Advances in heterocyclic ketene aminals*

WANG Meixiang and HUANG Zhitang**

(Center for Molecular Science, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, China)

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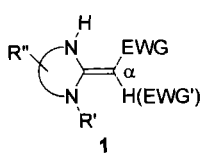
Abstract Recent developments in the study of the reactions of heterocyclic ketene aminals are reviewed with the emphases on regioselective alkylation, acylation and glycosylation reactions, and on the aza-ene reactions with α, β-unsaturated compounds, azo and carbonyl compounds. Reactions with 1, 3-dipoles and other reagents to synthesize fused heterocycles are also discussed.

Keywords: heterocyclic ketene aminals, regioselective reaction, aza-ene reaction, 1, 3-dipoles, fused heterocycles.

Heterocyclic ketene aminals **1** (Fig. 1), also known as cyclic 1, 1-endiamines, are powerful and versatile intermediates of synthetic value. One of the notable features of heterocyclic ketene aminals is the enhanced electron density on the α-carbon leading to higher nucleophilicity than that of nitrogen, owing to the conjugation effect of the electron-donating amino groups and the electron-withdrawing substituents. Considerable effort has been made therefore during the past decades to study enaminic carbon reactions. Since, in addition, the secondary amino group can also participate in the reaction, heterocyclic ketene aminals may serve as bis-nucleophilic reagents. Hence the annulation of heterocyclic ketene aminals with bis-electrophilic reagents gives rise to a wide variety of fused heterocyclic compounds which are hardly accessible to other synthetic methods. It is worth noting that some heterocyclic ketene aminals and their derivatives have been shown to possess certain biological activities, which has drawn the attention of medicinal chemists and agrochemists.



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EWG, EWG' = NO_2, CN, COR, CO_2R....
R', R" = H, alkyl, aryl

Fig. 1. Structure of heterocyclic ketene aminals.

The literature up to 1994 regarding the chemistry of heterocyclic ketene aminals has been summarized in our previous review article[1]. Since then, however, progress has been made in the study of heterocyclic ketene aminals. The purpose of this paper is to review the recent advances in reactions of these intermediates and the emphases will be laid on the work carried out in our laboratory.

1 Regioselective reaction of benzoyl-substituted heterocyclic ketene aminals

Although heterocyclic ketene aminals always undergo nucleophilic reactions at the α-carbon atom under neutral conditions, study of the structural properties[2] has revealed that acyl-substituted heterocyclic ketene aminals could utilize both secondary amino nitrogen and carbonyl oxygen sites to interact with electrophiles. Preferential *N*- or *O*-reactions over α-*C* would be expected if reaction conditions are optimized. Benzoyl-substituted heterocyclic ketene aminals have been shown indeed recently to undergo nucleophilic reactions regioselectively or regiospecifically.

1.1 Regiospecific alkylations

When a mixture of heterocyclic ketene aminals **2** and ethyl bromoacetate **3** was refluxed in acetonitrile, alkylation took place regiospecifically at enaminic carbon center to produce compounds **4**. Intramolecular cyclocondensation of **4** afforded γ-lactam-fused heterocyclic products **5**[3]. In the presence of sodium hydride, however, *N*-alkylation was affected efficiently, leading to compounds **6** which underwent cyclocondensation to yield 3-pyrrolidinone derivatives **7**[4] (Scheme 1).

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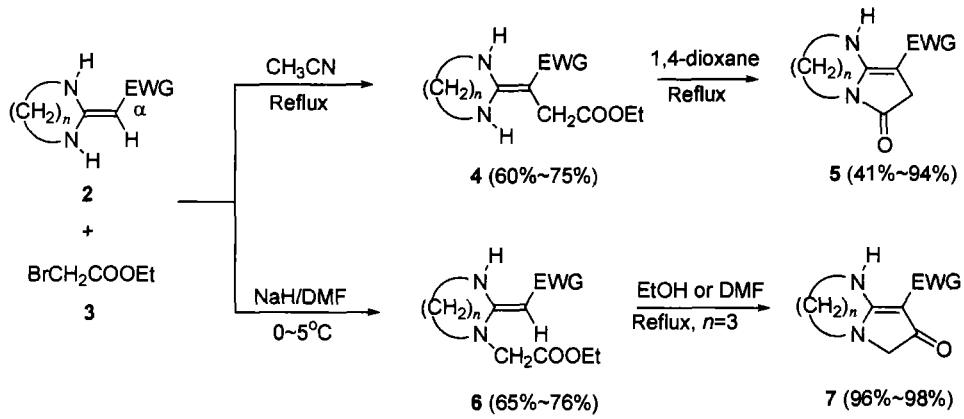
** To whom correspondence should be addressed. E-mail: huangzt@public.bta.net.cn

