorinated product (34). Since vinyl chlorides are relatively inert to electrophilic attack, radical chlorination of (27) appears to be a likely explanation for the formation of (35).

2.3 REACTION OF PHENYLPROPIOLIC ACID AND ITS METHYL ESTER WITH SULFUR MONOCHLORIDE

Nakagawa et al.[11] reported that cinnamic acid and several related systems could be converted to benzo[b]thiophenes by using sulfur monochloride (S_2Cl_2). However, they made no mention of any reaction of PPA or its esters with this reagent.

Reid and Ochs[25] have very recently shown that sulfur monochloride adds to acetylenic systems in both Markownikoff and anti-Markownikoff directions. Oxidation of the initial adducts gave mixtures of divinyl sulfones and a benzo[b]thiophene derivative if an arylacetylene was used. In particular ethyl phenylpropiolate gave a good yield (80%) of a benzo[b]thiophene-1,1-dioxide (37, R=$CO_2C_2H_5$) and a small amount (2%) of a thiophene-1,1-dioxide, which was considered to arise from a secondary reaction of the corresponding divinyl sulfones (38).

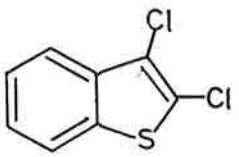
The results of the present study of the products formed in the reactions of PPA and MPP with sulfur monochloride are shown in Table 4. When PPA was refluxed with sulfur monochloride and pyridine for three hours and the mixture worked up as usual with methanol,



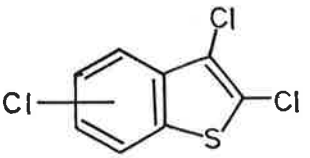
(37) (38)

v.p.c. data indicated the presence of only three products. Preparative t.l.c. enabled (25) to be obtained pure. The other two components could not be separated by adsorption chromatography, but n.m.r. and mass spectral data showed that the mixture consisted of (39) and (40). Fractional crystallisation of the mixture enabled (39) to be separated and its identity confirmed by melting point data. The n.m.r. data suggests that (40) is fully substituted in the thiophene ring

but does not enable the final chlorine to be placed.



(39)



(40)

When the same reaction was conducted in the absence of pyridine (25), (39) and (40) were formed in approximately the same ratio as before (Table 4). Small amounts of (26) and (27) were obtained as well, in contrast to the initial reaction where these products were not detected. Conducting the reaction at a lower temperature with pyridine altered the product ratio considerably as only a trace of (40) was detected. When MPP was used instead of the acid, relatively less of (39) was obtained and relatively more of the adduct (26) and (27) were noticed. In addition a new product was observed by v.p.c. with a longer retention time than (25). Unfortunately it was not possible to separate this material by preparative t.l.c. and no spectral information could be obtained for it.

Table 4

Relative ratio of products from sulfur monochloride and PPA or MPP

Starting material	Products (25)	(39)	(40)	(27)	(26)
PPA/pyridine[a]	5(23)[c]	6(31)	1(5)	-	-
PPA[a]	15	23	4	3	1
PPA/pyridine[b]	9	11	trace	-	-
MPP/pyridine[a]	12(17)	8(18)	1(2)	4	2[d]

a bath temperature 140-160°, reaction time three hours.

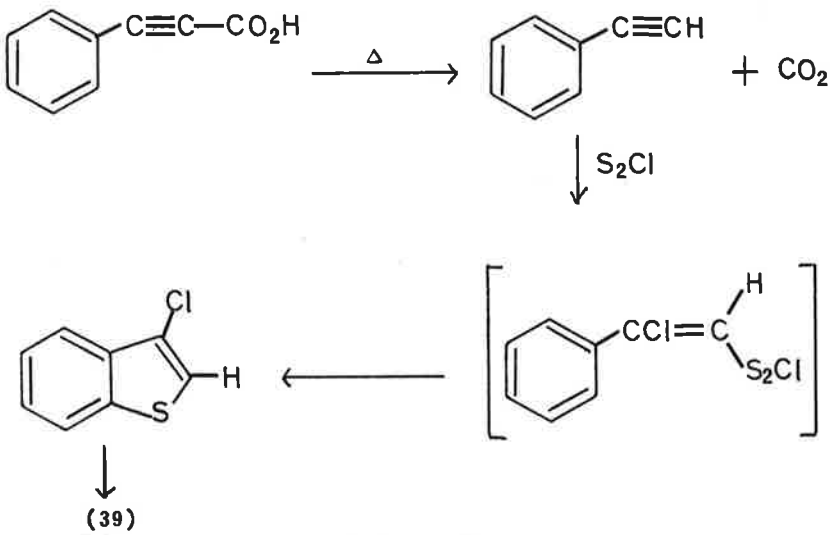
b bath temperature 95-100°, reaction time three hours.

c percentage yields after partial separation of the products by preparative t.l.c. are given in brackets.

d the relative ratio of the unidentified product is 6.

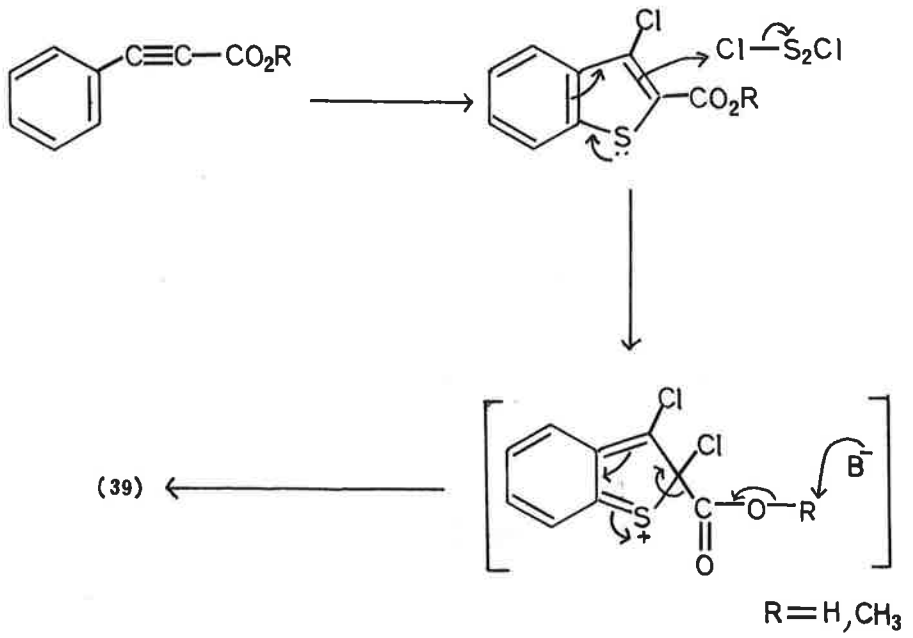
2,3-Dichlorobenzo[b]thiophene (39) has been obtained[11] in 41% yield from styrene and sulfur monochloride and is also formed[26] by the action of chlorine on benzo[b]thiophene. These results and the known[27] behaviour of thiophene and benzo[b]thiophene and benzo[b]thiophene esters and acids suggest two likely mechanisms for the formation of (39). It is possible that PPA decarboxylates thermally under the reaction conditions forming phenylacetylene. Addition of sulfur monochloride across the triple bond, followed

by ring closure and further chlorination would give (39) in a manner that is presumably very similar to that for the formation of (39) from styrene (scheme 6). It would not be expected that MPP would be readily decarboxymethylated by sulfur monochloride;



Scheme 6

however, pyridine hydrochloride may be generated during the reaction in sufficient quantity to at least partially saponify the starting ester which then could react as outlined in scheme 6. An alternative mechanism, shown in scheme 7, suggests that (39) arises from (25), or the corresponding acid, as the result of an electrophilic substitution involving displacement of a carboxylic acid or ester. The relative decrease in the yield



Scheme 7

of (39) starting from the ester compared to the acid (Table 4) could then be explained by the difficulty in decarboxymethylating (or saponifying) the intermediate in this scheme compared to the decarboxylation of the acid as the starting material. However, when (25) was treated with sulfur monochloride and pyridine under these reaction conditions (39) could not be detected by v.p.c. of the product and infrared and t.l.c. data showed that (25) was essentially unreacted.

The available data does not permit a definite conclusion to be made on the mechanism for the formation of (25) and (39) under these conditions and it is quite possible that radical, not ionic, processes are involved.

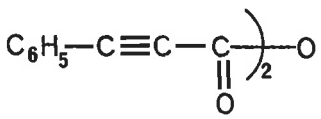
2.4. REACTION OF PHENYLPROPIOLIC ACID AND ITS METHYL ESTER WITH SULFURYL CHLORIDE

The reaction of acetylenic systems with sulfuryl chloride (SO_2Cl_2) has received little attention. Russian workers[28] have claimed that but-2-yne and sulfuryl chloride formed 3,4-dichloro-1,2,3,4-tetramethylcyclobutene in low yield as well as 2,3-dichloro-but-2-ene. The addition of chlorine has also been observed with olefins; in this case β-chlorosulfones were also formed[29] and a radical mechanism was involved. Amiel[30] has recently reported that sulfonyl chlorides added to the triple bond, in the presence of a copper catalyst to give β-chlorovinylsulfones. A similar reaction has been reported[31] with sulfonyl iodides. Chlorosulphonic acid reacts[32] with butyrophenones and valerophenones to form 3-chloro-2-alkylbenzo[b]thiophene-1,1-dioxides.

When MPP was refluxed with sulfuryl chloride for three hours an oil was obtained, which by v.p.c. analysis was shown to consist of six products. The cis and trans isomers of (27), in a 4:1 ratio, made up half of this total volatile material; with (34) (both isomers, relative yield 15%) and (35) (21%) being the other major components. A small amount (ca. 3%) of (26) was the other product.

