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REVIEW

α-Chlorocarbonyl Compounds

—— Their Synthesis and Applications ——

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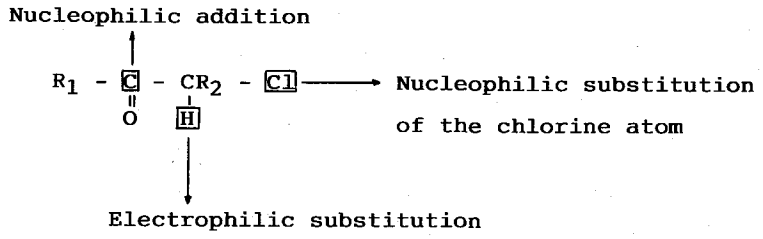
1. Introduction

α-Chlorocarbonyl compounds are very useful starting materials for indutrial scale production of various agrochemicals, pharmaceuticals, dyestuffs and polymers because of their highly reactive multifunctional character through the symergism of carbonyl group and chlorine atom. Their chemical reactions can basically be classified as shown in Scheme 1.

Scheme 1



R_1, R_2 = low alkyl, H, CO_2R, etc.

R = alkyl

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(a) Electrophilic substitution of hydrogen

The hydrogen atom is strongly activated by the inductive effect of the carbonyl group as well as the chlorine atom and is very susceptible to an electrophilic substitution.

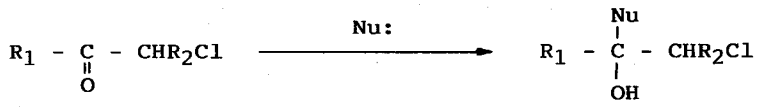
(b) Nucleophilic substitution of the chlorine atom

The chlorine atom can be replaced quite readily by nucleophilic agents because of the strong inductive effect of the carbonyl group.

(c) Nucleophilic addition to the carbonyl group

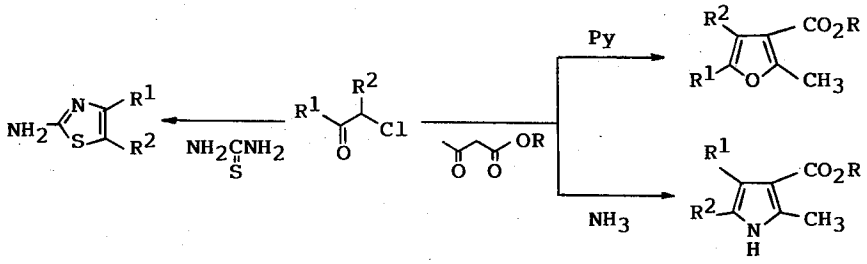
Additional positive polarization of the C atom of the carbonyl group takes place with the aid of α-chlorine atom leading to a facile addition of nucleophilic agents (Scheme 2).

Scheme 2



Nu: = Nucleophile

Scheme 3



Suitable combination of these reactions gives the convenient procedures for the preparation of various heterocyclic compounds containing oxygen, nitrogen, and sulfur as shown in Scheme 3. For instance, by combining a nucleophilic addition (c) with a nucleophilic substitution (b), 2-aminothiazoles can be synthesized from α-chlorocarbonyl compounds and thiourea. 2-Aminothiazoles are heavily used as key intermediates for sulfur drugs and dyestuffs. Furans and pyrroles are also obtainable by combining two reactions of α-chlorocarbonyl compounds, which are known as Feist-Benary Synthesis[1),2)]. Those are especially useful starting materials for pharmaceutical and agrochemical synthesis.

A great number of α-chlorocarbonyl compounds, therefore, have been synthesized so far on both laboratory and industrial scales. Among them α-chlorocarbonyl compounds having two, three, and four C units have been mainly industrialized as important intermediates because multiple uses can be expected. In a practical manner, they have mostly used by synthetic chemists for the introduction of functionalized C_2, C_3 and C_4 units into various sorts of organic compounds. Essntial

industrially available C_2, C_3 and C_4 α–chlorocarbonyl compounds are as follows:

C_2: Chloracetaldehydes
Chloroacetic acid and its esters
C_3: Chlorinated acetones
Chloropropionic acid and its esters
C_4: Chlorinated acetoacetates
Chlorinated methyl ethyl ketone

Here we describe the synthetic method for the above α–chlorocarbonyl compounds together with their industrially important applications. We do not refer to acid derivatives which are simply used in synthesis just by chlorine substitution in many cases. This review article may give some clues for the development of synthetic studies of new active substances which have destinies to be synthesized on an industrial scale.

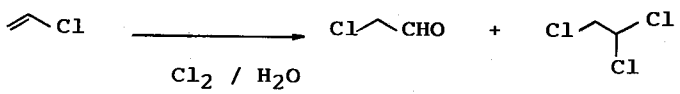
2. Chloroacetaldehydes

2-1 Preparation of chloroacetaldehyde

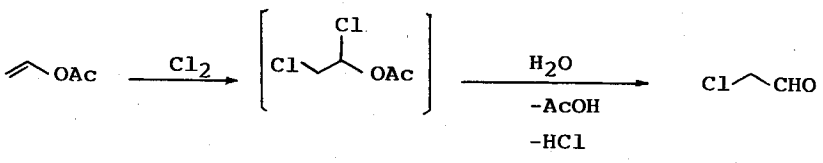
It has long been known that chloroacetaldehyde can be synthesized simply by the chlorination of acetaldehyde or para acetaldehyde. In accordance with this method however over–chlorinated acetaldehyde such as chloroacetaldehyde and chloral are generated as side products under most conditions. To avoid the generation of over–chlorinated acetaldehyde, the preparation way of chloroacetaldehyde from vinyl chloride has been proposed[3]. Simultaneous introduction of vinyl chloride and chlorine into water at ca. 20℃ can forms chloroacetaldehyde in a nearly quantitative yield if its concentration in the reaction solution is not allowed to rise sbove ca. 5 wt%. At a higher concentration however increasing amounts of 1,1,2–trichloroethane are formed. (Scheme 4)

This method is not suitable for industrial use because of the dilute solution required. It has therefore been found that chloroacetaldehyde aqueous solution can be obtained even in concentrated aqueous solution in a quantitative yield by the

Scheme 4



Scheme 5



reaction of vinyl acetate with chlorine[4)-6)]. This reaction is preferably carried out in two steps. Chlorine is first added to vinyl acetate at room temperature with cooling to form 1,2-dichloroethyl acetate, which is then hydrolyzed at 50-60℃. (Scheme 5)

2-2 Preparation of chloroacetaldehyde derivatives and their industrial uses

Chloroacetaldehyde is present in the form of the hydrate in aqueous solution. In case of anhydrous condition required in chemical reaction, water free chloroacetaldehyde must be prepared by removing the water by azeotropic distillation with chloroform, toluene[7)], or carbon tetrachloride[8)]. Further, after the preparation of water free chloroacetaldehyde, it must be used immediately because water free chloroacetaldehyde readily polymerizes to form cyclic or linear polyacetals. Some of chloroacetaldehyde derivatives therefore have been synthesized as synthetic equivalents of chloroacetaldehyde according to respective requirment. The derivatives can be classified into the following four groups based on reaction pattern.

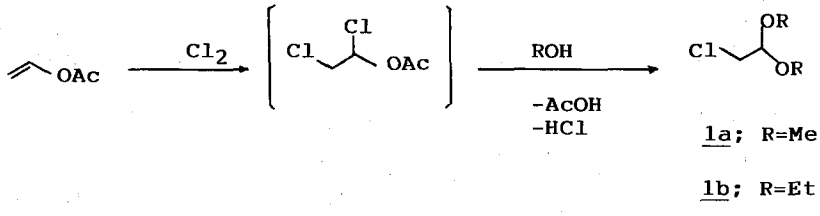
2-2-1 Derivatives by reaction of the aldehyde group
2-2-2 Derivatives by reaction of the chloromethyl group
2-2-3 Open-chain derivatives by reaction of the aldehyde and the chloromethyl groups
2-2-4 Heterocyclic derivatives by reaction of the aldehyde and the chloromethyl groups

2-2-1 Derivatives by reaction of the aldehyde group

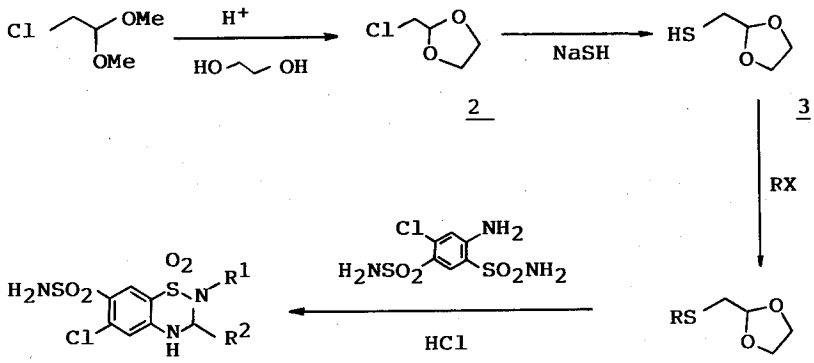
Chloroacetaldehyde dialkylacetals (**1a**; R=Me, **1b**; R=Et) have been synthesized as synthetic equivalents of chloroacetaldehyde which have greater chemical stability than water free chloroacetaldehyde and can be used under anhydrous condition. It has been reported that the reaction of vinyl chloride with chlorine in ethanol gives **1b** as a major product by controlling temperature carefully[9)]. But small amounts of 1,1,2-trichloroethane are formed under any condition. To overcome the problem for the side product, the procedure using vinyl acetate as a starting material has been taken up for industrial production. Thus, without any side product, **1a** and **1b** can be produced by the reaction of vinylacetate with chlorine in corresponding alcohol solution[10)]. (Scheme 6)

Diethylacetal and dimethylacetal are readily deacetalized even under weak acidic condition to form corresponding aldehyde. More stable cyclic acetales are re-

Scheme 6



Scheme 7



5 R^1= $CH_2SCH_2CF_3$, R^2= H Epitizide

R^1= $CH_2SCH_2CH{=}CH_2$, R^2= H Altizide

R^1= CH_2SCH_2Ph, R^2= H Hydrobentizide

R^1= $CH_2SCH_2CF_3$, R^2= Me Polythazide

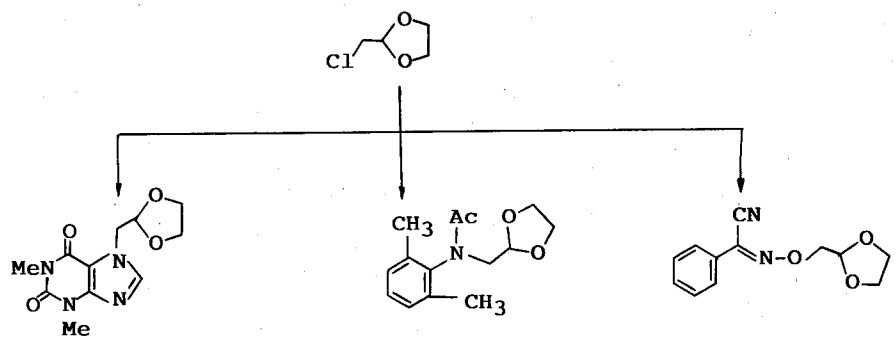
R^1= $CH_2SCH_2CH{=}CH_2$, R^2= Me Methylthiazide

4 R= CH_2CF_3

R= $CH_2CH{=}CH_2$

R= CH_2Ph

Scheme 8



Doxophylline 6 VEL-5052 7 CGA-92194 8

commendable in case that the protection of aldehyde group is required during several reaction steps including acidic reaction condition. 2-chloromethyl-1,3-dioxolane (**2**) has been synthesized for this purpose from **1a** and ethylene glycol under acidic condition. For example 2-mercaptomethyl-1,3-dioxolane (**3**) possessing acidic mercapto group can be prepared from **2**. **3** is a key intermediate for several types of 2-alkylthiomethyl-1,3-dioxolane (**4**) which are converted into diuretic 1,2,4-benzothiadiazine derivatives (**5**)[11]. They are highly effective, are quickly

resorbed by the organism and relatively non-toxic. (Scheme 7)

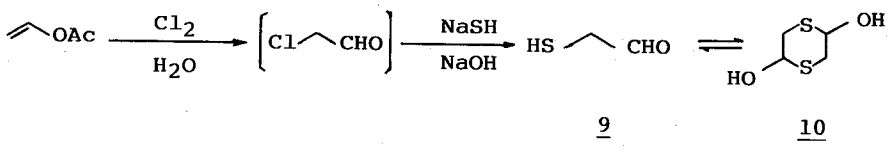
In addition there are some examples for characteristic use of **2** to improve the bioavailabilities or to reduce the toxicities of some known active substances by the introduction of 1,3-dioxolane group into the molecules. Xanthine compounds are widely used clinically as vasodilatator. Doxophylline (**6**), derived from **2**, is known as a drug which has much less by-effect than its analogues[12]. VEL-5051 (**7**) and CGA-92194 (**8**) have been developed as effective herbicides[13)-14)]. Those possess 1,3-dioxolane group introduced using **2**. (Scheme 8)

2-2-2 Derivative by reaction of the chlomethyl group.

