HETEROCYCLES FROM INTRAMOLECULAR WITTIG, HORNER AND WADSWORTH-EMMONS REACTIONS

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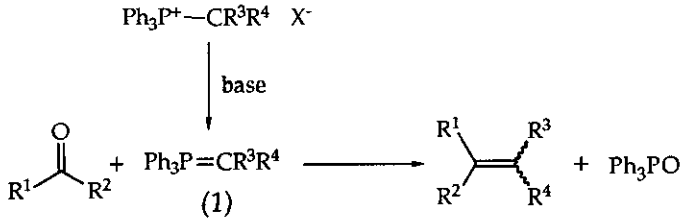
Abstract- *The synthesis of a range of heterocyclic systems based on intramolecular reactions of phosphorus ylides and phosphinoxy and phosphonate carbanions is reviewed.*

CONTENTS

1. INTRODUCTION

The condensation of an alkylidene(triphenyl)phosphorane (1) with a carbonyl compound to afford an alkene and triphenylphosphine oxide, the Wittig reaction,[1] dates back to 1953 (Scheme 1). The effectiveness and generality of this reaction have ensured its continued development and numerous reviews detailing its application have been published.[2]

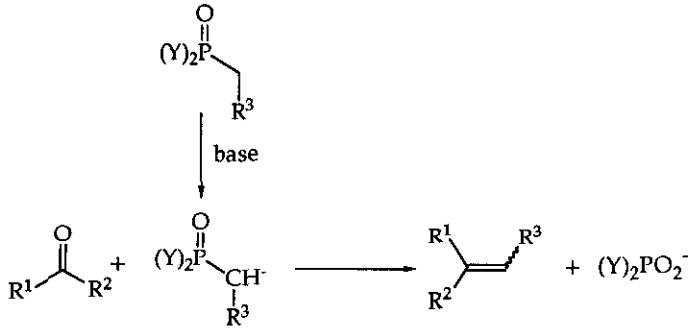


Scheme 1

The chemistry of phosphinoxy carbanions (2, Y = Ph) was first investigated by Horner *et al.*[3] who found that these carbanions reacted with carbonyl compounds to form alkenes through the elimination of diphenylphosphinate (Scheme 2).

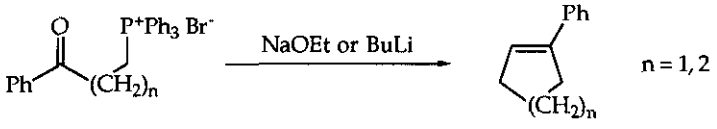
Shortly after this account, the application of phosphonate carbanions (2, Y = EtO) to alkene synthesis was developed by Wadsworth and Emmons[4] (Scheme 2).

The refinement of the Horner[5] and Wadsworth-Emmons[6] strategies has resulted in versatile alkene syntheses which today rival the Wittig reaction in value.



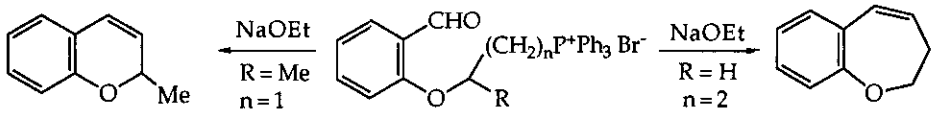
Scheme 2

The first examples of an intramolecular Wittig reaction were reported in 1962 and described the synthesis of 1-phenyl- cyclohexene and cyclopentene[7] (Scheme 3).



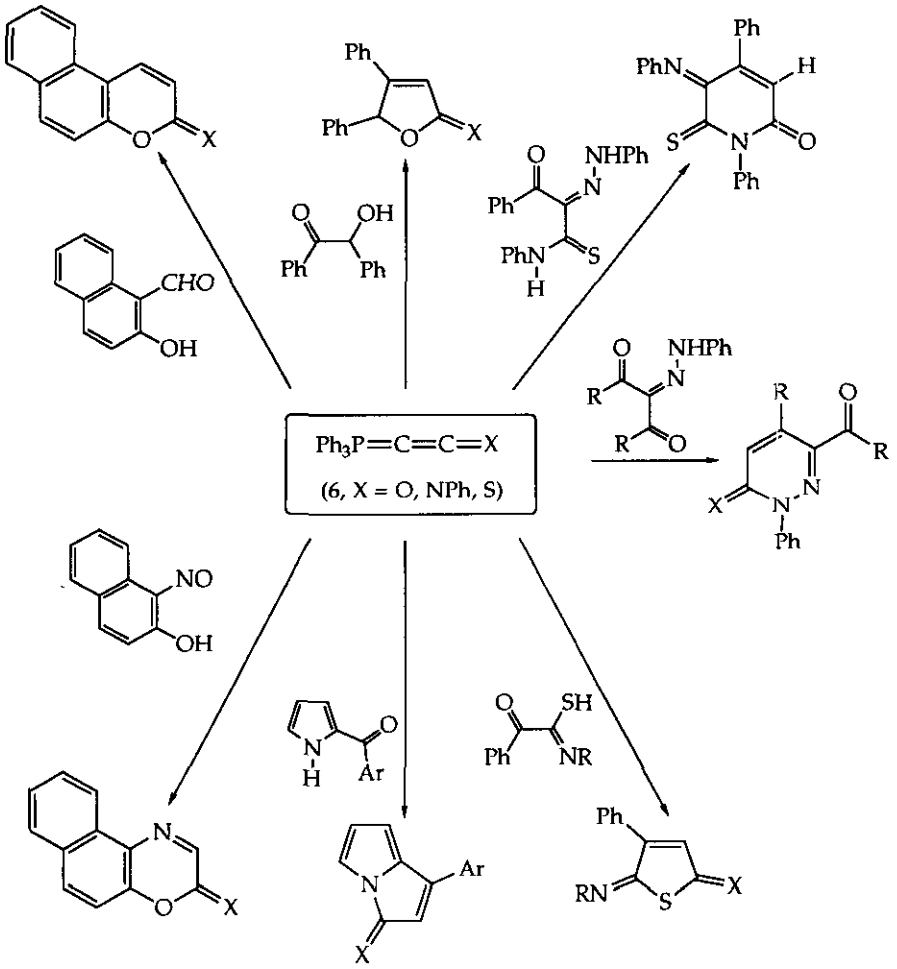
Scheme 3

This initial work was quickly followed by the synthesis of 2-methyl-2*H*[1]benzopyran (4) and 2,3-dihydro[1]benzoxepin (5) through the cyclisation of the phosphonium salt (3) with sodium ethoxide.[8]



The first comprehensive survey of the application of the Wittig, aza-Wittig, Horner and Wadsworth-Emmons reactions to the synthesis of heterocyclic compounds was produced by Zbiral in 1974,[9] whilst the synthesis of cycloalkenes and a limited number of heterocyclic compounds using Wittig methodology

has featured in a review.[10] A more selective technical report dedicated to the synthesis of heterocycles using an intramolecular Wittig reaction appeared some 11 years later.[11] The synthesis of some heterocyclic compounds using vinylphosphonates has been described in a short review of vinylphosphonate chemistry.[12] An excellent general review on the Wittig reaction with carbonyl compounds other than aldehydes and ketones,[13] often termed a non-classical Wittig reaction, appeared in 1988 and contained several examples of intramolecular Wittig reactions leading to heterocyclic compounds. Prominent among the many examples in this review was the application of phosphacumulenes to heterocyclic synthesis, an area dominated by Bestmann and his group.[14] The potential of triphenylphosphoranylidene ketene (6, X = O) and related compounds (6, X = NPh, S) is illustrated in a single paper by Bestmann and workers, which described the synthesis of seven classes of heterocycle[15] (Scheme 4).



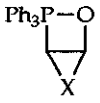
Scheme 4

It is the aim of this review to survey the application of intramolecular Wittig, Horner and Wadsworth-Emmons reactions which lead to heterocyclic systems containing N, O and S atoms or multiples thereof. The aza-Wittig reaction has been employed to obtain a diversity of nitrogen containing heterocycles and has been the subject of numerous recent reviews[16] and is omitted from this current work.

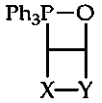
2 DISCUSSION

2.1 Small Rings

The mechanism of the Wittig and related phosphorus stabilised carbanion reactions is thought to rely upon the formation of a 1,2-oxaphosphetane system prior to the *cis*-elimination of Ph_3PO, $Ph_2PO_2^-$ or $(RO)_2PO_2^-$. Thus it comes as no surprise to find that 3- and 4- membered heterocyclic or carbocyclic[10] systems are not accessible by this methodology since highly strained bicyclic intermediates of the type (7a,b) would be required to facilitate the transformations.



(7a) X = O, NR, S

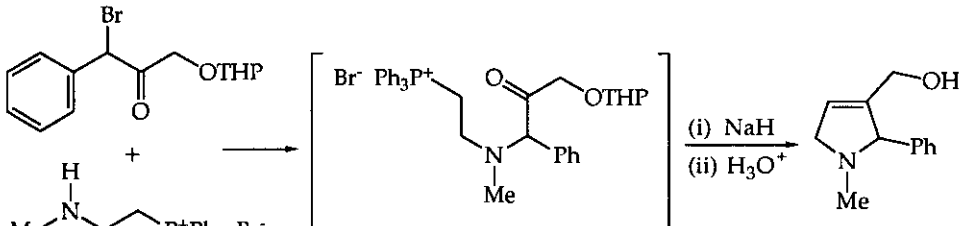


(7b) X = CH_2; Y = O, NR, S
X = O, NR, S; Y = CH_2

2.2 5-Membered Rings and Their Benzologues

2.2.1 Rings Containing Nitrogen

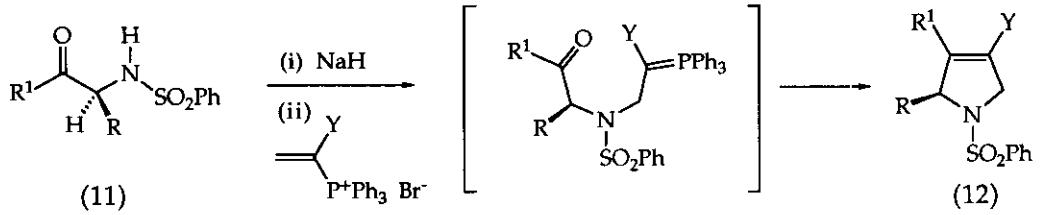
α-Amino ketones are frequently employed in the synthesis of pyrroles,[17] although these 1,2-difunctional compounds are not particularly easy to prepare and additionally often require careful storage. Several Wittig based routes to 2,5-dihydropyrroles circumvent the need to isolate such reagents. Thus, coupling a β-aminophosphonium salt (8) with an α-bromo ketone affords a trialkyl-α-amino ketone (9). Subsequent generation of the ylide with sodium hydride readily effected the cyclisation to the 2,5-dihydropyrrole ring (10).[18]



(8) (9) (10)

When α-amino ketones are required, they may be conveniently protected as their *N*-arylsulfonyl derivatives. Rapoport *et al.* have devised a simple preparation of these compounds from the reaction of

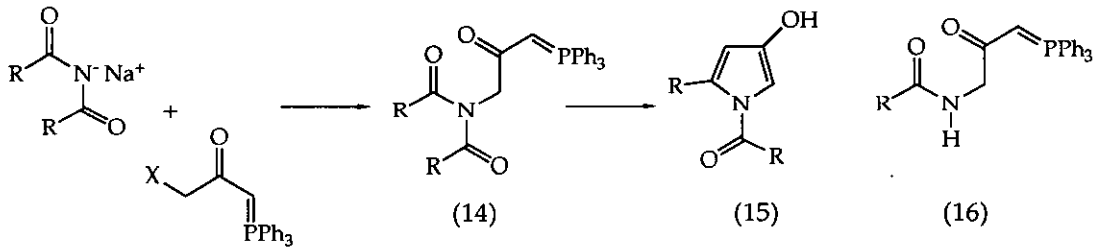
organolithium reagents with *N*-arylsulfonyl-α-amino acids.[19] This methodology has been utilised for the preparation of several optically pure *N*-arylsulfonyl-α-amino ketones (11), which on treatment with sodium hydride undergo a Michael addition to vinyl phosphonium salts which proceeds with retention of stereochemistry. Concomitant cyclisation affords the 2,5-dihydropyrroles (12) in high enantiomeric excess and good overall yield.[20]



