

HETEROCYCLIC KETENE AMINALS

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Abstract - Heterocyclic ketene aminals are presented in view of their synthesis, reactions and applications in the preparation of fused heterocycles.

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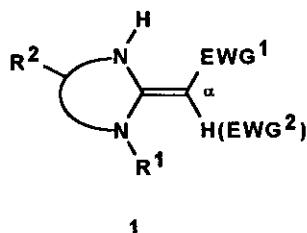
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Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.

9. References

1. INTRODUCTION

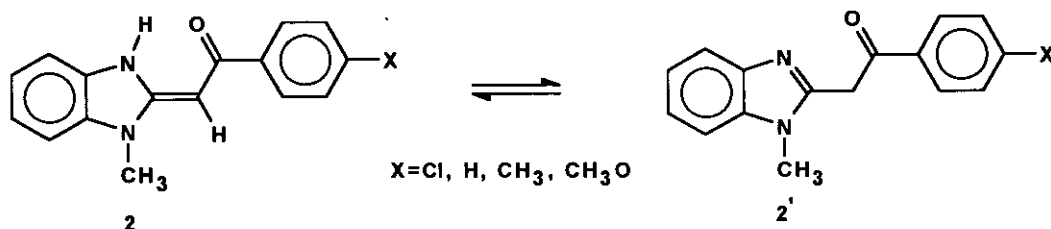
Heterocyclic ketene amins, also known as cyclic 1,1-enediamines, can be generally described by formula (1).



$R^1, R^2 = \text{H, alkyl, aryl}$

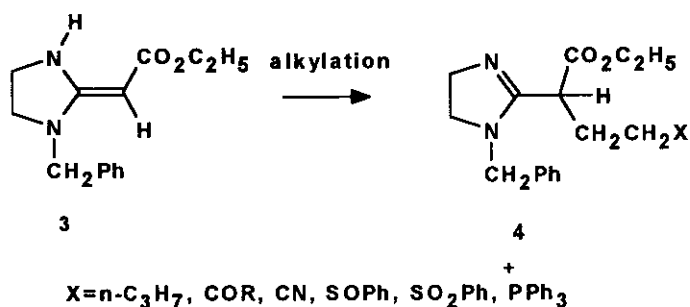
$\text{EWG}^1, \text{EWG}^2 = \text{NO}_2, \text{CN, COR, COAr, CO}_2\text{R, etc.}$

Owing to the conjugation effect of electron-donating amino groups and electron-withdrawing substituents, the double bond is highly polarized. X-Ray diffraction analyses have shown that the double bond length is about 1.38-1.47 Å,¹⁻⁸ being much longer than that of normal olefins. Delocalization of lone-pair electrons of nitrogen atoms into the double bond results in the increase of electron density on α -carbon atom. Thus, the nucleophilicity of α -carbon atom is greater than that of nitrogen atom, and the carbon center always attacks the electropositive site of electrophiles, even 1,3-dipoles (*vide infra*). Heterocyclic ketene amins are polyfunctionalized molecule, in addition to the α -carbon site, β -carbon, α -substituents and particularly the secondary amino group may also participate in the reactions. An important application of heterocyclic ketene amins is that they may serve as bis-nucleophiles to synthesize a wide variety of fused heterocyclic compounds by nucleophilic addition or substitution (*via* α -carbon atom) and cyclocondensation (*via* NH) reaction sequences. Although heterocyclic ketene amins (1) are possible to tautomerize to amidine isomers, spectroscopic data⁹⁻¹¹ obtained so far are consistent with the 1,1-enediamine structure. Only in the case of imidazoline^{12,13} and benzimidazoline-substituted ketene amins,¹⁴ have amidine tautomers been isolated or observed in tautomeric



equilibrium with ketene amins. Apparently, the aromaticity gained in compound (2') leads to the tautomerization of 2. The equilibrium between 2 and 2' has been investigated in terms of substituent X on

phenyl ring, temperature and solvent. Polar solvents such as dimethyl sulfoxide especially favor the ketene aminal tautomer (2).¹⁴ Besides, steric effect may also play an important role in determining the tautomeric equilibrium.^{15,16} It has been reported¹⁶ that the alkylation products of heterocyclic ketene amins (4) exist predominantly in amidine form, while their precursor (3) is in ketene aminal form.

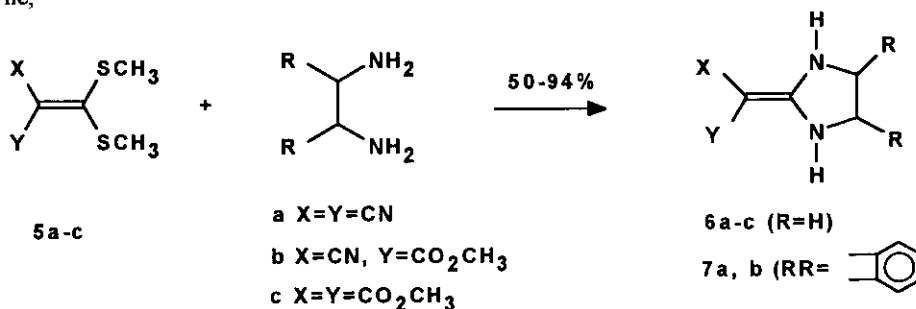


The first report¹⁷ of heterocyclic ketene amins may date back to 1950s, however, they had not attracted the curiosity of chemists, nor had they been considered as building blocks for further synthetic manipulations until 1980s. Much attention has been given to them in recent years. In this review, we present the synthesis and reactions of heterocyclic ketene amins. Emphasis is placed on the applications of this versatile synthon in the preparation of heterocycles, especially fused heterocycles. Acyclic ketene amins are excluded in this survey. As push-pull ethylene compounds, *N,N'*-fully substituted heterocyclic ketene amins have been extensively studied and reviewed,¹⁸ and they are not included.

2. SYNTHESIS

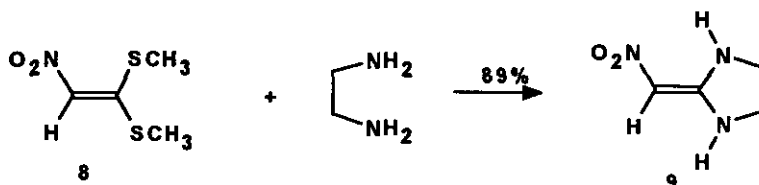
2.1. Reaction of diamines with ketene dithioacetals

At the beginning of 1960s, Gompper and Topel¹⁹ reported that ketene dithioacetals reacted with diamines to give heterocyclic ketene amins. Cyclocondensation between ketene dithioacetals (5), derived from malononitrile,



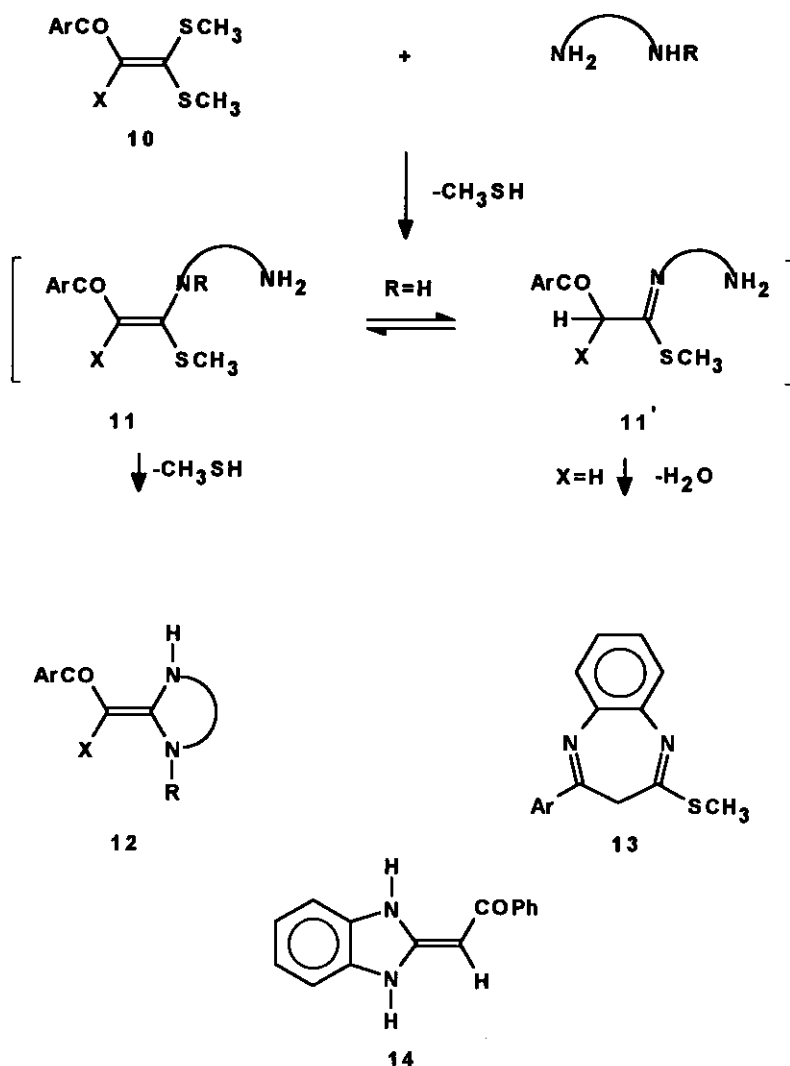
methyl cyanoacetate and dimethyl malonate, respectively, and ethylenediamine or *o*-phenylenediamine afforded five-membered heterocyclic ketene amins (6) or (7) in moderate to excellent yields.

Nitro-substituted heterocyclic ketene amins (9) was similarly obtained.²⁰



This preparative method provides several advantages. First, the starting material ketene dithioacetals are easily accessible. Active methyl and methylene compounds react with carbon disulfide in the presence of an appropriate base to form the salts of ketene mercaptols, and they are transformed into dithioacetals by reaction with alkylation reagents, usually the alkyl halides. The reaction can be carried out in a one-pot procedure. Thus, on successive treatment with a base, carbon disulfide and methyl iodide, active methyl and methylene compounds are converted into ketene dithioacetals in moderate to excellent yields.²¹⁻²⁶ Second, ketene dithioacetals are reactive toward diamines and they react readily with both aliphatic and *ortho* aromatic diamines to give heterocyclic ketene amins. In addition, the cyclocondensation reaction between ketene dithioacetals and diamines can be conveniently controlled by monitoring the bubbling of methanethiol. Furthermore, the yield of the reaction is generally good. A great number of heterocyclic ketene amins has been synthesized by this procedure from active methyl and methylene substrates including nitromethane,^{20,27-31} acetophenones,^{32,33} acetone,³⁴ cyclic ketones,³⁵⁻³⁷ 1,3-diketones,³⁸⁻⁴⁰ malonates,^{19,40,41} β -ketoacetates,^{40,42} α -cyanoketones,⁴²⁻⁴⁴ cyanoacetates,^{11,19} arylacetoneitriles,⁵ malononitrile,^{11,19} and other precursors.⁴⁵⁻⁴⁸

Although this method is applicable to the synthesis of a wide variety of heterocyclic ketene amins, 2-(arylmethylene)benzimidazoline compounds (14) can not be obtained from benzoyl-substituted ketene acetals (10) ($X=H$) and *o*-phenylenediamine. Instead of (14), 3*H*-1,5-benzodiazepines (13) are isolated.⁴² Similar results have been encountered in the reaction between 10 ($X=H$) and other *ortho* primary aromatic diamines.^{49,50} A recent investigation⁴² has revealed that an enamine-imine tautomeric intermediate is involved in reaction process. The tautomeric equilibrium between 11 and 11' is affected by the substituent X and diamines employed. In the case of aliphatic diamines, the enamine form 11 can be stabilized either one or two electron-withdrawing groups ($X=H$ or EWG); therefore, heterocyclic ketene amins (12) are obtained. When *o*-phenylenediamine is used, enamine intermediate (11) is stable only when two electron-withdrawing groups are presented ($X=EWG$).