In marked contrast PPA and sulfuryl chloride under similar conditions gave a product whose infrared spectrum suggested the presence of an anhydride as one of the products. This material appeared to be formed to its greatest extent, when the reaction time was prolonged to twenty hours. In this case a crystalline acid was obtained, in 40% yield, whose spectral data and physical properties are consistent with it being cis-αβ-dichlorocinnamic acid. In particular it had a melting point of 116-120°, which is greater than that of the trans isomer[33] but very similar to that quoted for the cis isomer.[33] A mixture of the two acids melts lower than that of either pure acid.[33] In addition a chlorine containing anhydride was isolated in 15% yield. The n.m.r. and mass spectrum of this compound suggested, particularly after comparison with those of similar compounds,[34] the structure (42). Esterification of the total product with diazomethane and analysis of the mixture by v.p.c. showed that (27) was the major component (84% of total volatile material, cis:trans ratio 4:1). Small amounts of (26) and one isomer of (34) were also obtained. The chloroanhydride (42) is not sufficiently volatile to be detected by v.p.c. under the usual conditions. No benzo[b]thiophene products were detected in either of these reactions.

It is known[34] that phenylpropiolic anhydrides (41) heating will cyclise to form 1-phenylnaphthalene anhydride (43). Trans-cinnamyl phenylpropiolates (44) also cyclise when heated in acetic anhydride.[35] Cadby[36] has demonstrated



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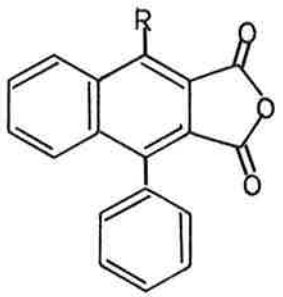
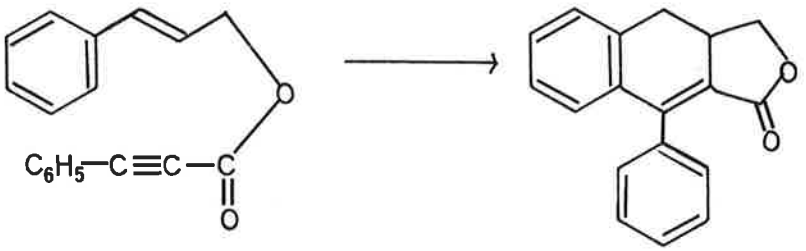


(42) R=Cl
(43) R=H
(47) R=I

that the trans-enynic ester (44) cyclises whereas the cis isomer is resistant to cyclisation. A study of molecular models and a consideration of the molecular orbitals involved suggested that the required geometry for a Diels-Alder reaction between the cinnamoyl moiety (the diene) and the triple bond (the dienophile) could only occur with the trans geometry for the double bond.

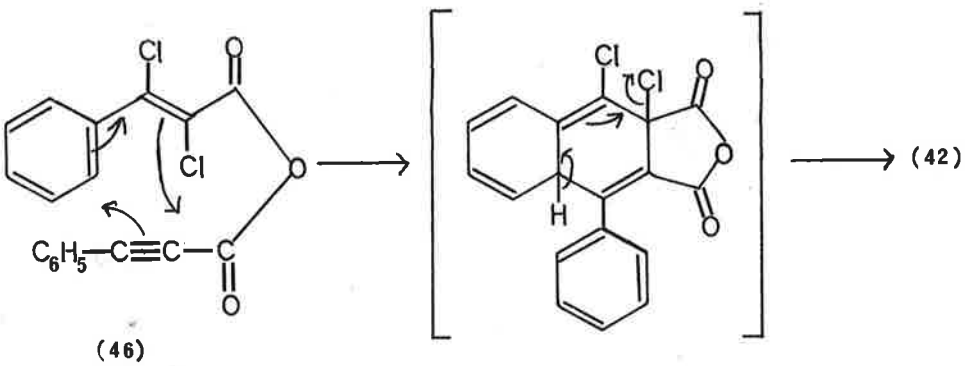


(44)

(45)

It is thus reasonable to suggest that of the mixture of anhydrides that could be formed under the reaction conditions, only that (46) formed from trans-αβ-dichlorocinnamic acid and PPA could cyclise to a 1-phenylnaphthalene derivative. Since the trans acid is formed in smaller amounts than the cis in these reactions it also accounts for the lower yield of (42) compared to the yield of cis-αβ-dichlorocinnamic acid. Since no (43) was detected among the reaction products, it suggests that the activation energy required to form (43) is considerably higher than that to form (42), assuming comparable reaction rates for both cyclisation processes. Usually the formation of (43) from PPA requires strong heating in a dehydrating medium and the

cyclisation of phenylpropiolic anhydride is slow at 100°.[36] It is reasonable to expect such a difference in activation energies since the enynic system (46) is better suited, both electronically and sterically, to a Diels-Alder reaction and the subsequent aromatisation process (scheme 8). A variation on this mechanism



Scheme 8

involving chlorination of one of the triple bonds of phenylpropiolic anhydride, followed by cyclisation is also a possibility.

When the cis-αβ-dichlorocinnamic acid and PPA were refluxed in benzene containing some acetic anhydride for twenty-four hours, the self-condensation product (43) was the only anhydride isolated. The cis acid is known[37] to be partially converted to the trans isomer (45% yield) when irradiated under

ultraviolet light for a prolonged time. When the cis acid was heated in chloroform under ultraviolet light for twelve hours and then PPA and acetic anhydride added and the irradiation continued for a further twenty-four hours no anhydride products were observed when the mixture was worked up.

Since the literature indicated that the trans-dichloro and the trans-dibromocinnamic acid were either difficult or very time consuming to prepare,[9,37] an attempt was made to prepare trans-αβ-diiodocinnamic acid. It was found[9] that the acid had a tendency to revert to PPA. When it was refluxed with PPA and acetic anhydride in chloroform with the solution protected from ambient light by aluminium foil, an anhydride material was obtained. The mass spectrum and infrared spectrum of this product indicated that both (47) and (43) were present. It was not possible to fully characterise (47) as it tended to liberate iodine when crystallisation was attempted. Though these results are somewhat inconclusive, they do tend to support the suggestion that (42) arises from the cyclisation of the trans-anhydride (46).

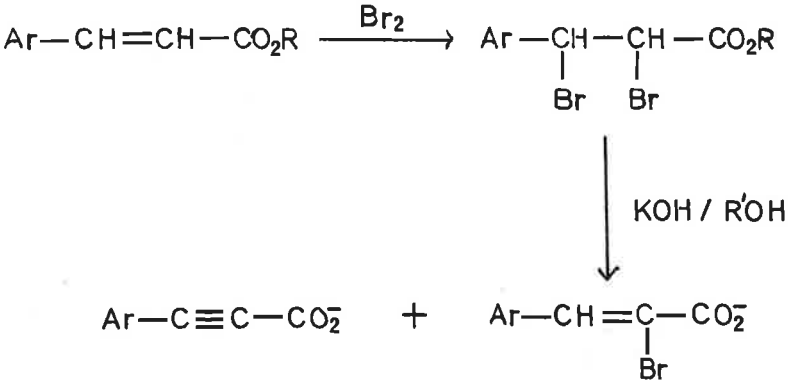
CHAPTER 3

SYNTHESIS AND REACTIONS OF PYRIDYLPROPIOLIC ACIDS AND ESTERS

The catalytic effect of small amounts of pyridine on the reaction of arylpropiolic acids with sulfur halides, particularly thionyl chloride, has been described in Chapter 2 and by others.[11,12,14,1 It was thus of interest to examine the reaction of thionyl chloride with pyridylpropiolic acids, to see whether this catalytic effect could be incorporated into the substrate. A search of the literature revealed that the pyridylpropiolic acids and esters had not been reported and accordingly an investigation into possible routes for the synthesis of these acids and related systems was undertaken.

3.1 SYNTHESIS OF PYRIDYLPROPIOLIC ACIDS AND ESTERS

The classical method for the synthesis of arylpropiolic acids involves a bromination - dehydrobromination sequence with a substituted cinnamic acid or ester. Although this reaction is of some value, the nature of the base used for the dehydrobromination step is of some importance. It has been found[34] that treatment of substituted cinnamyl esters with potassium hydroxide in alcoholic solvents gives variable yields of the acetylenic acid and that often considerable amount of the 2-bromocinnamic acid are also formed (scheme 9). In the benzene series this problem can be overcome[34] by

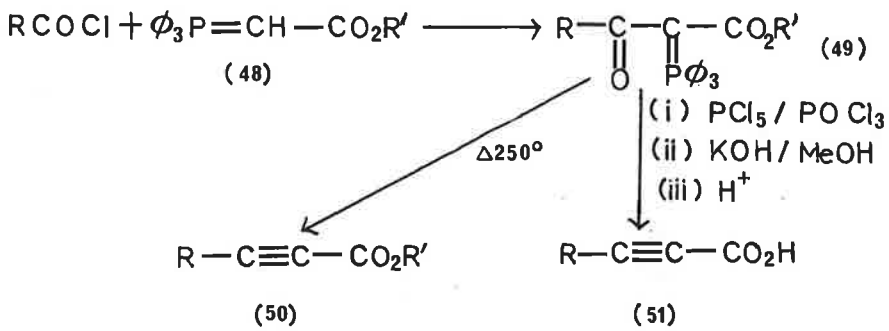


Scheme 9

the use of stronger bases in aprotic media or the use of sodamide in liquid ammonia. However, although bromination of pyridylacrylic acids occurs quite readily it has been shown[38] that

treatment of these dibromoacids with a variety of bases leads almost entirely via debromination to starting material rather than via dehydrobromination to yield a triple bond. More recently the dehydrobromination of dibromopyridylethylenes, to yield pyridylacetylenes, has been achieved[39] but the reaction was found to be very sensitive to reaction conditions and only slight changes dramatically lowered the yield of acetylenic material. It was considered, in the light of these results, that it would not be profitable to attempt to synthesise pyridylpropiolic acids or esters by this route, particularly since other routes seemed more attractive.