(11) (12)

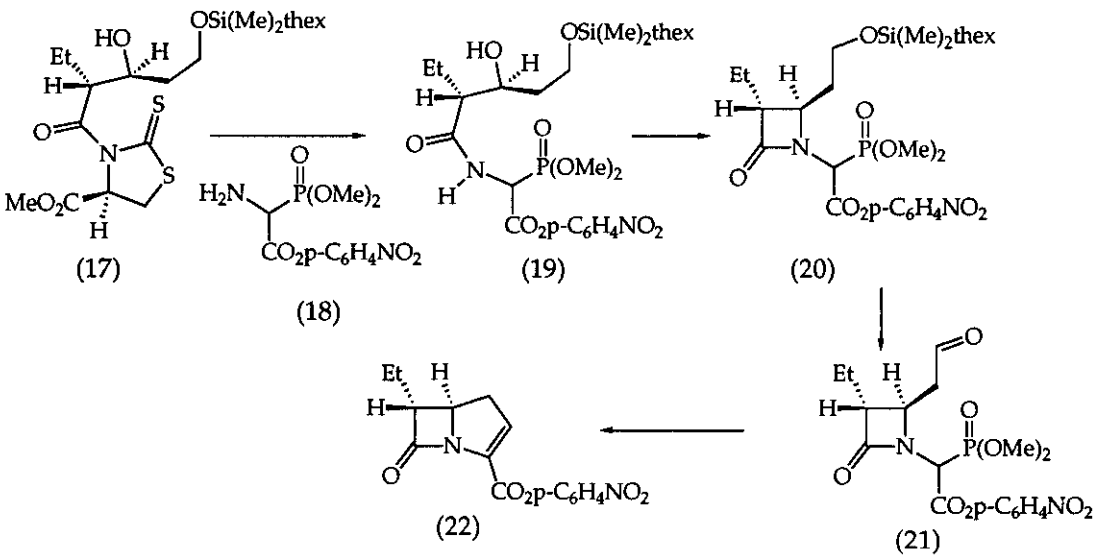
Y = H, SPh; R^1 = Me, Ph; R = CH_2OH, Me, $CH_2OTBDMS$

Symmetrical imides have also been used as a source of α-amino ketones. Displacement of the halide from (α-haloacetylmethylene)triphenylphosphoranes (13) on treatment with the anion derived from symmetrical imides resulted in isolable (α-imidoacetylmethylene)triphenylphosphoranes (14). Attempts to effect the cyclisation of these new ylides to the *N*-acyl-3-hydroxypyrroles (15) using NaH or lithium diisopropylamide (LDA) under a range of conditions was unsuccessful, the major product isolated being characterised as the monoacylaminophosphorane (16). However, efficient cyclisation to the pyrroles was accomplished on heating the ylides (14) in either toluene or mesitylene.[21]

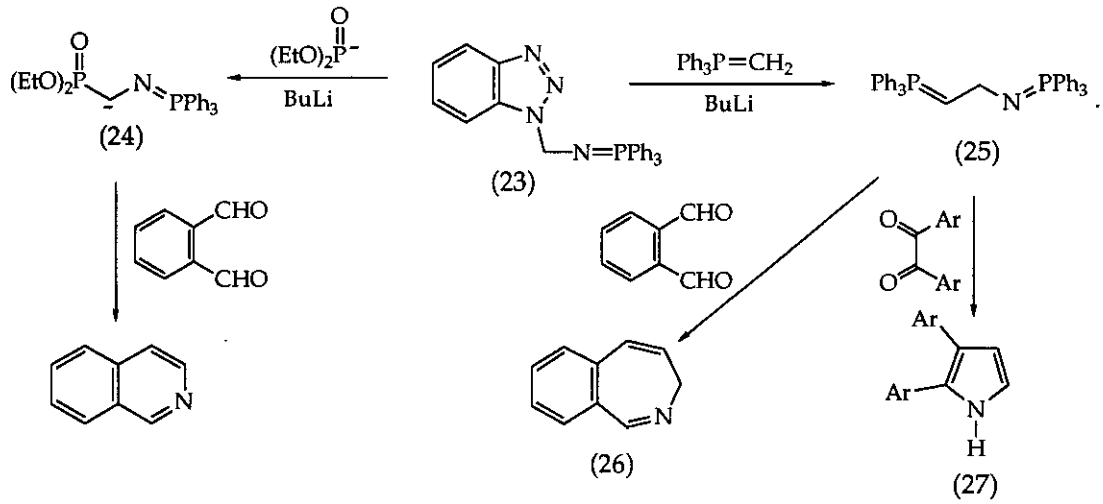


(13) (14) (15) (16)

An intramolecular Wadsworth-Emmons reaction features as the key step in a new approach to the carbapenem unit. Transamidation of the acylthiazolidinethione (17) with the aminophosphonoacetate (18) in the presence of 4-dimethylaminopyridine (DMAP) gave the amide (19), which was cleanly cyclised to the β-lactam (20) using Mitsunobu conditions (di-*tert*-butyl azodicarboxylate, Ph_3P). Removal of the protecting silyl function (tetrabutylammonium fluoride) and subsequent oxidation of the alcohol (pyridinium chlorochromate/alumina) afforded the phosphono aldehyde (21) which , on treatment with NaH in THF cyclised to the optically active carbapenem (22).[22]



An ingenious variation of the bis-Wittig reaction employing monoazabis-ylides for the synthesis of 5-, 6- and 7-membered nitrogen containing heterocycles has been described by Katritzky *et al.* Displacement of the labile benzotriazole function from 1-{[(triphenylphosphoranylidene)amino]methyl}benzotriazole (23) with the anion generated from diethyl phosphite and excess butyllithium affords the 1,2-bis-ylide (24), whereas reaction of 23 with methylenetriphenylphosphorane and butyllithium results in the 1,3-bis-ylide (25). The potential of these ylides is illustrated by their reaction with phthalaldehyde and diaryl 1,2-diketones to afford isoquinoline, 2-(3*H*)-benzazepine (26) and 2,3-diarylpyrroles (27) in good yields (Scheme 5).[23]

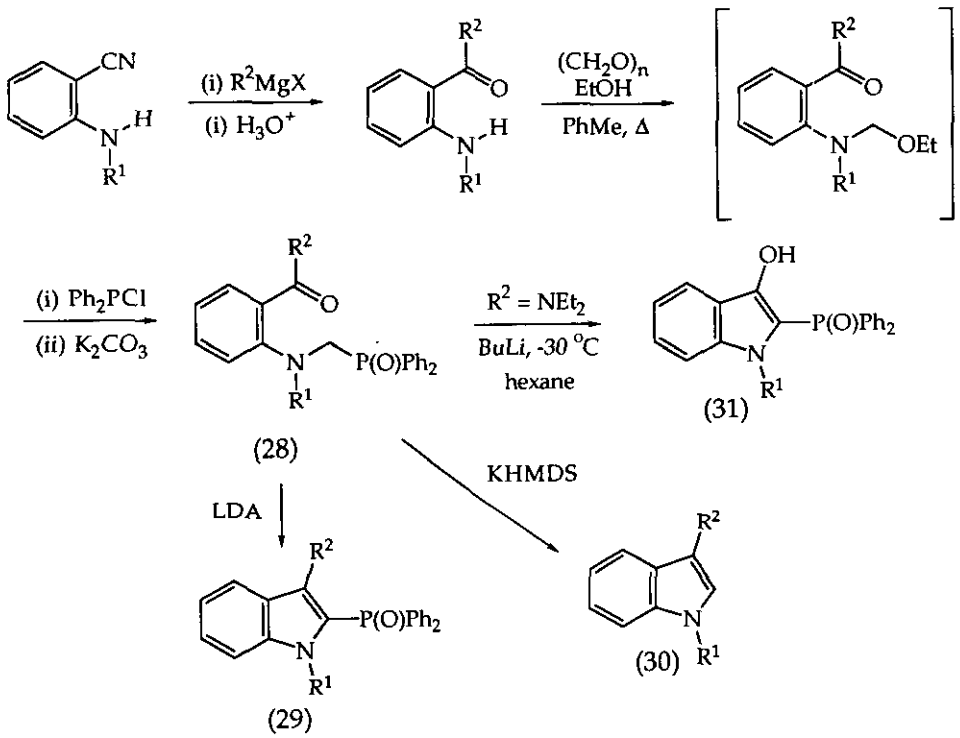


Scheme 5

An efficient synthesis of 3-substituted indoles from *N*-methyl or *N*-benzyl anthranilonitriles has been described. Initial treatment of the nitrile with a Grignard reagent affords the *o*-acylanilines which are

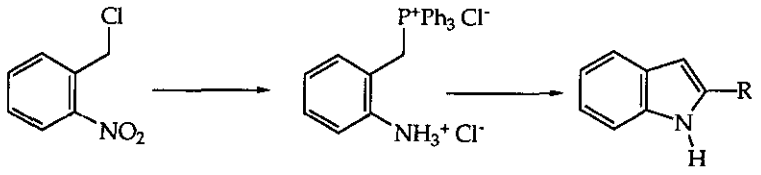
readily converted into the *o*-[diphenylphosphinoylmethyl(alkyl)amino]aryl ketones (28) *via* a one-pot three step sequence entailing a Mannich reaction, Arbusov reaction of the intermediate *O,N*-acetal with chlorodiphenylphosphine and basification with potassium carbonate (Scheme 6). The choice of base for the generation of the P=O stabilised anion derived from 28 has a marked effect on the outcome of the Horner cyclisation process. The use of LDA promotes the formation of 2-diphenylphosphinoyl-3-substituted indoles (29) presumably by an overall dehydration process, whereas potassium bis(trimethylsilyl)amide (KHMDS) favours the formation of the 3-substituted indole (30) as a consequence of elimination of potassium diphenylphosphinate.[24]

In a previous report by these workers, the cyclisation of the amide intermediates (28, $R^2 = NEt_2$), obtained by a similar reaction sequence, was achieved using butyllithium as the base and led to the exclusive formation of the 2-diphenylphosphinoyl-3-hydroxyindoles (31).[25]



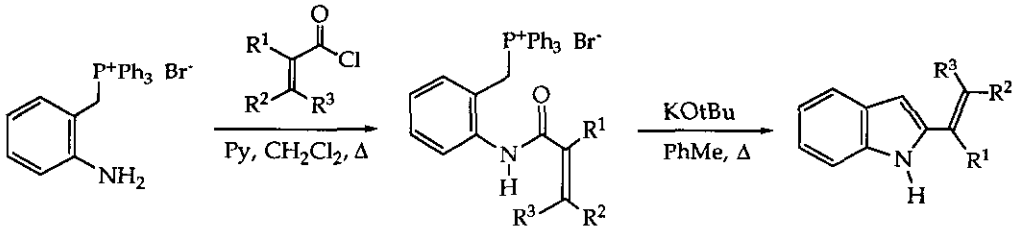
Scheme 6

2-Alkylindoles (33) have been obtained in good yield from 2-nitrobenzyl chloride in four steps. Displacement of chloride with triphenylphosphine and reduction of the nitro function with zinc in acetic acid gave 2-aminobenzyl(triphenyl)phosphonium chloride hydrochloride (32). Reaction with an acid chloride and subsequent treatment with potassium *tert*-butoxide (KOtBu) in refluxing toluene completed the sequence.[26]



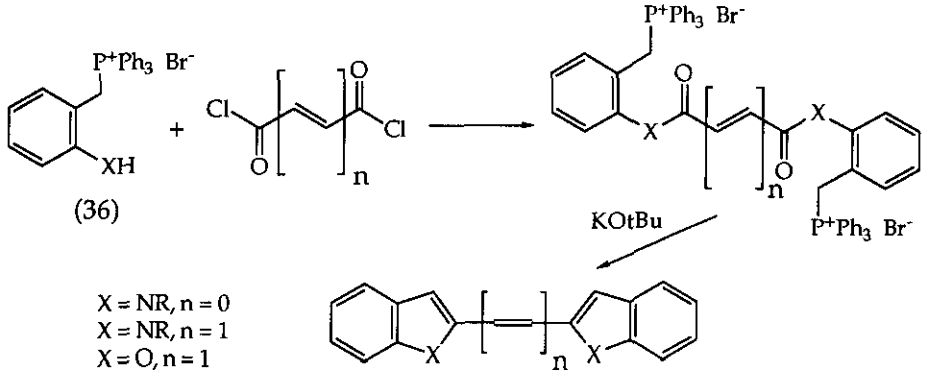
(32) (33)