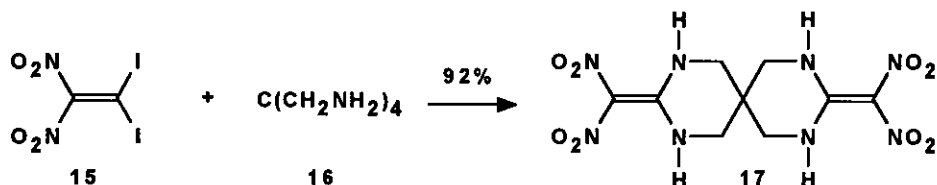


With one aroyl substituent (X=H), enamine intermediate tautomerize to imine form (11') due to conjugation with the aromatic ring, and seven-membered heterocyclic compounds (13) are finally obtained. When *N*-methyl-*o*-phenylenediamine is used, the first substitution occurs on the methylamino group, enamine intermediate (11) thus formed can not tautomerize to the imine form (11'), therefore, ketene amins with benzimidazoline ring (2) are formed.

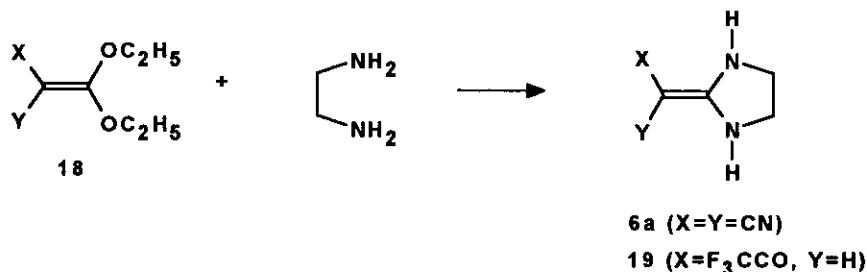
2.2. Reaction of diamines with *gem*-dihaloethylene compounds and ketene *O,O*-; *N,O*- acetals.

The reaction of *gem*-dihaloethylene compounds with diamines provides another synthetic route to heterocyclic ketene amins.^{8,51,52} Halogen atoms, like methylthio in ketene dithioacetals, act as leaving groups to be

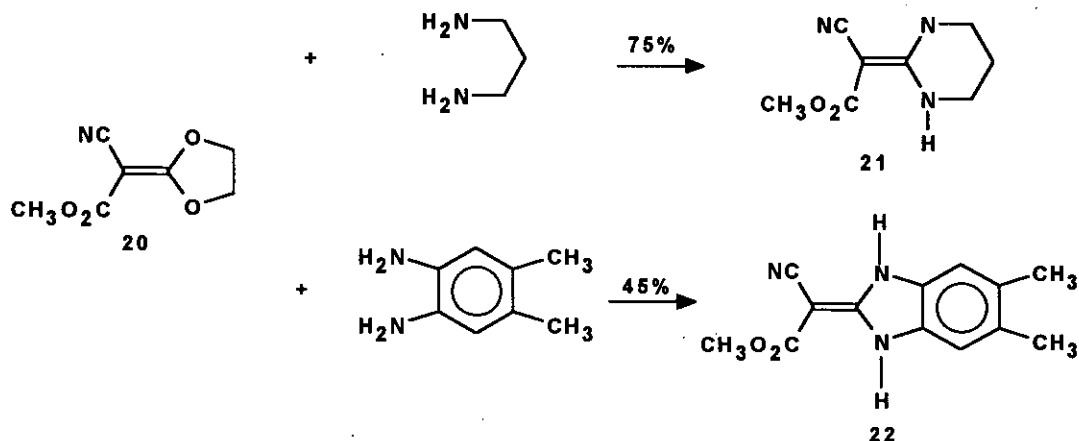
substituted by amino groups. Benzimidazoline-substituted ketene aminal (14) has been synthesized by the reaction of 1,1-dichlorobenzoyl ethene and *o*-phenylenediamine.⁵¹ 1,1-Diiodonitroethylene compound (15), derived from the nitration of tetraiodoethylene, reacted with both aliphatic and aromatic diamines to afford heterocyclic ketene aminals. A spiro product (17) was obtained in excellent yield when tetrakis(aminomethyl)methane (16) was used.⁸



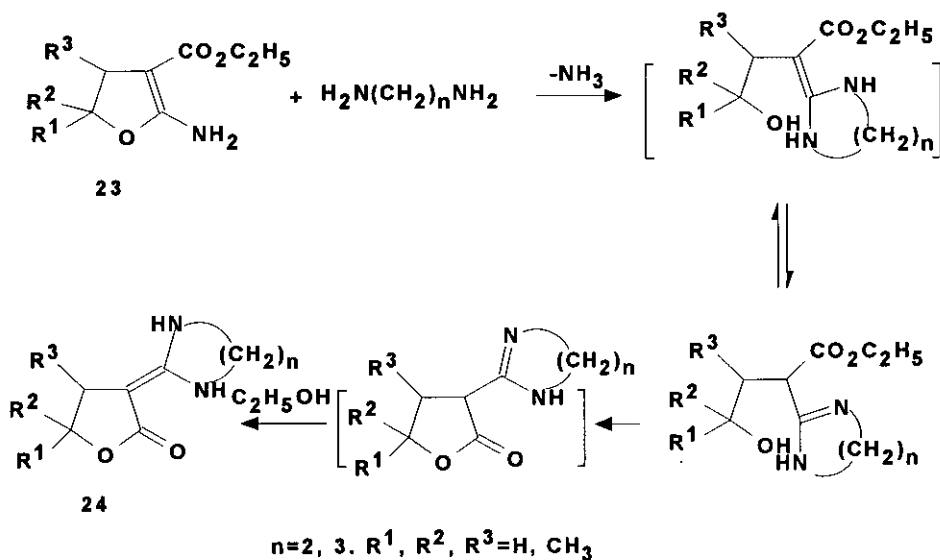
Similar to ketene dithioacetals and *gem*-dihaloethylene compounds, ketene *O,O*-acetals reacted with diamines to yield heterocyclic ketene aminals with elimination of alcohol.^{17,53}



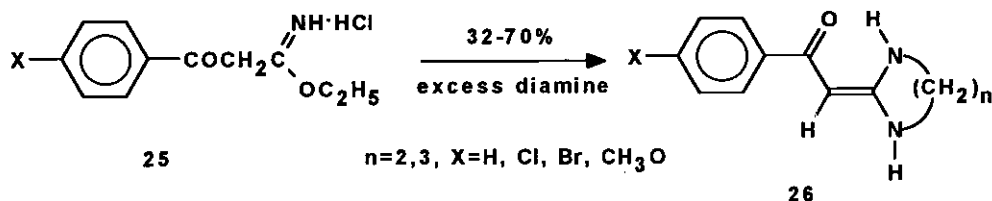
Cyclic ketene *O,O*-acetal (20) behaved analogously, and ethylene glycol was displaced by diamines in the reaction.⁵⁴



The reaction of 2-amino-4,5-dihydro-3-furancarboxylates (**23**) with diamines appeared intriguing. In contrast to the structure assigned earlier,⁵⁵⁻⁵⁷ the reaction product has been identified as heterocyclic ketene amins attached to a lactone moiety (**24**).⁵⁸ Apparently, 4,5-dihydrofuran ring opening and lactone formation steps were involved in the reaction.



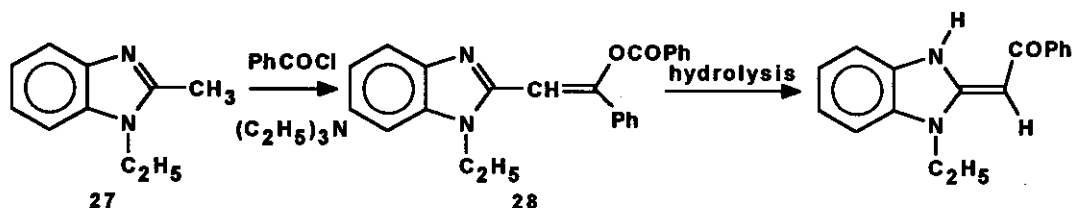
Ketene *N,O*-acetals and imino esters, derived from benzoyl-,¹⁰ nitro-⁵⁹ and ester-substituted acetonitrile⁶⁰ gave heterocyclic ketene amins when treated with diamines.



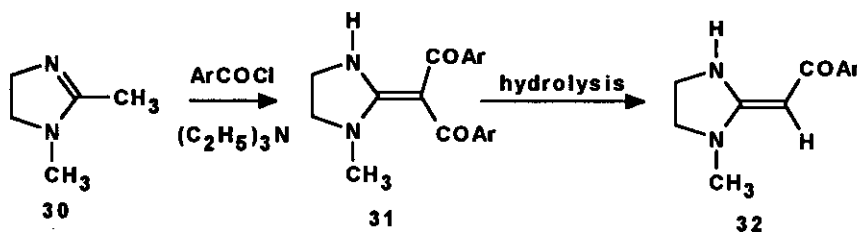
2.3. Acylation of 1-alkyl-2-methylamidine derivatives

The key point of the synthetic methods described in 2.1 and 2.2 is to construct a heterocyclic ring by using diamines. Strategy presented in this and following sections is to use 1,3-diazoheterocyclic compounds as building block. 2-Methylimidazole and 2-methylbenzimidazole derivatives are unique starting materials, since 2-methyl

group in these compounds is weak acidic. It has been reported that acylation of 1,3-dimethylimidazole¹² and 1-ethyl-2-methylbenzimidazole¹³ with benzoyl chloride in the presence of a base gave enol benzoate products, and ketene amins or amidines after hydrolysis.



The reaction of compound (30) with aroyl chloride produced diacylated compound (31). Hydrolysis of 31 led to cleavage of one acyl group, and monobenzoyl substituted heterocyclic ketene aminal (32) was formed in moderate yield.⁶¹



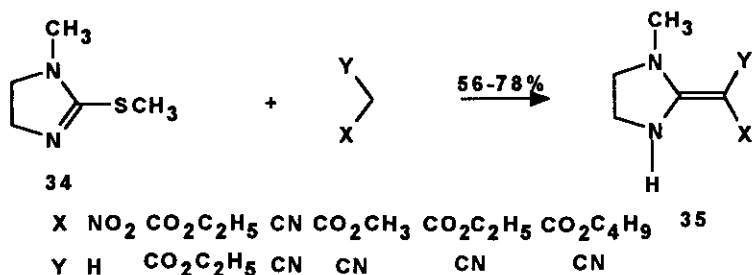
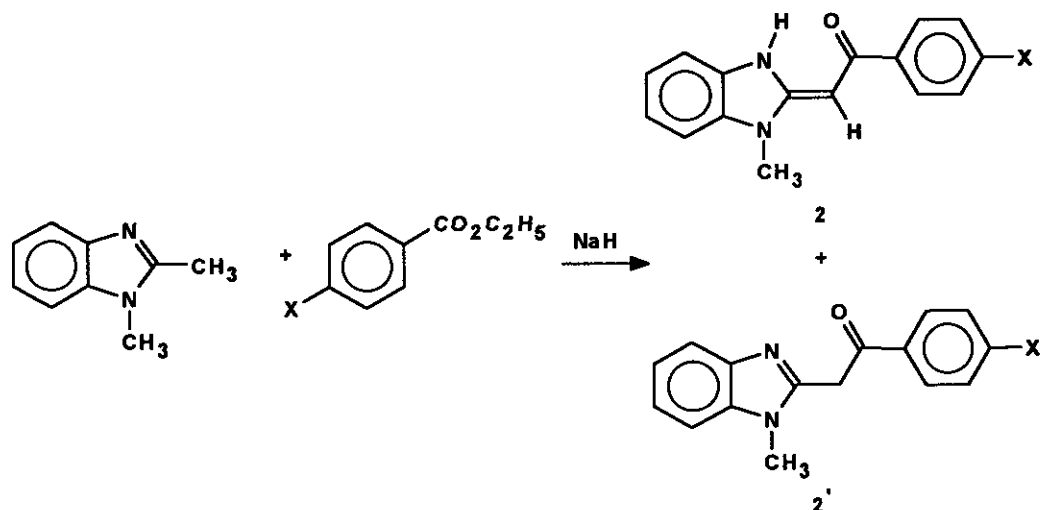
Esters have been used as acylation reagents, but a strong base was usually required, and the reaction afforded directly monoacylated product.^{4,62} The reaction between 1,2-dimethylbenzimidazole (33) and ethyl benzoate with the aid of sodium hydride resulted in the formation of ketene amins (2) and their amidine tautomers (2').¹⁴ Relevant to the acylation, 2-methyl substituent of 1-alkyl-2-methylamidine compounds have been esterified⁴ by diethyl carbonate and thioacylated⁶³ by the Willgerodt-Kindler reaction, respectively, but the yields were low.