Several modifications of the Wittig reaction have recently been described which lead to acetylenic acids or esters in acceptable yields.[40,41,42] Of these the route shown in scheme 10 was considered to be the most suitable for synthesis of pyridylpropiolic esters and hence the corresponding acids. This route[40] required the



Scheme 10

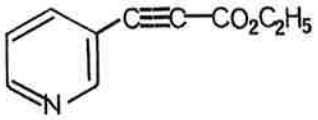
preparation of the various pyridyl acid chlorides and then reaction with the methylidenephosphorane (48) to produce the acylphosphoranes (49).

In agreement with the literature,[43] it was observed that in several cases the attempted distillation of the product from the reaction of the pyridylcarboxylic acid and thionyl chloride leads to a coloured volatile material and low yields of the required acid chloride. It was found that by using a threefold excess of the phosphorane (48) on the crude reaction mixture obtained after removal of the excess thionyl chloride, a satisfactory yield of the acylphosphorane (49) could be achieved without the need to distil the acid chloride. In the cases where the acid chloride could be satisfactorily obtained by distillation it reacted in the usual manner[34] with two moles of the methylidenephosphorane (48) to form the acyl derivative (49).

In general the acyl systems (49) can be converted to the acetylenic ester (50) by pyrolysis[40] at ca. 250° or to the acetylenic acid (51) by reaction[41] with phosphorus pentachloride in phosphorus oxychloride as solvent, followed by a basic hydrolysis. It was felt that the latter method may prove difficult because of difficulties associated with the reactivity of the pyridine system towards the acidic reagents. In practice this proved to be the case as the

acylphosphorane derived from nicotinyl chloride gave a poor yield of acetylenic material by this route. No other product could be obtained from the reaction mixture in this case.

However, the pyrolysis of the acylphosphoranes obtained from all three isomers of pyridyl acid chloride proceeded satisfactorily at the temperatures in the range 200-250° and good yields of the pyridylpropiolyl esters (52-54) were obtained. These esters were



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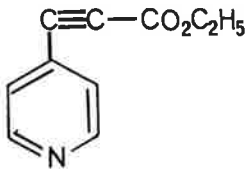

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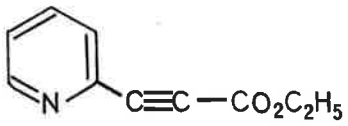


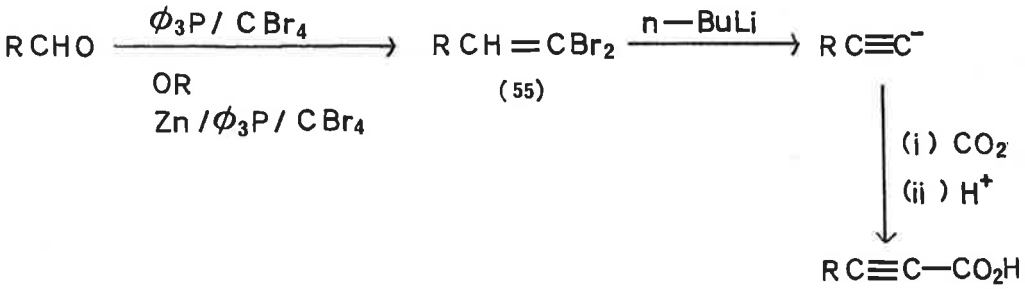
(54)

colourless liquids that rapidly darkened on standing, even in sealed containers. The decomposition of ethyl 2-pyridylpropiolate (54) was so rapid that the material had noticeably darkened in colour by the time it reached the receiving flask in the distillation apparatus. The order of stability of the esters was in the order (52) > (53) > (54). Although an acceptable analysis was obtained for the most stable isomer (52), it was considered that instability problems would prevent satisfactory analytical figures being obtained for the other isomers. In all cases the esters had n.m.r. and mass spectral data in full agreement with their structures.

The esters could be hydrolysed to the corresponding acids

although care had to be taken in acidifying the basic hydrolysis medium to ensure that the acid and not the acid hydrochloride was obtained. Careful neutralisation of the solution to pH≈7 resulted in the precipitation of the potassium salt of the acid on several occasions. It was also necessary to maintain the pH of the hydrolysis solution at about 10, for it was found that at higher pH's rapid darkening in colour of the solution occurred with the formation of tarry intractable material.

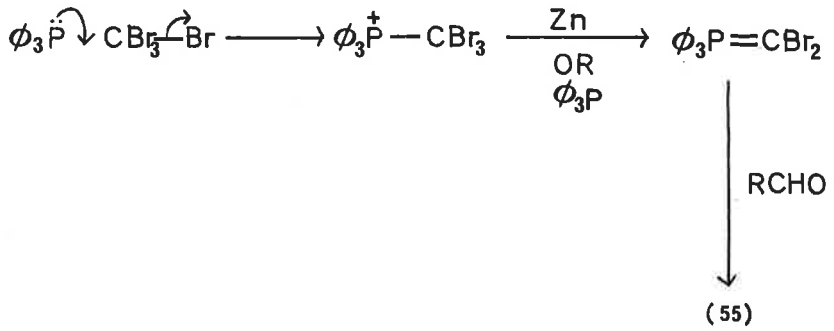
Recently a new method for the synthesis of acetylenic acid has been described by Corey and Fuchs[44] (scheme 11). They found that aldehydes on treatment with four equivalents of triphenylphosphine and two equivalents of carbontetrabromide gave high yields of



Scheme 11

1,1-dibromoethylenes (55), which on treatment with two equivalents

of n-butyllithium underwent dehydrobromination and halogen-metal exchange to form the acetylide. Carboxylation of this intermediate resulted in high yields of the corresponding acetylenic acid. As an alternative, but very similar procedure, zinc metal could be used as the base instead of triphenylphosphine (scheme 12).

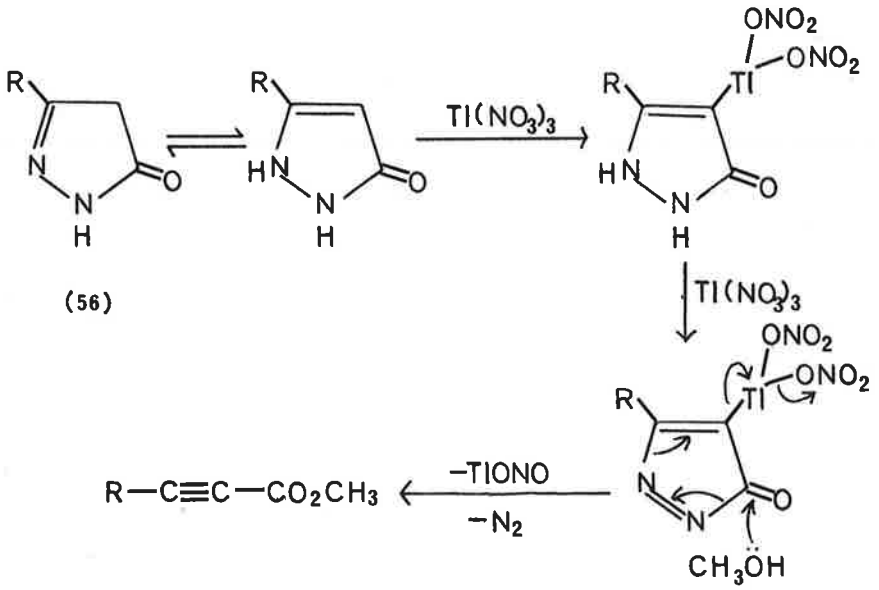


Scheme 12

Attempts to form the intermediate (55) from pyridine-3-aldehyde using the zinc/triphenylphosphine route gave only a low yield (16%) of the desired product after a long reaction time (two days). At least in part this low yield appeared to be caused by the tendency of the pyridine system to complex strongly with zinc salts resulting in a mixture that was difficult to work up satisfactorily. In contrast the alternative procedure, using only triphenylphosphene and carbontetrabromide, gave the desired olefin

in 60% yield after only forty-five minutes. The product was not stable and decomposed slowly on standing. It had the same Rf on silica as the starting aldehyde, which necessitated separating the two by washing the reaction solution with sodium bisulphite to extract the aldehyde. Treatment of the dibromo olefin (55) with n-butyllithium using the literature procedure[44] followed by acidifying of the total crude product gave a complex mixture, which could not be resolved by alumina chromatography. One fraction obtained from the column contained an acetylene band in its infrared spectrum but no carbonyl band suggesting the presence of 3-pyridylacetylene. Whether this in turn suggests the failure of carboxylation step or the presence of a decarboxylation process can not be ascertained. In view of the complex mixture obtained by this process, the reaction sequence was not further investigated.

Another recently developed method for the preparation of arylacetylenic esters involves[45] the oxidation of 5-arylpyrazol-3-ones (56) with thallium nitrate (scheme 13). The pyrazol-3-ones (56) are in turn prepared from the corresponding β-keto-ester using hydrazine hydrate. Reaction of ethyl nicotinoylacetate[46] with hydrazine hydrate, according to the literature method,[45] gave a pale yellow solid. Attempts to recrystallise this material from ethanol gave a product of lower and much broader melting point.