2-Vinylindoles (35) have been obtained in an identical manner to the indoles above. The key steps are the direct acylation of 2-aminobenzyl(triphenyl)phosphonium bromide with an α,β-unsaturated acid chloride in the presence of pyridine (py) followed by intramolecular cyclisation of the 2-(*N*-acyl)aminobenzyl(triphenyl)-phosphonium bromides (34) on treatment with KOtBu in refluxing toluene.[27]



(34) (35)

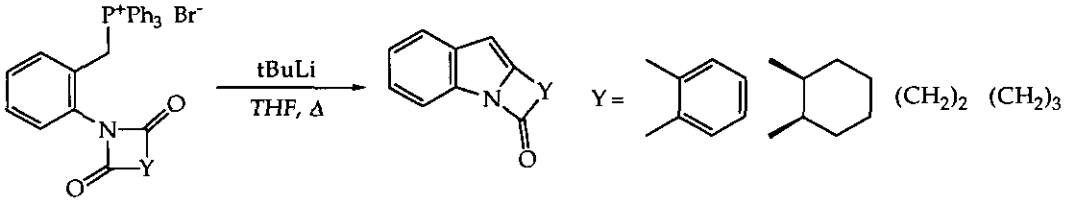
An extension of this methodology relies upon acylation of either 2-amino- or 2-hydroxybenzyltriphenylphosphonium bromides (36) with a diacid chloride to afford the bis[benzyl(triphenyl)-phosphonium bromides]. Routine ring closure of these compounds with KOtBu gave the 2,2'-biindolyls (37, X = NR, n = 0) or the ethylene bridged analogues (37, X = NR or O, n = 1).[28]



(36) (37)

The key intermediate in the synthesis of the pyrrolo- and pyrido[1,2-*a*]indoles (39) is the phosphonium salt (38), which is readily obtained by acylation of *o*-toluidine with the appropriate anhydride followed by allylic bromination and nucleophilic displacement of bromide ion by triphenylphosphine. Generation of

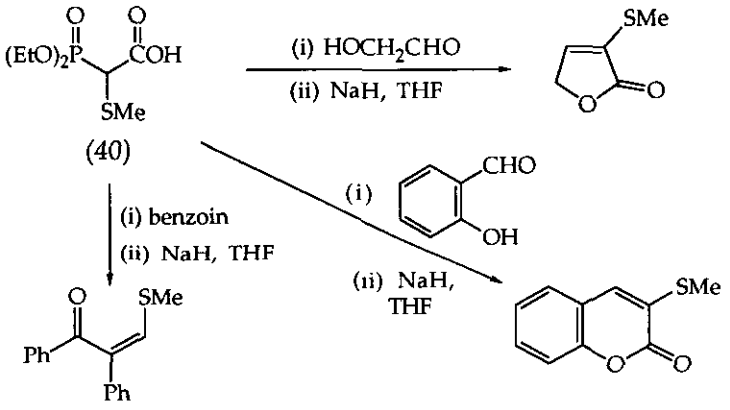
the ylide and subsequent cyclisation was accomplished with *tert*-butyllithium in refluxing tetrahydrofuran (THF).[29]



(38) (39)

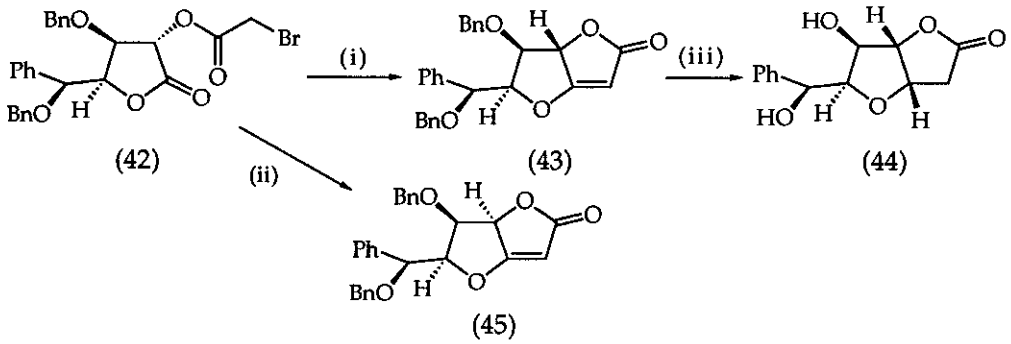
2.2.2 Rings Containing Oxygen

A versatile route to 5- and 6- membered α-methylthiolactones has been described which utilises diethyl α-methylthiophosphonoacetic acid (40) as the key reagent. Esterification of 40 with a hydroxycarbonyl compound using dicyclohexylcarbodiimide followed by treatment with NaH in THF effected the ring closure to the lactones. Interestingly, reaction of 40 with benzoin gave the methylthiomethylene compound (41) instead of the expected lactone.[30]



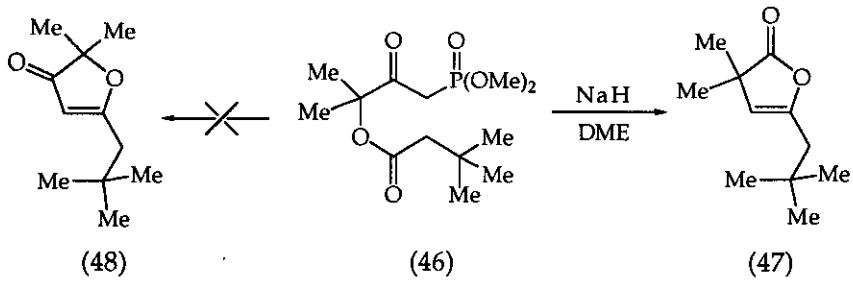
(41)

An intramolecular Wittig reaction features as the key step in a total synthesis of (+)-goniofufurone (44), a styryllactone isolated from the stem bark of *Goniothalamus giganteus*. Formation of the phosphonium salt from the bromoacetyl derivative (42) with concomitant cyclisation on treatment with Ph_3P and one equivalent of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile gave the bicyclic lactone (43) in excellent yield. Selective hydrogenation of the conjugated double bond with simultaneous deprotection of the hydroxyl functions afforded the natural product. Interestingly, the use of a slight excess of DBU resulted in the isolation of a mixture of 44 and a new product (45) in which the C-4 position has been epimerised.[31]

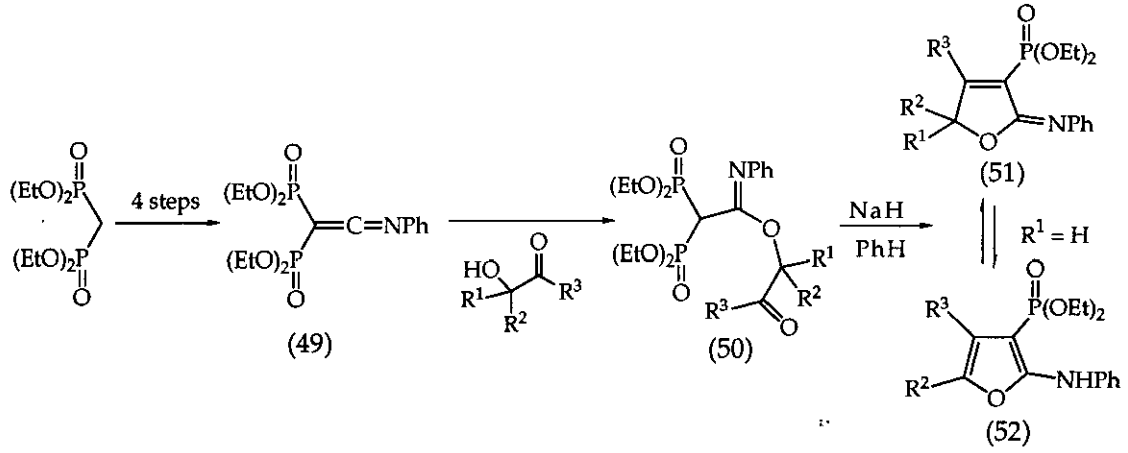


Reagents: (i) Ph_3P, DBU, MeCN, (ii) Ph_3P, excess DBU, MeCN, (iii) H_2, 10% Pd/C

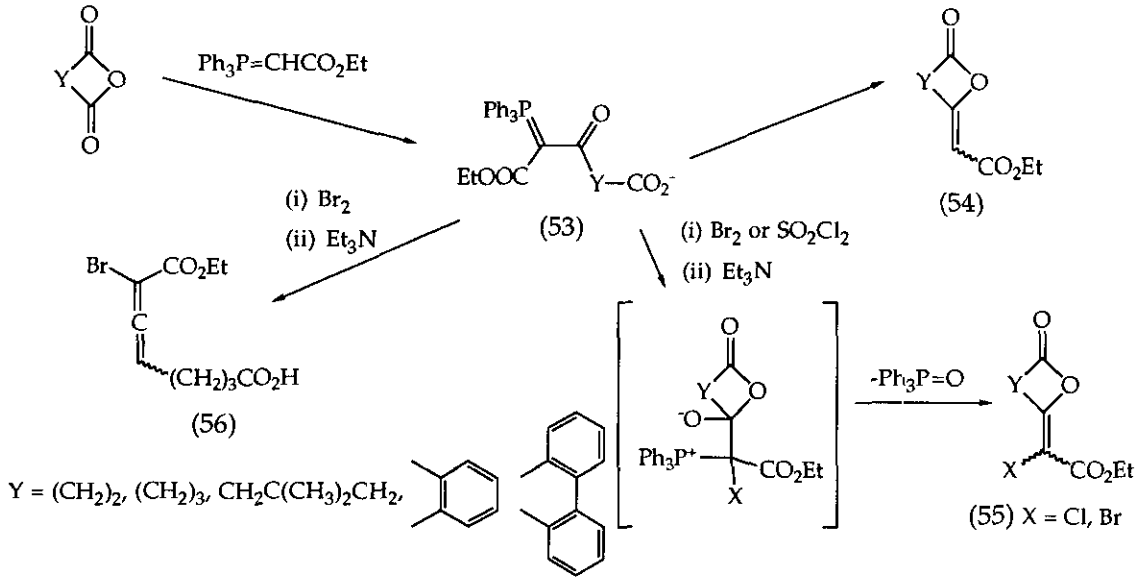
Treatment of the phosphonate (46) with NaH in 1,2-dimethoxyethane (DME) resulted in the unexpected formation of the 2,3-dihydrofuran-2-one (47) rather than the expected 2,3-dihydrofuran-3-one (48). Attempts to elucidate the mechanism of this unusual skeletal rearrangement were unsuccessful.[32]



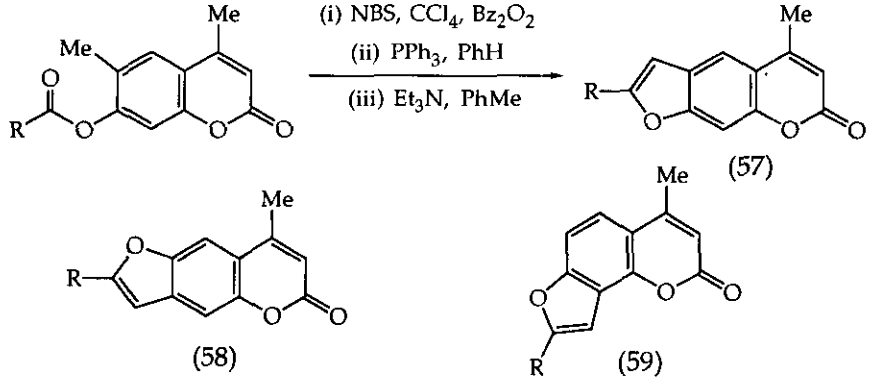
N-Phenyl-bis(diethylphosphonato)ketene imine (49) has been prepared from tetraethylmethylene-diphosphonate in four steps. This phosphacumulene reacts with α-hydroxyketones to afford 1,5-keto-bis(phosphonates) (50) which undergo an intramolecular Wadsworth-Emmons reaction on deprotonation with NaH in benzene to yield 2-*N*-phenylimino-2,5-dihydrofurans (51), which tautomerise to the diethyl 2-aminofuran-3-phosphonates (52).[33]