2.4. Reaction of active methyl and methylene compounds with *S*-methylated thioureas

Condensation reaction between 1-methyl-2-methylthio-4,5-dihydroimidazole, or 1,4,5,6-tetrahydropyrimidine and active methyl and methylene compounds gives heterocyclic ketene amins with elimination of methanethiol.^{64,65} Compounds (35) have been obtained in good yield from corresponding active substrates.⁹

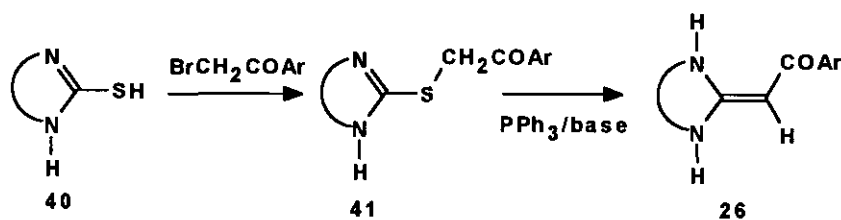
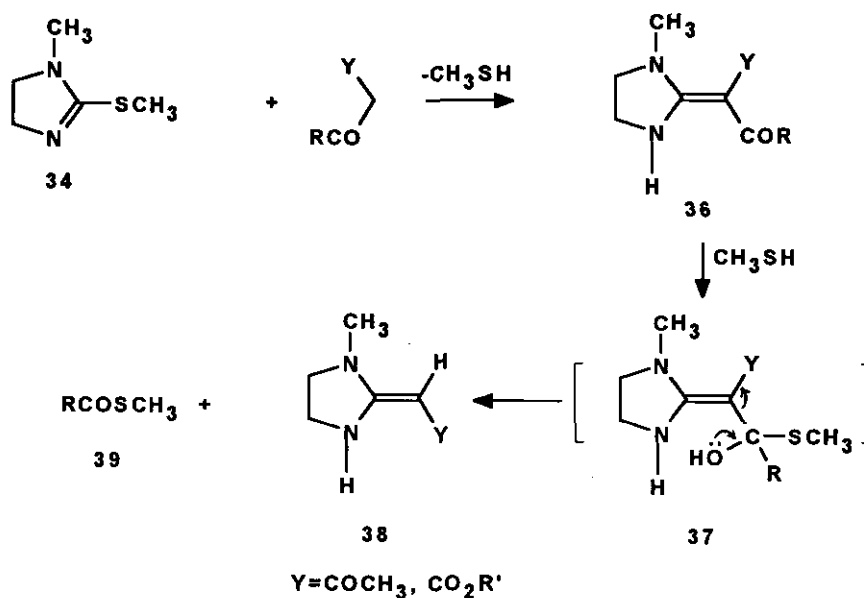
Reaction between 34 and β -ketoacetate or acetylactone under same conditions, however, gave product (38) with loss of one acetyl group.^{9,66} Evidence available indicated the involvement of secondary reaction between heterocyclic ketene amins and methanethiol released from the condensation step. Thus, methanethiol attacked the more active carbonyl group of the primary formed ketene amins (36) to form intermediate (37). The

intermediate (37) underwent elimination to give deacetylation product (38) and by-product (39). The ketene amins (36) can be obtained from the reaction if methanethiol is removed as soon as it is formed. The same deacetylation reaction of 36 can also be effected by using a base.⁴⁰



2-Methylthioimidazoline, analogue of 34, is able to undergo the same condensation reaction, but more active methylene compounds are required.⁹

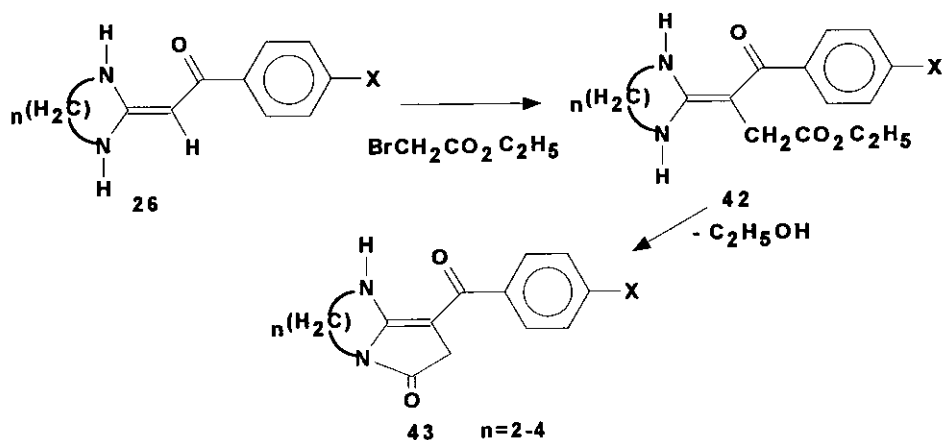
Except for the preparative methods displayed above, it has been reported⁶⁷ that acylmethylisothiureas (41) were converted to heterocyclic ketene amins (26) when treated with triphenylphosphine in the presence of a base. However, no reaction occurred in the case of benzimidazole and diazepine analogues, and reaction yield for *N*-methylated reactants appeared low.



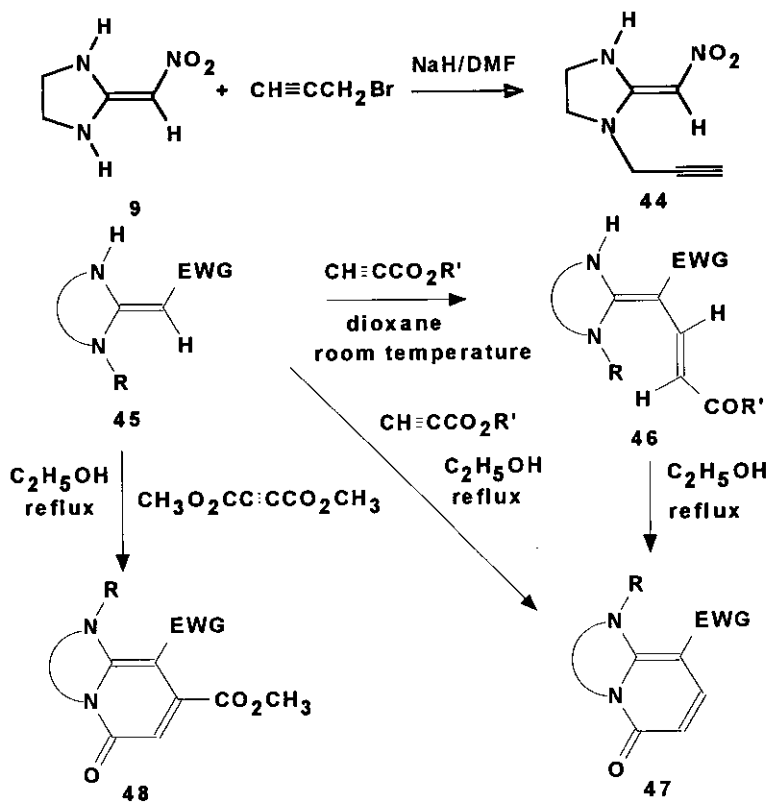
3. ALKYLATION REACTION

3.1. With alkyl halides

The reaction between heterocyclic ketene aminals with alkyl halides such as benzyl chloride,⁶⁸ *n*-pentyl iodide⁶⁹ under neutral condition gave exclusively *C*-alkylated products due to the greater nucleophilicity on α -carbon than on nitrogen atom. Heterocyclic ketene aminals (26) reacted smoothly in reflux acetonitrile or dioxane with ethyl bromoacetate to afford γ -lactam-fused diazoheterocycles (43) in moderate yield. The reaction proceeded through *C*-alkylation and cyclocondensation sequences.⁶⁸

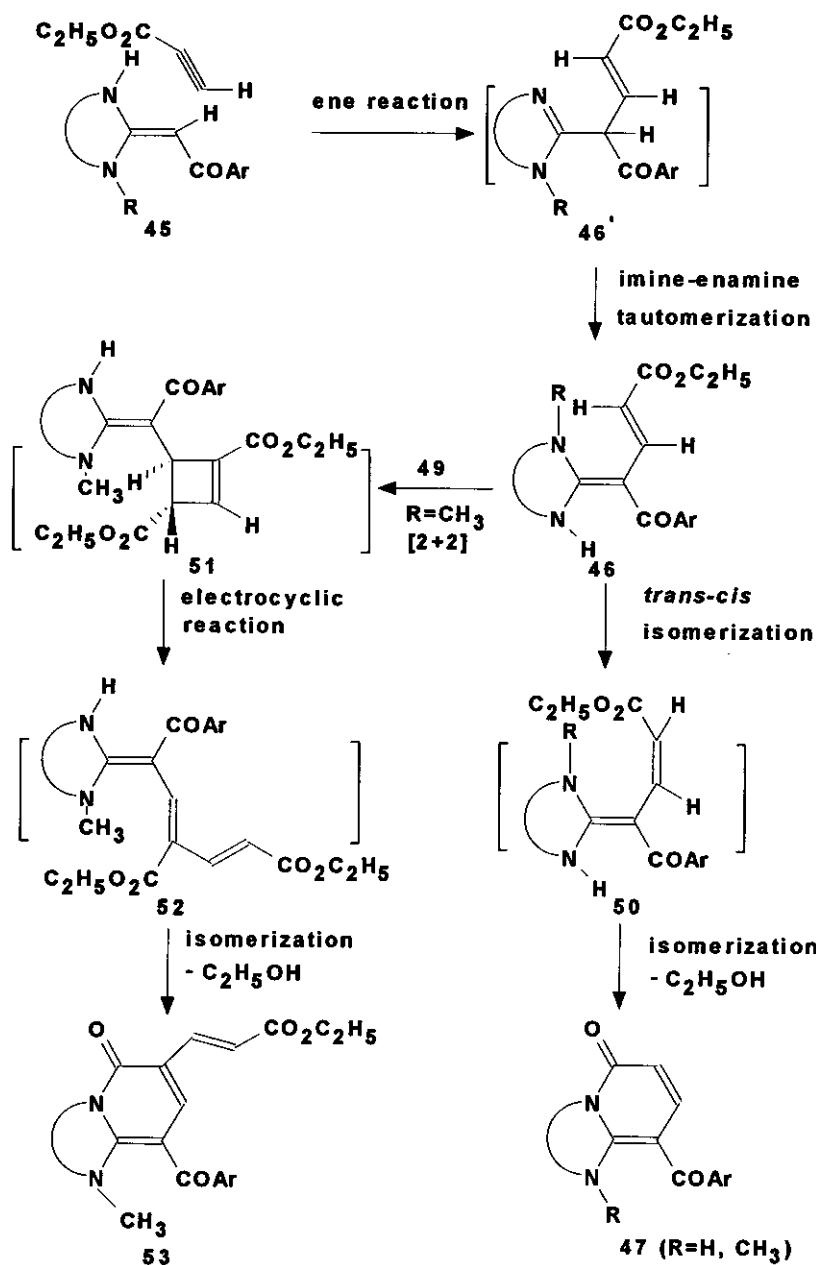


It should be noted that although heterocyclic ketene amins always undergo C-alkylation under neutral condition, *N*-alkylation has been effected with the aid of a strong base.^{28,29} Nitro-substituted heterocyclic ketene aminal (9) reacted with propargyl bromide in the presence of sodium hydride to afford exclusively *N*-alkylated compound (44).²⁸