Mercaptoacetaldehyde (**9**) is present in the form of the dimer as a stable 6-membered ring, 2,5-dihydroxy-1,4-dithiane (**10**) so that it can be handled easily under anhydrous reaction conditions in contrast to chloroacetaldehyde. The synthetic route from vinylacetate has been developed for economical production[15]. The reaction of vinylacetate with chlorine in aqueous solution gives chloroacetaldehyde, which provides **10** without isolation of chloroacetaldehyde by treatment with sodium sulfide. (Scheme 9)

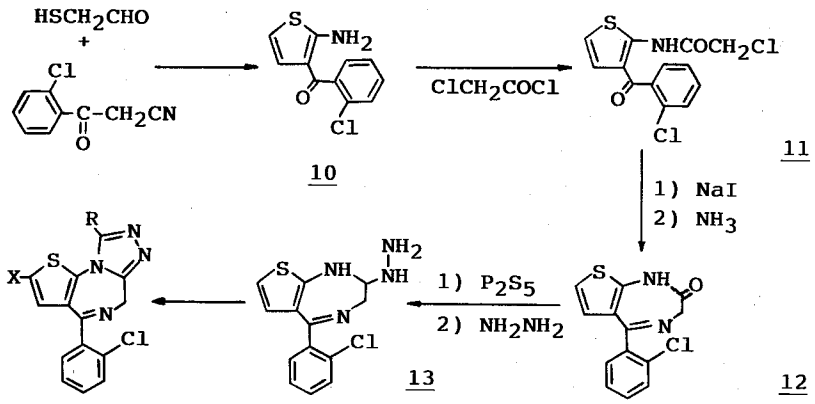
9 is a useful intermediate for synthesizing some tranquilizers which have three

Scheme 9



9 10

Scheme 10



14 Brotizolam (R=CH_3, X=Br)

15 Ciclotizolam (R=C_6H_{11}, X=H)

rings system containing thiophene ring such as Brotizolam (**14**)[16] and Ciclotizolam (**15**)[17]. **9** reacts with acylacetonitrile to afford 2-amino-3-acylthiophene (**10**). The three rings system can be constructed from **10** by the clue of amino functionality. (Scheme 10)

2-2-3 Open-chain derivatives by reaction of the aldehyde and the chloromethyl groups

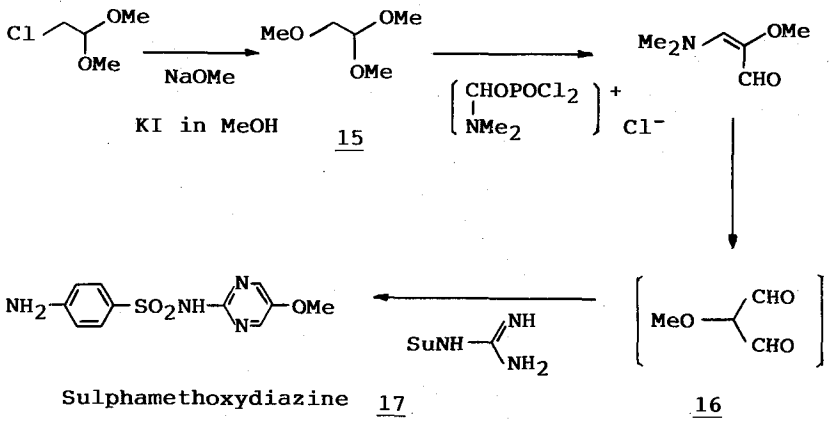
Chloroacetaldehyde dimethylacetal (**2**) combines with various alcohols to give alkoxyacetaldehyde dimethylacetal. In the simplest example, the reaction of **2** with sodium methoxide in the presence of potassium iodide in methanol gives 1,2,2-trimethoxyethane (**15**)[18]. A formylation reaction developed by Vilsmeier can be used to prepare methoxylated malonic dialdehyde (**16**) from **15**. **16** is converted into sulfonamide sulphamethoxydiazine (**17**)[19]. **17** has an especially favourable elimination half-life period, which enables it to be used in a 24 hour cycle. (Scheme 11)

A number of liquid crystal compounds based on 5-alkoxy substituted pyrimidines have recently been prepared. For example, it was proposed that 2-(alkylthiophenyl)-5-alkoxy pyrimidines (**23**) are the useful components for ferroelectric liquid crystals.[20] **23** can be derived from **2** through the same synthetic method as sulphamethoxydiazine's. (Scheme 12)

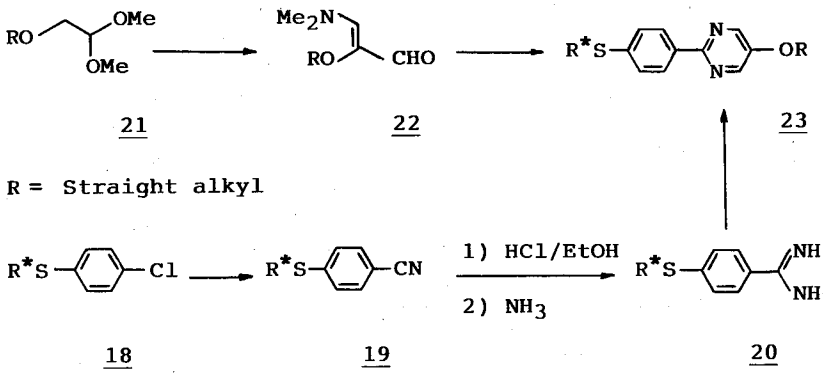
Another important example for use of **15** is the synthesis of the herbicide 1,3-dioxepinen (**24**) by acetal exchange reaction. Under acidic condition, cis-pent-2-en-1,4-diol is readily cyclized with **15** to afford **24**[21]. (Scheme 13)

Under pressure at 20 atm, **1a** reacts with methylamine to afford N-methylaminoacetaldehyde dimethylacetal (**25**), although chlomethyl group of **1a** is much less reactive than that of chloroacetaldehyde due to the acetal protection of carbonyl group. **25** is a useful intermediate as a synthetic equivalent of N-methylaminoacetaldehyde for making N-methyl heterochyles since N-methylaminoacetaldehyde is not obtainable due to the high nuclephilicity of the secondary amine to lead self-con-

Scheme 11

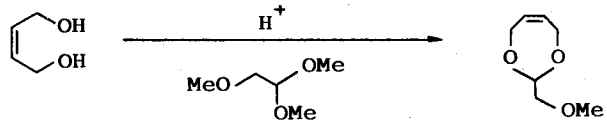


Scheme 12



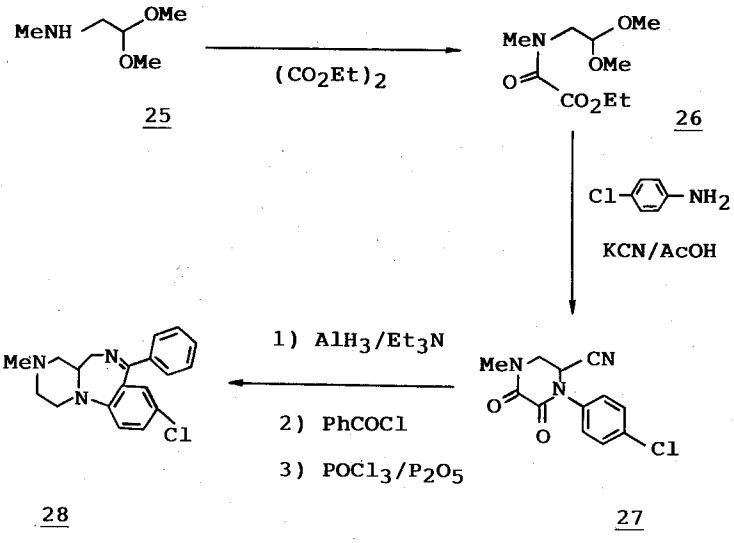
R* = Alkyl group possessing chiral carbon

Scheme 13

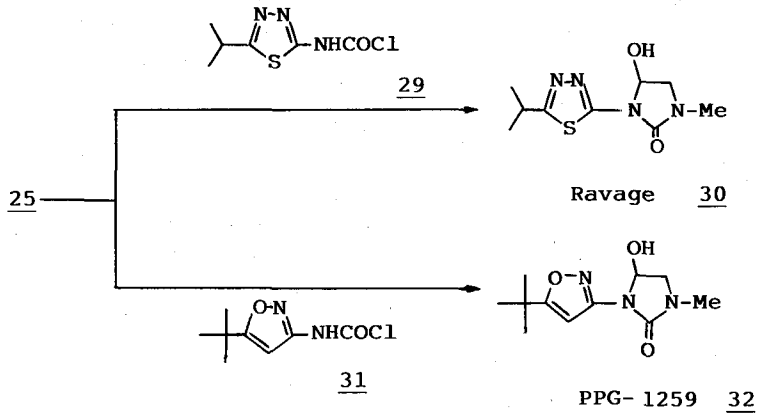


24 1,3-Dioxepinen

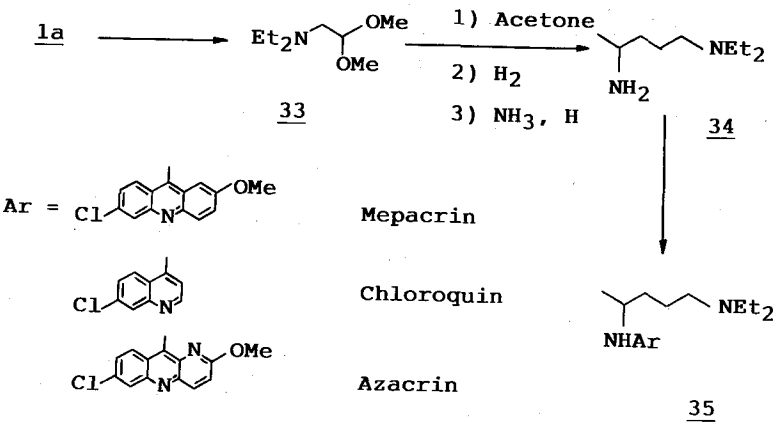
Scheme 14



Scheme 15



Scheme 16



densation. Amide ester (**26**) derived from **25** reacts with p-chloroaniline and potassium cyanide to form N-methyl heterocycle (**27**). **27** can be converted into **28**, which is claimed to be useful as a tranqulizer drug[22]. (Scheme 14)

Ravage (**30**) is well-known herbicide possessing N-methyl diazolone ring which is effective against broad-leaved weeds such as cane sugar, pineapple and maize plantations[23]. **30** is currently synthesized by cyclization of 2-aminothiadiazole derivative (**29**) with **25**. Similar herbicidal diazolone, PPG-1259 (**32**), has also been prepared with the same synthetic method[24]. (Scheme 15) This is highly effectve against dicotyldenous weeds in corn, millet and can sugar fields.

Another industrially important use of **25** is the modification of starch. **25** can be used to prepare starch ether containing methylamino group. This increases the wet strength of paper and card, and is also used in starch based adhesives and coating

compositions[25].

As well as **25** under pressure diethylamine reacts with **1a** to give the tertially amine, diethylaminoacetaldehyde dimethylacetal (**33**), which is converted into 2-amino-5-diethylaminopentane (**34**) via acetone condensation/ reduction/ reductive amination sequence[26]. **34** is useful as a side chain of antimaralia, Mepacrine[27], and its analogues. (Socheme 16)

2-2-4 Heterocyclic derivatives by reaction of the aldehyde and the chloromethyl groups

Among numerous heterocycles obtained from chloroacetaldehyde, 2-aminothiazole (**36**) is of special interest in the synthesis of dyestuffs and sulpha-drugs. It has long been known that **36** can be synthesized from chloroacetaldehyde. For economical production, however, the synthetic method has been improved starting from vinylacetate[28]. Thus, crude **36** (purity 94 %) is synthesized by the reaction of thiourea with 1,2-dichloro-1-acetoxyethane, prepared from vinylacetate. The crude **36** is purified by the distillation in the presence of 0.1 wt % of H_3BO_3 to give **36** with purity at 99.4 %. (Scheme 17)

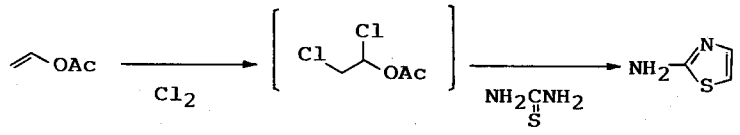
The chemotherapeutics possessing thiazole ring are of great importance. Sulphathiazole (**37**) prepared from **36** is now only used in veterinary medicine. Derivatives such as succinly (**38**), phthaloyl (**39**), maleyl (**40**), and formosulphathiazole (**41**) are, however, used in human medicine where they are used to treat infections of the stomach and intestinal tract because of their sparing solubility and low resorption[29)-33]. (Scheme 18)

Besed on **36**, numerous number of dyestuffs have been developed. **36** can be diazotized and coupled with aromatic amines or aromatic alcohols to prepare 2-thiazolylazo dyes[34] and basic thiazolylazo dyes[35]. Nitrothiazolylazo dyes can be obtained in a similar manner from 2-amino-5-nitrothiazole[36]. **36** itself is used as a coupling agent to prepare 5-(2-aminothiazolyl)azo dyes[37].