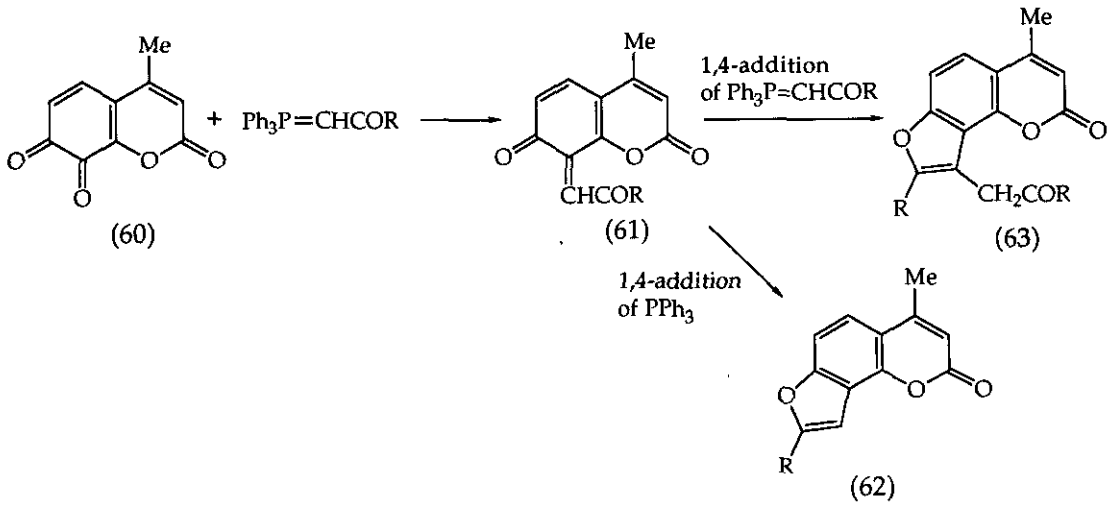
The non-classical Wittig reaction between stabilised ylides and cyclic anhydrides is well documented and provides an efficient route to enol lactones (54) through the intermediate keto acid phosphoranes (53).[34] Halogenation of these phosphoranes with Br_2 or SO_2Cl_2 gives access to novel 5-, 6- and 7-membered halo enol lactones (55). The addition of the halogen is thought to promote lactonisation which generates the β-oxido function that is essential for oxaphosphorane formation; loss of triphenylphosphine oxide completes the sequence. Bromination of the keto-acid phosphorane derived from adipic anhydride failed to give the 7-membered ring lactone upon treatment with Et_3N and instead resulted in the formation of the bromoallene (56).[35]



Two routes to furocoumarins utilising intramolecular Wittig methodology have been reported. One relies upon the established methodology of free radical bromination of an arylmethyl function with subsequent displacement of bromide ion by triphenylphosphine to generate the phosponium salt. This salt undergoes cyclisation on treatment with a mild base, and is applicable to the synthesis of linear (57) and (58) and angular (59) furocoumarin isomers.[36]

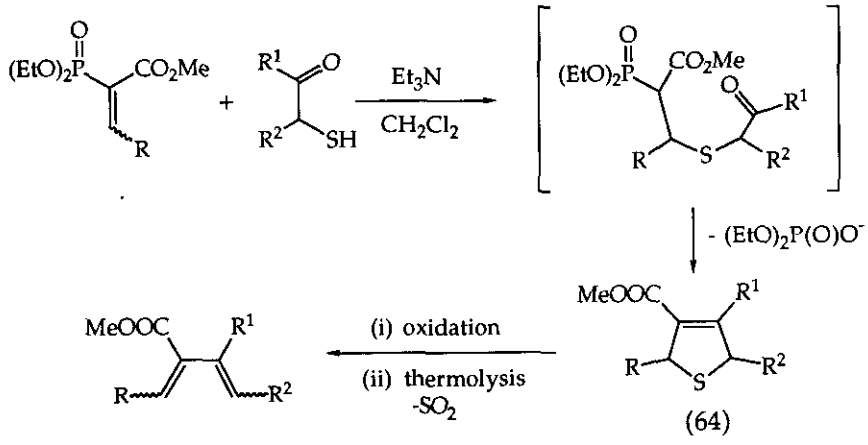


The second approach affords a mixture of angular furocoumarins (62, 63) from the reaction of the heterocyclic *o*-quinone (60) with two equivalents of a stabilised phosphorane. Michael addition of Ph_3P or a second equivalent of the phosphorane to the initially formed α,β-unsaturated system (61) have been postulated as the key steps in the formation of the products.[37]



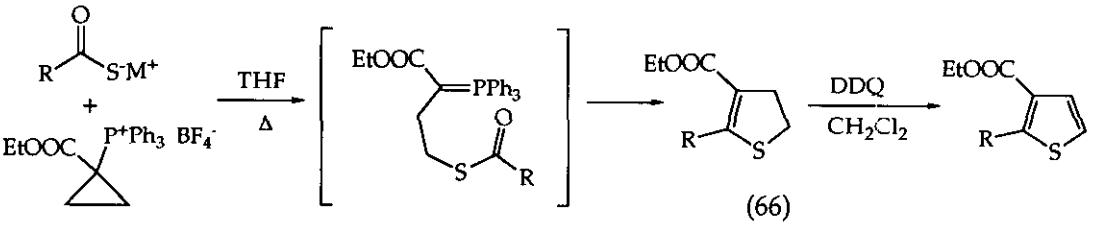
2.2.3 Rings Containing Sulfur

McIntosh has continued to exploit the established 2,5-dihydrothiophene synthesis from α-mercapto ketones and vinylphosphonium salts.[38] In this related study, 2,5-dihydrothiophenes (64) result from the Michael addition of α-mercapto carbonyl compounds to carbomethoxyvinylphosphonates (Scheme 7). These thiophene derivatives provide stereoisomeric mixtures of 2-carboxylated 1,3-butadienes by oxidation of the sulfur atom and chelotropic extrusion of SO_2 from the 2,5-dihydrothiophene 1,1-dioxides.[39]



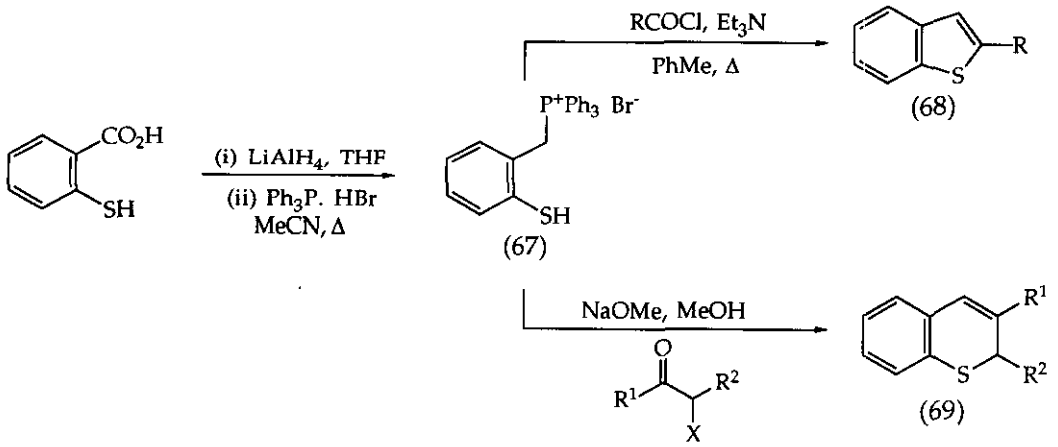
Scheme 7

Nucleophilic ring opening of 2-ethoxycarbonylcyclopropyl(triphenyl)phosphonium fluoroborate (65) with alkali metal thiolates affords 2,3-disubstituted 4,5-dihydrothiophenes (66) in good yield. Aromatisation is readily accomplished by treatment with DDQ in dichloromethane.[40]



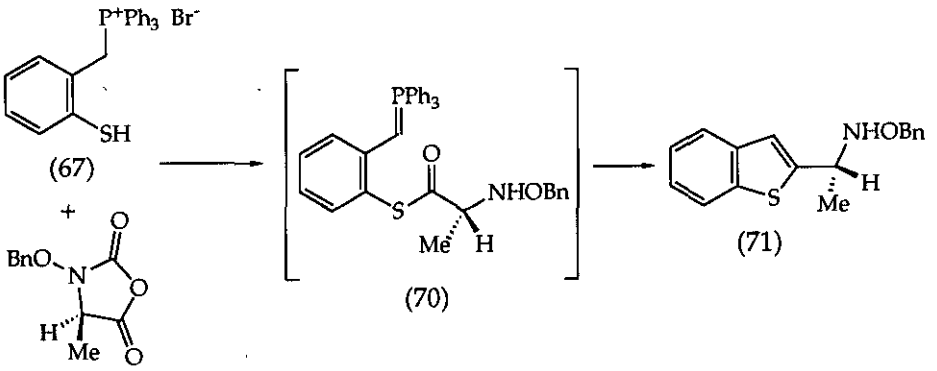
(65) (66)

Reduction of 2-mercaptobenzoic acid with lithium aluminium hydride followed by reaction of the resulting methanol with triphenylphosphine hydrobromide in acetonitrile affords (2-mercaptophenyl)-methyltriphenyl phosphonium bromide (67) in good yield. This compound is the key intermediate in a versatile synthesis of 2-substituted benzo[*b*]thiophenes (68) and 2,3-disubstituted 2*H*[1]benzothiopyrans (69) and is analogous to the route devised by Le Corre for the synthesis of benzo[*b*]furans.[41] Acylation of the phosphonium salt (67) with an acid chloride in toluene containing triethylamine readily affords the benzo[*b*]thiophene system, whereas reaction with an α–halo ketone in the presence of methoxide provides access to the 2*H*[1]benzothiopyran moiety in moderate overall yield.[42]

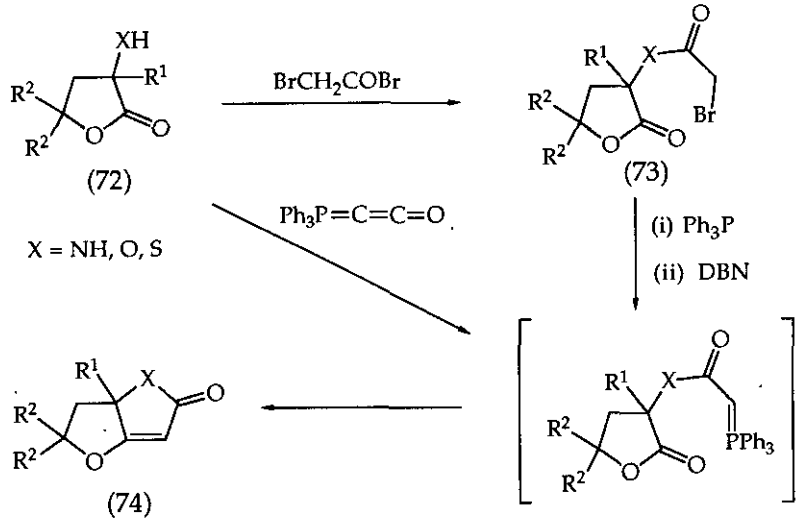


(67) (68) (69)

(2-Mercaptophenyl)methyltriphenylphosphonium bromide (67) has also been used to form the benzo[*b*]thiophene ring of zileuton,™ a potent inhibitor of 5-lipoxygenase. Cross coupling- cyclisation of this phosphonium salt with *N*-benzyloxy-D-alanine anhydride readily effected the formation of the benzo[*b*]thiophene system. However, the choice of base and solvent system proved critical for the transformation, with the optimised conditions of NaH in THF containing 5% dimethyl formamide (DMF) affording (71) in 86% yield. It is also noteworthy that the stereochemical integrity of the intermediate ylide (70), in which C-2 is highly epimerisable, is preserved during the intramolecular cyclisation.[43]