3.2. With acetylenes

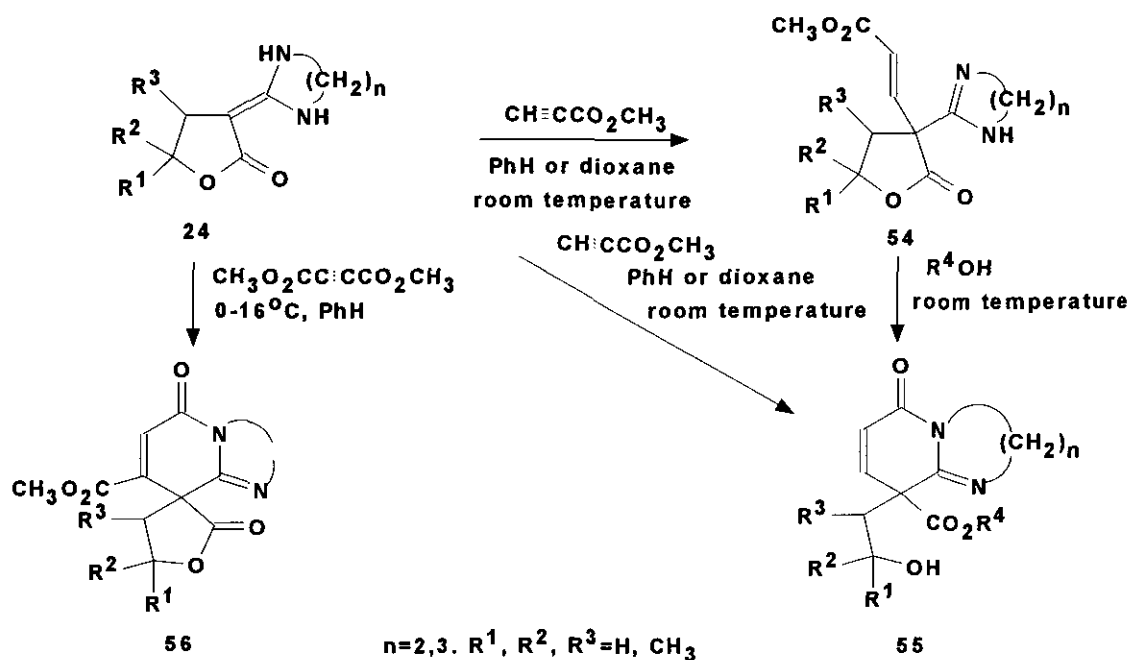
Heterocyclic ketene aminals react readily with activated acetylenes, and several papers have published in this aspect.^{9,70,71} In aprotic solvents such as benzene and dioxane, 45 adds to propiolic acid esters at ambient



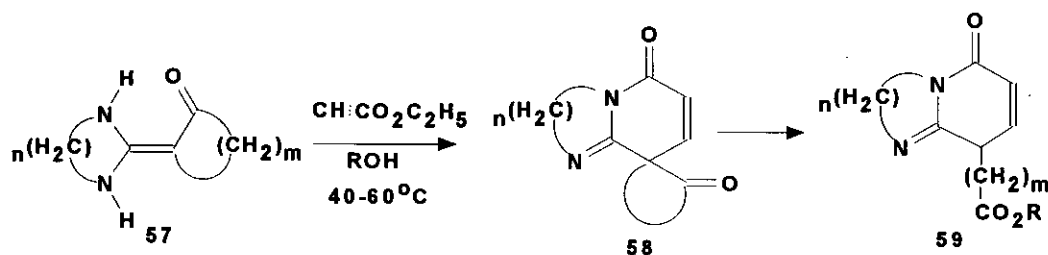
temperature to give almost quantitatively *C*-alkylated products (46). In reflux ethanol, *C*-adducts (46) are converted into fused heterocycles (47). The transformation of 45 to 47 is easily achieved in alcoholic solvents.⁷⁰ When dimethyl acetylenedicarboxylate is used, similar reaction occurs leading to heterocyclic compounds with an alkoxycarbonyl substituent on pyridinone ring 48.^{9,70}

A very recent investigation⁷² has demonstrated convincingly that heterocyclic ketene amins add to triple bond of acetylene *via* ene-mechanism. When secondary amino groups are fully substituted, 1,3-dimethyl-2-benzoylmethyleneimidazolidine did not add to ethyl propiolate (49). With one methylated nitrogen, the heterocyclic ketene amins (45) ($R=CH_3$) reacted with 49 to give the fused heterocycles (47) ($R=CH_3$) and ethoxycarbonylvinyl-substituted heterocyclic compounds (53). The yield of 53 increased when excess amount of (49) was used. Reaction pathway has been proposed.

Heterocyclic ketene amins with a lactone moiety (24) underwent same addition reaction with methyl propiolate in benzene or dioxane and consecutive cyclocondensation reaction in alcoholic solvents, but the lactone ring was opened.⁷³ Interestingly, lactone moiety survived when (24) was treated with dimethyl acetylenedicarboxylate, thus spiro compounds (56) were obtained at 0-10°C in benzene solution.⁷⁴



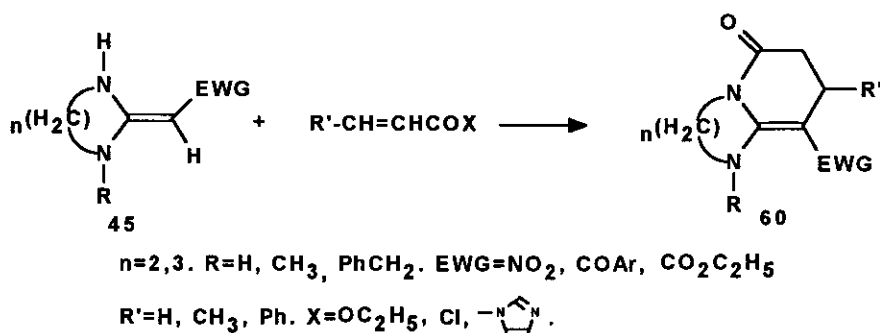
The synthesis of spiro compounds (58) has been attempted^{37,75} from heterocyclic ketene amins 57 which were prepared from cyclic ketones. In contrast to the expectation, cyclic ketone ring was cleaved under very mild reaction conditions and fused heterocycles (59) were isolated in good yield.



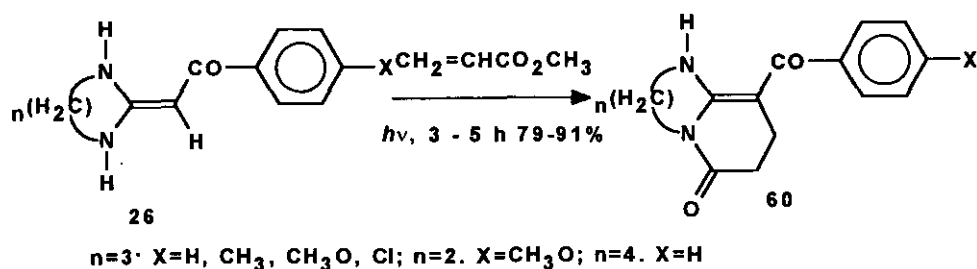
3.3. With electrophilic olefins

C-Alkylation of heterocyclic ketene amins takes place readily when they react with electrophilic olefins including α,β -unsaturated aldehydes, ketones and carboxylic acid derivatives. Fused heterocyclic compounds are usually obtained as final products because of the simultaneously intramolecular cyclocondensation reaction between secondary amino and carbonyl groups of the primary formed adducts.

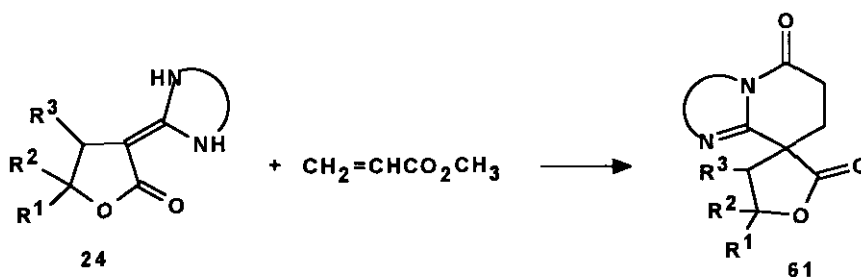
δ -Lactam-fused heterocyclic compounds (60) are given by the reaction of 45 with methyl acrylate,^{9,70} propenoyl chloride (with pyridine as an acid acceptor)⁷¹ and α,β -unsaturated carbonylimidazole.⁷¹



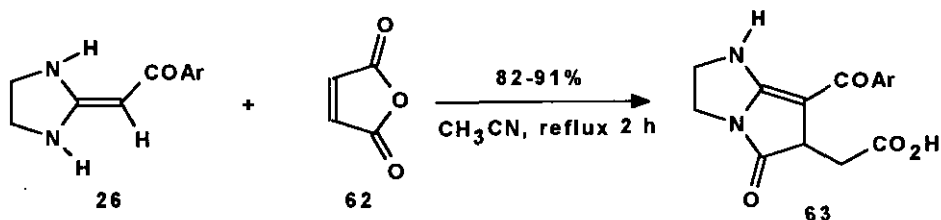
The photochemical reaction of heterocyclic ketene amins (26) with methyl acrylate has been reported recently.⁷⁶ This photochemical reaction appeared clear-cut, the reaction gave high yield of product, otherwise it showed no reaction.



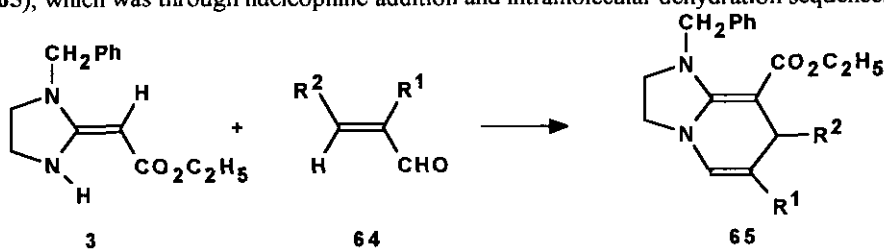
The reaction between heterocyclic ketene aminals (24) and methyl acrylate leads to the spiro products (61).⁷⁴



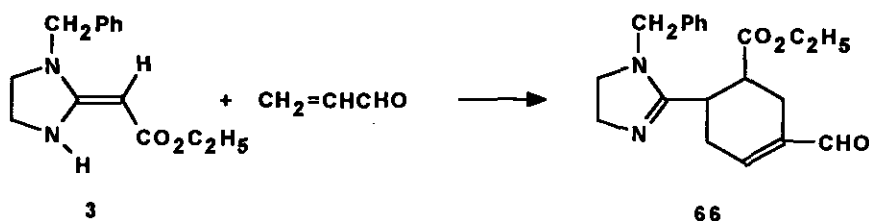
It has been reported⁷⁷ that heterocyclic ketene aminals (26) reacted with maleic anhydride (62) to give the products to which γ -lactam-fused heterocycle (63) had been assigned.



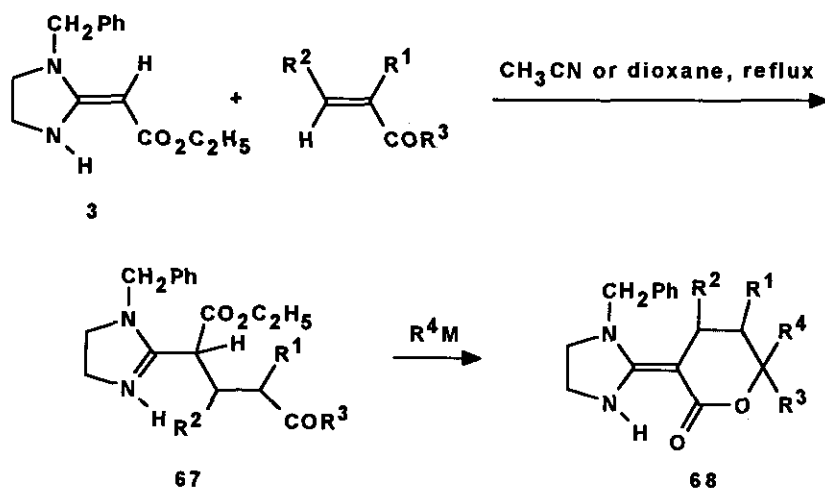
An investigation of alkylation of heterocyclic ketene animals with α,β -unsaturated aldehydes and ketones has been conducted by Jones *et al.*¹⁶ The reaction of (3) with α,β -enals (64) afforded the fused 1,4-dihydropyridine compounds (65), which was through nucleophilic addition and intramolecular dehydration sequences.