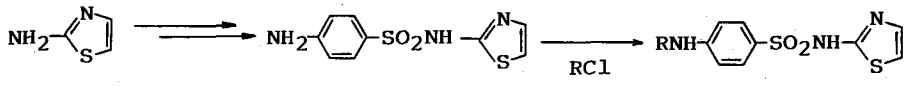
Chloroacetaldehyde reacts with nucleophilic amines and carbonyl compounds to afford various pyrroles. By the use of this reaction, many drugs have been synthesized from chloroacetaldehyde. One of the most important uses is the synthesis of tolmetine (**44**) which has outstanding antiphlogistic properties. The pyrrole ring (**42**) is constructed from chloroacetaldehyde, acetone dicarboxylic acid and methylamine[38]. The decarboxylation of **42** provides N-methyl-2-pyrrolyl acetic acid (**43**), which is acylated to give **44**. (Scheme 19)

Without nucleophilic amine, chloroacetaldehyde reacts with β-ketoesters to

Scheme 17

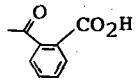


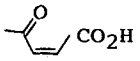
Scheme 18

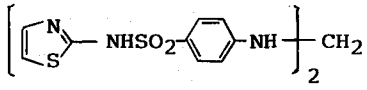


Sulphathiazole 37

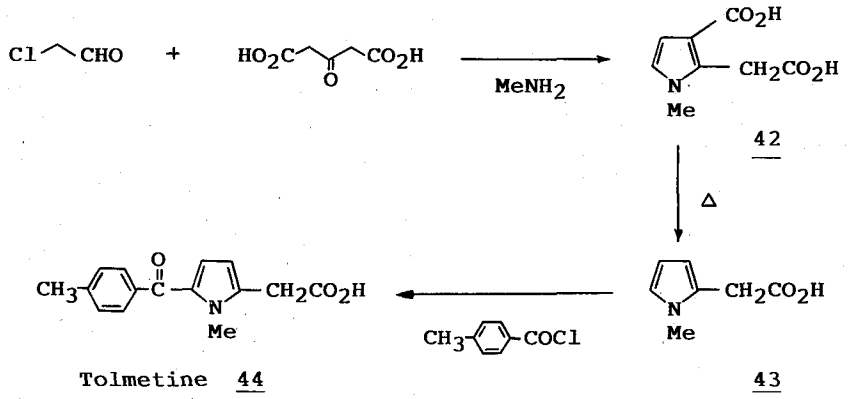
R = $-COCH_2CH_2CO_2H$ Succinylsulphathazole 38

R =  Phthaloylsulphathiazole 39

R =  Maleylsulphathazole 40

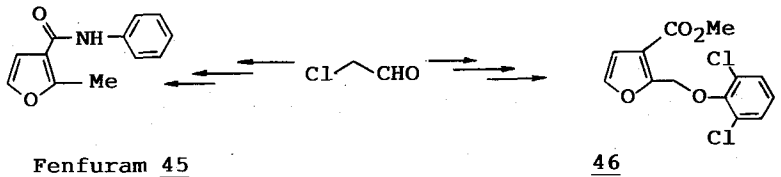
 Formosulphathiazole 41

Scheme 19



Tolmetine 44

Scheme 20



Fenfuram 45

46

afford various furanes (Feist–Benary reaction). The fungicide fenfuram (**45**)[39] and the herbicide (**46**)[40] have been synthesized based on this reaction. (Scheme 20)

2-3 Preparation of dichloroacetaldehyde and its main uses

Dichloroacetaldehyde (**47**) is a useful synthon for heterocyclic chemistry and an efficient symmetric and asymmetric crosslinking agent for macromolecules due to its two adjacent carbonyl and carbonyl equivalent functionalities. Further, **47** is also useful for the synthesis of pharmaceuticals and agrochemicals possessing dichloromethyl group. Therefore, much attention has been directed to find the industrial synthetic method for **47**.

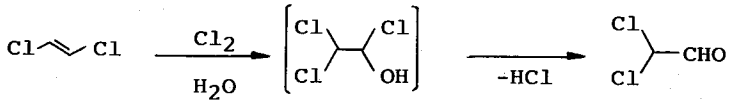
It has been reported that **47** is obtainable from the rectification tower of acetaldehyde passed over ferrous powder in the preparation of acetaldehyde by the oxidation of ethylene with air (Wacker process)[41]. On the other hand, the direct synthesis of **47** has also been found starting from 1,2-dichloroethylene. **47** can be prepared without impurities such as chloral and monochloroacetaldehyde, by treating 1,2-dichloroethylene with chlorine at 0-20℃ in aqueous dioxane[42] or in water alone with vigorous mixing[43]. (Scheme 21)

Anhydrous **47** is an unstable compound and can be readily polymerized. Heating (ca. 150℃) is needed to decompose polymerized materials into **47**. Therefore, **47** is normally treated with the form of the monohydrate. In case of anhydrous **47** required, it can be obtained from the monohydrate by treating with sulfuric acid.

Condensation of **47** with ethylbenzene yields p,p′-diethyl-1,1-diphenyl-2,2-dichloroethane (**48**), which is known as the insecticide perthane. Cholorobenzene reacts similarly with **47** to give p,p′-dichloro-1,1-diphenyl-2,2-ddichloroethane named rothane (**49**), which is also used as an insecticide. (Scheme 22)

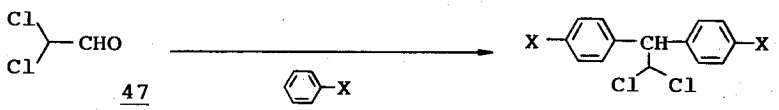
Trichloromethiazide (**51**), which has an excellent diuretic activity, also pos-

Scheme 21



47

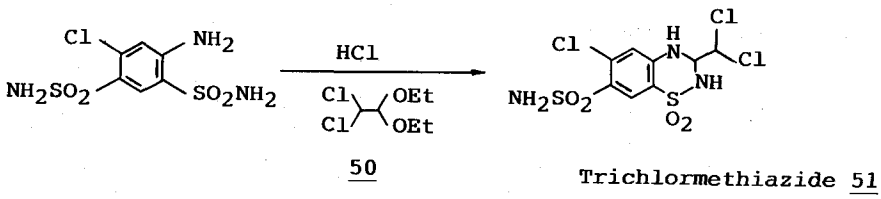
Scheme 22



X = Et, Perthane 48

X = Cl, Rothane 49

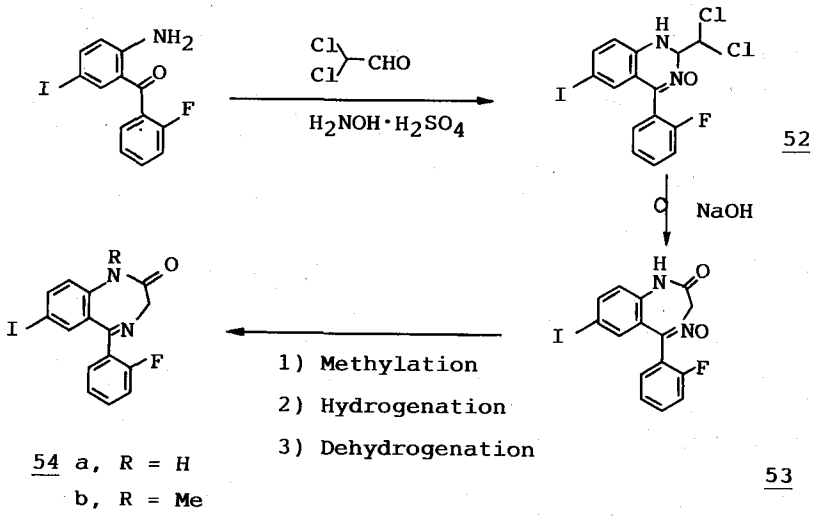
Scheme 23



50

Trichlormethiazide 51

Scheme 24



52

53

54 a, R = H
b, R = Me

sesses dichloromethyl group. **51** can be obtained by the condensation of 6-amino-4-chloro-1,3-diaminosulfonyl benzene with dichloroacetaldehyde diethylacetal (**50**), which is prepared from **45** and ethanol, in the presence of hydrogen chloride[44]. (Scheme 23)

The cyclization of 2-amino-2′-fluoro-5-iodobenzophenone with hydroxyamine sulfuric acid salt and **47** gives 2-dichloromethyl-4-(2-fluorophenyl)-1,2-dihydro-6-iodoquinazoline-3-oxide (**52**). In the presence of sodium hydroxide, **52** is rearranged to give 1,4-benzodiazepine-4-oxide (**53**), which is converted into 1,4-benzodiazepine derivatives (**54a** and **54b**) via methylation/hydrogenation/dehydrogenation sequence. **54a** and **54b** are used as sedatives, muscle relaxants, and anticonvulsants[45]. (Scheme 24)

Dichloroacetaldehyde polymers of high molecular weight are obtainable under essentially anhydrous conditions and in the presence of a catalyst comprising a Lewis acid or its organic complex at a temperature below 0 ℃[46]. These products have a polyoxymethylene (polyacetal) structure and more or less soluble in common organic solvents, depending on the degree of polymerization. The copolymers of chloral and dichloroacetaldehyde are also formed with organometallic compounds as

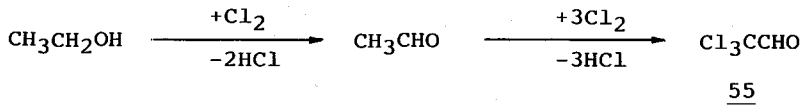
catalysts at low temperature, i, e., $<-40℃$[47]. It is well known that these polymers are fire-resistant materials and have an excellent thermal stability.

2-4 Preparation of trichloroacetaldehyde and its main uses

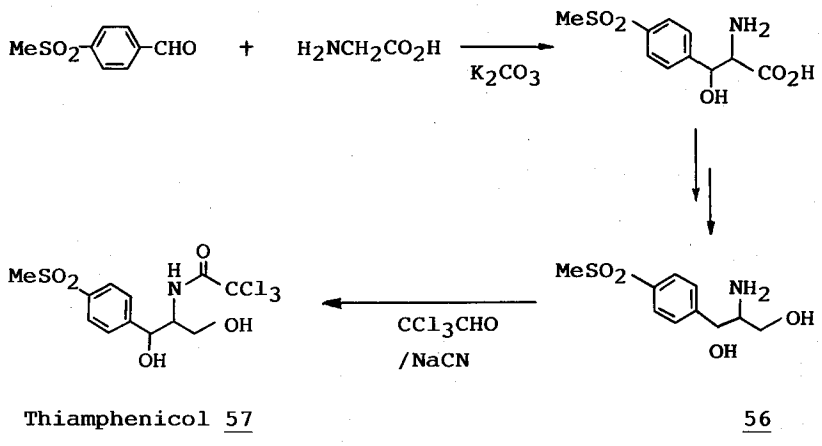
Trichloroacetaldehyde (**55**) was an important raw material in agricultural field in the 1960 s, but its importance has steadily declined since the use of the insecticide DDT derived from **55** and other chlorinated insecticides have been restricted. However a number of application possibilities of **55** for other fields such as pharmaceutical and polymer fields have still remained. In fact, **55** has often been taken up as a useful synthetic intermediate so far.

55 was first synthesized by J. von Liebig in 1832 by chlorination of ethanol. In this reaction chlorination of a mole of ethanol requires 4 mol of chlorine, with first serving to oxideze the ethanol to aldehyde. (Scheme 25) Since acetaldehyde is usually the more economical starting material than ethanol, nowadays, **55** is produced by the chlorination of acetaldehyde[48]. The reaction is carried out in hydrochloric acid in order to repress condensation and aldehyde-oxidation reactions and facilitate temperature control from 0 ℃ to 90℃ for the stepwise chlorination. After the reaction, **55** is distilled from reaction mixture as the hydrate. Anhydrous **55** is also obtainable by the distillation of the hydrate mixed with concentrated sulfuric acid.

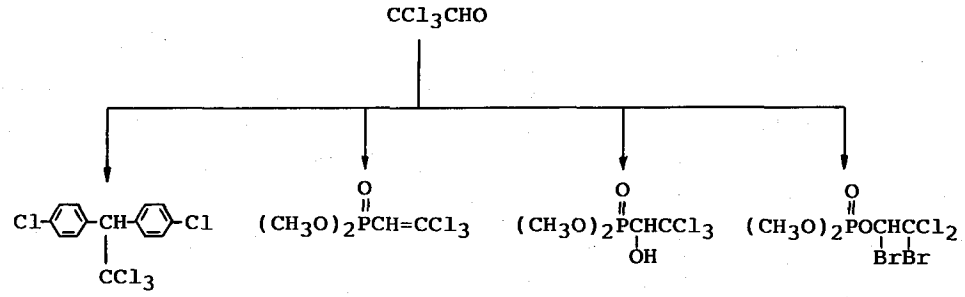
Scheme 25



Scheme 26



Scheme 27



DDT 58 Dichlorvos 59 Trichlorfon 60 Naled 61

In pharmaceutical field, the hydrate itself is known as an anticonvulsive, hypnotic drug. The hydrate is also used as a sedative by the combination with betain.