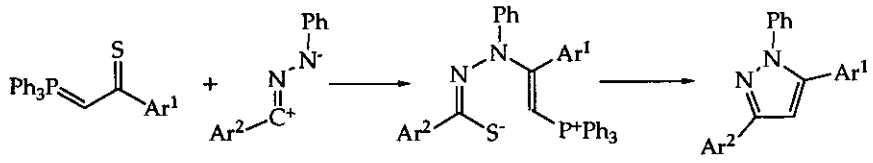


Two efficient routes to the bicyclic systems (74, X = NH, O, S) from the related α-substituted lactones (72) have been described. In one approach, the lactones are converted to their bromoacetyl derivatives (73) and thence to the phosphonium bromides. Treatment with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) generated the corresponding ylides which cyclised under the reaction conditions to furnish the fused heterocycles. The alternative approach relies upon the reaction of the α-substituted lactones with triphenylphosphoranylidene ketene to generate the ylides and hence the fused heterocycles in a single step.[44]



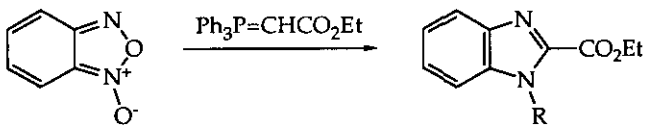
2.2.4 Rings Containing More Than One Heteroatom

Thioarylmethylene(triphenyl)phosphoranes react with benzonitrile imines to give the stable, red hydrazono(triphenyl)phosphoniothiolates (75) *via* a thiadiazole intermediate. On heating, these compounds cyclise with loss of Ph_3PS to afford the 2,4-diarylpyrazoles (76).[45]



(75) (76)

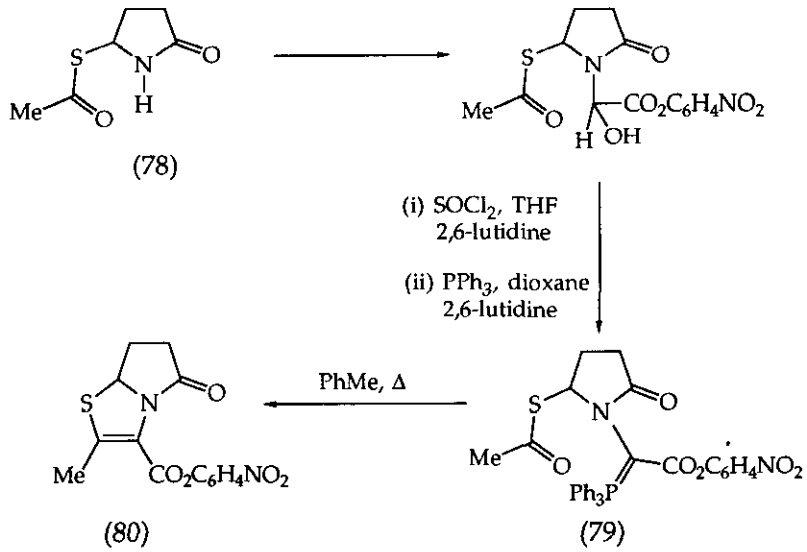
An elaborate mechanism involving an intramolecular Wittig reaction has been proposed to account for the formation of a mixture of ethyl benzimidazole-2-carboxylate (77, R = H) and its 1-ethoxy derivative (77, R = OEt) from the reaction of benzofuroxan with excess ethoxycarbonylmethylene(triphenyl)-phosphorane.[46]



(77)

The pioneering work of Woodward[47] on the synthesis of penems using a Wittig reaction as the ring forming step continues to be used.

Condensation of the lactam (78) with 4-nitrobenzyl glyoxylate afforded a diastereoisomeric mixture of hemiaminals, which was transformed to the chloro compound on treatment with thionyl chloride. Formation of the thiazole ring (80) was achieved by displacement of the chloride ion by triphenylphosphine in dioxan containing 2,6-lutidine and subsequent cyclisation of the phosphorane (79) on heating in toluene.[48]

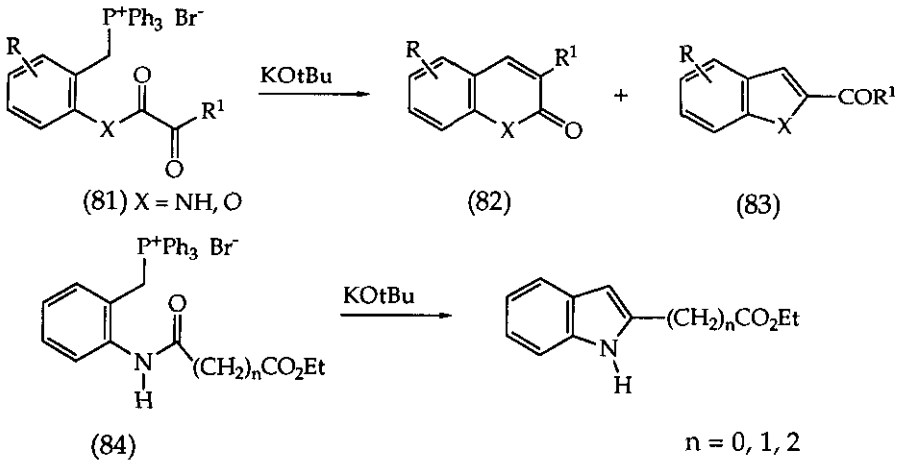


(78) (80) (79)

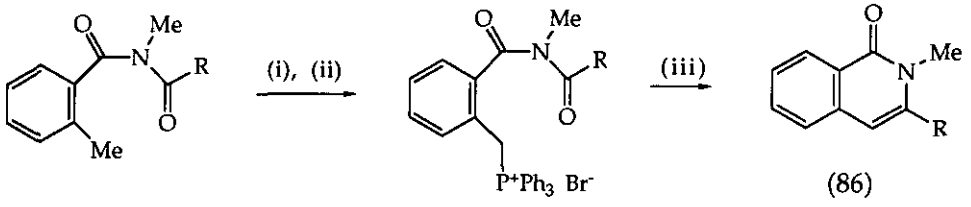
2.3 6-Membered Rings and Their Benzologues

2.3.1 Rings Containing Nitrogen

An interesting study by Capuano *et al.* revealed that the intramolecular cyclisation of the benzyl(triphenyl)phosphonium bromide derivatives (81, X = NH) gave mixtures of 2-quinolones (82) and 2-acylindoles (83, X = NH), in which the former predominated. The formation of the six-membered ring was favoured as a consequence of attack by the ylide at the more electrophilic carbonyl function. However, when 81, (X = O) was cyclised under identical reaction conditions the 2-acylbenzo[*b*]furan (83, X = O) was obtained as the exclusive product. Cyclisation of the related phosphonium salts (84) also led to the formation of the 5-membered heterocycle, despite the potential for attack by the ylide at the ester function.[49]



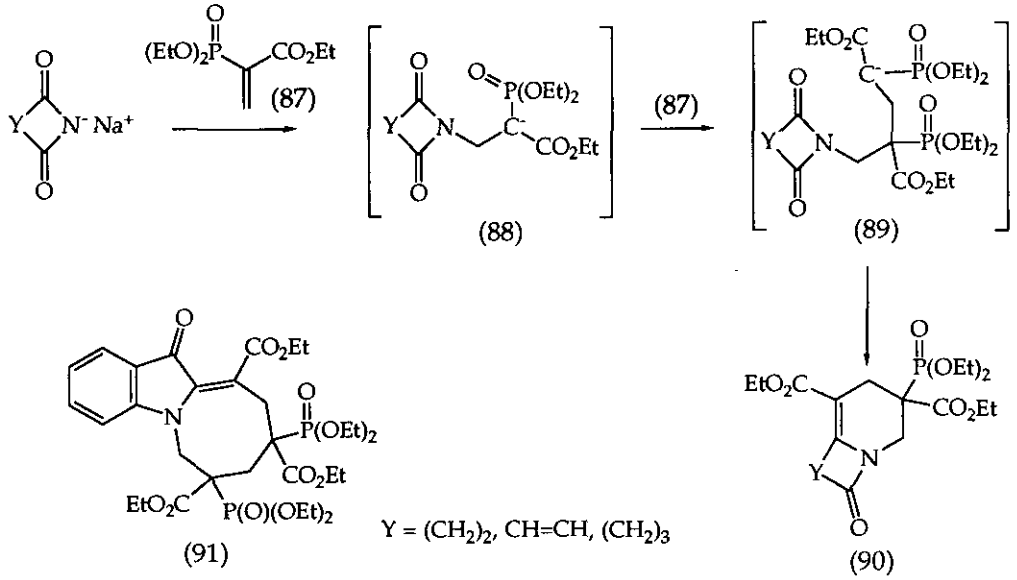
Intramolecular cyclisation of the phosphonium salts (85) derived from *N*-acyl-*N*-methyl-*o*-toluamides by the established protocol of photoinduced allylic bromination and subsequent displacement of bromide with PPh_3, gave a range of 3-substituted isoquinolones (86) in good yield.[50]



Reagents: (i) Br_2, CCl_4, hυ; (ii) Ph_3P, PhMe, Δ; (iii) Et_3N, PhMe, Δ.

The reaction of a range cyclic amide anions with two equivalents of carboethoxyvinyl phosphonate (87) proceeds *via* an initial Michael addition to afford the phosphonate (88) which then undergoes a further Michael addition to the second equivalent of the vinyl phosphonate rather than cyclising to produce a

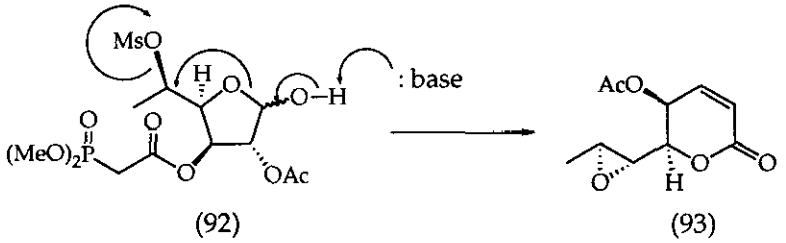
four-membered ring. The resulting bis-phosphonate (89), readily cyclises to the fused ring system (90). Surprisingly, the reaction of sodioisatin with two equivalents of (87) failed to afford the pyridine ring and instead resulted in the fused azocine (91) albeit in low yield. The application of three equivalents of 87 with sodioisatin resulted in an improved yield (38 %) of 91.[51]



2.3.2 Rings Containing Oxygen

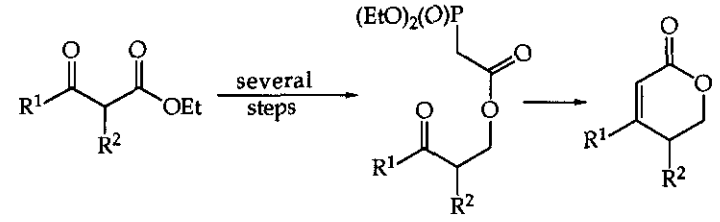
Of all of the heterocyclic systems obtained by application of the intramolecular Wittig or Wadsworth-Emmons reaction, the greatest activity has been directed towards the synthesis of six-membered oxygen containing heterocycles, a feature which may be attributed to the frequent occurrence of this heterocyclic unit in nature and to the pharmacological properties often associated with it.