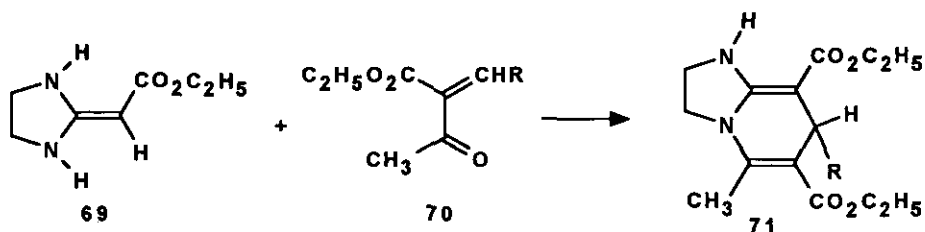
Compound (3) reacted with propenal, however, gave cyclohexene compound (66) in almost quantitative yield based on aldehyde. The formation of 66 was most probably through addition of 3 to two propenal molecules followed by intramolecular aldol condensation, and these reactions were faster than the formation of 1,4-dihydropyridine ring.



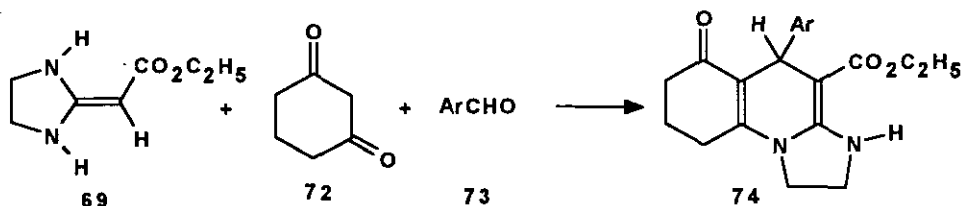
Heterocyclic ketene aminal (3) underwent an easy C-alkylation with α,β -unsaturated ketones under comparable conditions and no cyclocondensation products were observed. Similar C-alkylation reaction with other electrophilic olefins such as unsaturated lactones, acrylonitrile, vinyl sulfoxide, vinyl sulphone and vinylphenylphosphonium bromide have been achieved. All the products existed predominantly as the imine tautomers (67). Treatment with organometallic reagents transformed C-alkylated products (67) into ketene aminals with lactone moiety (68).⁶⁹



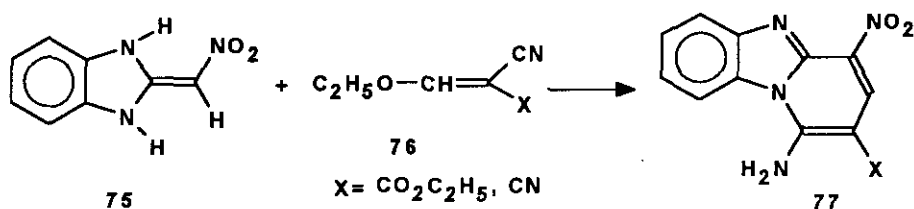
Meyer and co-workers^{78,79} have shown that heterocyclic ketene aminal (69) can add to alkylidene or aralkylideneacetoacetic esters (70) to give products (71). It is worth noting that the amino group condensed selectively with ketonic rather than ester carbonyl site.



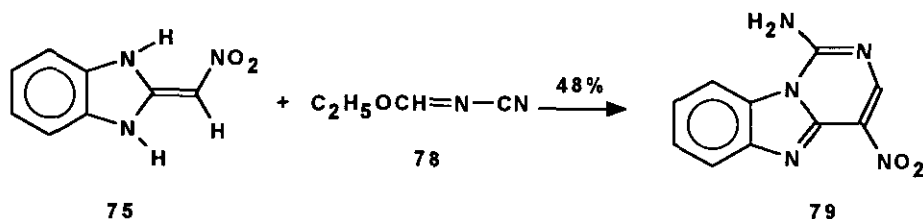
Tricyclic compounds (74) were obtained when 69 was treated with 1,3-cyclohexanedione (72) and aromatic aldehydes (73). The reaction proceeded *via* the addition and cyclization steps between (69) and 2-alkylidene-1,3-cyclohexanediones formed *in situ* from 72 and 73.



Apart from the addition reaction to electrophilic olefins, α -carbon of heterocyclic ketene amins can also act as nucleophilic center to substitute the leaving group attached to double bond. Shafer and Gewald⁸⁰ have reported that ketene aminal (75) reacted with 76 to give product (77) in moderate to good yields. Ketene dithioacetals derived from cyanoacetate and molononitrile behaved similarly to 76.⁸¹

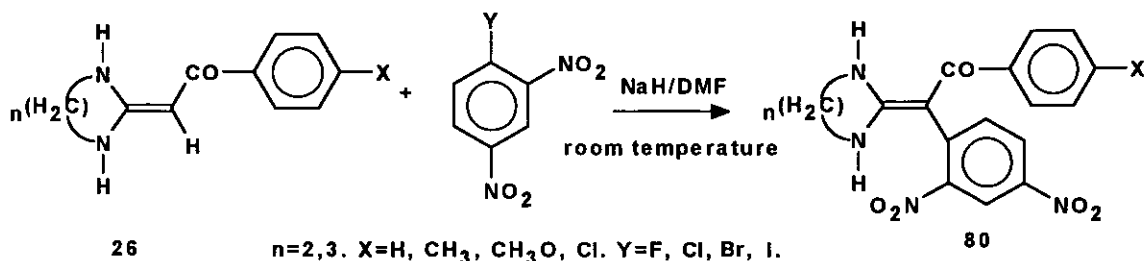


When imine (78) was employed, reaction gave rise to the formation of heterocyclic compound (79).⁸⁰ Apparently, displacement of ethoxy by α -carbon of heterocyclic ketene aminal and cyclocondensation of amino with nitrile group were the key steps.

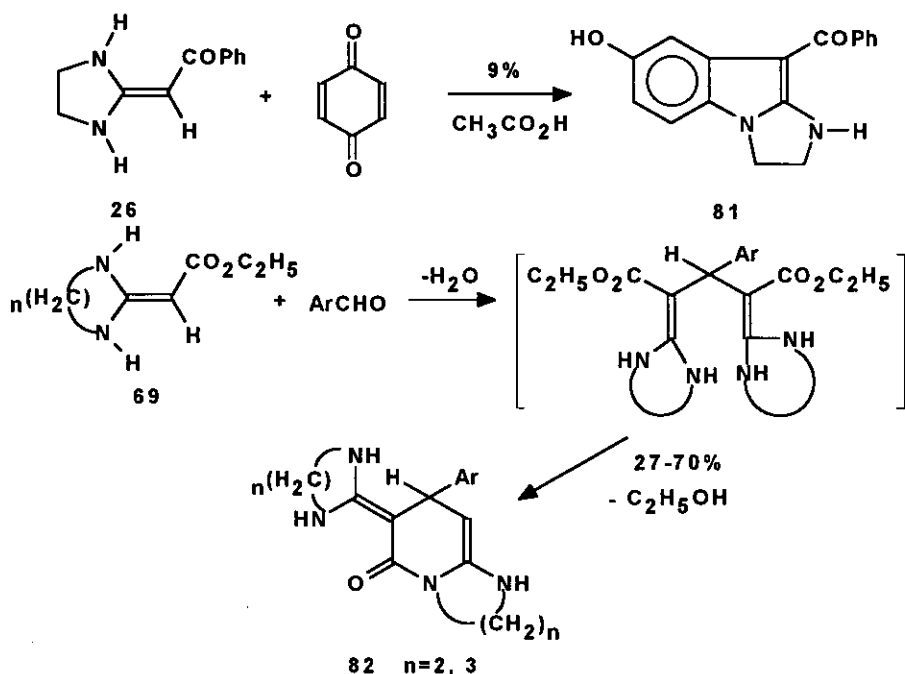


3.4. Arylation

No arylation was observed between heterocyclic ketene aminals (**26**) and halobenzenes under neutral condition. However, the anion of **26** which was prepared with sodium hydride in DMF can react with 2,4-dinitrohalobenzenes to afford *C*-arylated products (**80**). 2,4-Dinitrofluorobenzene gave the best yield. It has been demonstrated that the reaction proceeded through a radical nucleophilic substitution ($S_{RN}1$) mechanism.⁸²



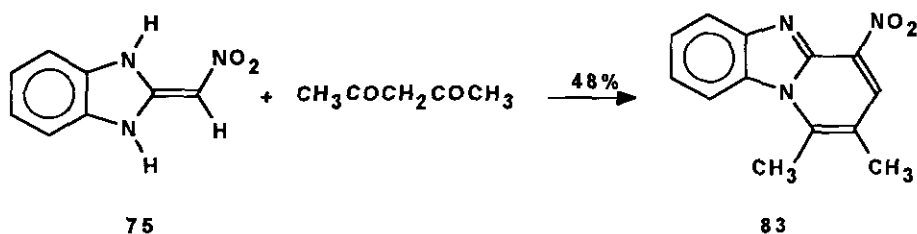
The reaction of heterocyclic ketene aminals (**26**) with 1,4-benzoquinone has been examined, and an exclusively tricyclic indole (**81**) was obtained in very low yield.⁸³



3.5. With aldehydes and ketones

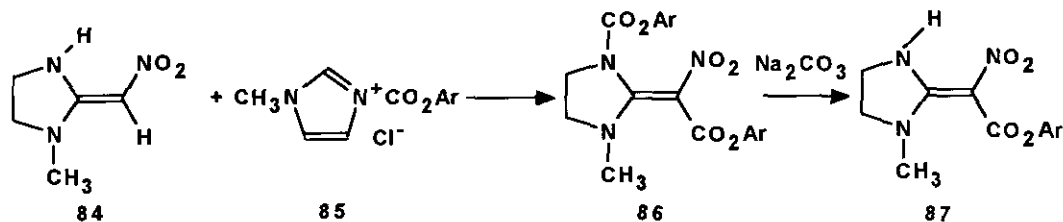
Only few cases are known for the alkylation of heterocyclic ketene aminals by aldehydes and ketones. Compounds (69) reacted with aldehydes to give fused heterocycles (82) with elimination of water and ethanol.⁸⁴

Heterocyclic ketene aminaI (75) reacted with acetylacetone to afford condensed product (83).⁸⁵



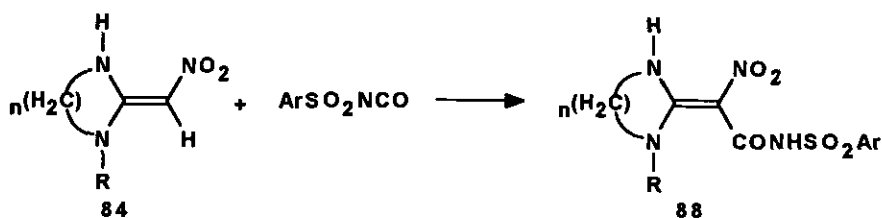
4. ACYLATION

Acylation of heterocyclic ketene aminals with carboxylic acid halides has been reported to occur on α -carbon⁶¹ and oxygen^{12,13} of carbonyl group attached at α -carbon. These have already been discussed in section 2.3. In addition, secondary amino group can also be acylated. For example, nitro-substituted heterocyclic ketene aminaI (84) reacted with 1-methyl-3-phenoxycarbonylimidazolium chloride (85), prepared from the reaction of phenoxycarbonyl chloride and imidazole, to give bis-acylated product (86). Hydrolysis of 86 led to α -carbon acylated product (87).⁸⁶

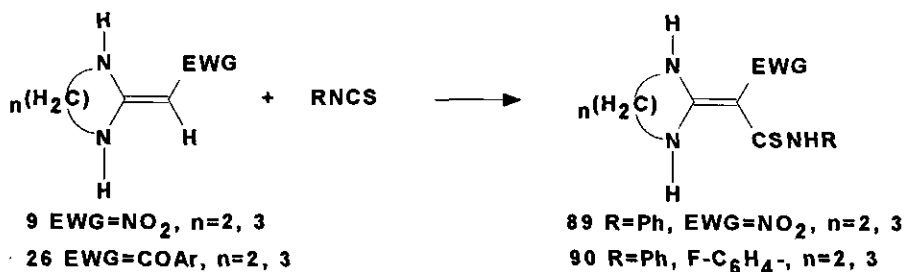


From the acylation reaction, we can found that three reaction sites (α -C, N and O) of heterocyclic ketene aminals are sensitive to carboxylic acid chloride.