Thiamphenicol (**57**) is a useful antibiotic, and a synthetic route using **55** has been developed[49]. Thus, aminoalcohol (**56**), derived from 4-methylsulfonylbenzaldehyde and glycin, reacts with **55** in the presence of sodium cyanide to afford 2,2-dichloroacetylated product (**57**). (Scheme 26)

DDT (**58**) has not been so important insecticide any longer. However dichlorvos (**59**)[50], trichlorfon (**60**)[51] and naled (**61**)[52] are still important phosphate insecticides synthesized from **55**. Those three have insecticidal activities against mosquitoes, fruit flies, and flies on crop plants, respectively. (Scheme 27)

55 can be converted into an insoluble, non-flammable high polymer with the aid of anionic initiators such as lithium tert-butoxide[53], although it has not found commercial use.

3. Chlorinated acetones

Acetone, propionaldehyde, propionates, malonates can be chlorinated to afford C_3 α-chlorocarbonyl compounds generally. However only chlorinated acetones have been industrialized as versatile intermediates so far due to the limited application possibilities for other C_3 α-chlorocarbonyl compounds such as 2-chloropropionaldehyde.

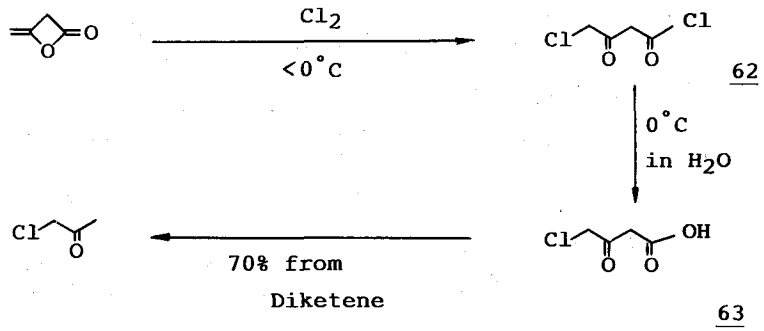
3-1 Monochloroacetone

Monochloroacetone is the simplest member of chlorinated acetone. Due to its simple feature and high reactivity, monochloroacetone offers a wide range of applications for the synthesis of drugs, pesticides, dyestuffs, etc.

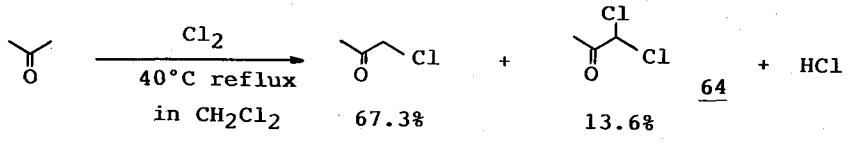
3-1-1 Preparation of monochloroacetone

Elemental chlorine and diketene react to form 4-chloroacetoacetyl chloride (**62**). At low temperatures, treatment of **62** with a stoichiometric amount of water is used to form 4-chloroacetoacetic acid (**63**), at elevated temperatures, decarboxy-

Scheme 28



Scheme 29



lation of **63** provides monochloroacetone[54]. (Scheme 28) This procedure is an excellent method for selective preparation of monochloroacetone.

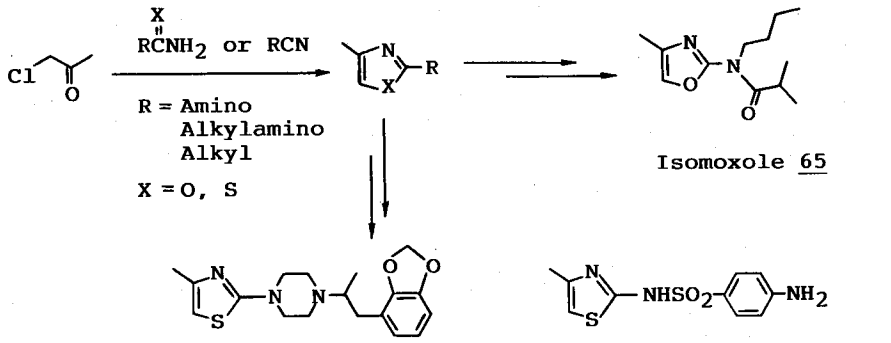
From economical point of view however monochloroacetone is now synthesized by chlorination of acetone in a continuous process. The example procedure is that acetone is refluxed in a five-plate distillation tower at 40℃ while bubbling with chlorine and adding methylene dichloride from the top of the tower to keep the overhead temperature at 39-40℃ for 4 hrs. to give a reaction mixture containing monochloroacetone (67.3%), 1,1-dichloroacetone (**64**) (13.6%) and no mesityl oxide and other condensation products[55)56)]. (Scheme 29)

3-1-2 Preparation of heterocyclic compounds and their uses

Monochloroacetone reacts with amides, ureas, thioamides, thioureas and nitriles to give 4-methyl substituted oxazoles and thiazoles which are especially used in pharmaceutical field, for example, in the synthesis of antiasthmatic isamoxole **65**[57], hypotensive podilfin **67**[58] and chemotherapeutic methylsulfathiazole **66**[59]. (Scheme 30) On the other hand, 5-methyl thiazoles are also obtainable from 2-chloropropionaldehyde or its dimethylacetal as a starting material instead of monochloro acetone. However the production for 2-chloropropionaldehyde has not yet been industrialized due to the lmitted applications[60].

The reaction of monochloroacetone with substituted salicyl aldehydes or o-hydroxyacetophenones affords 2-acetylbenzofuranes (**68**), which are useful as key heterobicyclic intermediates for the preparation of various pharmaceuticals possessing benzofurane skeleton. (Scheme 31) 2-Acetylbenzofurane (**68 a**) can be converted into ethylbenzofurane (**69**) by the reduction of acetyl group of **68 a** with

Scheme 30



Scheme 31

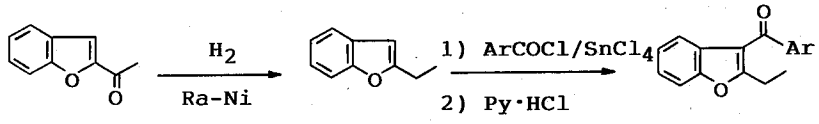
a; R^1 = H, R^2 = H

b; R^1 =  , R^2 = Me

c; R^1 = OMe, R^2 = H

68 a, b, c

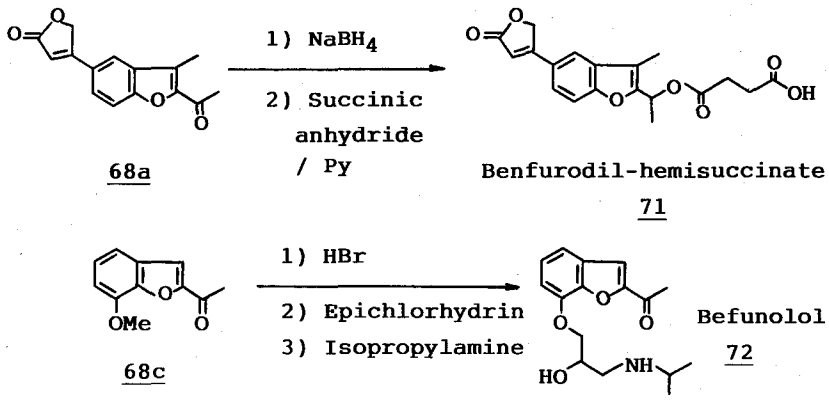
Scheme 32



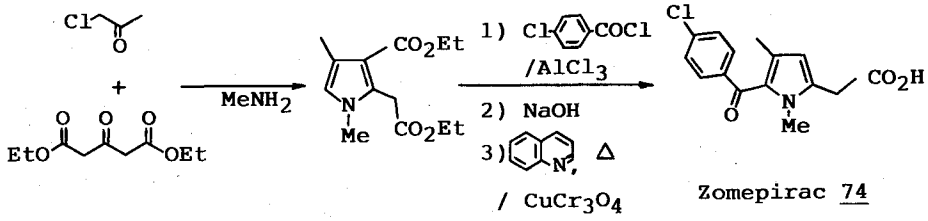
68a 69 70

70a;	Ar = 	Benzarone
70b;	Ar = 	Benziodarone
70c;	Ar = 	Benzbromarone

Scheme 33



Scheme 34

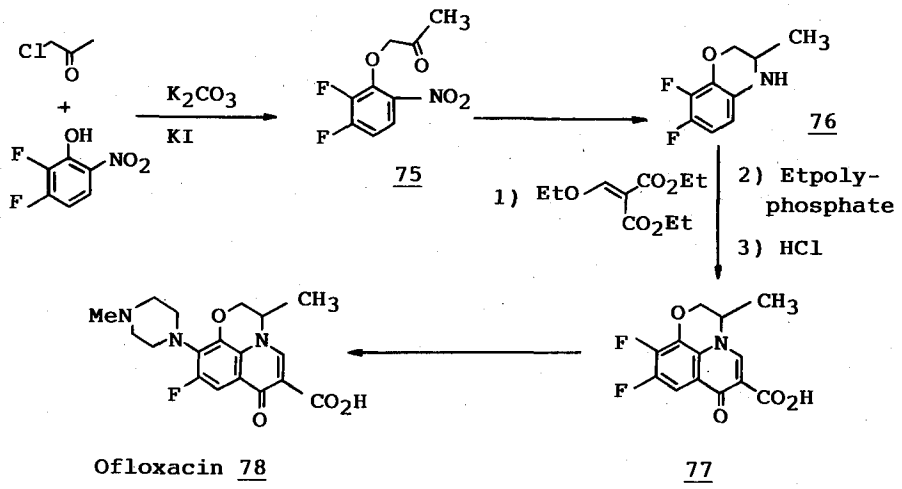


hydrogen in the presence of Raney nickel, **69** is used as a common intermediate for a series of benzofurane drug such as antihemorrhagic benzarone (**70 a**), coronary dilator benziodarone (**70 b**) and benzbromarone (**70 c**), which are prepared via acylation/demethylation sequence[61)62)]. (Scheme 32) Cardiotonic benfurodil-hemisuccinate (**71**)[63)] and β-blocker, befunolol (**72**)[64)] are also synthesized based on above-mentioned 2-acetylbenzofurane synthesis from **68 b** and **68 c** respectively. (Scheme 33)

It is well known that methyl substituted pyrrole or furane ring can be formed from monochloroacetone and β-ketoester under basic condition in accordance with Feist-Benary reaction[1)2)]. A typical example is the synthesis of analgesic zomepirac (**74**)[65)] as a strong pain-killing substance. Monochloroacetone reacts with acetone dicarboxylic acid ethyl ester and methylamine to give 4-methylpyrrole (**73**), which is converted into **74** via acylation/hydrolysis/decarboxylation (at 200℃ under basic condition) sequence. (Scheme 34)

The use of monochloroacetone for the preparation of ofloxacin (**78**) should be noted in particular because of a broad spectrum of antibacteria activity against gram-negative and gram-positive bacteria, and more effective than norfloxacin[66)]. 2-Hydroxy-3,4-difluoronitrophenol reacts with monochloroacetone in the presence of potassium carbonate and catalytic amount of potassium iodide to give acetonyl

Scheme 35



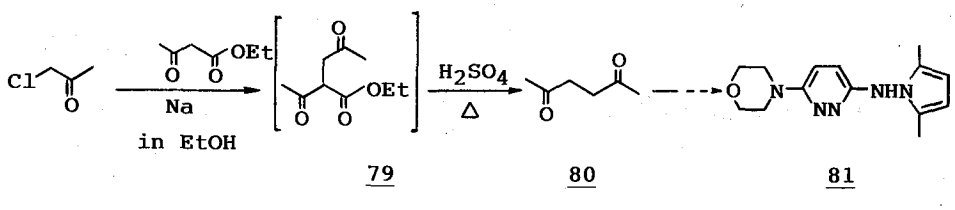
ether (**75**), which is reductively cyclized with hydrogen/Raney Nickel to form benzoxazine (**76**). **78** is synthesized from **76** with four reaction steps shown in scheme 35[67].