The pyran-2-one ring of asperlin (93), a secondary metabolite isolated from cultures of the fungus *Aspergillus nidulans*, has been constructed by an ingenious tandem epoxide formation and intramolecular Wadsworth-Emmons cyclisation of the lactol (92) on treatment with mild base.[52]



An efficient annulation protocol for the transformation of β-ketoesters to α,β-unsaturated δ-lactones (95) using an intramolecular Wadsworth-Emmons reaction of the phosphonate (94) has been described by

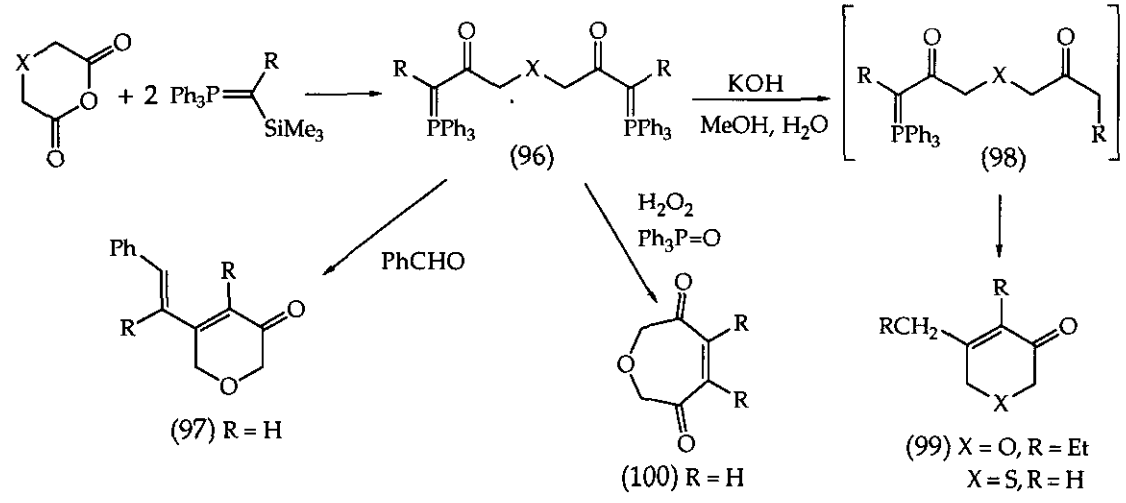
Nangia *et al.* Mild reaction conditions (LiCl, DBU, CH_3CN) are essential to minimise deleterious side reactions and to promote efficient cyclisation to the lactones.[53] The same workers have exploited this methodology for the partial synthesis of some iridoid monoterpene lactones from (+)-pulegone.[54]



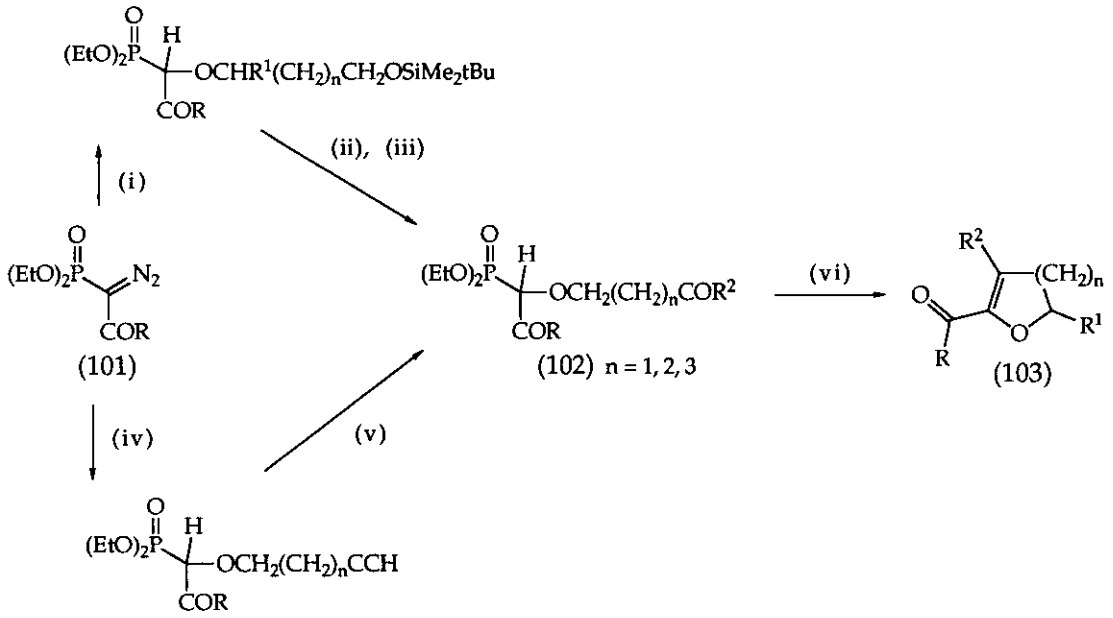
$R^1 = R^2 = H$; $R^1 = H$, $R^2 = Bz$
$R^1 = R^2 = (CH_2)_3$; $R^1 = R^2 = (CH_2)_4$

(94) (95)

Bis[(1-acylalkylidene)triphenylphosphoranes] (96), derived from cyclic anhydrides and two equivalents of a [1-(trimethylsiliyl)alkylidenetriphenylphosphorane,[55] are versatile reagents for the formation of heterocyclic compounds. Reaction with one equivalent of benzaldehyde results in the formation of 3,6-dihydro-5-(2-phenylvinyl)-2*H*-pyran-3-one (97). Alkaline hydrolysis of 96 affords the monoacyl ylides (98), which readily cyclise to afford the 3,6-dihydro-2*H*-pyran-3-ones and the sulfur analogues (99) in good yield. The oxidative hydrolysis of 96 with the hydrogen peroxide/triphenylphosphine oxide complex results in the transformation of the more reactive phosphorane function to an aldehyde group which is then 'captured' by the remaining terminal phosphorane moiety to give the 1,2,5,6-tetrahydrooxepin-3,6-dione (100).[56]



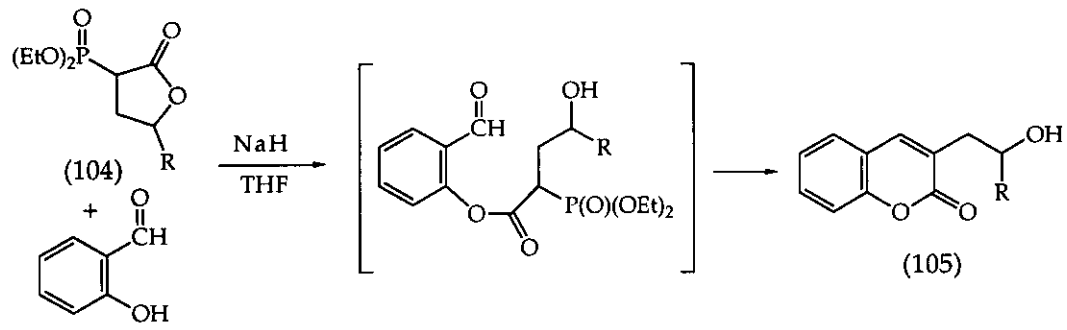
Aldehyde and ketone phosphonates (102) derived from the rhodium carbenoid mediated O-H insertion reaction of triethyl diazophosphonoacetate (101) with either mono-protected diols or terminal alkynols, undergo an intramolecular Wadsworth-Emmons reaction on treatment with NaH in THF to afford 5-, 6- and 7-membered cyclic ethers (103) (Scheme 8).[57]



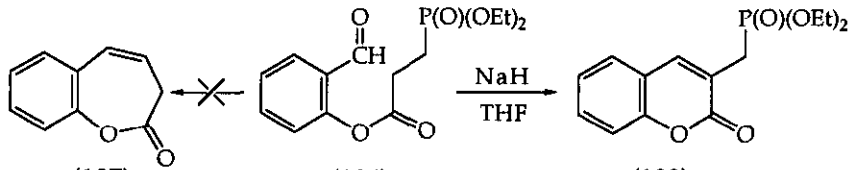
Reagents and conditions: (i) $tBuMe_2SiOCH_2(CH_2)_nCHR^1OH$, cat. $Rh_2(OAc)_4$, PhH, Δ, (ii) AcOH, H_2O, THF, (iii) PDC, CH_2Cl_2, (iv) $HOCH_2(CH_2)_nCCH$, cat. $Rh_2(OAc)_4$, PhH, Δ, (v) $HgSO_4$, H_2O, THF, (vi) NaH, THF.

Scheme 8

The reaction of α-diethylphosphono-γ-butyrolactones (104) with salicyl aldehyde gave the 3-(2-hydroxyethyl)-2*H*[1]benzopyran-2-ones (105) in excellent yield. Further manipulation of these compounds provided access to a range of benzopyranones with a heterocyclic or carbocyclic ring fused across the 3,4-bond.[58]

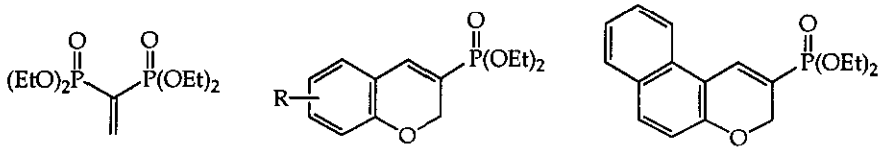


Generation of the anion from 2-formyl-3-(diethoxyphosphoryl)propionate (106), obtained by acylation of salicylaldehyde with 3-(diethoxyphosphoryl)propionyl chloride, effected an intramolecular aldol condensation yielding 3-diethoxyphosphorylmethyl-2*H*[1]benzopyran-2-one (108) rather than a Wadsworth-Emmons reaction leading to the benzoxepin-2-one (107).[59]



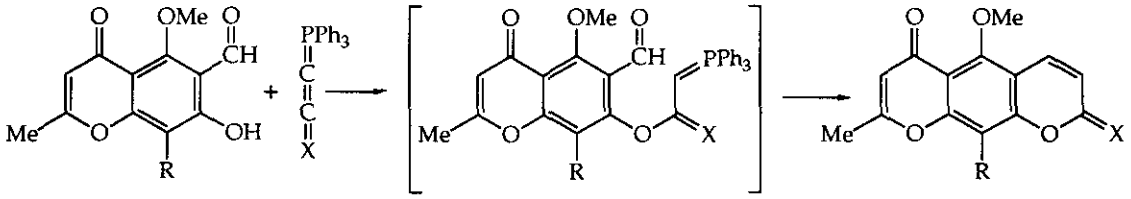
(107) (106) (108)

The reaction of the tetraethylethylidene *gem* bisphosphonate (109) with substituted salicyl aldehydes to yield 2*H*[1]benzopyran-3-phosphonates (110) or 3*H*-naphtho[2,1-*b*]pyran-2-phosphonates (111) proceeds *via* an initial Michael addition and subsequent intramolecular Wadsworth-Emmons reaction.[60] The formation of the 2,5-dihydrofuran ring system from 2-hydroxycyclohexane and (84) is also described.



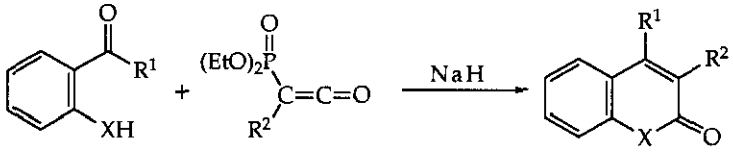
(109) (110) (111)

The 2*H*-pyran-2-one ring of the linear benzodipyran (113) has been constructed by union of the triphenyphosphoranylidene ketene and the 7-hydroxychromone-6-carboxaldehyde (112). The thione analogue was obtained by an identical procedure from the corresponding thioketene.[61]



(112) (113) X = O, S

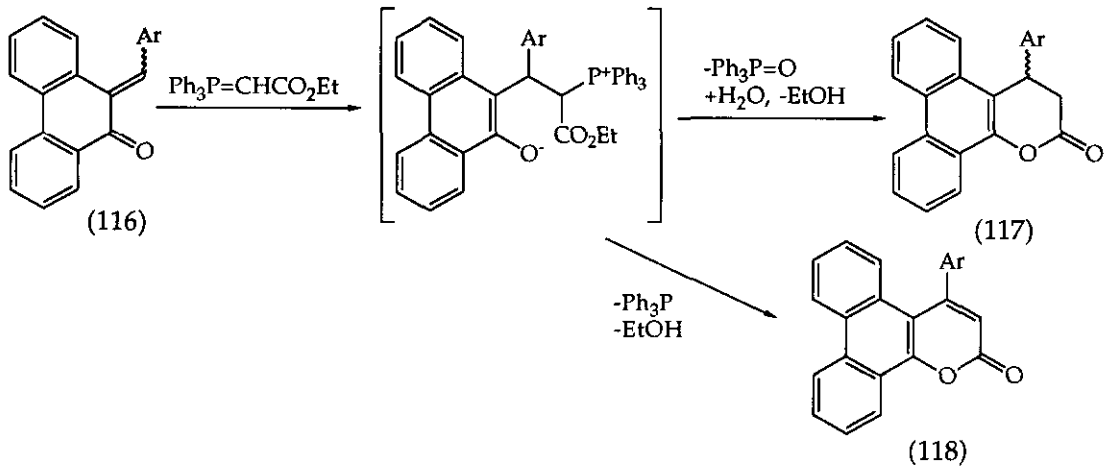
Diethylphosphonoketenes (114) have been used in a similar fashion with salicyl aldehydes and related *o*-functionalised compounds to afford benzopyran-2-ones (115, X = O) and 2-quinolones (115, X = NMe).[62]