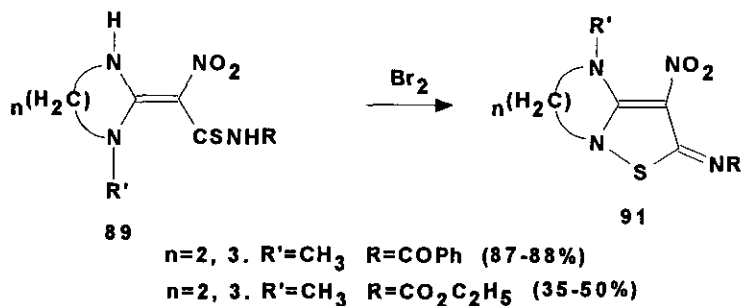
In contrast to the carboxylic acid chloride, acylation of heterocyclic ketene aminals with isocyanates and isothiocyanates gave clearly α -acylated product. Carbonyl-substituted heterocyclic ketene aminals (88) have been obtained from 84 and arylsulphonyl isocyanates.⁸⁷



Rajappa *et al.*²⁷ have used isothiocyanates as probe to examine the enaminic reactivity of nitro substituted enamines and 1,1-enediamines, and they found that compounds (9) were unreactive toward aryl and alkyl isothiocyanates. Very recently, same reaction has been re-examined and it has been found that 9 reacted readily with aryl isothiocyanate to give α -carbon adducts (89) in 54-64%.⁸⁸ The reaction of benzoyl-substituted heterocyclic ketene amins (26) with aryl isothiocyanates proceeded successfully, and always gave excellent yield of 90.⁸⁸

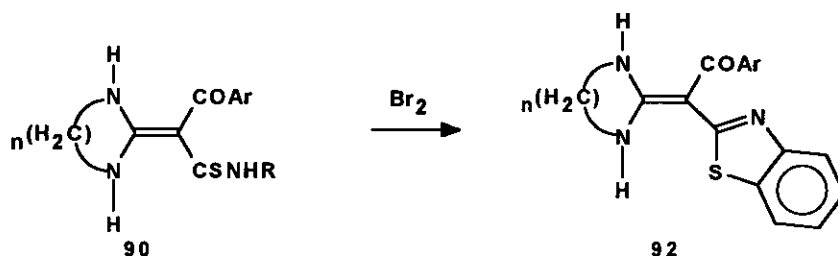


Oxidation of 89 with bromine resulted in the formation of isothiazole derivatives (91).^{88,89} The yield of oxidation-cyclization reaction depended on the substituent R drastically.

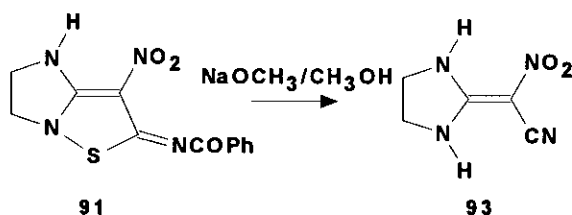


Oxidation of 90 under same conditions, however, did not furnish isothiazole compounds. Instead, benzothiazoles (92) were formed.⁸⁸ The different outcome of the oxidation reaction reveals that the reactivity of

secondary amino group in heterocyclic ketene amins is affected greatly by the electron-withdrawing substituents on α -carbon atom.



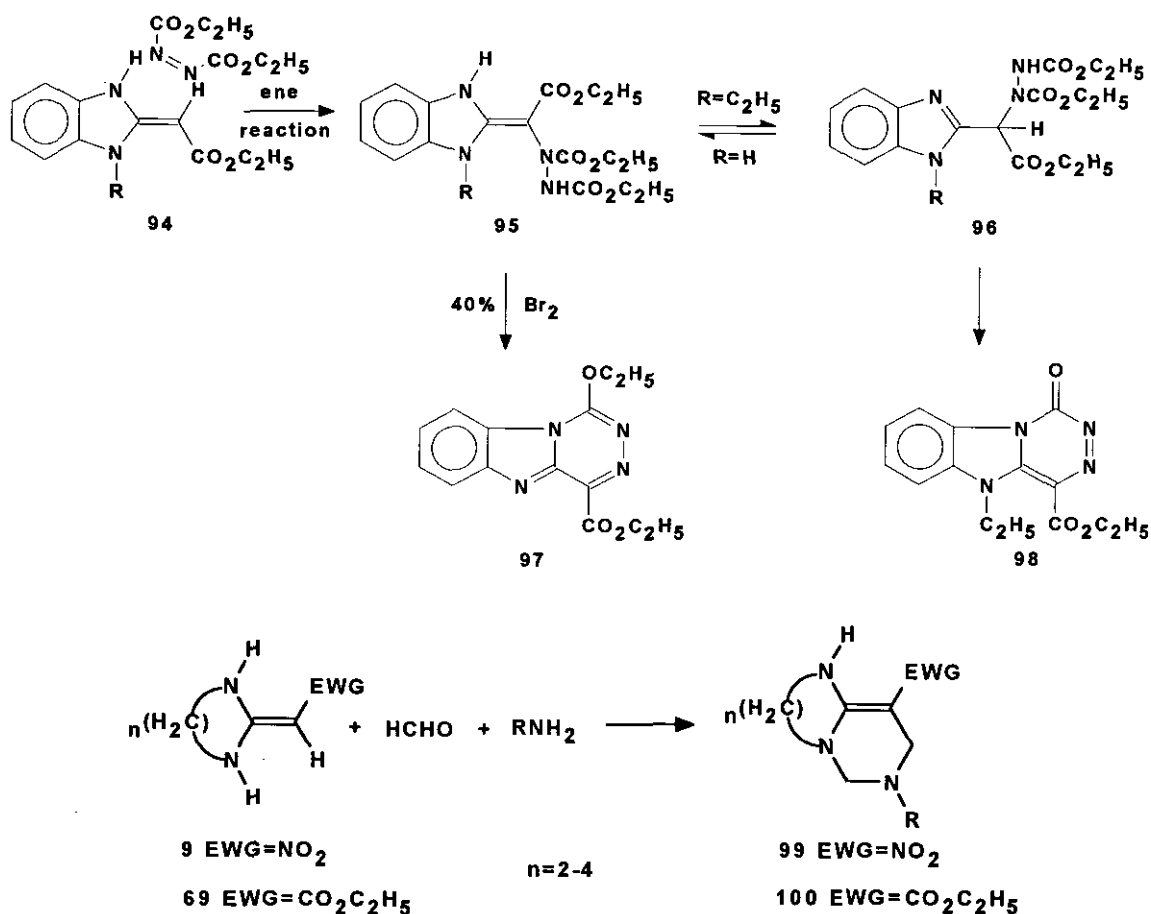
Further transformation of isothiazoles has been made. On treatment of **91** with sodium methoxide in methanol, fragmentation reaction occurred to give **93**.^{65,90}



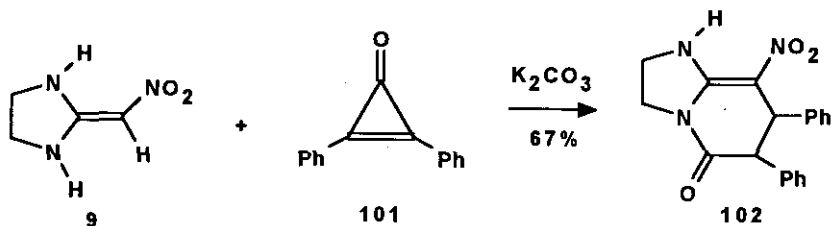
5. REACTION WITH OTHER ELECTROPHILES

Except for the electrophilic reagents presented above, heterocyclic ketene amins can react with a variety of other electrophiles. Protonation,^{10,58} halogenation^{58,91,92} and nitration⁹³ have been reported. In addition, their reactions with phenylsulfenyl chloride^{92,94} and aryldiazo cation^{95,96} have also been known. These reactions all occurred on α -carbon atom. Heterocyclic ketene amins (**26**) reacted with diethyl azodicarboxylate smoothly at room temperature to afford excellent yield of *C*-adduct.^{9,10} Benzimidazoline-substituted ketene amins (**94**) also led to *C*-adducts (**95**) or (**96**) when refluxed with diethyl azodicarboxylate in methylene chloride.¹⁵ Ene-reaction was suggested by the authors. Oxidation of **95** and **96** with bromine and diisopropylethylamine varied greatly. In cold methylene chloride, **95** was oxidized to tricyclic compound (**97**) in moderate yield, whereas only tiny amount of **98** was given from **96** under various oxidizing conditions.⁹⁷

Mannich reaction of heterocyclic ketene amins has been reported. Compounds (**9**) and (**69**) reacted with formaldehyde and primary amines readily to form fused heterocycles (**99**) and (**100**). Normally, the reaction was through the Mannich reaction followed by condensation between amino group and second formaldehyde molecule.^{30,98,99}

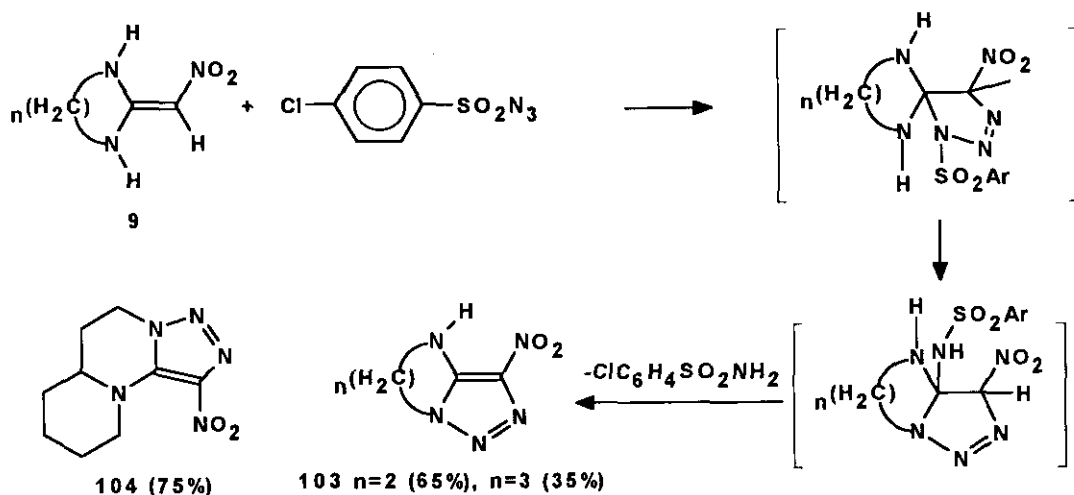


Diphenylcyclopropanone (**101**) has been used to react with nitro-substituted heterocyclic ketene amination. In the presence of K_2CO_3 , the reaction between **9** and **101** led to the γ -lactam-fused heterocyclic product (**102**). Mechanism proposed for this reaction starts with attack of the enamine nitrogen on the carbonyl moiety of **101**.¹⁰⁰

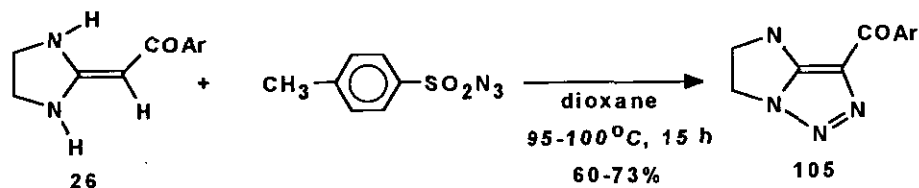


6. REACTION WITH 1,3-DIPOLES

The reaction of heterocyclic ketene amins with azides has been studied extensively. It was reported in 1979¹⁰¹ that nitro-substituted compounds (**9**) reacted with *p*-chlorobenzenesulphonyl azide to give the triazole-fused heterocycles (**103**) in moderate yield. Compound (**104**) was also obtained in 75%. The reaction was postulated to proceed *via* 1,3-dipolar cycloaddition, the Dimroth rearrangement and deamination sequences.