3-1-3 Preparation of 2,5-hexanedione and its uses

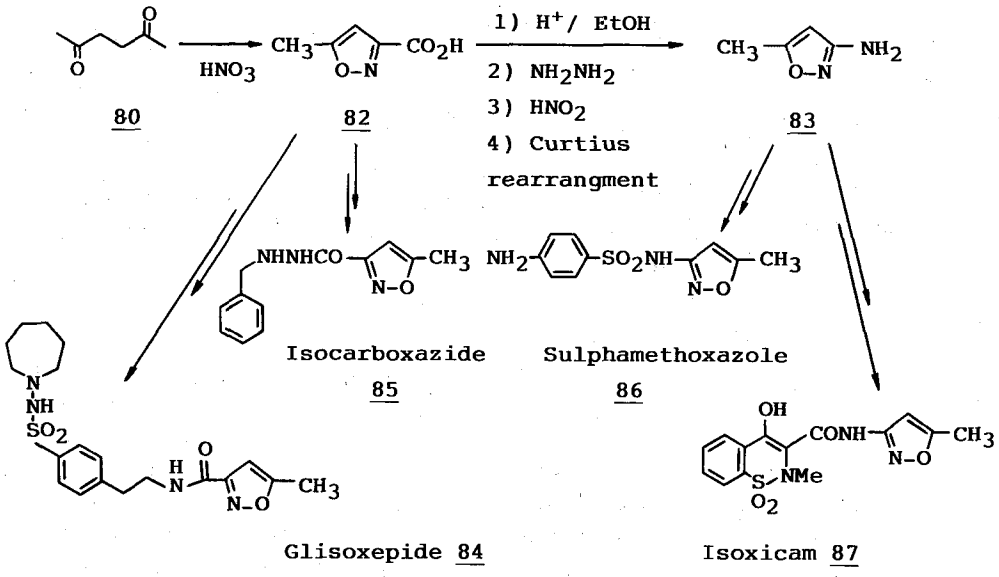
2,5-Hexanedione (**80**) has been prepared by acetonylation reaction of ethylacetoacetate with monochloroacetone in the presence of bases in ethanol, followed by saponification and decarboxylation with sulfuric acid[68]. (Scheme 36) **80** is a useful synthetic intermediate especially for heterocycles because of its symmetric bifunctional character. For example, 2,5-dimethylpyrroles are obtainable by condensation of **80** with amine or hydrazine derivatives. By using this reaction, pyridazinamine derivative (**81**) with antihypertensive activity has been synthesized[69].

An important role is played by 5-methyl-3-carboxy isoxazole (**82**), derived from 2,5-hexanedione, as well as 5-methyl-3-aminoisoxazole (**83**), which is obtained from **82** by curtius rearrangement involving acid azide degradation. Anti-diabetic glisoxepide (**84**)[70] and anti-depressive isocarboxazide (**85**)[71] are prepared from **82**. The synthesis of sulphamethoxazole (**86**)[72] and anti-rheumatic isoxicam[73] (**87**) are typical examples for use of **83**. (Scheme 37)

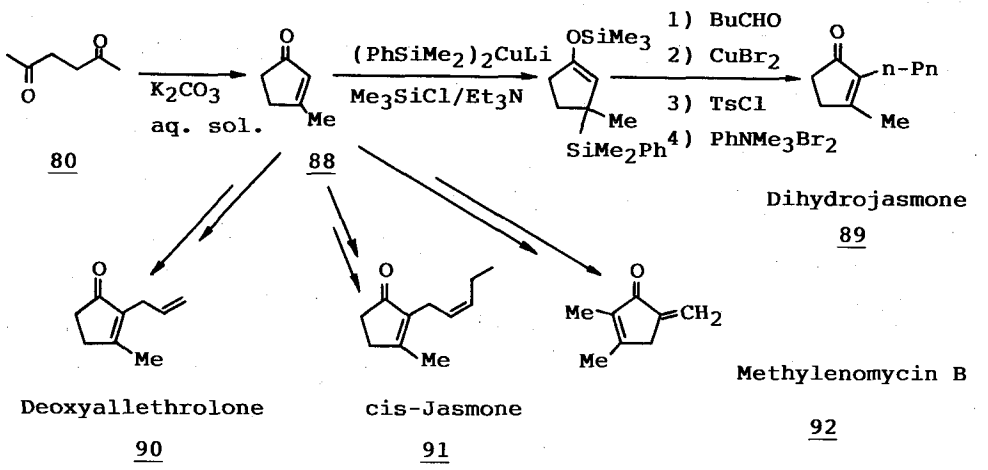
Scheme 36



Scheme 37

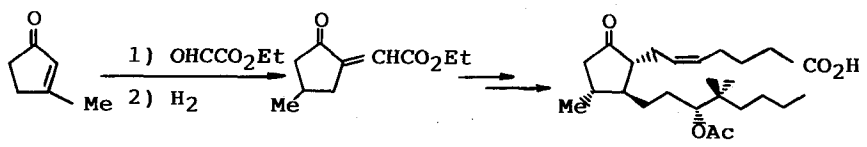


Scheme 38



80 is cyclized by refluxing in 1% aqueous potassium carbonate solution to obtain 3-methyl-2-cyclopentenone (88). By protecting α, β-unsaturation, 88 can be alkylated in α-position. Using this method, dihydrojasmone (89) is prepared by condensation / desilylation of silylated 88 with n-pentanal, followed by tosylation, hydrogenation, and deprotection[74]. (Scheme 38) The applications to the synthesis of deoxyallethrolone (90), cis-jasmone (91), and methylenomycin B (92) are also possible[75]. Besides, 88 has been converted into a useful prostaglandin intermediate

Scheme 39



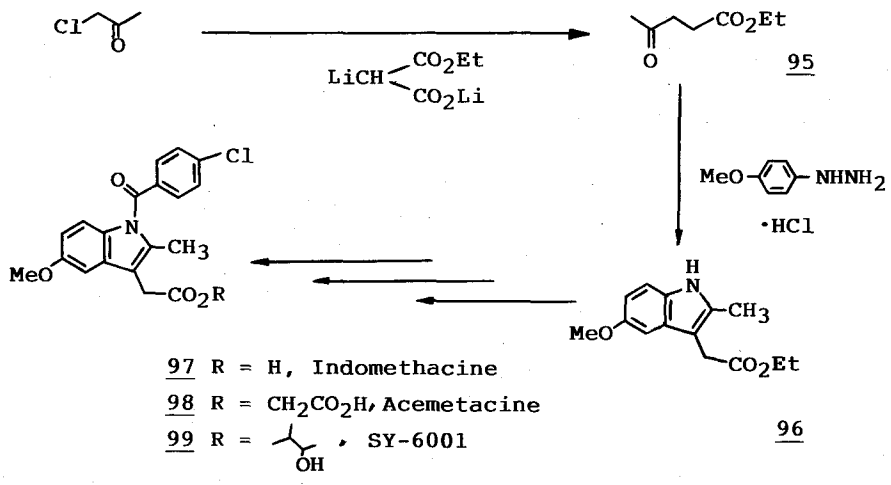
88 93 94

(**93**) via condensation/hydrogenation/dehydration sequence[76]. The synthetic prostanoid 15-(acetyloxy)-11, 16, 16-trimethyl-9-oxoprosta-5,13-dien-1-onic acid (**94**), derived from (**93**), has a significant fastric antisecretory activity[77]. (Scheme 39)

3-1-4 Preparation of ethyl 4-oxopentanoate and its uses

Ethyl 4-oxopentanoate (**95**)[78] has also been prepared from monochloroacetone as a key intermediate for the synthesis of indomethacin (**97**) and its analogue. Monochloroacetone reacts with dilithium salt of malonic acid monoethyl ester to give **95**. The mother skeleton of **97**, 2-methylindole-3-acetic acid, is readily formed by the reaction of diazonium salt with **95**[79]. By molecular modification of **97**, acemetacine (**98**) and SY-6001 (**99**) have also been synthesized. These compounds have proved to be highly effective antiphlogistic drugs for rheumatic diseases[79]. (Scheme 40)

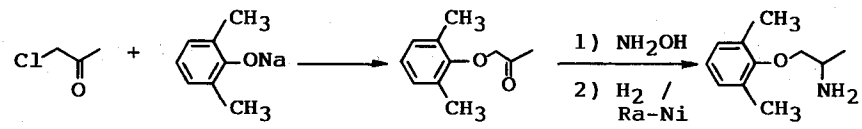
Scheme 40



3-1-5 Uses for 1-substituted isopropylamine derivatives

Various drougs possessing 1-substituted isopropylamine unit have been synthesized from monochloroacetone so far by the conversion of carbonyl group into amino group as a key reaction step[80)-83]. Among them, antiarrhythmic mexiletin

Scheme 41



Mexiletin

100

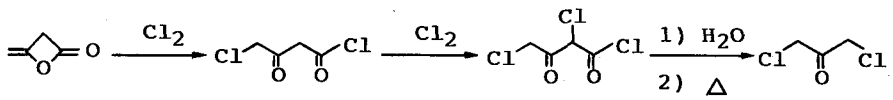
(**100**) should be noted as a practical use[80]. **100** is synthesized from monochloroacetone via etherification/oximation/reduction sequence as shown in Scheme 41.

3-2 1,3-Dichloroacetone

3-2-1 Preparation of 1,3-dichloroacetone

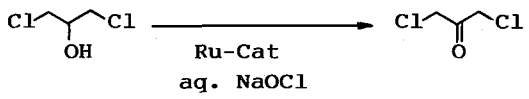
It has been reported that acetone-monochloroacetone mixture is chlorinated over iodine contiguous promoters to yield 1,3-dichloroacetone as a major product together with 1,1-dichloro acetone and 1,1,3-trichloroacetone[84]. The oxidation of epichlorhydrin by means of chlorine also gives 1,3-dichloroacetone[85]. Under any condition, however, 1,2,3-trichloropropane is generated as a side product in this reaction. A synthetic method starting from diketene seems to be partly superior to above mentioned methods because of its high selectivity. The reaction of diketene with chlorine at 10℃ gives 4-chloro acetoacethyl chloride (**101**), which reacts further with chlorine to afford 2,4-dichloroacetoacetyl chloride (**102**). Treatment of **102** without isolation with a stoichiometric amount of water at 0℃ gives 2,4-dichloroacetoacetic acid, which is decarboxylated in situ at elevated temperature to provide 1,3-dichloroacetone in yield of 77% from diketene[86]. (Scheme 42) On the other hand, recent patents have also decribed a process for selective preparation of 1,3-dichloroacetone by oxidation of 1,3-dichloroisopropanol[87, 88]. By the treatment

Scheme 42



101 102

Scheme 43

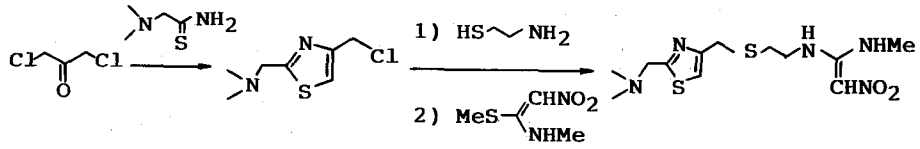


of 1,3-dichloroisopropanol with high valent Ruthenium compounds as catalysts under dropwise addition of aqueous sodium hypochloride at 20-30℃ and pH 1-2 to give 1,3-dichloroacetone in 96% yield. (Scheme 43)

3-2-2 Preparation of 4-Chloromethylthiazoles and their uses

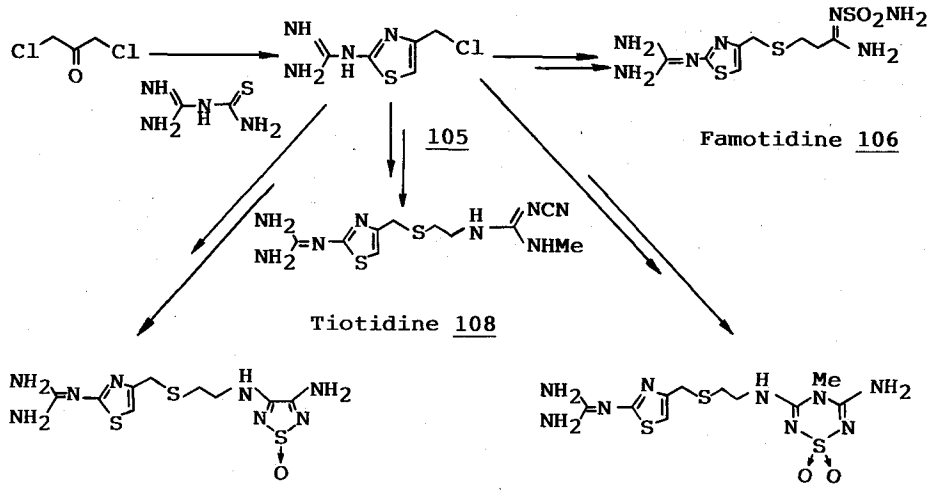
1,3-Dichloroacetone reacts various thioamides and thioureas to give 4-chloromethyl-2-substituted thiazoles[89)-92)], which are specially suited for the synthesis of numerous anti-ulcer drugs. For examples, 2-(dimethylaminomethyl)-4-chloromethylthiazole (**103**), obtained from N, N-dimethylaminothioacetamide and 1,3-dichloroacetone, can be converted into nizatidine (**104**) by the condensation with 2-aminoethanethiol and 1-methylthio-2-nitro-N-methylethyleneamine[93)]. (Scheme 44) **104** 100mg proved to be as potent as well known cimetidine 300mg in reducing pentagestrin-stimulated gastric acid output[94)]. 2-Guanidino-4-chloromethylthiazole (**105**), obtained from guanidinothiourea and 1,3-dichloroacetone, is a key intermedi-

Scheme 44



103 Nizatidine 104

Scheme 45



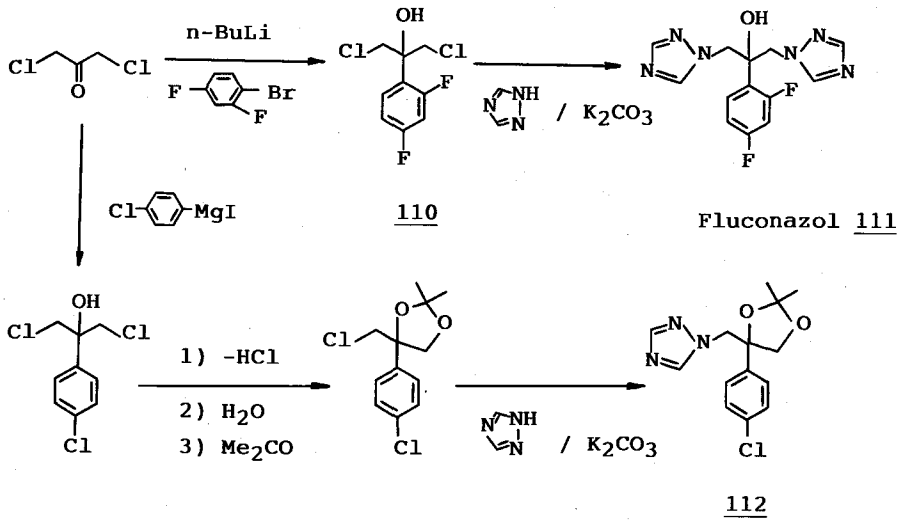
ate for preparation of some anti-ulcers, famotidine (**106**)[95], BL-6341A (**107**)[96], tiotidine (**108**)[92], and tuvatidine (**109**). (Scheme 45) Those are also noted for their strong, long-lasting inhibiting effect upon the secretion of gastric acid.