(114) (115)

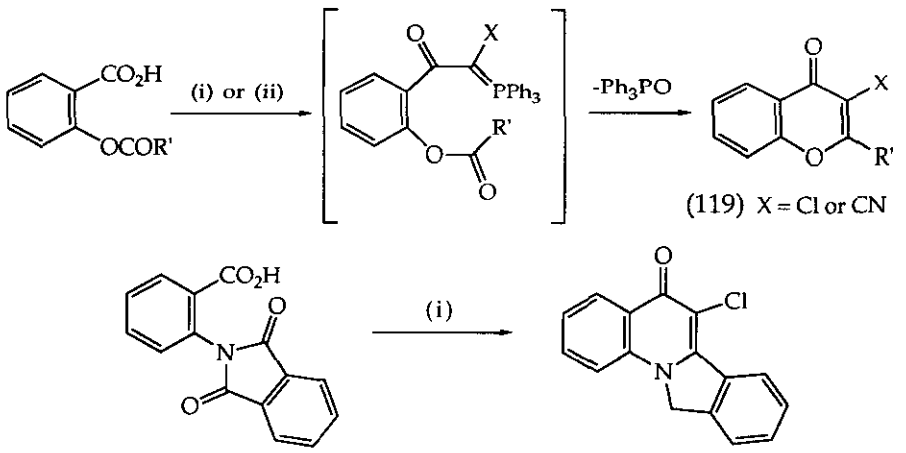
The two benzopyran-2-ones (117) and (118) result from the Michael addition of ethoxycarbonylmethylene(triphenyl)phosphorane to the stable *o*-quinone methanide (116). Formation of

the former compound relies upon loss of triphenylphosphine oxide and hydrolysis of the enol ether to generate the lactone carbonyl, whereas the fully aromatic product (118) requires the elimination of triphenylphosphine and ethanol.[63]



(116) (117) (118)

2-Acyloxy- and 2-phthalimido-benzoic acids are readily cyclised on treatment with an excess of Ph_3P/CCl_4 under mild conditions to afford the corresponding 3-chloro-4*H*[1]benzopyran-4-one (119, X = Cl) or 3-chloro-quinoline-4-one (120) respectively (Scheme 9). The use of trichloroacetonitrile in place of CCl_4 and higher reaction temperatures resulted in the formation of the 3-cyano-4*H*[1]benzopyran-4-one (119, X = CN) from 2-acyloxybenzoic acid.[64]

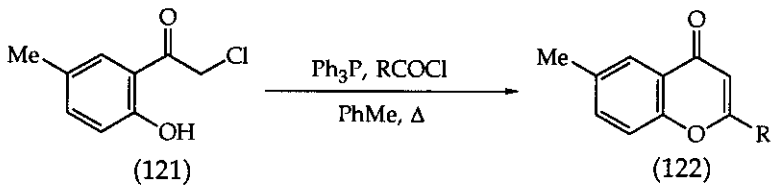


(120)

Reagents (i) Ph_3P, CCl_4, CH_2Cl_2, 24 °C (X = Cl); (ii) Ph_3P, Cl_3CCN, 180 °C (X = CN).

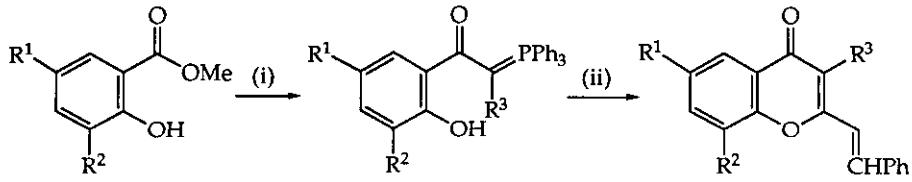
Scheme 9

2-Substituted-4*H*[1]benzopyran-4-ones (122) result from a base free intramolecular Wittig reaction on refluxing the *o*-hydroxyphenacyl chloride (121) in toluene containing Ph_3P and an acid chloride.[65]



(121) (122)

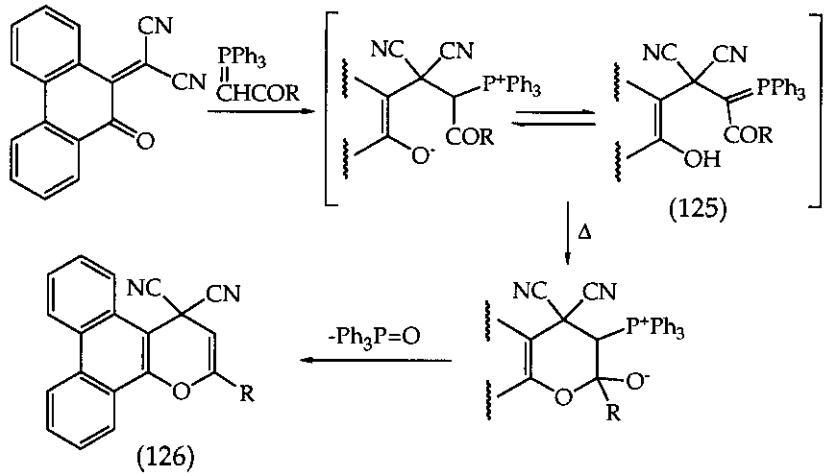
2-Styryl-4*H*[1]benzopyran-4-ones (124) have been obtained in two steps from the readily available and inexpensive methyl salicylates. Initial reaction with alkylidene(triphenyl)phosphoranes affords the acyl phosphoranes (123) through displacement of methoxide. Subsequent acylation with an excess of cinnamoyl chloride in pyridine is followed by cyclisation to the heterocycle.[66]



(123) (124)

Reagents: (i) $Ph_3P{=}CHR^3$; (ii) 3PhCH=CHCOCl, py.

Heating the stable ylide (125), obtained from 10-dicyanomethylene-9-(10*H*)phenanthrone and alkoxycarbonymethylene(triphenyl)phosphoranes, resulted in the elimination of triphenylphosphine oxide to afford the 4,4-dicyano-4*H*[1]benzopyrans (126) in moderate yields (Scheme 10).[67]

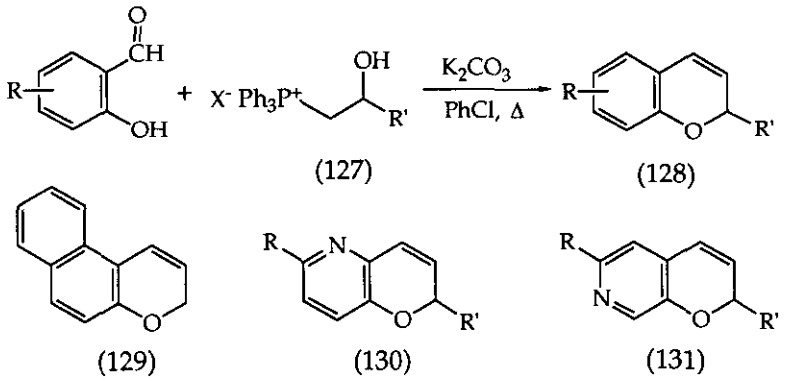


(126)

Scheme 10

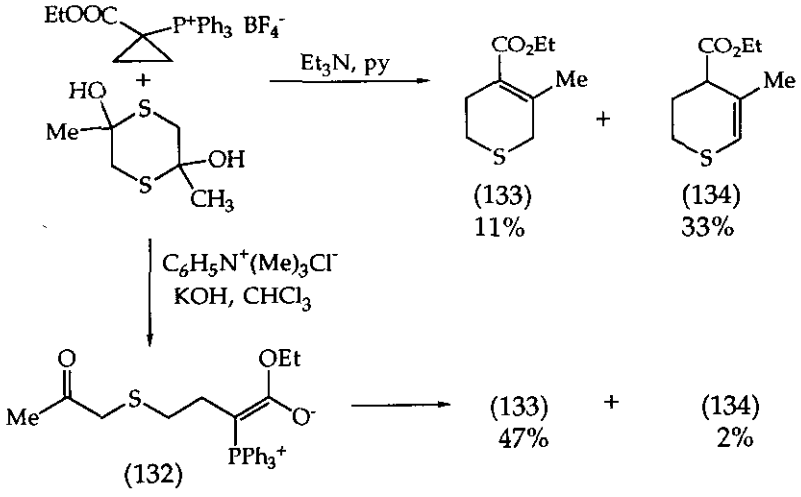
An intramolecular Wittig reaction has been postulated to account for the formation of the 2*H*[1]benzopyrans (128) from substituted salicylaldehydes and 2-hydroxyalkyl(triphenyl)phosphonium salts (127) in the presence of potassium carbonate in refluxing chlorobenzene. The naphthopyran (129)

and the novel fused heterocyclic systems, the pyrano[3,2-*b*]- (130) and pyrano[2,3-*c*]pyridines (131) were obtained by an identical protocol from the appropriate *o*-hydroxy aldehydes.[68]

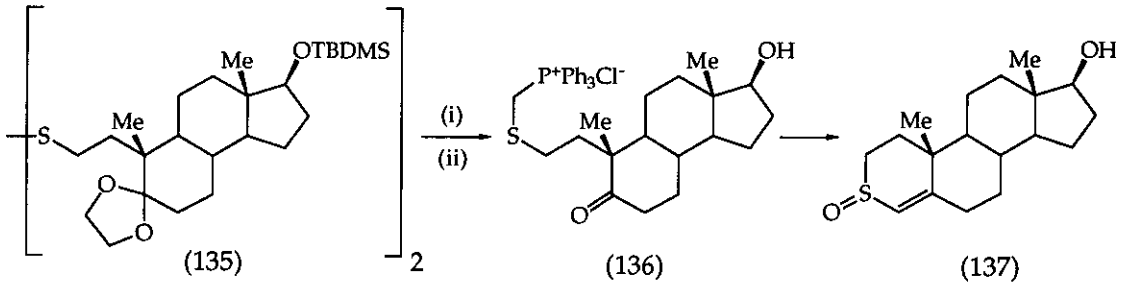


2.3.3 Rings Containing Sulfur

Mixtures of isomeric dihydro-2*H*-thiopyrans (133) and (134) are obtained when 1-ethoxycarbonyl-cyclopropyl(triphenyl)phosphonium fluoroborate is reacted with α-mercapto ketones in the presence of triethylamine and pyridine. Alternative base catalysis with benzyltrimethylammonium chloride and potassium hydroxide in chloroform results in formation of the stable betaine (132) which can subsequently be cyclised to the same isomeric thiopyrans, though now (133) is obtained in significant excess.[69]

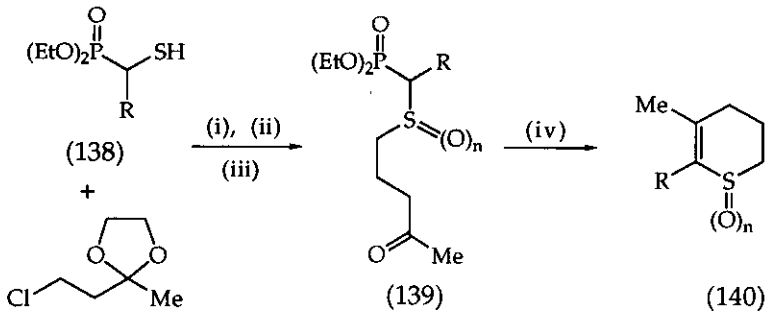


Cleavage of the disulfide (135) with methylene(triphenyl)phosphorane gave the phosphonium salt (136) which readily cyclised in the presence KOtBu/dimethyl sulfoxide (DMSO) to the 3-thiatestosterone analogue. Oxidation to the sulfoxide (137) was accomplished with sodium periodate.[70]



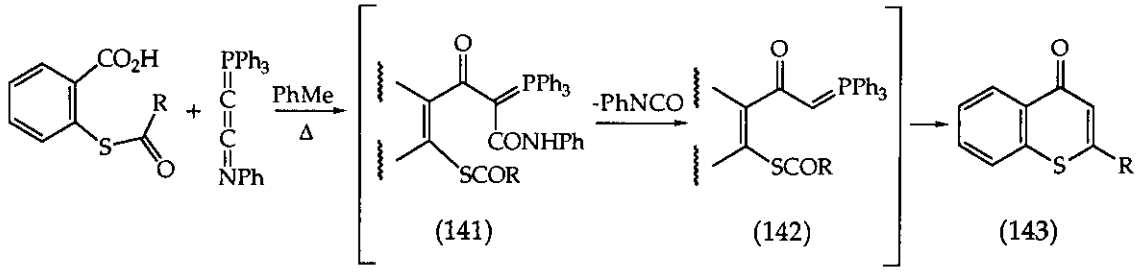
Reagents: (i) $Ph_3P{=}CH_2$, (ii) HCl, (iii) KOtBu, DMSO, (iv) $NaIO_4$.