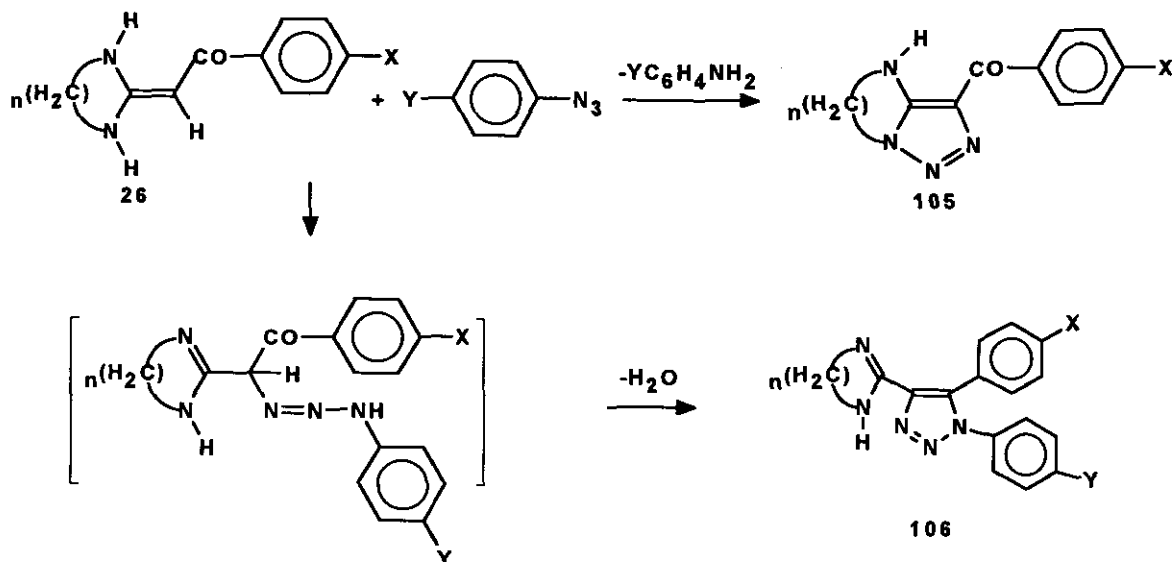


Later, similar result was reported by Junjappa *et al.*²⁵ Fused heterocyclic compounds (**105**) were obtained from benzoyl-substituted heterocyclic ketene amins (**26**) and *p*-methylbenzenesulphonyl azide.

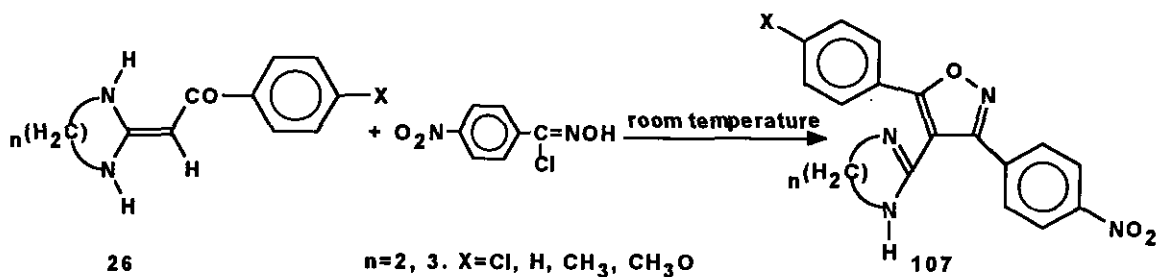


In contrast to benzenesulphonyl azide, the reaction between **26** and aryl azides gives only small amount of **105**, instead, highly substituted triazoles (**106**) are formed as major product.^{102,103} When *p*-nitrophenyl azide is used, reaction furnishes **106** exclusively. It has been believed that there are two competition reaction pathways involved in the reaction, and benzoyl-substituted heterocyclic ketene amins act mainly as nucleophiles rather than 1,3-dipolarophiles toward aryl azides. Therefore, they undergo nucleophilic addition to azido group,

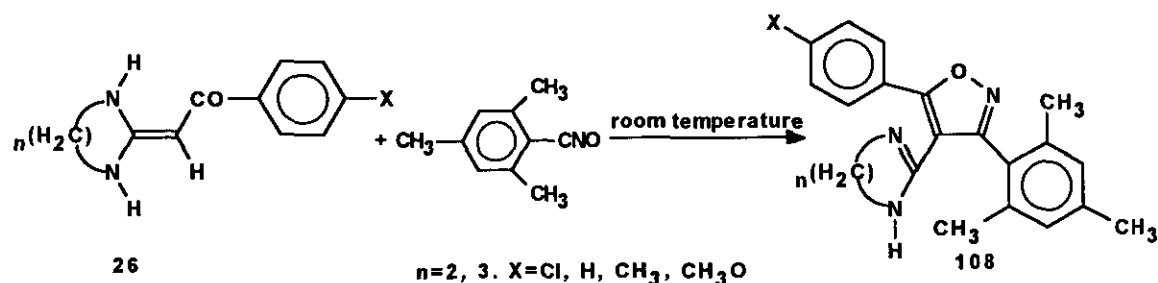
followed by intramolecular cyclocondensation, to give products (106). Only in the case of unfavorable electronic factors, do 1,3-dipolar cycloaddition reaction take place.¹⁰³



Nitrile oxides have been examined to react with benzoyl-substituted heterocyclic ketene aminals (26). Due to the rapid dimerization of nitrile oxide, no reaction happens between 26 and *p*-nitrobenzonitrile oxide. However, 26 reacts smoothly with *p*-nitrobenzhydroxamic acid chloride, precursor of nitrile oxide, to give isoxazoles (107).¹⁰⁴



When 2,4,6-trimethylbenzonitrile oxide, which is hardly dimerized because of steric effect, is used, 26 adds to it at ambient temperature to give isoxazoles (108) in moderate to excellent yields.¹⁰⁵ In these cases, benzoyl-substituted heterocyclic ketene aminals (26) are only nucleophiles rather than 1,3-dipolarophiles.

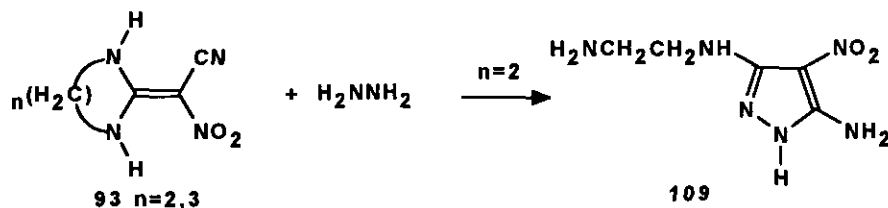


The reaction for heterocyclic ketene aminals (26) not behaving like 1,3-dipolarophiles has been rationalized as a levelling effect¹⁰⁶ arising from the amino and electron-withdrawing groups in the molecule. Based on the frontier electron theory of Fukui, MO perturbation treatment of the reaction between phenyl azide and olefins shows that attaching either an electron-donating or an electron-withdrawing group to the olefins accelerates 1,3-dipolar addition but decreases the reactivity when both kinds of substituents are incorporated in one molecule.¹⁰⁶ The influence of the electron-donating amino groups in 26 may be compensated by that of electron-withdrawing benzoyl group, *i.e.*, the accelerating effect led by amino groups is at least partially cancelled by benzoyl substituent. In addition, strong conjugation effect weakens the double bond character in heterocyclic ketene aminals.

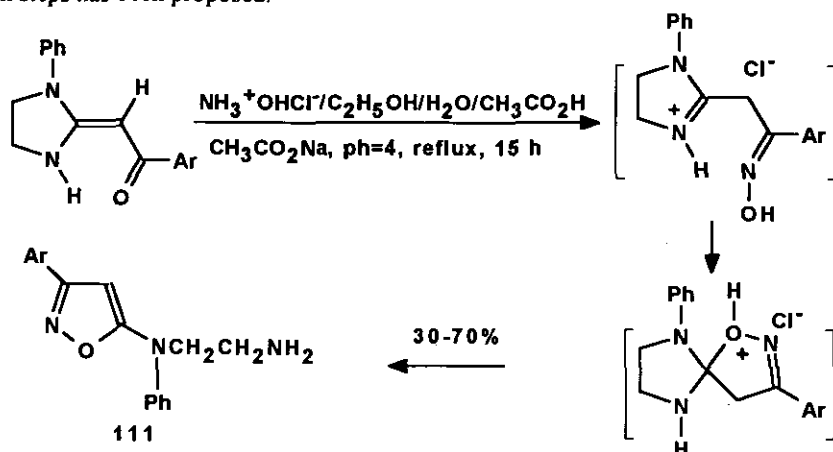
7. MISCELLANEOUS REACTIONS

Catalytic reduction of nitro-substituted heterocyclic ketene aminals gave the 2-aminomethylamidine products in which only nitro group was reduced.¹⁰⁷ Attempts to reduce the benzoyl-substituted heterocyclic ketene aminals (26) were unsuccessful.¹⁰⁸ These results are not unexpected, since the double bond character of the molecules in weakened owing to the strong conjugation effect.

Treatment of five-membered heterocyclic ketene aminal (93) ($n=2$) with hydrazine gave rise to pyrazole compound (109), but strangely, no any characterizable products was obtained when the six-membered analogue (93) ($n=3$) was employed in the reaction.¹⁰⁹



Ring transformation from benzoyl-substituted heterocyclic aminals (110) to isoxazoles (111) has been achieved recently.⁶² In acidic media, 110 reacted with hydroxylamine to give moderate yield of 5-(2-aminoethylamino)isoxazoles (111). A reasonable mechanism which involves protonation, oximation, cyclization and deamination steps has been proposed.



8. CONCLUSION

Heterocyclic ketene aminals are versatile starting materials for the synthesis of a wide variety of heterocyclic compounds, particularly the fused heterocyclic compounds. Studies of heterocyclic ketene aminals have been focused on their nucleophilic reactions of α -carbon atom. Nevertheless, reactions of other sites such as nitrogen atom, β -carbon atom and α -substituents should be of interest. We hope that this review will stimulate chemists' interest in exploring the reactions of heterocyclic ketene aminals and their applications in synthesis.

REFERENCES

1. B.-M. Chen and Z.-T. Huang, *J. Struct. Chem.*, 1984, **3**, 27.
2. X.-J. Wang, N.-J. Zhu, F. Guo, Z.-R. Liu, and Z.-T. Huang, *J. Struct. Chem.*, 1987, **6**, 62.
3. X.-J. Wang, N.-J. Zhu, F. Guo, Z.-R. Liu, and Z.-T. Huang, *J. Struct. Chem.*, 1991, **10**, 103.
4. M. W. Anderson, M. J. Begley, R. C. F. Jones, and J. Saunders, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2599.
5. Z.-T. Huang, W.-X. Gan, and X.-J. Wang, *J. Prakt. Chem.*, 1988, **330**, 724.
6. D. Adhikesavalu and K. Venkatesan, *Acta Crystallogr. Sect. C*, 1983, **39**, 1044.
7. R. Destro, U. Cosentino, G. Moro, E. Ortoleva, and T. Pilati, *J. Mol. Struct.*, 1989, **212**, 97.