3-2-3 Preparation of 2-Aryl-1,3-isopropanols and their uses

Without substitution of chlorine atom, 1,3-dichloroacetone reacts with aryl halides in the presence of lithium or Grignard reagents to a afford 2-aryl-1,3-isopropanols exclusively due to the appropriate stability of chlorine atom.

By utilizing this reaction, fluconazol (**111**), which has fungicidal properties, can by synthesized. Thus, the reaction of 1,3-dichloroacetone with 2,4-difluoro-1-bromobenzene in the presence of n-butyl lithium gives isopropanol (**110**), which is treated with triazole to provide **111**[97]. As the same type of fungicide, **112** has been similarly prepared using Grignard reagent instead of lithium reagent as shown in Scheme 46[98].

Scheme 46



3-2-4 Ketal protection of 1,3-dichloroacetone

Because of the handling difficulty of 1,3-dichloroacetone by a strong irritating effect on the eyes, mucous membrances and skin and a mutagenic effect on microorganisims[99], its synthetic equivalents, such as 1,3-dichloroacetone dimethylketal, diethylketal and 2,2-bis (chloromethyl)-1,3-dioxolane have been developed. They are very useful in case that the reaction of 1,3-dichloroacetone can proceed in situ after deprotection of the ketals by means of acid catalyst. These ketals can be prepared by the reaction of 1,3-dichloroacetone with corresponding alcohols, methanol, ethanol and ethylene glycol in the presence of hydrochloric acid[100].

3-3 1,1-Dichloroacetone

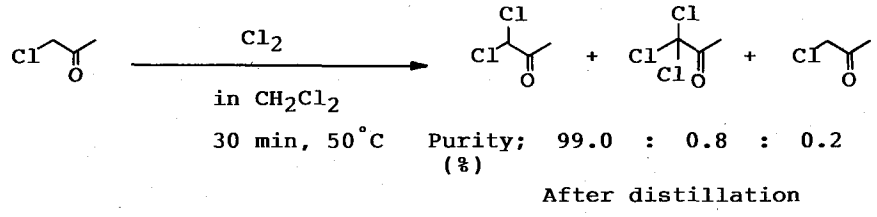
The dichlomethyl and the keto group are two reactive centers which make 1,1-dichloroacetone an interesting starting material for aromatic heterocycles. 1,1-dichloroacetone is also used for the preparation of 1,1,3-trichloroacetone and 1,1,1-trichloro acetone on industrial scale which are described in next section.

3-3-1 Preparation of 1,1-dichloroacetone and its uses

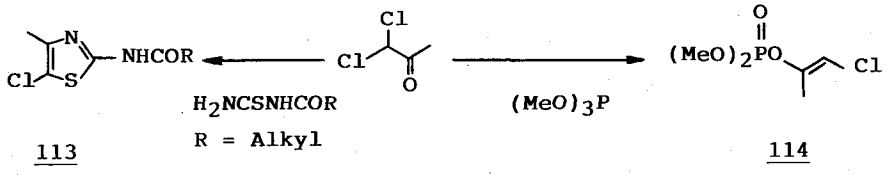
It has long been known that 1,1-dichloroacetone can be prepared by the chlorination of acetone with chlorine in water or methanol solvent. Due to the generation of hydrogen chloride, however, sticky side products are formed in those solvents. And they cause the purification difficulty of 1,1-dichloroacetone. It has therefore been proposed to use organic solvents inert to hydrogen chloride[101]. The treatment of monochloroacetone with chlorine at 50℃ in methylene chloride gives a mixture containing 70% 1,1-dichloroacetone, which can be distilled readily to give 1,1-dichloroacetone of 99.0% purity. (Scheme 47)

1,1-Dichloroacetone reacts with acylated thiourea to give 2-acylamino-5-chloro-4-methylthiazoles (**113**) which have herbicidal activities[102]. Chlorinated vinyl phosphates (**114**), have been synthesized from trialkyl phosphites and 1,1-dichloroacetone, are suitable as insect repellents[103]. (Scheme 48)

Scheme 47



Scheme 48



113 114

3-4 1,1,3-Trichloroacetone

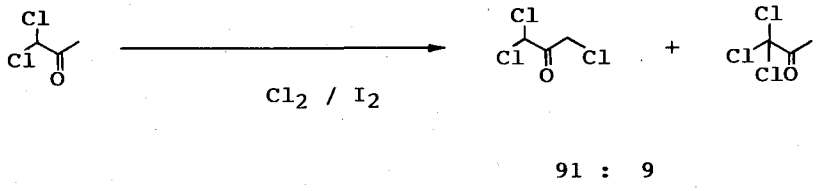
Due to the inductive effects of the chlorine atoms and the carbonyl group, the hydrogen atoms can be electrophilically substituted. In addition, the carbon atom of the carbonyl group is positively polarized by the three chlorine atoms in the alpha position so that nucleophilic addition reactions readily proceed. These chemical properties provide various application possibilities.

3-4-1 Preparation of 1,1,3-trichloroacetone

It has been reported that the chlorination of acetone controlling the feeding rate of chlorine (initially at a rate of 0.8-1 g/min. and at the end at a rate of 1.62 g/min. for 1 g acetone) in the presence of amine catalyst such as pyridine gives 1,1,3-trichloroacetone as a major product, which can be separated by the extraction with water[104] or aqueous acid, e. g. hydrochloric acid or sulfuric acid[105].

To inhibit formation of polychlorinated byproducts it has been proposed to add small amount of iodine during the chlorination for the preparation of 1,1,3-trichloroacetone. The reaction of 1,1-dichloroacetone 190.5 g with chlorine 63 g in the presence of iodine 6 g for 3.5 hrs. at 35℃ gives a mixture of 1,1-dichloroacetone (34%), 1,1,1-trichloroacetone (6.5%), 1,1,3-trichloroacetone (53%), tetrachloroacetone (0.7%) and 1,1-dichloro-3-iodoacetone (4%), distillation of which gives 1,1,3-trichloroacetone with the purity at 98%[106]. (Scheme 49)

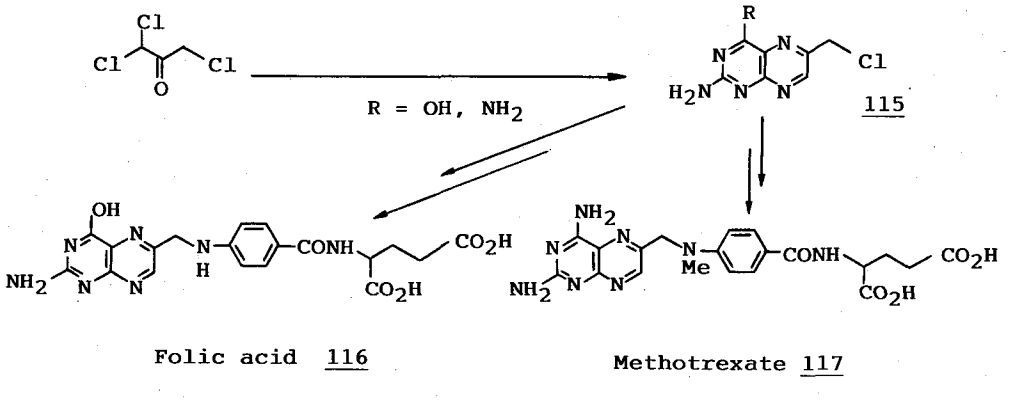
Scheme 49



3-4-2 Preparation of pteridines and their uses

2,4,5-Triamino pyrimidines are cyclocondensed with 1,1,3-trichloroacetone to afford pteridines (**115**)[107]. Folic acid (**116**) and methotrexate (**117**) are synthesized by the reaction of **115** with the Schotten-Baumann reaction products as shown in Scheme 50[108][109]. **116** is used as a vitamin nutrient that promotes growth in poultry and is also an essential nutrient for infants and lactating mothers. **117** is a cytostatic drug.

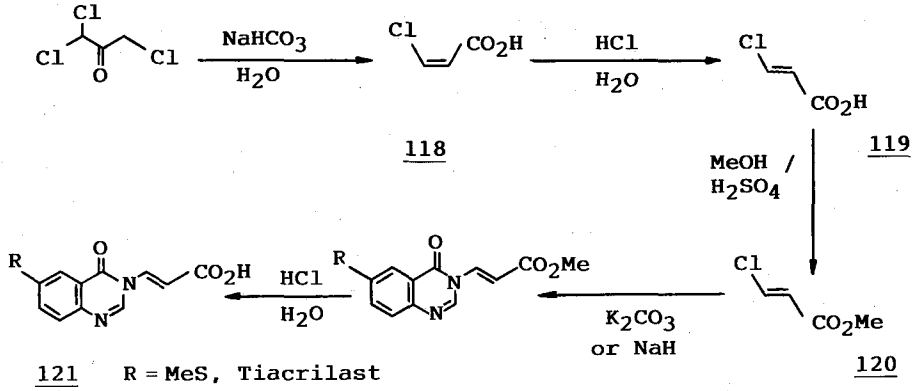
Scheme 50



3-4-3 Preparation of trans-β-chloroacrylic acid and their uses

The Favorskii rearrangement of 1,1,3-trichloroacetone in the presence of sodium bicarbonate in water gives cis-β-chloroacrylic acid (**118**). Isomerization of **118** with aqueous hydrochloric acid gives the E-isomer (**119**), which is converted in high yield to the corresponding methyl ester (**120**). **120** is an important intermediate for preparation of substituted (E)-3-(4-oxo-4H-quinazolin-3-yl)-propeoic acids (**121**) as a new series of antiallergy agents. For example, Tiacrilast has been prepared through the route described in Scheme 51[110].

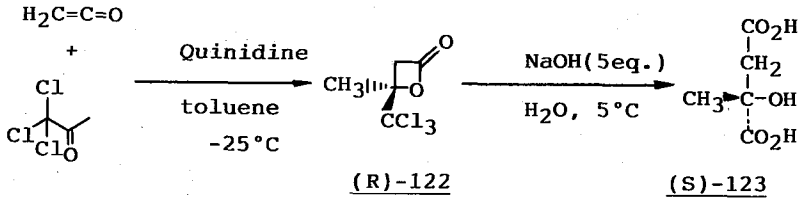
Scheme 51



3-4-4 Uses of 1,1,1-trichloroacetone

1,1,1-Trichloroactone, obtained as a side product in the preparation of 1,1,3-trichloroacetone, can be used for the synthesis of (R)- and (S)-citramalic acid (**123**) via the enantiomers of 4-methyl-4-(trichloromethyl)-2-oxetanone (**122**). Thus, catalytic cycloaddition of ketene to 1,1,1-trichloroacetone in the presence of quinidine in toluene gives optically pure **122**. The alkaline hydrolysis of **122** proceeds with inversion of configuration at the chiral center so that (S)- and(R)-**123** are prepared from (R)- and (S)- **122** respectively. The synthetic route is depicted in Scheme 52[111]. Optically pure **123** is a promising synthon for natural products, because of its isoprenoid structure.

Scheme 52



4. Chlorinated acetoacetates

Chlorinated acetoacetates, derived from inexpensive diketene, are reactive and versatile compounds which are used for the introduction of functional C_4 unit into organic compounds.