Scheme 13

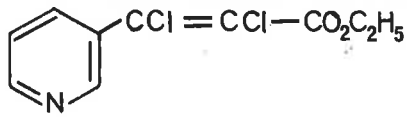
This latter product had a molecular ion consistent with that expected for the pyrazolone but did not give the correct analytical figures. Its infrared spectrum indicated that it was a mixture of the desired material (the original product showed no carbonyl absorption, consistent with that expected for a 5-arylpyrazol-3-one[47]) and a carbonyl containing product (medium intensity band at 1700 cm^{-1}). Both products were too insoluble for a n.m.r. spectrum to be obtained in the normal solvents. When the non-ethanol-treated material was reacted with thallium nitrate by the literature procedure[45] a product was obtained after distillation, that had an acetylene band in the

infrared spectrum. However v.p.c. showed that this material was a mixture of at least three compounds. The n.m.r. spectrum of the distillate indicated the presence of the expected acetylenic ester within the mixture. The components of this mixture could not be separated on an alumina t.l.c. plate.

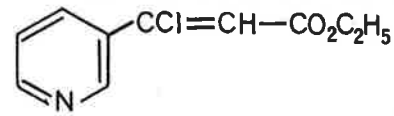
The preliminary survey described above, clearly indicates that the pyrolysis of the corresponding acylidenephosphorane is the most satisfactory route to the pyridylpropiolic acids and esters. However, it must be stressed that it is possible further work on some of the alternative methods may enable satisfactory yields to be obtained by these routes as well.

3.2 REACTIONS OF PYRIDYLPROPIOLIC ACIDS AND ITS ETHYL ESTERS WITH THIONYL CHLORIDE

When 3-pyridylpropiolic acid was refluxed with thionyl chloride for twenty hours and the residue treated with ethanol, a dark coloured product was obtained. Analysis of this material by v.p.c. showed that the volatile material consisted of four components, one of which amounted to 60% of the total volatile material. These components could not be sufficiently well resolved to enable them to be obtained in a pure form by preparative v.p.c. However, mass spectral data of the fractions collected in this manner showed the presence of a product arising from the addition of two chlorine atoms to the starting material. By analogy with products obtained in the benzene series, this material could be assigned the ethyl 2,3-dichloro-3-(3-pyridyl)propenoate structure (57), and the existence of *cis* and *trans* forms would then account for two of the observed peaks. N.m.r. signals at δ 6.60 and 6.43 in some fractions obtained by preparative t.l.c. are compatible with the presence of both isomers of (58). These signals were also observed in some fractions obtained from a similar reaction on ethyl 3-pyridylpropiolate (52). However, no pure material could be obtained from either reaction, a result



(57)



(58)

which was not unexpected since the analogous compounds in the benzene series also failed to separate by adsorption chromatography.

When the reaction was repeated on the acid with a much longer reaction time (six days), a small amount (ca. 4%) of crystalline material was isolated by preparative t.l.c. This material had a molecular weight of 241, consistent with that expected for structure (59). From a consideration of the coupling patterns of the aromatic signals of the starting material and this product; it was clear that the product lacked the C-2 hydrogen of the starting material. There was no indication of the presence of the other

possible cyclised system (60) in any of the fractions obtained from the preparative plate. No other products could be obtained

(59)

(60)

in a pure form from the preparative plate. Analysis of the total reaction product by v.p.c. again indicated the presence of the same four volatile compounds, only this time the major product was present to a much greater extent (ca. 90%) with only small amounts of the other products. By analogy with the benzene series it is suggested that this major compound is one of the isomers of the chlorine addition product (57).

The formation of the thieno[2,3-b]pyridine (59) is of interest from the mechanistic point of view. It would be expected that the pyridine system would be coordinated under the reaction conditions, to either thionyl chloride or to any liberated hydrogen chloride, and would thus be present as a pyridinium

species. Electrophilic ring substitution on a pyridinium species normally occurs only under very vigorous conditions,[43] and this in turn suggests the possibility that the cyclisation process involved in the formation of (59) is not electrophilic in nature. However, the long reaction time and low yield of this product would allow for an electrophilic attack occurring or the very small amount of non-coordinated pyridine present at equilibrium. The slightly greater electron density at C-2 rather than C-4 of the pyridine ring could account for the observed preference for cyclisation to occur into the 2-position. Hence the observation of cyclisation in this reaction with the formation of (59) does not necessarily shed light on the mechanism of the cyclisation process.

Hydrolysis of ethyl 4-pyridylpropiolate (53) gave 4-pyridylpropiolic acid as a very insoluble solid. This material was too insoluble in all the common solvents to obtain a n.m.r. spectrum, and its spectrum was eventually obtained in D_2O containing anhydrous sodium carbonate. It had the correct molecular ion in its mass spectrum. The infrared spectrum was notable for the very weak acetylene bond. This in turn made it very difficult to ascertain whether any starting material was present in the total reaction product. When the acid was refluxed with thionyl chloride for ten hours and the crude reaction product

treated with methanol, no crystalline material would be obtained after preparative t.l.c. on either silica or alumina. Analysis of each fraction by n.m.r. showed that in each case the ratio of the α-hydrogens to β-hydrogens of the pyridine ring was 1:1 indicating that no cyclised products were present to any significant extent. Essentially the same result was obtained when the corresponding ester (53) was refluxed with thionyl chloride for six days. As expected a considerable amount of product appeared to arise from the decomposition of the starting ester.

When freshly distilled ethyl 2-pyridylpropiolate (54) was refluxed for six days with thionyl chloride, the n.m.r. spectrum of the product obtained after separation of tarry material by means of a short alumina column, did not contain the C-6 hydrogen signal at δ 8.6 present in the starting material. Integration of the aromatic and ester proton signals suggested the presence of only three aromatic protons. Preparative t.l.c. of this material did not yield any crystalline material. The n.m.r. data suggests that the C-6 hydrogen of the starting material has been replaced by another atom or group. If nucleophilic attack has occureed at this position, the most likely possibility is the introduction of a chlorine atom at position 6. However, if this is the case it is surprising that a similar result was not observed in the reaction of the isomeric esters (52 and 53).

Whatever the explanation for these results, it is clear from these preliminary investigations that the reaction is of little value for the synthesis of a thienopyridine ring system. It is possible that improvements in the separation of the various products obtained in the benzene series could enable a similar improvement in the pyridine series to be achieved. The present results suggest, however, that this would only enable the dichloro-products (e.g. 57) to be more readily obtained.

CHAPTER 4

EXPERIMENTAL

4.1 PREAMBLE

General

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. X4 and X60 refer to the light petroleum fractions boiling between 40-60° and 60-70° respectively. All organic solvent extracts were dried over anhydrous magnesium sulphate. Solvent was evaporated at reduced pressure using a rotary evaporator, unless otherwise stated. Column chromatographic absorbants used were Whatman Sorbsil, or Spence Alumina. Preparative and qualitative thin layer chromatography were carried out with a 1:1 mixture of Merck Kieselgel G and Kieselgel HF254 or with Merck Aluminiumoxid G. Analyses were carried out by Australian Microanalytical Service, Melbourne.

Spectroscopic

Infrared spectra (i.r.) were recorded as Nujol Mulls, unless otherwise specified, on either a Perkin-Elmer 337 or an Unicam SP.200 spectrophotometer. The intensities of i.r. absorptions are expressed as follows: s, strong; m, medium; w, weak; b, broad.

Nuclear magnetic resonance (n.m.r.) spectra were measured

on a Varian T60 spectrometer operating at 60MHz, chemical shifts are expressed in δ values (p.p.m.) downfield from tetramethylsilane as an internal standard. Multiplicity is expressed as follows: s, singlet; d, doublet; t, triplet; q, quartet and m, multiplet.

Mass spectral data were obtained from a Hitachi Perkin-Elmer RMU-7D double focusing mass spectrometer operating at 70 eV. Accurate mass spectra (H.R.-M.S.) were obtained from the Research School of Chemistry, A.N.U.

Vapour Phase Chromatography (v.p.c.)

Analytical and preparative gas chromatography was performed on a Pye-Unicam 104 instrument, which incorporated a flame ionisation detector. Three 5' x 1/8" stainless steel columns were used (A) 5% FFAP on varaport 30, 100-120 mesh. (B) 10% QF1 on varaport 30, 100-120 mesh. (C) 15% FFAP on varaport 30, 100-120 mesh. Nitrogen was used as the carrier gas with a flow rate of approximately 30 ml/min.

Combined v.p.c.-mass spectrometry (VPC/MS) were recorded on a Perkin-Elmer F11 gas chromatograph linked to an A.E.I. MS30 mass spectrometer operating at 20 eV. A 10' x 1/8" metal column packed with 10% QF1 on varaport 30, 100-120 mesh was used, with argon as the carrier gas with a flow rate of approximately 30 ml/min.

A summary of the retention time (Rt) is given in the following table.

Table 5

VPC/MS and v.p.c. data for the product studies

Sample		Mol. wt. requires	m/e[a]	Retention time[b]
(26)[c]	$C_{10}H_9OCl$	196.5	198,196	3'05", 6'40"[d]
(27)[c]	$C_{10}H_8O_2Cl_2$	231	234,232,230	cis 4'40" trans 5'30"
(25)[c]	$C_{10}H_7O_2SCl$	226.5	228,226	21'
MPP	$C_{10}H_8O_2$	160	160	3'30"
(34)[c]	$C_{10}H_7O_2Cl_3$	265.5	268,266,264	7'30", 10'[d]
(35)[c]	$C_{10}H_8O_2Cl_4$	302	307,305,303	15'50"

[a] these peaks showed the expected[49] relative intensities.

[b] column B, T=150°

[c] structure assignments are based on the molecular ions and their isotopic cluster and to some extent on the fragmentation patterns.

[d] it is not possible, with the available data, to allocate the cis or trans structure to these peaks.

Reagents

Thionyl chloride was purified by the method of Friedman and Wetter[50]; sulfur monochloride, sulfur dichloride and sulfuryl chloride were freshly distilled before use. Pyridine, toluene, benzene, chloroform, ethanol and methanol were purified by literature procedures.[51] Tetrahydrofuran was distilled from lithium aluminium hydride.