3,4-Dihydro-2*H*-thiopyran 1-oxides (140, n = 1) and 1,1-dioxides (140, n = 2) have been obtained by an intramolecular Wadsworth-Emmons reaction of the ketophosphonates (139) derived from 5-chloro-2-pentanone ethyleneacetal and the α-mercaptoalkylphosphonates (138).[71]



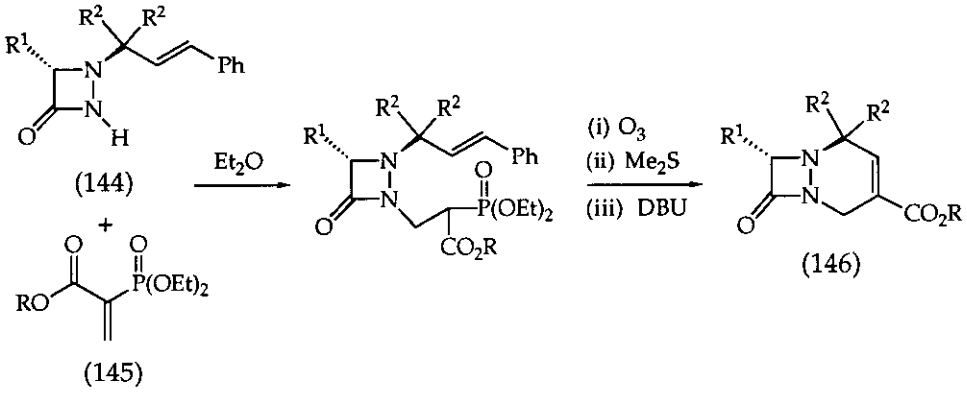
Reagents: (i) NaOEt, EtOH; (ii) n = 1, $NaIO_4$, $(Me)_2CO$, H_2O or n = 2, *m*CPBA, $CHCl_3$; (iii) H_3O^+; (iv) BuLi, THF.

2-Substituted 4*H*[1]benzothiopyran-4-ones (143) result from the reaction of *S*-acyl(aroyl)thiosalicylic acids with *N*-phenyl(triphenylphosphoranylidene) ethenimine. It is likely that the reaction proceeds *via* the phosphoranes (142) which arise by the loss of phenyl isocyanate from the initial adduct (141). Evidence for the process includes trapping the liberated phenyl isocyanate as a carbamate when ethanol was introduced into the reaction media. The rate of formation of the products was greatly influenced by the electronic character of the thioester carbonyl group, with electron withdrawing substituents enhancing the intramolecular cyclisation step.[72]



2.3.4 Rings Containing More Than One Heteroatom

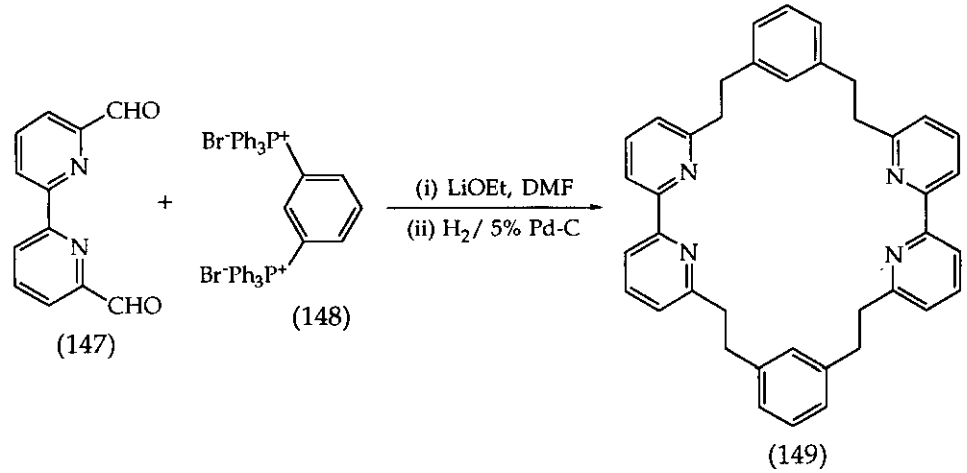
The diazeto[1,2-*a*]pyridazine ring system (146) has been obtained from a three step sequence initiated by Michael addition of the diazetidinone (144) to the vinyl phosphonate (145). Ozonolysis of the styryl function generates the aldehyde which is cyclised directly to (146) on treatment with DBU.[73]



2.4 Large Rings

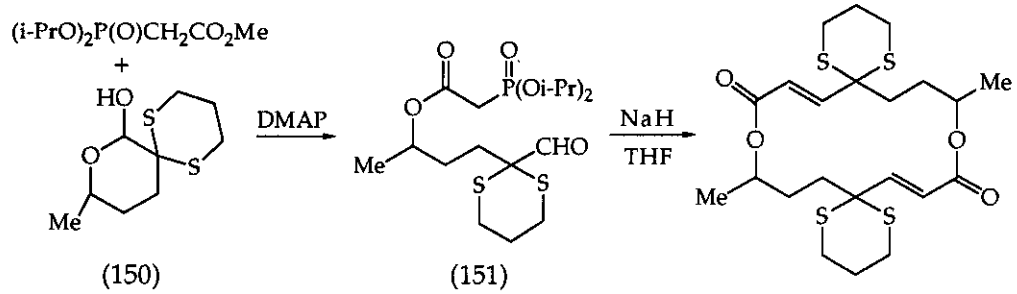
There are very few examples of the synthesis of large heterocyclic rings *via* an intramolecular Wittig, Horner or Wadsworth-Emmons reaction, although an early review on the bis-Wittig reaction includes the synthesis of some heterocyclic rings ranging in size from 5 to 18 atoms.[74]

More recently, bis-Wittig methodology has been employed to obtain the 26-membered pyridinophane (149), through the lithium ethoxide catalysed union of the bipyridinecarboxaldehyde (147) with the bis[(triphenyl)phosphonium bromide] (148) and subsequent hydrogenation.[75]



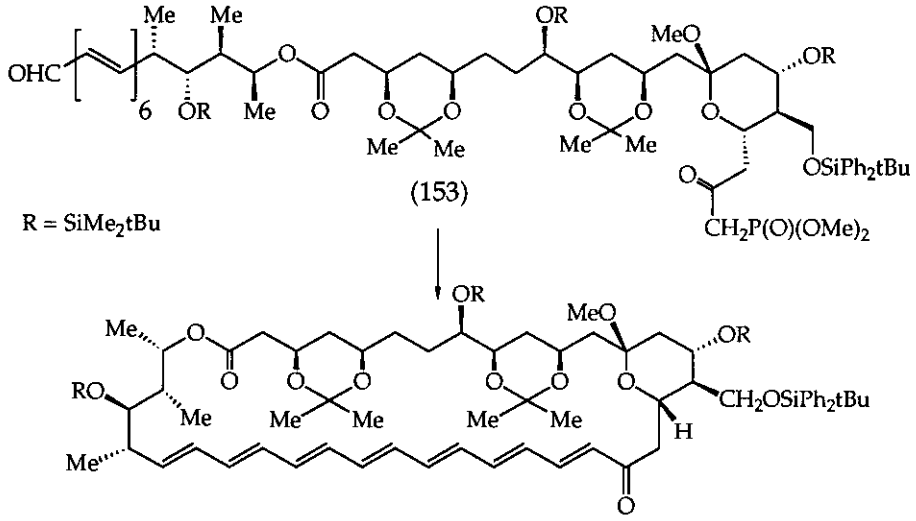
The synthesis of macrorings has attracted considerable attention and although not normally classed as heterocycles the following examples of lactone ring syntheses have been included to illustrate the

versatility of the Wadsworth-Emmons and Wittig reactions. Indeed, the intramolecular Wadsworth-Emmons reaction has been described as the most powerful method for the construction of macrocycles.[76] Base promoted dimerisation of the phosphono aldehyde (151) derived from ester exchange of the phosphonoaceate with the hemiacetal (150) afforded the 16-membered bis-lactone (152).[77]



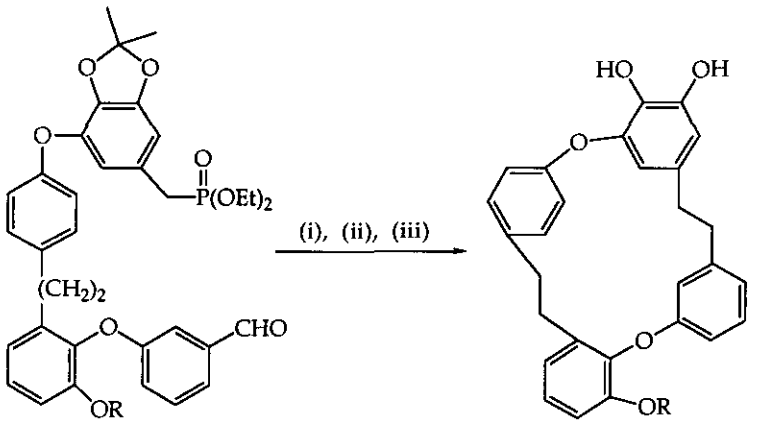
(150) (151) (152)

The key step in Nicolaou's synthesis of amphotericin B, cyclisation of the polyene (153) to the 38-membered cyclic product (154), was accomplished by an intramolecular Wadsworth-Emmons reaction carried out at high dilution using either DBU/LiCl in acetonitrile or K_2CO_3/18-crown-6 in toluene as the basic reagent system .[78]



(153) (154)

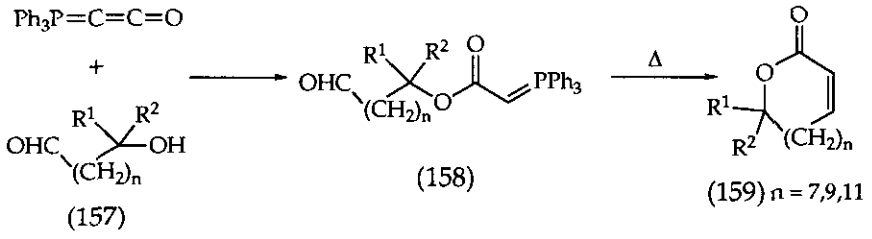
The synthesis of the macrocyclic ethers marchantin A (156, R = H) and riccardin B, isolated from liverworts, has been accomplished using intramolecular Wadsworth-Emmons methodology. The cyclisation step was shown to be markedly dependent on the concentration of the reactant, with the lower concentration giving 156 as a result of intramolecular cyclisation of the phosponate (155), whilst higher concentrations facilitated an intermolecular reaction followed by ring closure to a 36-membered product.[79]



(155) (156)

Reagents: (i) tBuOK, DMF, 1.4 mmol; (ii) H_2/ 5% Pd-C; (iii) HCl

Ring closure to give macrocyclic lactones (159) has also been achieved by a Wittig reaction of (ω-oxoalkoxy)carbonylmethylenetriphenylphosphoranes (158).[80] These ylides were conveniently obtained by the addition of an ω-hydroxy aldehyde (157) or ketal to triphenylphosphoranylidene ketene generated from methoxycarbonylmethylenetriphenylphosphorane and sodamide.



3 CONCLUSION

The variety of ylides and carbanions readily accessible from a range of phosphorus based substrates, together with the reactivity they show towards a carbonyl functionality in many different environments enable many heterocyclic systems to be synthesised by intramolecular variations of the Wittig, Horner and Wadsworth-Emmons reactions. These approaches are particularly valuable for the synthesis of 5- and 6- membered rings containing N, O and S, but have considerable potential for the formation of larger heterocycles.

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