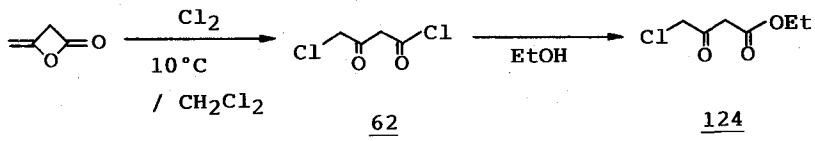
4-1 4-Chloroacetoacetates

Utilizing four reactive centers, chloromethyl, carbonyl, active methylene and ester, of 4-chloroacetoacetates, a number of important chemicals have been synthesized. They are particularly useful in the field of pharmaceutical.

4-1-1 Preparation of 4-chloroacetoacetates

The reaction diketene in a dichloromethane solution with chlorine at 10℃ gives 4-chloroacetoacetyl chloride (**62**), which is treated in situ with ethanol to provide ethyl-4-chloroacetoacetate (**124**). The product is isolated in 90% yield and is free of 2-chloro isomer[112]. (Scheme 53) Other alkyl esters are also obtainable with similar manner by treating with the corresponding alcohols. The reaction of diketene with bromine are similar to that of diketene with chlorine, and 4-bromoacetoacetates can thus be prepared. 4-Bromoacetoacetates, however, are less stable than 4-chloroacetoacetates and may rearrange to other bromoacetoacetate isomers. Therefore, 4-chloroacetoacetates are recommendable for industrial chemical synthesis.

Scheme 53



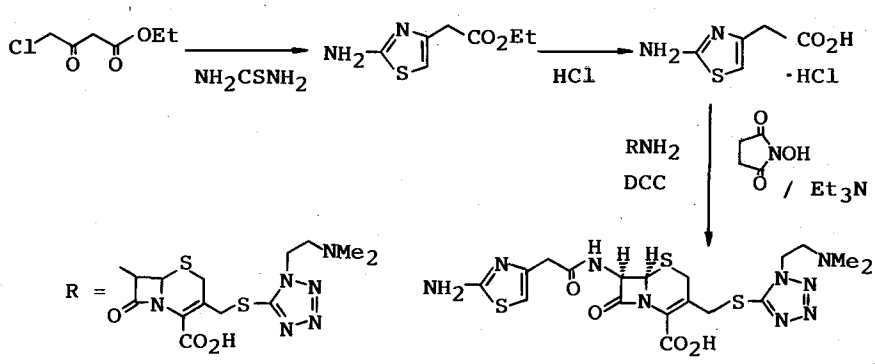
4-1-2 Preparation of thiazolylacetate derivatives and their uses

Cephalosporin antibiotics bearing 2-(2-aminothiazol-4-yl) acetamido group in the 7-position, has a strong enhancing effect on the activity against gram-negative bacilli. It has also been known that the high antibiotic activity against a broad spectrum of species can be expected by the introduction of alkoxim group on 2-(2-aminothiazol-4-yl) acetamido unit. Those side chains have been constructed starting from 4-halogenated acetoacetates without exception.

The reaction of ethyl-4-chloroacetoacetates (**124**) with thiourea provides ethyl-2-aminothiazol-4-ylacetate (**125**)[113], which is hydrolized to give the acid and used, for example, in the synthesis of well-known cefotiam (**126**)[114]. (Scheme 54)

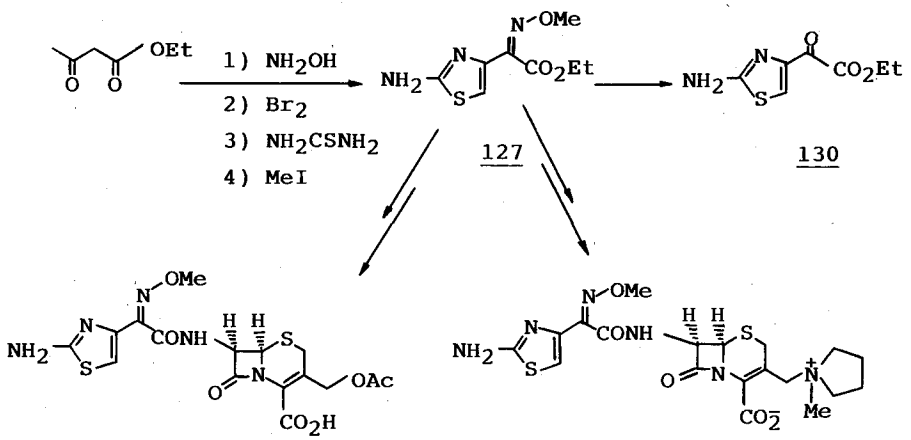
Ethyl-2-methoxyimino-2-(2-aminothiazol-4-yl)acetate (**127**) is synthesized from ethyl acetoacetate via hydroximation/bromination/thiazole formationg/methylation sequence[115]. **127** is used for the preparation of cephalosporins bearing

Scheme 54



Cefotiam 126

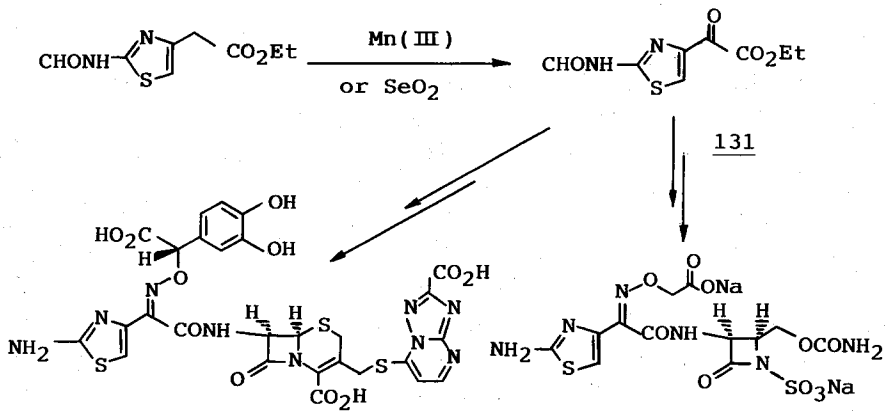
Scheme 55



Cefotaxime 128 Cefepime 129

2-methoxyimino-2-(2-aminothiazol-4-yl) acetoamido group in the 7-position such as cefotaxime (**128**)[116] and cefepime (**129**)[117]. (Scheme 55) However, to construct the aminothiazole side chain having heavy alkoxim or carboxylic alkoxim group instead of methoxim group, ethyl-2-aminothiazol-4-yl glyoxylate (**130**) is more useful in may cases from synthetic point of view. Although **130** is obtainable by deoximation of **127** with hydrochloric acid in ethanol, the preparation way of **130** from **125** is more economical as the reaction steps can be shorten. Thus, the oxidation of formylated **125** in the presence of catalytic amount of Mn(Ⅲ) or selenium dioxide provides glyoxylate (**131**). It has been shown that M-14659 (**132**) can be synthesized efficiently from **130**[118]. (Scheme 56) **130** is applicable for synthesizing not only cephalosporins but also monocyclic β-lactam antibiotic such as carumonam

Scheme 56



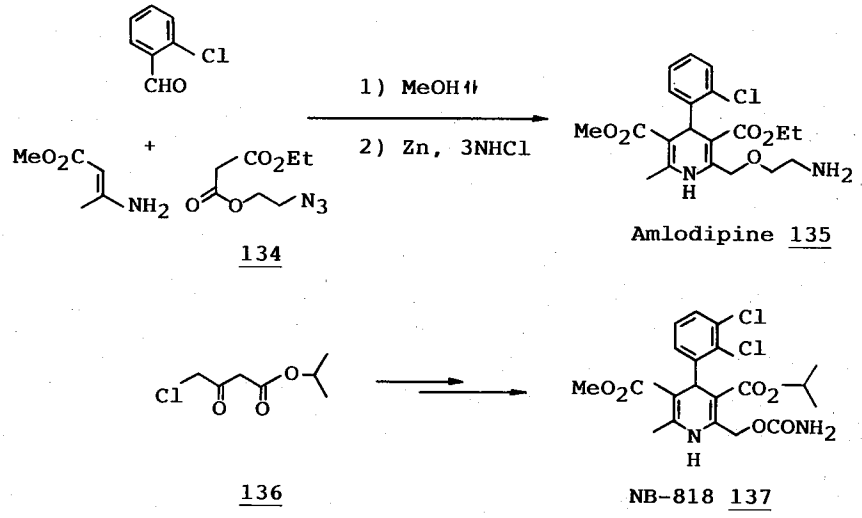
M-14659 132 Carumonam Sodium 133

sodium (**133**)[119].

4-1-3 Preparation of dihydropyridine derivatives

A number of dihydropyridines possessing substituent on methyl group in the 2-position have recently been developed as a new type of dihydropyridines. For instance, amlodipine (**135**) possesses 2-aminoethoxy group and is a novel anti-hypertensive drug which has long duration time of action, allowing daily dosing. **135** is prepared by the Hantzsch cyclocondensation of azide **134**, derived from ethyl-4-

Scheme 57

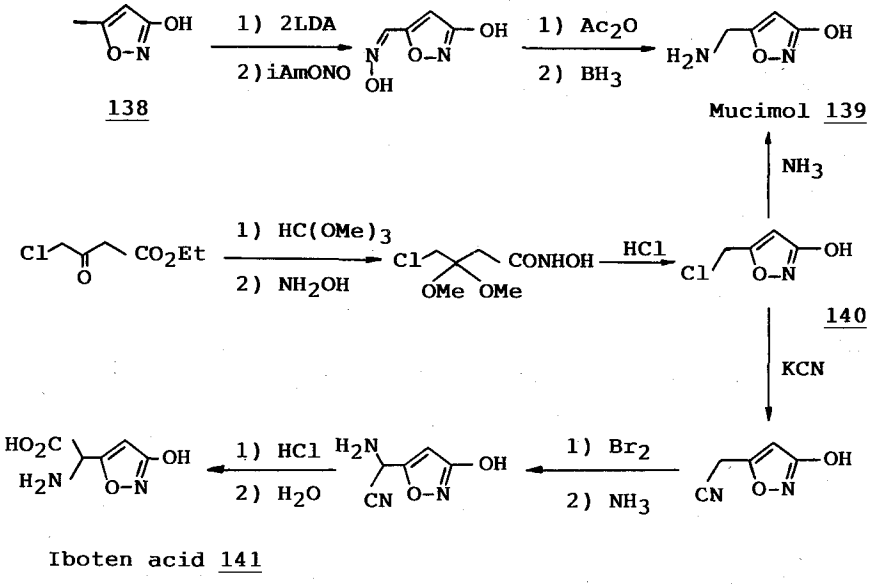


chloroacetoacetate, with methyl-3-aminocrotonate and 2-chlorobenzaldehyde[120]. (Scheme 57) NB-818 (**137**) is also synthesized with similar manner from isopropyl-4-chloroacetoacetate (**136**)[121]

4-1-4 Preparation of 5-chloromethyl-3-hydroxyisoxazole and its uses

The 3-hydroxy-5-methylisoxazole (**138**) is a useful plant protecting agent, known as Tachigaren or Hymexazol. Since **138** is commercially available, the synthetic route to the analgetic drug, muscimol (**139**), a hallucinogen found in muschrooms, from **138** has been elaborated[122]. However it was accessible only when using expensive agents such as lithium diisopropylamide with long reaction steps. Therefore, 5-chloromethyl-3-hydroxyisoxazole (**140**) is useful as a key intermediate for the preparation of **139** via ketalization/amidation/cyclization sequence. **140** is readily converted into **139**[123]. Iboten acid **141**, which has an insecticidal activity, has also been synthesized from **140**[123]. (Scheme 58)

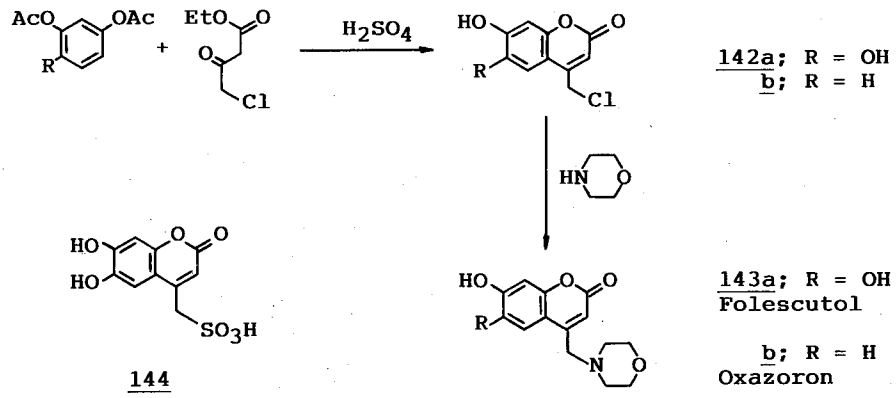
Scheme 58



4-1-5 Preparation of benzopyranone derivatives

4-chloromethylbenzopyranones can be obtained from acetoxybenzenes and 4-chloroacetoacetates. Based on the synthesis, capillary therapeutic folescutol (**143 a**) and its analogue, choleretic oxazorone (**143 b**) have been synthesized. Thus, the reaction of acetoxybenzenes with ethyl-4-chloroacetoacetate in the presence of sulfuric acid give (**142 a, b**), followed by treating with morphorin to obtain **143 a** and **143 b** as shown in Scheme 59[124]. 4-Sulfomethylbenzopyranone (**144**) has also

Scheme 59



been prepared with similar manner.