4.2. WORK DESCRIBED IN CHAPTER 2

Phenylpropiolic acid

This acid (65%), m.p. 133-134° (lit.[51] 135-136°), was prepared by the method of Vogel.[51]

Methyl phenylpropiolate

Using the method of Hearn,[52] methyl phenylpropiolate (80%) was obtained as a colourless liquid, b.p. 90-95°/1.5 mm (lit.[53] 132-133°/16 mm).

Methyl-3-chloro-benzo[b]thiophene-2-carboxylate (25).

This compound was prepared by adding thionyl chloride (2 ml) to a solution of cinnamic acid (1.019 g) and pyridine (4 ml) at 0°C. Reflux of the mixture (oil bath ca. 95°) for 6 days followed by treatment in methanol and the solvent evaporated, gave a dark tarry material. Chromatography of this material on a sorbsil column and elution with chloroform/X4 (2:1) gave a fraction, which was crystallised from chloroform/X60 as the methyl-3-chloro-benzo[b]thiophene-2-carboxylate (25) (210 mg, 14%), m.p. 80-81° (lit.[14] 81-82°). (Found: C, 52.8; H, 3.3; Cl, 16.0; M^+ at m/e 228 and 226. $C_{10}H_7ClO_2S$ requires C, 53.0; H, 3.1; Cl, 15.6%; M, 226.5).

Reaction of phenylpropiolic acid (PPA) and its methyl ester (MPP) with sulfur halides.

An example of the reaction procedure for each sulfur halide is described below. Usually several experiments of an identical or very similar nature were conducted depending on the type of information required. However, the experimental details or work up procedure were normally very similar to those described below, which can therefore be regarded as the general procedures.

Reaction of MPP with thionyl chloride in presence of pyridine.

Pyridine (1 ml, 14 mmole) was added dropwise to a vigorously stirred solution of MPP (520 mg, 3.25 mmole) in thionyl chloride (4 ml, 50.0 mmole) at 0°C. The mixture was refluxed (oil bath ca. 95°) and the reaction mixture examined by t.l.c. After two days no further change in the reaction products was noticed and the mixture was poured into methanol. The solvent was evaporated and the dark brown residue dissolved in chloroform. Tarry material was removed by filtration through celite, the filtrate was washed with dil. HCl (2 x 20 ml) dried and the solvent evaporated to give a brown oil. The oily product was chromatographed on preparative silica plates, developed with

chloroform/X4 (1:1) and the band (Rf 0.4-0.6) that fluoresced dark blue under an ultraviolet lamp extracted with chloroform to yield the benzo[b]thiophene (25), which crystallised from chloroform/X60 (190 mg, 26%) m.p. 78-80°; this material was identical in all respects with an authentic sample prepared from cinnamic acid. Results of similar experiments in which the mole ratio of pyridine and thionyl chloride were varied are shown in Table 1.

Investigation of the reaction of MPP with thionyl chloride and pyridine by VPC/MS and v.p.c.

(a) VPC/MS was performed on a reaction mixture that was obtained from MPP after reflux for 6 hr with thionyl chloride and pyridine (4 ml:1 ml) and worked up in the usual manner. The results are shown in Table 2.

(b) V.p.c. analysis of the reaction mixture obtained after MPP had been refluxed with thionyl chloride and pyridine for 24 hr and injected, without work up, onto Column B (150°) showed four peaks corresponding to MPP, (25), cis (27) and an unknown (ca. 30% overall volatile material). After work up in the usual manner, two new peaks with the same retention times as

(26) were obtained and the unknown peak was decreased to ca. 2%*. A similar result was obtained after 36 hr. V.p.c. analysis of the mixture obtained after reflux for 2 days and work up in the usual manner are shown in Table 2.

Reaction of MPP with HCl in methanol.

MPP (50 mg) was refluxed with HCl in methanol and the reaction progress was followed by v.p.c. analysis (B, 150°). Reflux times of 15 min to 1 hr showed only the starting material peak. After 24 hr the reaction mixture showed the presence of a trace amount of (26) (Rt 3'05").

Reaction of PPA with thionyl chloride and pyridine

Pyridine (1 ml, 14 mmole) was added portionwise to a well stirred solution of PPA (578 mg, 3.95 mmole) in thionyl chloride (4 ml, 50.0 mmole) at 0°C, and the mixture was refluxed

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* This peak had the same retention time as trans (27) and it was not possible to determine whether it was in fact due to trans (27) or represented a small amount of the unknown compound.

(oil bath ca. 95°). The progress of the reaction was followed by t.l.c. After 6 hr the solution was poured into methanol and worked up in the same manner as described for MPP with thionyl chloride and pyridine. Crystallisation of the mixture gave (25) (332 mg, 37%) m.p. 77-78°.

Investigation of the reaction of PPA with thionyl chloride and pyridine by v.p.c.

V.p.c. analysis (B, 150°) of the reaction mixture obtained from PPA, thionyl chloride and pyridine (4:1 volume ratio) after reflux for 6 hr and work up in the usual manner are shown in Table 2.

Reaction of MPP with sulfur dichloride

(a) MPP (243 mg) was dissolved in methylene dichloride (5 ml) and excess sulfur dichloride (2 ml) was added. The mixture was left at room temperature for 1 hr; t.l.c. suggested that most of the starting material had reacted. After another addition further stirring for 2 hr at room temperature, an excess of ethanol was added and a yellow gum removed by filtration, the filtrate was left overnight at room temperature then refiltered to remove further gum and the solvent evaporated. The residue was dissolved in methylene chloride, washed with sodium carbonate solution, dried and the solvent evaporated to give an oil. V.p.c. (B, 150°)

analysis of the material are summarised in Table 3. All the compounds indicated had satisfactory molecular ions with the expected isotopic ratio when examined by VPC/MS.

(b) MPP (280 mg, 1.75 mmole) was stirred at room temperature with excess sulfur dichloride (1.5 ml) in ether (7 ml) for 3 hr. The solvent was removed under reduced pressure to give a yellow oil, which was dissolved in methylene chloride, washed with sodium bicarbonate solution, dried and the solvent evaporated. V.p.c. data (B, 150°) for the resulting oil [ν_{max} (film) 2290 (b), 2250 (m), 1710 (s), 1640 (m), 1580 (m), 1540 cm^{-1} (m)] is shown in Table 3.

Reaction of PPA with sulfur monochloride and pyridine

(a) PPA (447 mg, 3.06 mmole) was refluxed with excess sulfur monochloride (3 ml) and pyridine (0.2 ml) for 3 hr (bath temperature 140-160°). The reaction mixture was poured into methanol stirred for 10 min, and the solvent was evaporated. The residue was extracted with hot ethanol and the extract was filtered (celite) to give an oil on removal of the solvent, this residue was dissolved in methylene chloride, washed with dil. HCl solution, dried and the solvent evaporated to give an oil (487 mg), which was shown by v.p.c. analysis (B, 150°) to contain 3 peaks (Table 4). (39) Rt 3'15", (40) Rt 1'20" and (25).

The resulting mixture was chromatographed on preparative silica plates. Elution with chloroform/X4 (1:1) gave two bands, that fluoresced blue under an ultraviolet lamp (Rf 0.8 and 0.4 respectively). The material with higher Rf value crystallised from X4 to yield a solid (230 mg), m.p. 43-45°. The i.r. spectrum of this material showed no carbonyl band and the n.m.r. spectrum showed only aromatic signals. V.p.c. analysis showed two peaks (Rt 1'20", 3'15" in a 1:6 ratio). The mass spectrum had peaks of 242, 240, 238 and 236 that were consistent with trichloro product and a further set of peak at 206, 204, 204 consistent with a dichloro product. This material was further purified by preparative t.l.c. (X4). Crystallisation of the material from the major band gave 2,3-dichlorobenzo[b]thiophene (39) as needles, m.p. 52-54° (lit.[26] 55.5-56.5°), which had Rt 3'15" on column B (150°).

The lower band from the original preparative plate gave (25) (160 mg, 23%); which was identified by its i.r. and n.m.r. spectrum.

(b) PPA (87 mg) was refluxed (bath temperature 95-100°) with excess sulfur monochloride (2 ml) and pyridine (0.2 ml) in benzene (4 ml) for 3 hr. Worked up as described above gave an oil which was analysed by v.p.c. (B, 150°). The results are shown in Table 4.

Reaction of PPA with sulfur monochloride

A mixture of PPA (107 mg) and excess sulfur monochloride

was refluxed (bath temperature 140-160°) for 3 hr. After a similar work up an oil was obtained, ν_{max} (film) 3000 (b), 1720 (s), 1690 cm^{-1} (s). This material was analysed by v.p.c. (B, 150°). The results are summarised in Table 4.

Reaction of MPP with sulfur monochloride and pyridine

MPP (594 mg, 3.7 mmole) was refluxed (bath temperature 140-160°) with sulfur monochloride (3 ml) and pyridine (0.1 ml) for 3 hr. The reaction mixture was poured into ethanol, the insoluble material filtered (celite) and the residue was washed with hot ethanol. Evaporation of the solvent gave a residue which was dissolved in chloroform, washed with dil. HCl solution, dried and the solvent evaporated to give an oil (715 mg). V.p.c. analysis (B, 150°) data are shown in Table 4. An unidentified compound (Rt 25'35") was also observed.

Chromatography of this oil on preparative silica plates and elution with $CHCl_3$/X4 (1:1) gave two bands. The band (160 mg) with Rf 0.8, was shown by v.p.c. analysis (B, 150°) and spectral data to be a mixture of (39) and (40). Crystallisation of the material obtained from the band with Rf 0.4 gave (25) (150 mg, 17%) m.p. 78-80°.