8. K. Baum, S. S. Bigelow, N. V. Nauyen, T. G. Archibald, R. Gilardi, J. L. Flippen-Anderson, and C. Georeg, *J. Org. Chem.*, 1992, **57**, 235.
9. Z.-T. Huang and L.-H. Tzai, *Chem. Ber.*, 1986, **119**, 2208.
10. Z.-T. Huang and Z.-R. Liu, *Synthesis*, 1987, 357.
11. X.-J. Wang and Z.-T. Huang, *Acta Chim. Sinica*, 1989, **47**, 890.
12. J. D. Albright and R. C. Schepherd, *J. Heterocycl. Chem.*, 1973, **10**, 899.
13. E. F. Godefroi and J. H. Geenen, *J. Med. Chem.*, 1975, **18**, 530.
14. Z.-T. Huang and M.-X. Wang, *Tetrahedron*, 1992, **48**, 2325.
15. N. Finch and C. W. gemenden, *Tetrahedron Lett.*, 1969, 1203.
16. R. C. F. Jones and S. C. Hirst, *Tetrahedron Lett.*, 1989, **30**, 5361.
17. W. J. Middleton and V. A. Engelhardt, *J. Am. Chem. Soc.*, 1958, **80**, 2788.
18. J. Sandstrom, *Top. Stereochem.*, 1983, **14**, 83.
19. R. Gompper and W Topel, *Chem. Ber.*, 1962, **95**, 2871.
20. R. Gompper and H. Schaefer, *Chem. Ber.*, 1967, **100**, 591.
21. R. K. Dieter, *Tetrahedron*, 1986, **42**, 3029.
22. M. Yokoyama and T. Imamoto, *Synthesis*, 1984, 797.
23. Y. Tominaga and Y. Matsuda, *J. Heterocycl. Chem.*, 1985, **22**, 937.
24. M. Kolb, *Synthesis*, 1990, 171.
25. H. Junjappa, H. Ila, and C. V. Asokan, *Tetrahedron*, 1990, **46**, 5423.
26. D. Villemain and A. B. Alloum, *Synthesis*, 1991, 301.
27. S. Rajappa, R. Sreenivasan, B. G. Advani, R. H. Summerville, and R. Hoffmann, *Indian J. Chem.*, 1977, **15b**, 297.
28. C. H. Tieman, W. D. Kollmeyer, and S. A. Steven, Ger. Offen, 2445421 (*Chem. Abstr.*, 1975, **83**, 97297b).
29. K. Shiokawa, S. Tsuboi, S. Kagabu, K. Moriya, and B. Baasner, Eur. Pat. Appl. EP, 212600 (*Chem. Abstr.*, 1987, **107**, 7209m).
30. M. Sone, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, 1977, **97**, 262 (*Chem. Abstr.*, 1977, **87**, 53195v).
31. H. Schaefer, B. Bartho, and K. Gewald, *J. Prakt. Chem.*, 1977, **319**, 149.

32. W.-D. Rudolf, A. Schierhorn, and M. Augustin, *Tetrahedron*, 1979, **35**, 551.
33. Z.-T. Huang and Z.-R. Liu, *Synth. Commun.*, 1989, **19**, 943.
34. Z.-H. Huang and X.-J. Wang, unpublished results.
35. M. Augustin and Ch. Groth, *J. Prakt. Chem.*, 1979, **321**, 215.
36. S. Seube, A.-M. Lamazouere, and L. Sotiropoulos, *J. Heterocycl. Chem.*, 1978, **15**, 343.
37. Z.-T. Huang and X.-J. Wang, *Chem. Ber.*, 1987, **120**, 1803.
38. M. Augustin and Ch. Groth, *J. Prakt. Chem.*, 1979, **321**, 215.
39. M. Augustin and S. Bielka, *Z. Chem.*, 1980, **20**, 90.
40. H.-T. Wang, X.-J. Wang, and Z.-T. Huang, *Chem. Ber.*, 1990, **123**, 2141.
41. Z.-T. Huang and X. Shi, *Synth. Commun.*, 1990, **20**, 1321.
42. Z.-T. Huang and M.-X. Wang, *Synthesis*, 1992, 1273.
43. M. Augustin and G. Jahreis, *J. Prakt. Chem.*, 1979, **321**, 699.
44. W.-D. Rudolf and M. Augustin, *J. Prakt. Chem.*, 1977, **319**, 545.
45. M. Augustin and W. Dolling, *J. Prakt. Chem.*, 1982, **324**, 3.
46. W. Dolling, M. Augustin, and H. Bohrer, *Z. Chem.*, 1985, **25**, 176.
47. W. Dolling, K. Khoudary, and M. Augustin, *J. Prakt. Chem.*, 1989, **331**, 573.
48. R. Neidlein and T. Eichinger, *Synthesis*, 1991, 1228.
49. A. Ushiroguchi, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Heterocycles*, 1980, **14**, 7.
50. Y. Tominaya, H. Fujito, N. Norisue, A. Ushiroguchi, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, 1980, **100**, 699 (*Chem. Abstr.*, 1981, **94**, 472285c).
51. G. G. Levkovskaya, A. N. Mirskova, I. D. Kalikhman, and M. G. Voronkov, *Zh. Org. Khim.*, 1984, **20**, 634 (*Chem. Abstr.*, 1984, **101**, 90823b).
52. K. Shiokawa, S. Toshibe, and K. Moriie, Jpn. Kokai Tokkyo Kono JP, 6248681 (*Chem. Abstr.*, 1987, **107**, 198324).
53. M. Hojo, R. Masuda, E. Okada, H. Yamamoto, and K. Okada, *Synthesis*, 1990, 195.
54. R. Neidlein, D. Kikelj, and W. Kramer, *J. Heterocycl. Chem.*, 1989, **26**, 1335.
55. H. Wamhoff and C. Meterne, *Liebigs Ann. Chem.*, 1971, **754**, 113.
56. H. Wamhoff, C. Meterne, and F. Knoll, *Chem. Ber.*, 1972, **105**, 753.
57. H. Wamhoff and C. Meterne, *Chem. Ber.*, 1974, **107**, 1784.

58. Z.-T. Huang and H. Wamhoff, *Chem. Ber.*, 1984, **117**, 622.
59. W. Reid and A. Sinharay, *Chem. Ber.*, 1963, **96**, 3306.
60. H. Wamhoff and C. Materne, *Liebigs Ann. Chem.*, 1973, 573.
61. M. D. Nair, S. Rajappa, and J. A. Desai, *Indian J. Chem.*, 1982, **21b**, 1.
62. G. Dannhardt and S. Laufer, *Synthesis*, 1989, 12.
63. S. Rajappa, M. D. Nair, S. Sreenivasan, and B. G. Advani, *Tetrahedron*, 1982, **38**, 1673.
64. W. D. Kollmeyer, U. S. Pat., 4053622 (*Chem. Abstr.*, 1978, **88**, 37798).
65. S. Rajappa, M. D. Nair, B. G. Advani, and R. Sreenivasan, *J. Chem. Soc., Perkin Trans. 1*, 1981, 3161.
66. Z.-T. Huang and L.-H. Tzai, *Chinese Chem. Lett.*, 1991, **2**, 267.
67. M. D. Nair and J. A. Desai, *Indian J. Chem.*, 1982, **21B**, 4.
68. Z.-T. Huang and Z.-R. Liu, *Chem. Ber.*, 1989, **122**, 95.
69. R. C. F. Jones and S. C. Hirst, *Tetrahedron Lett.*, 1989, **30**, 5365.
70. Z.-T. Huang and Z.-R. Liu, *Heterocycles*, 1986, **24**, 2247.
71. R. C. F. Jones and M. J. Smallridge, *Tetrahedron Lett.*, 1988, **29**, 5005.
72. Z.-T. Huang and M.-X. Wang, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1085.
73. Z.-T. Huang and H. Wamhoff, *Chem. Ber.*, 1984, **117**, 1856.
74. Z.-T. Huang and H. Wamhoff, *Chem. Ber.*, 1984, **117**, 1926.
75. Z.-T. Huang and X.-J. Wang, *Tetrahedron Lett.*, 1987, **28**, 1527.
76. W.-Y. Zhao and Z.-T. Huang, *Synth. Commun.* 1993, **23**, 1039.
77. A. K. Gupta, H. Ila, and H. Junjappa, *Synthesis*, 1988, 285.
78. H. Meyer, F. Bossert, and H. Horstmann, *Liebigs Ann. Chem.*, 1977, 1888.
79. H. Meyer, F. Bossert, and H. Horstmann, *Liebigs Ann. Chem.*, 1977, 1895.
80. H. Schafer and K. Gewald, *Z. Chem.*, 1978, **18**, 335.
81. K. Kurata, H. Awaya, Y. Tominaga, Y. Matsuda, and G. Kobayashi, Bunseki Kiki, 15413 (*Chem. Abstr.*, 1978, **88**, 121047w).
82. W.-Y. Zhao and Z.-T. Huang, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1967.
83. V. Aggarwal, A. Kumar, H. Ila, and H. Junjappa, *Synthesis*, 1981, 157.
84. H. Meyer, F. Bossert, and H. Horstmann, *Liebigs Ann. Chem.*, 1978, 1483.
85. H. Schafer and K. Gewald, *Z. Chem.*, 1976, **16**, 272.

86. W. D. Kollmeyer, U. S. Pat., 4053622 (*Chem. Abstr.*, 1978, **88**, 37797h).
87. W. D. Kollmeyer, S. A. Roman, and S. B. Soloway, U. S. Pat., 4029791 (*Chem. Abstr.*, 1977, **87**, 117871x).
88. Z.-T. Huang and J.-K. Yang, *Heteroatom Chem.*, 1992, **3**, 487.
89. S. Rajappa, B. G. Advani, and R. Sreenivasan, *Indian J. Chem.*, 1977, **15B**, 886.
90. S. Rajappa, B. G. Advani, and R. Sreenivasan, *Tetrahedron*, 1977, **33**, 1057.
91. C. H. Tieman, W. D. Kollmeyer, and S. A. Roman, U. S. Pat., 3969354 (*Chem. Abstr.*, 1976, **85**, 192727s).
92. C. H. Tieman, W. D. Kollmeyer, and S. A. Eoman, U. S. Pat., 3971774 (*Chem. Abstr.*, 1977, **86**, 5460k).
93. K. Baum, N. V. Nguyen, R. Gilardi, J. L. Flippen-Anderson, and C. George, *J. Org. Chem.*, 1992, **57**, 3026.
94. W. D. Kollmeyer, U. S. Pat., 3996372 (*Chem. Abstr.*, 1977, **86**, 121332u).
95. H. Shafer and K. Gewald, *J. Prakt. Chem.*, 1980, **22**, 87.
96. M.-D. Ruan, W.-Q. Fan, Y.-Z. Gu, H.-J. Jiang, and Y.-F. Bu, *Synth. Commun.*, 1991, **21**, 1307.
97. N. Finch and C. W. Gemenden, *J. Org. Chem.*, 1970, **35**, 3114.
98. W. Hilmar, B. Benedikt, H. Bernhard, and S. Wilhelm, EP 247477 (*Chem. Abstr.*, 1988, **108**, 94588w).
99. M. Augustin and E. Gunther, *Z. Chem.*, 1988, **28**, 436.
100. M. Takahashi, C. Nozaki, and Y. Shibasaki, *Chem. Lett.*, 1987, 1229.
101. N. I. Viswanathan and V. Balakrishnan, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2361.
102. Z.-T. Huang and M.-X. Wang, *Chinese Chem. Lett.*, 1990, **1**, 5.
103. Z.-T. Huang and M.-X. Wang, *J. Org. Chem.*, 1992, **57**, 184.
104. Z.-T. Huang and M.-X. Wang, *Synth. Commun.*, 1991, **21**, 1167.
105. Z.-T. Huang and M.-X. Wang, *Synth. Commun.*, 1991, **21**, 1909.
106. R. Sustmann, *Pure Appl. Chem.*, 1974, **40**, 569 and references cited therein.
107. S. Rajappa and R. Sreenivasan, *Indian J. Chem.*, 1979, **17B**, 339.
108. Z.-T. Huang and M.-X. Wang, unpublished results.
109. S. Rajappa and B. G. Advani, *Indian J. Chem.*, 1977, **15B**, 890.

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