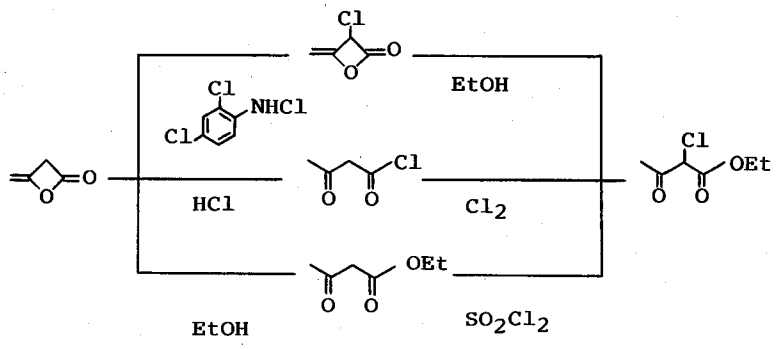
4-2 2-Chloroacetoacetates

The bifunctional reactants such as thioamides, dithiocarbamates, formamide, ureas, thiocarbamates, semicarbazides, and thiosemicarbazides react with chlorine and keto groups of 2-chloroacetoacetates to afford heterocycles bearing adjacent methyl and carboxylic acid ester groups. Among numerous reaction possibilities of 2-chloroacetoacetates, paticularly this reaction makes 2-chloroacetoacetates important starting materials for pharmaceutical and agrochemical products.

4-2-1 Preparation of 2-chloroacetoacetates

Diketene has been chlorinated in the 3-position with N, 2,4-trichloroaniline to provide 3-chloro-4-methylene-2-oxetanone, which is converted in situ into ethyl-2-chloroacetoacetate by the treatment with ethanol[125]. It has also been know that acetoacetyl chloride, prepared from diketene with hydrochloric acid, reacts with

Scheme 60

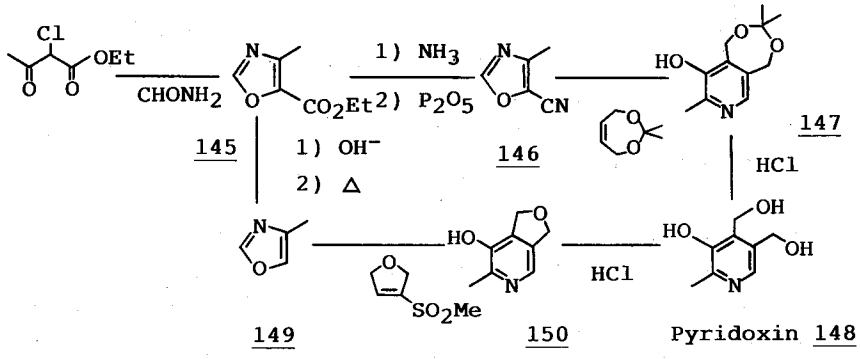


clorine at − 20℃ to give 2-chloroacetoacetyl chloride, which is treated with ethanol to provide ethyl-2-chloroacetoacetate[126]. These two routes contain steps for the formation of unstable intermediates which must be treated at low temperature. The synthetic method for ethyl-2-chloroacetoacetate by the reaction of ethyl acetoacetate with sulfuryl chloride has therefore been suggested as an industrial method. (Scheme 60) Methyl-2-chloroacetoacetate can also be prepared with similar manner.

4-2-2 Pyridoxin (Vitamin B_6) synthesis

Ethyl-2-chloroacetoacetate reacts with formamide to give ethyl-4-methyloxazole-5-carboxylate (**145**), which is a common intermediate for two different synthetic routes to pyridoxin (**148**). The Diels-Alder reaction of 5-cyano-4-methyloxazole (**146**), prepared by amidation and dehydration of **145**, with 2-butene-1,4-diol acetone adduct to give pyridine (**147**), which is deprotected to afford **148**[127]. 4-Methyloxazole (**149**), decarboxylation product of **145**, is also used as a diene for the Diels-Alder reaction. **149** reacts with methylsulfonyldihydrofurane to afford pyridoxin precursor (**150**)[128] (Scheme 61)

Scheme 61



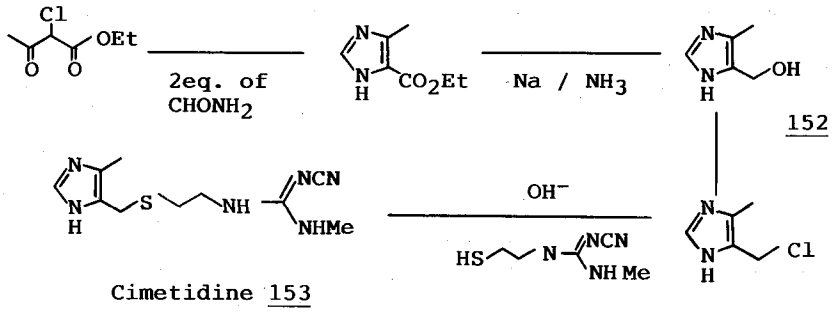
4-2-3 Cimetidine synthesis

Reaction of ethyl-2-chloroacetoacetate with two equivalents of formamide gives ethyl-4-methylimidazole-5-carboxylate (**151**), although oxazole (**145**) is formed using one equivalent of formamide as mentioned above. The reduction of ester group of **151** with sodium in ammonia provides 4-hydroxymethyl-5-methylimidazole **152**, which is used to prepare cimetidine (**153**) via chlorination/sulfide formation sequence[129]. (Scheme 62) **153** is a H_2-receptor antagonist especially used for the treatment of duodenal ulcer.

4-2-4 Preparation of other heterocycles bearing adjacent methyl and carbonyl groups and their uses

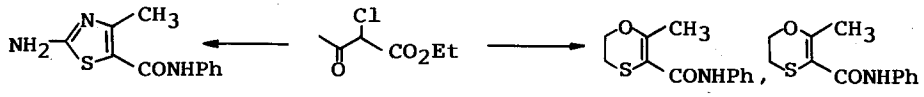
Mainly in the field of agrochemical, heterocycles bearing adjacent methyl and carbonyl groups have become known. For example, Oxathiin (**154**) is produced

Scheme 62



Cimetidine 153

Scheme 63



Oxathiin 154 Oxycarboxin 155

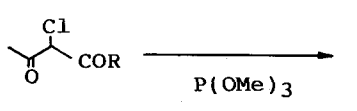
156

from ethyl-2-chloroacetoacetate, 2-mercaptoethanol and aniline[130]. **154** and its sulfone analogue, oxycarboxin (**155**) are fungicides used for the treatment of rust diseases of cereals, ornamentals and vegetables. Anilide (**156**) from thiazolcarboxylic acid ester have also become known as a fungicide and, additionally, as a growth regulator[131]. (Scheme 63)

4-2-5 Preparation of enol phosphates and their uses

The Perkow reaction of 2-chloroacetoacetic acid derivative with trialkyl phosphites give enol phosphates having insecticidal activities. Well-known compounds for example are mevinphos (**157**)[132] and crotoxyphos(**158**)[133]. Its N-methylamide analogue, monocrotophos (**159**) is also noteworthy[134]. (Scheme 64)

Scheme 64



157 R = OMe, Mevinphos
158 R = OCHMePh, Crotoxyphos
159 R = NHMe, Monocrotophos

5 3-Chlorobutanone-2

3-chlorobutanone-2 is an another important C_4 α-chlorocarbonyl compound. There are numerous active substances which possess adjacent dimethyl unit particularly in agrochemical field. 3-Chlorobutanone-2 is suitable starting material for including the adjacent dimethyl unit in the molecules by the use of a wide range of the reaction of 3-chlorobutanone-2 as well as above-mentioned α-chlorocarbonyl compounds.

5-1 Preparation of 3-chlorobutanone-2

It has been reported that 3-chlorobutanone-2 can be prepared by the chlorination of 2-butanone with sulfuryl chloride in Carbon tetrachloride (Carbon tetrachloride : 2-butanone=5 : 1-2) at 60-78℃[135]. Here sulfuryl chloride is used for the selective chlorination inhibiting the formation of over-chlorinated products. However, this procedure has not been applicable on industrial scale due to the generation of sulfur compounds which requires a severe separation process. The chlorination of 2-butanone with chlorine has therefore been suggested from economical point of view although it also requires a separation process of over-chlorinated butanone-2.

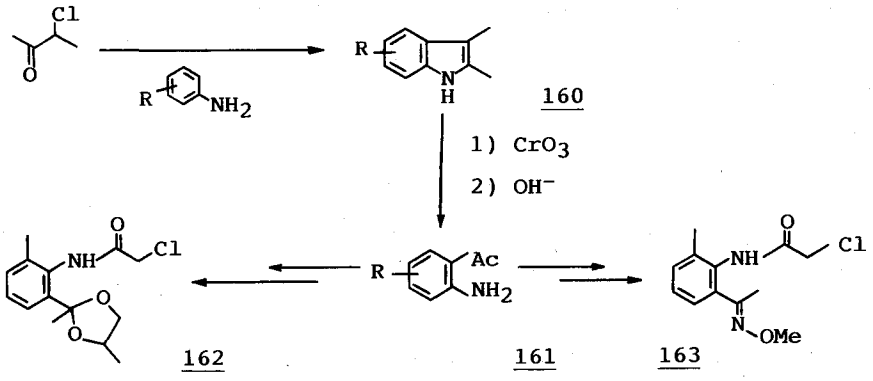
5-2 Preparation of 2, 3-dimethylindoles and their uses

The condensation of 3-chlorobutanone-2 with anilines gives 2,3-dimethylindoles (**160**), which can be converted into ortho-acetylanilines (**161**) via oxidative ring-opening reaction/hydrolysis sequence[136]. By the use of this orheo-acetylation process of anilines, some compounds (**162, 163**) having herbicial activities have been synthesized. (Scheme 65)

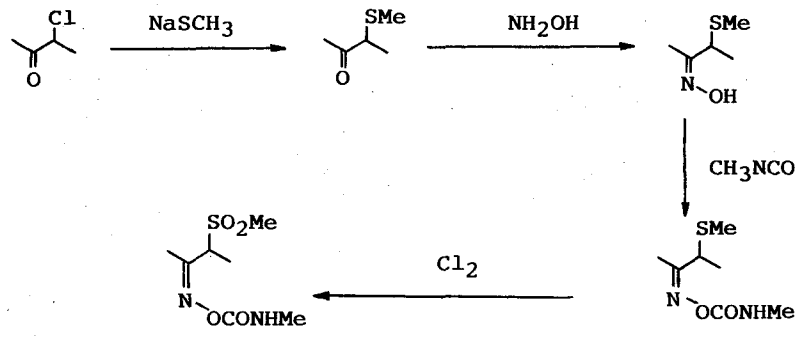
5-3 Synthesis of butocarboxim and butoxicarboxim

Insecticides, butocarboxim (**165**) and butoxicarboxim (**166**) have been prepared

Scheme 65



Scheme 66



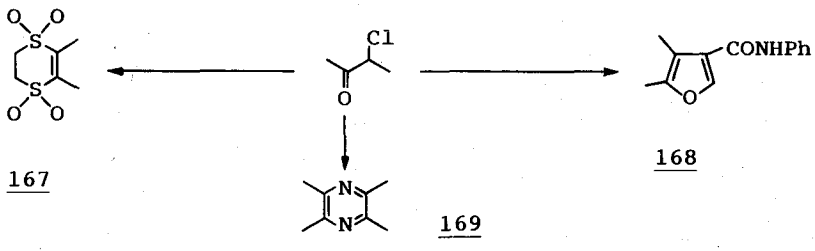
Butoxicarboxim 166 Butocarboxim 165

from 3-chlorobutanone-2. Thus, 3-chlorobutanone-2 reacts with sodium methylthiolate to give methylthioether (**164**). The carbamoyloximation of **164** provides **165**. By the treatment of **165** with chlorine, **166** is also prepared. (Scheme 66) **165** is effective against sucking insects. **166** is effective against aphids and mites[137].

5-4 Other heterocycles derived from 3-chlorobutanone-2

2,3-Dihydro-5,6-dimethyl-1,4-dithi-ine tetraoxide (**167**) out of 3-chlorobutanone-2 has been developed as an effective defoliant for cotton, nursery stock, rubber trees and vines. It is known as dimethipin[138]. 2,3-dimethylfurane-4-carboxylic acid derivative by Feist-Benary reaction of 3-chlorobutanone-2 has been developed as a fungicide named trivax (**168**)[139]. The cyclocondensation of 3-chlorobutanone-2 with ammonia gives tetramethylpyrazine (**169**)[140], which is used as synthetic, nontoxic flavouring in cocoa, coffee, galbanum oil, etc. **169** has also been developed as a new drug to improve blood flow and relieve circulatory stasis[141]. (Scheme 67)

Scheme 67



167 168 169

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