Methyl-3-chloro-benzo[b]thiophene-2-carboxylate (25) with sulfur monochloride and pyridine.

The ester (25) (10 mg) in sulfur monochloride (2 ml) and pyridine (0.1 ml) was heated under reflux (bath temperature ca. 150°) for 3 hr and worked up in the same manner as described above. V.p.c. analysis (B, 150°) and t.l.c. data showed the presence of starting material only.

Reaction of PPA with sulfuryl chloride

(a) PPA (1.078 g) was refluxed with excess sulfuryl chloride for 3 hr and the solvent was removed. Addition of methanol resulted in the precipitation of 1-phenyl-4-chloronaphthalene-2,3-dicarboxylate (42) (30 mg, 3%). Recrystallisation from chloroform gave (42) as pale yellow needles, m.p. 298-299°. ν_{max} (nujol) 1820 (s), 1760 (s), 1610 (m), 1590 cm^{-1} (m); mass spectrum m/e 310 (M^+), 308 (M^+, base peak); n.m.r. (DMSO) δ 7.5-8.0 (m, aromatic ring protons). (Found: C, 70.2; H, 3.0; Cl, 11.8; $C_{18}H_9ClO_3$ requires C, 70.0; H, 2.9; Cl, 11.5%).

Evaporation of the filtrate gave an oil whose i.r. spectrum showed a strong acetylene bond at 2250 cm^{-1} and carbonyl absorption at 1700 cm^{-1}. V.p.c. analysis (B, 150°) indicated the presence of several compounds, which could not be isolated in pure form.

(b) PPA (1.0407 g) was refluxed with sulfuryl chloride for 20 hr and the solvent was evaporated. Addition of methanol

precipitated anhydride (42) (167 mg, 15%). Evaporation of the filtrate gave an oil, which was crystallised from chloroform/X60 to yield cis-α,β-dichlorocinnamic acid, m.p. 116-120° (lit.[37] 120-121°) (695 mg, 40%). ν_{max} (nujol) 3200-2500 (b), 1680 (s), 1570 cm^{-1} (m); n.m.r. ($CDCl_3$) δ 7.05 (s, 5H, Ar-H), 10.2 (s, 1H, $-\overset{O}{\overset{\|}{C}}-OH$); mass spectrum M^+ at m/e 220, 218, 216; identical with material prepared by literature procedure.[37]

The mother liquor from the crystallisation was evaporated to give an oil, t.l.c. of this material showed that it consisted of a mixture of at least four compounds. ν_{max} (film) 3200-2500 (b), 1700 (s), 1580 cm^{-1} (s).

(c) PPA was refluxed with excess sulfuryl chloride for 20 hr, the solvent was evaporated; methanol was added and (42) was removed by filtration. The filtrate was concentrated under reduced pressure to give an oil, which was esterified using diazomethane. Evaporation of the solvent gave an oil which was shown by v.p.c. analysis (B, 150°) to contain (27), (26) and (34). (See page 33).

Reaction of MPP with sulfuryl chloride

MPP (254 mg) was refluxed with sulfuryl chloride for 3 hr. The remaining sulfuryl chloride was removed under reduced pressure and methanol added. The excess solvent was evaporated and the

residue was dissolved in chloroform, washed with sodium bicarbonate solution, dried and the solvent removed. T.l.c. ($CHCl_3$/X4, 1:1) of the residue showed only one spot apart from at the origin [ν_{max} (film) 2990 (b), 1745 (s), 1720 (s), 1580 cm^{-1} (m)] proved intractable. V.p.c. analysis (B, 150°) showed 6 peaks, identified by comparison of retention times, as a mixture of (27), (34), (35) and (26). (See page 32).

Attempted cyclisation of cis-α,β-dichlorocinnamic acid and PPA

(a) A mixture of cis-α,β-dichlorocinnamic acid (344 mg, 1.58 mmole) and PPA (232 mg, 1.58 mmole) in benzene (5 ml), 10 µl acetic acid and acetic anhydride (723 mg, 7.1 mmole) was refluxed (bath temperature ca. 100°) for 24 hr. Mixture of methylene chloride and X4 (1:2) was added. 1-Phenylnaphthalene-2,3-dicarboxylate (43) was crystallised as colourless plates (170 mg), m.p. 254-256°) (lit.[34] 255-256°). Crystallisation of the mother liquor material gave the starting material cis-α,β-dichlorocinnamic acid, which was identified by its i.r. spectrum.

The starting materials were quantitatively recovered, when the reaction was repeated using chloroform instead of benzene and at either room temperature or heated under reflux.

(b) Cis-α,β-Dichlorocinnamic acid (387 mg, 1.78 mmole) was

dissolved in chloroform and refluxed under U.V. light for 12 hr. PPA (260 mg, 1.78 mmole) and acetic anhydride (1.1300 g, 11.07 mmole) were added to this solution and the mixture was refluxed (bath temperature ca. 80°) for a further 24 hr. Evaporation of the solvent under low pressure (ca. 2 mm Hg) gave an oil, ν_{max} (film) 3000 (b), 2200 (s), 1700 (s), 1600 cm^{-1} (m).

α,β-Diiodocinnamic acid.

This compound (64%) was prepared[54] as colourless needles, m.p. 170-172° (lit.[54] 172°).

Cyclisation of the mixture of α,β-diiodocinnamic acid and PPA.

(a) Acetic anhydride (2 ml) was added to a solution of PPA (65 mg, 0.445 mmole) and α,β-diiodocinnamic acid in chloroform (2 ml) and the mixture stirred for 2 days at 60°. The colourless solution gradually turned pink. Addition of chloroform/X4 (1:1) to the solution precipitated a material (5 mg), m.p. 205-210°; ν_{max} (nujol) 1810 (m), 1760 (s), 1610 cm^{-1} (w); mass spectrum m/e 400 (16% $C_{18}H_9O_3I$); m/e 274 (84% $C_{18}H_{10}O_3$); which appeared to be a mixture of 1-phenyl-4-iodo-naphthalene-2,3-dicarboxylate (47) and 1-phenyl-naphthalene-2,3-dicarboxylate (43).

The filtrate was evaporated and the residue was dissolved in methylene chloride and washed with sodium carbonate solution

(2 x 10 ml). The basic solution was acidified with dil. HCl, saturated with salt and extracted with methylene chloride (2 x 10 ml), dried. Removal of the solvent from the extract and crystallisation of the residue from methylene chloride/X4 gave α,β-diiodocinnamic acid (48 mg). The mother liquor from the crystallisation showed an acetylene band in its i.r. spectrum [ν_{max} (nujol) 2250 (m), 1710 (s), 1670 (s), 1610 (s), 1590 cm^{-1} (m)] and appeared to be a mixture of the starting materials.

(b) The above reaction was repeated in the dark. After 2 days a mixture of the two cyclized anhydrides (47, 43) was isolated by the procedure described above from the pale yellow reaction mixture. 1-Phenyl-4-iodo-naphthalene-2,3-dicarboxylate (47) was too unstable to be purified; attempt to crystallise it from chloroform continually resulted in the development of an iodine colour in the solution.

4.3. WORK DESCRIBED IN CHAPTER 3

Nicotinyl chloride (73%), b.p. 98-100°/20 mm (lit.[55] 85°/12 mm) picolinyl chloride (82%), b.p. 80-100°/2 mm (lit.[56] m.p. 45-47°) and ethoxycarbonylmethylidentriphenylphosphorane (48) (70%), m.p. 126-127° (lit.[57] 125-127.5°) were prepared by literature procedures.

α-Ethoxycarbonylacylidenetriphenylphosphoranes

These compounds were prepared by modifying the procedure of Hearn[52] and Markl.[41]

(a) A solution of methylidene phosphorane (48) (0.02 mole) in benzene (400 ml) was added to the freshly distilled nicotinyl chloride (0.01 mole). After the addition was completed, the mixture was allowed to reflux overnight, the precipitated ethoxycarbonylmethylidenetriphenylphosphonium chloride was filtered and washed well with benzene and the filtrate and benzene washings were combined. The residue after removal of the solvent was dissolved in chloroform, washed with water, dried, concentrated and chromatographed over a silica gel column (eluent methylene chloride/X4

4:1); crystallisation of this material from chloroform/X60 gave α-ethoxycarbonyl-3-pyridacylidene-triphenylphosphorane (84%) as colourless prisms, m.p. 182°. ν_{max}(nujol) 1660 (s), 1580 (m), 1550 cm^{-1} (m); n.m.r. ($CDCl_3$) δ 0.6 (t, 3H, ester methyl protons), 3.7 (q, 2H, ester methylene protons), 7-8 (m, 17H, 15 benzene hydrogens plus C-4, C-5 pyridine hydrogens), 8.60 (m, 1H, C-6 pyridine hydrogen), 8.98 (m, 1H, C-2 pyridine hydrogen). (Found: C, 73.9; H, 5.6; N, 3.0. $C_{28}H_{24}NO_3P$ requires C, 74.2; H, 5.3; N, 3.0%).

α-ethoxycarbonyl-2-pyridacylidene-triphenylphosphorane (82%), m.p. 160-161°, was similarly obtained as straw-coloured prisms from chloroform/X60. ν_{max}(nujol) 1665 (s), 1590 (w), 1540 cm^{-1} (m); n.m.r. ($CDCl_3$) δ 0.58 (t, 3H, ester methyl protons), 3.67 (q, 2H, ester methylene protons), 7.1-8.1 (m, 18H, 15 benzene hydrogens plus C-3, C-4 and C-5 pyridine hydrogens), 8.6 (m, 1H, C-6 pyridine hydrogen). (Found: C, 74.1; H, 5.5; N, 2.9. $C_{28}H_{24}NO_3P$ requires C, 74.2; H, 5.3; N, 3.0%.)

(b) The pyridylcarboxylic acid (0.01 mole) and excess thionyl chloride (3 ml) in dry benzene (6 ml) was refluxed for 20 min, and the solvent evaporated. A solution of ethoxycarbonylmethylidenetriphenylphosphorane (0.03 mole) in benzene was added to the residue and the mixture refluxed overnight. Similar work-up of the

mixture as described in (a), yielded the following compounds.

α-ethoxycarbonyl-3-pyridacylidenetriphenephosphorane (53%), m.p. 178-180°.

α-ethoxycarbonyl-4-pyridacylidenetriphenephosphorane (87%), m.p. 146°, as colourless prisms from chloroform/X60. ν_{max}(nujol) 1670 (s), 1600 (w), 1560 (m), 1530 cm^{-1} (s); n.m.r. ($CDCl_3$) δ 0.58 (t, 3H, ester methyl protons), 3.67 (q, 2H, ester methylene protons), 7.2-7.8 (m, 17H, 15 benzene hydrogens plus C-3 and C-5 pyridine hydrogens), 8.60 (d, 2H, C-2 and C-6 pyridine hydrogens). (Found: C, 74.0; H, 5.3; N, 3.1. $C_{28}H_{24}NO_3P$ requires C, 74.2; H, 5.3; N, 3.0%.)

α-ethoxycarbonyl-2-pyridacylidenetriphenephosphorane (80%), m.p. 160-161°.

Ethyl pyridylpropiolates

These esters were obtained by pyrolysis of the α-ethoxycarbonylacylidenetriphenylphosphoranes by the method of Hearn.[52]

Ethyl 3-pyridylpropiolate (80%), b.p. 103-105°/1.1 mm, which became deep red after about 15 min but was sufficiently stable in a sealed ampoule to permit an analysis. (Found:

C, 68.6; H, 5.36; N, 8.3. $C_{10}H_9NO_2$ requires C, 68.6; H, 5.2; N, 8.0%.) ν_{max}(film) 2950 (m), 2200(s), 1700 (s), 1580 (m), 1560 cm^{-1} (m); n.m.r. ($CDCl_3$) δ 1.35 (t, 3H, ester methyl protons), 4.33 (q, 2H, ester methylene protons), 7.33 (m, 1H, C-5 pyridine hydrogen), 7.87 (m, 1H, C-4 pyridine hydrogen), 8.7 (m, 2H, C-2 and C-6 pyridine hydrogens); mass spectrum m/e 175 (M^+) and 130 (base peak), $C_{10}H_9NO_2$ requires mol.wt. 175.

Ethyl 2-pyridylpropiolate (58%), b.p. 131°/2.6 mm, which rapidly darkened. ν_{max}(film) 2950 (m), 2200 (m), 1700 (s), 1580 (m), 1560 cm^{-1} (m); n.m.r. (CCl_4) δ 1.37 (t, 3H, ester methyl protons), 4.27 (q, 2H, ester methylene protons), 7.5 (m, 3H, C-3, C-4 and C-5 pyridine hydrogens), 8.60 (m, 1H, C-6 pyridine hydrogen; mass spectrum m/e 175 (M^+) and 130 (base peak), $C_{10}H_9NO_2$ requires mol.wt. 175.

Ethyl 4-pyridylpropiolate (68%), b.p. 123/0.9 mm, which darkened within 5 min; ν_{max}(film) 2950 (w), 2250 (m), 1700 (s), 1600 (m), 1540 (w), 1500 cm^{-1} (w); n.m.r. (CCl_4) δ 1.37 (t, 3H, ester methyl protons) 4.25 (q, 2H, ester methylene protons), 7.43 (d, 2H, C-3 and C-5 pyridine hydrogens), 8.63 (d, 2H, C-2 and C-6 pyridine hydrogens); mass spectrum m/e 175 (M^+) and 130 (base peak), $C_{10}H_9NO_2$ requires mol.wt. 175.

Pyridylpropiolic acid

(a) Ethanolic potassium hydroxide was added slowly to a solution of ethyl 3-pyridylpropiolate (3.4 g, 0.0194 mole) in ethanol (200 ml), the mixture was then refluxed for 30 min, while maintaining the pH at about 10. The reaction mixture was concentrated by evaporating the solvent carefully under reduced pressure. Methanolic HCl added dropwise to this solution until pH 7 was reached and the potassium chloride was filtered. Addition of benzene to the filtrate, precipitated potassium 3-pyridyl-propiolate. Recrystallisation from methanol/benzene gave colourless prism (3.2 g, 92%), m.p. 228-233° decomp. (Found: C, 51.2, 50.9; H, 2.1, 2.2; N, 7.5. $C_8H_4KNO_2$ requires C, 51.9; H, 2.2; N, 7.5%.) ν_{max}(nujol) 2200 (w), 1650 (m), 1610 (s), 1580 (m), 1560 cm^{-1} (w).

(b) Potassium 3-pyridylpropiolate (2.0 g) dissolved in methanol, and methanolic HCl was added until the pH reached 2-3. The potassium chloride was removed by filtration. Concentration of the filtrate gave 3-pyridylpropiolic acid, which was recrystallised from methanol to give colourless needles (1.5 g, 95%), m.p. 148-150° decomp. (Found: C, 65.3; H, 3.5; N, 9.5. $C_8H_5NO_2$ requires C, 65.3; H, 3.4; N, 9.5%). ν_{max}(nujol) 2240 (w), 2200 (m), 1700 (s), 1590 cm^{-1} (m).

(c) Methanolic HCl was added to a solution of 3-pyridylpropiolic acid (520 mg) dissolved in methanol, until the pH of the solution was less than 1. After careful addition of ether and cooling, 3-pyridylpropiolic acid hydrochloride was obtained as colourless needles (592 mg, 90%), m.p. 165-167° decomp. (Found: C, 52.4; H, 3.4; N, 7.8. $C_8H_6NO_2Cl$ requires C, 52.3; H, 3.3; N, 7.6%.) ν_{max}(nujol) 2600 (b, s), 2200 (m), 1680 (s), 1600 (w), 1550 cm^{-1} (m).

(d) 3-Pyridylpropiolic acid was also prepared by a method similar to that of Markl[41] in low yield.

Phosphorus pentachloride (939 mg, 0.0045 mole) was added to suspension of α-ethoxycarbonyl-3-pyridacylidenetriphenylphosphorane (906 mg, 0.002 mole) in phosphorus oxychloride (2 ml), and the mixture was stirred at 80° for 30 min. The phosphorus oxychloride was removed under reduced pressure, the residual dark oil was dissolved in water (20 ml), and the aqueous solution was neutralised with potassium carbonate and saturated with salt. Extraction of the solution with chloroform (3 x 15 ml) and removal of the solvent gave an oil. Methanolic potassium hydroxide was added to this oil until the solution had pH ∿ 10. Then the solution was refluxed for 45 min, cooled and acidified (pH ∿ 2) with methanolic HCl. 3-Pyridylpropiolic acid (23 mg, 8%) was

obtained as outlined in (b), its i.r. spectrum was identical with that of the sample previously prepared.

(e) Ethyl 4-pyridylpropiolate was refluxed with ethanolic potassium hydroxide maintaining pH 9-10, for 45 min, then worked up as in (a), with the exception that the solution was acidified to pH $\sim$ 4. 4-Pyridylpropiolic acid was obtained as crystals, m.p. 123-127° decomp.; mass spectrum m/e 147 (M^+), 130 (M^+ - OH), 119 (M^+ - CO), 103 (M^+ - CO_2 base peak); ν_{max}(nujol) 1685 (s), 1620 (m). The n.m.r. (D_2O, Na_2CO_3) spectrum showed two sets of doublets centred at δ = 7.63 (C-3 and C-5 pyridine hydrogens) and 8.70 (C-2 and C-6 pyridine hydrogens) with integration ratio 1:1, Jortho 6 cps. All attempts to further purify this material by crystallisation caused decomposition and formation of tars.

(f) Ethyl 2-pyridylpropiolate was refluxed with ethanolic potassium hydroxide as described in (a). Acidification of the solution with methanolic HCl to pH 4 $\sim$ 5, caused the solution to become dark green. Attempts to crystallise this material failed and only a tarry hygroscopic material was obtained which t.l.c. indicated was a complex mixture.

3-(β-Pyridyl)-5-pyrazolone

This compound (m.p. 264-266°)[47] was obtained in crude form

by the reaction of ethylnicotinoacetate[58] with excess hydrazine hydrate by the method of Gagnon et al.[47] Recrystallisation from ethanol gave material, m.p. 175-185°; mass spectrum m/e 161 (M^+, base peak), $C_{10}H_7N_3O$ requires mol.wt. 161.

Attempted preparation of methyl 3-pyridylpropiolate

The procedure was based on that described by Talylor et al.[45]

A solution of thallium (III) nitrate (0.002 mole) in methanol (5 ml) was added to a suspension of the material (0.001 mole) obtained above, the mixture was stirred for 15 min at room temperature, and then for an additional 20 min under reflux. The reaction mixture was filtered to remove precipitate thallium (I) nitrate and the filtrate diluted with water, saturated with salt and extracted with chloroform. Removal of the solvent from the dried extracts and distillation at 110-115°/2.3 mm gave a colourless liquid, which was chromatographed on an alumina preparative plate. Elution with chloroform/X4 (1:1) yielded a yellow fluorescent oil (Rf. 0.8); ν_{max}(film) 2295 (m), 2200 (s), 1710 (s), 1590 (m), 1560 cm^{-1} (w). V.p.c. analysis (C, 200°) showed the presence of 3 peaks.

Attempted preparation of 3-pyridylpropiolic acid

(a) 1,1-Dibromo-2-(β-pyridyl)ethene

(i) Carbontetrabromide (6.64 g, 0.02 mole) and triphenylphosphine (10.4 g, 0.04 mole) were stirred in dry methylene chloride (50 ml) under nitrogen at 0°C for 5 min, then pyridine-3-aldehyde (1.07 g, 0.01 mole) was added and the mixture stirred for 30 min at room temperature. The reaction mixture was extracted with dil. HCl solution (3 x 25 ml), the aqueous extracts were neutralised with sodium bicarbonate and extracted with chloroform (4 x 25 ml). The chloroform extracts were washed with saturated metabisulphite solution (2 x 20 ml), dried and evaporated to yield a dark gum. Chromatography on an alumina column and elution with chloroform/X4 (1:5) yielded 1,1-dibromo-2-(β-pyridyl) ethene as slightly brown crystals (1.74 g, 66%), m.p. 57-59°, which readily darkened. ν_{max}(nujol) 1600 (w), 1580 (w), 1560 (m); n.m.r. ($CDCl_3$) δ 7.44 (m, 1H, C-5 pyridine hydrogen), 7.55 (8, 1H, -CH=CBr_2), 8.0 (m, 1H, C-4 pyridine hydrogen), 8.7 (m, 2H, C-2 and C-6 pyridine hydrogens); mass spectrum m/e 265 (M^+), 263 (M^+), 261 (M^+), 184 (M^+ - Br), 182 (M^+ - Br), 103 (M^+ - Br_2 base peak).

(ii) Carbontetrabromide (31 g, 0.093 mole), triphenylphosphine (24.5 g, 0.093 mole) and zinc dust (6.4 g, 0.098 mole) in dry methylene chloride (200 ml) were stirred for 48 hr at

room temperature under nitrogen. Pyridine-3-aldehyde (5 g, 0.0467 mole) was then added and the reaction mixture was stirred for a further 2 hr at room temperature. The mixture was filtered and the filtrate concentrated and extracted with dil. HCl solution. The aqueous extract was worked up as in (i) to yield the dibromo-compound (1.97 g, 16%).

(b) 1,1-Dibromo-2-(β-pyridyl)ethene (1g, 3.8 mmole) was dissolved in tetrahydrofuran (20 ml) and the solution cooled to -78°. n-Butyllithium in hexane (3.5 ml, 7.6 mmole) was added under nitrogen to the mixture, which was stirred for 1 hr at -78° and allowed to warm to room temperature (ca. 15°) for a further 1 hr, while maintaining the nitrogen atmosphere. The reaction mixture was cooled to -70°, dry carbon dioxide was bubbled through the solution for 30 min and the mixture allowed to warm to room temperature. Removal of the solvent followed by addition of methanolic HCl to pH 3 ∿ 4 and concentration of the solution failed to give a crystalline product. The i.r. spectrum of this material did not have any strong absorption in the carbonyl region (1650 - 1740 cm^{-1}). T.l.c. indicated that the oil contained several compounds.

(c) The reaction was repeated with the exception that carbon dioxide was bubbled through the mixture for 1 hr. Worked

up as described in (b), gave a dark oil whose i.r. spectrum showed no absorption in the carbonyl region (1650 - 1740 cm^{-1}). This material was chromatographed on an alumina column; elution with chloroform gave an oil, whose n.m.r. and i.r. spectrum indicated that this fraction contained 3-pyridylacetylene. Further elution with chloroform/methanol (19:1) afforded dark resinous material, which could not be further purified.

Ethyl 3-pyridylpropiolate with thionyl chloride

Ethyl 3-pyridylpropiolate (474 mg) was refluxed with excess of thionyl chloride (6 ml). After 12 hr, the excess thionyl chloride was evaporated, ethanol was added and the mixture refluxed for 20 min. The residue obtained on removal of the ethanol was chromatographed on preparative alumina plates. Elution with chloroform gave a continuous band and no pure compounds could be obtained. The higher Rf material showed a multitude of signals in its n.m.r. spectrum due to the ester groups which indicated a complex mixture. Signals at δ 6.60, 6.43 (ratio 4:1) were observed as well as the expected complex aromatic signals. The lower Rf material had both acetylene and carbonyl absorption in its i.r. spectrum.

3-Pyridylpropiolic acid with thionyl chloride

(a) Excess of thionyl chloride (3 ml) was refluxed with 3-pyridylpropiolic acid (538 mg) for 20 hr. Ethanol was added to the cooled solution and the resulting mixture was refluxed for 10 min. Evaporation of the solvent gave a dark residue, which was dissolved in chloroform and washed with potassium carbonate solution. V.p.c. analysis (A, 220°) of the oil obtained on removal of the solvent showed four peaks; Rt 7'15", 9'40", 10'45" and 12'25" (ratio of peak area 1:7:1:3 respectively). The major peak was collected by preparative v.p.c. (Rt 9'40", 60% of total peak area). Spectral evidence showed one of the isomer of ethyl αβ-dichloro-β-(3-pyridyl)acrylate (57); mass spectrum m/e 249, 247, 245 (M^+); ν_{max}(film) 2950 (b), 1720 (s), 1620 (m), 1580 cm^{-1} (m); n.m.r. ($CDCl_3$) δ 1.05 (t, 3H, ester methyl protons), 4.05 (q, 2H, ester methylene protons), 7.2-8.8 (m, 4H, pyridine hydrogens).

Chromatography of the total oily reaction product on preparative plates, did not provide any worthwhile separation and all fractions proved intractable. Vinyl protons signals at δ 6.60, 6.43 (4:1 ratio respectively) were observed in the n.m.r. spectrum of some fractions. In general the n.m.r. spectrum of these fractions indicated that it was a complex mixture. The oil was

distilled under reduced pressure (80-100°/0.3 mm) to give material, whose n.m.r. spectrum was unchanged.

(b) A similar reaction was worked up as described above, after 6 days to give an oil. V.p.c. analysis (A, 220°) showed four peaks; Rt. 7'15", 9'43", 10'30" and 12'30" (Rt 9'43" and 10'30", 98% of the total peaks area with the ratio 12:1 respectively).

Chromatography of the oil on preparative silicaplates and elution with chloroform/X4 (4:1) gave several fractions. The band (Rf. 0.8-0.9) yielded a small amount of sulfur, m.p. ∿ 115° (lit.[59] 112.8-120°), on crystallisation from chloroform/X60. The band (Rf. 0.6-0.7) that fluoresced blue under an ultraviolet lamp extracted by chloroform to yield 2-carbethoxy-3-chlorothieno-[2,3-b]pyridine (59), (4%), which crystallised from $CHCl_3$/X60, m.p. 74-75°. ν_{max}(nujol) 1710 (s); 1570 (w), 1550 cm^{-1} (w); n.m.r. ($CDCl_3$) δ 1.42 (t, 3H, ester methyl protons), 4.45 (q, 2H, ester methylene protons), 7.42 (q, 1H, C-5 pyridine hydrogen, J 5,6 5 cps, J 4,5 7cps), 8.24 (q, 1H, C4 pyridine hydrogen, J 4,6 2 cps, J 4,5 7 cps), 8.78 (q, 1H, C-6 pyridine hydrogen J 5,6 5 cps, J 4,6 2 cps). (H.R. - M.S. $C_{10}H_8NO_2SCl$ calculated mass 240.9964, measured mass 240.9970).

The lower band from the original preparative plates yielded

an oil, which would not be further purified.

4-Pyridylpropiolic acid with thionyl chloride

The acid (77 mg) was refluxed with excess thionyl chloride (1 ml) for 10 hr. The excess thionyl chloride was evaporated, methanol was added and the mixture was stirred for 30 min at room temperature. After removal of the solvent the residue was dissolved in chloroform and washed with sodium bicarbonate solution, dried and the solvent evaporated to yield an oil; ν_{max}(film) 3050 (w), 2950 (w), 1720 (s), 1600 (m), 1590 (m), 1550 cm^{-1} (m); n.m.r. ($CDCl_3$) showed signals at δ 7.27 (C-β pyridine hydrogens) and 8.67 (C-α pyridine hydrogens) in a 1:1 ratio with methoxyl signals at 3.63, 3.93 and 4.00. The material could not be further purified.

Ethyl 4-pyridylpropiolate with thionyl chloride

The ester (535 mg) was refluxed with excess of thionyl chloride (4 ml) for 6 days. After evaporation of the solvent and treatment of the residue with ethanol, a dark residue was obtained which was dissolved in chloroform. Anhydrous sodium carbonate was added and the mixture was stirred for 30 min. Filtration (celite) and removal of the solvent gave a dark brown

oil, which failed to separate on preparative plates. The n.m.r. spectrum showed that no signals in the vinyl region and complex signals due to methylene and methyl signals of the ester protons. Aromatic signals at δ 7.2 (d, 2H, C-3 and C-5 pyridine hydrogens), 8.63 (d, 2H, C-2 and C-6 pyridine hydrogens) were present.

Ethyl 2-pyridylpropiolate with thionyl chloride

The ester (690 mg) was refluxed with excess thionyl chloride (4 ml) for 6 days. The black solution was evaporated and the residue was dissolved in chloroform, anhydrous sodium carbonate was added and the mixture stirred for 1 hr. After filtration, the solvent was evaporated to yield a tarry substance which was filtered through a short alumina column. Elution with chloroform gave a brown hygroscopic oil, which did not further separate by preparative t.l.c. plates. ν_{max}(film) 2950 (b), 1740 (s), 1570 cm^{-1} (m); n.m.r. ($CDCl_3$) spectrum showed that δ at 7.1-8.0 (m, C-3, C-4 and C-5 pyridine hydrogens) and a complex set of signals due to the various ester methylene and methyl groups present in a 3:2:3 ratio respectively. No signals corresponding to the C-6 hydrogen of the starting material were present in this product.

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