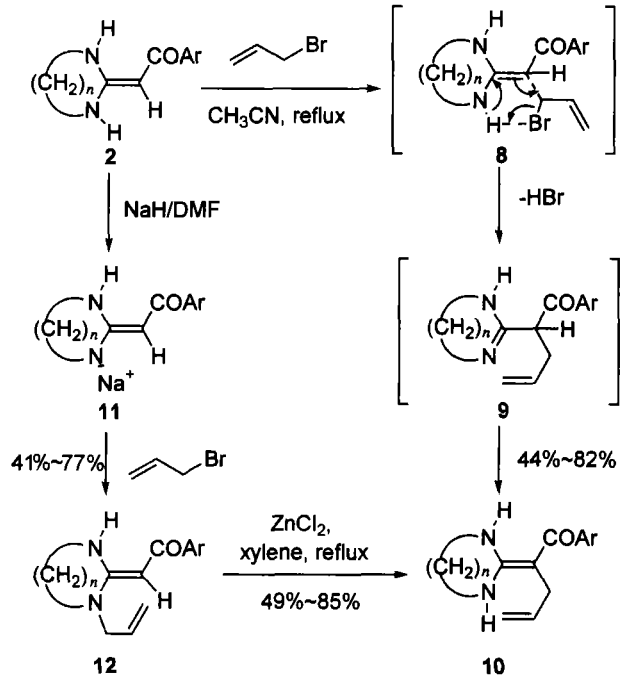


Scheme 1

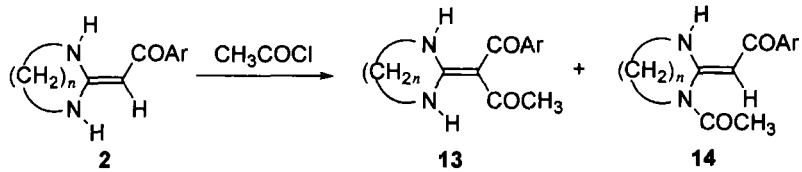
Under the same neutral and basic conditions, heterocyclic ketene aminals **2** have been reported to undergo respective *C*- and *N*-alkylations with benzyl chloride[3,5] and allyl bromide[6]. It has been found that no reaction occurred when a *N*, *N*′-dimethylated heterocyclic ketene aminals analogue was allowed to interact with allyl bromide. A concerted mechanism involving a six-membered transition state has been proposed[6]. In the same paper, a zinc chloride-promoted 3-aza-Cope rearrangement of *N*-allylated heterocyclic ketene aminals **12** to **10** has also been described[6] (Scheme 2).

1.2 Regioselective acylation

The reaction between heterocyclic ketene aminals and carboxylic acid chlorides proceeds readily, but with poor regioselectivity. This has been exemplified by the reactions of **2** with propionic acid chloride, which gave both *C*- and *N*-acyl products with a ratio from 1∶1 to 1∶4.[7] In order to improve the selectivity, different methods were attempted. It has been found that regioselectivity of acetylation of **2** at α-carbon was improved significantly when mercury (II) cyanide and triethylamine were present in the reaction mixture. *N*-acetylation of **2** was achieved exclusively when sodium hydride was used[8] (Scheme 3).



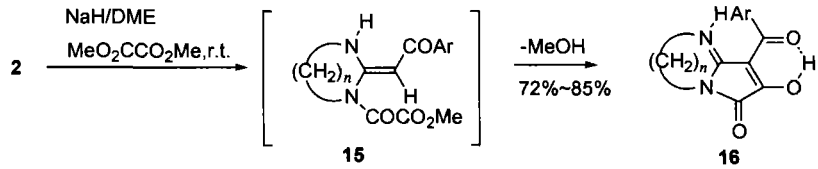
Scheme 2



$Hg(CN)_2/Et_3N$/-10°C	*n*=2:	58%~68%	12%~21%
	n=3:	74%~84%	2%~6%
NaH/DMF/-10°C	*n*=2:	0	75%~81%
	n=3:	0	64%~70%

Scheme 3

Successful acylation of heterocyclic ketene aminals at α-carbon position normally requires active acylation reagents such as carboxylic acid halides[7,8], isothiocyanates[9] and isocyanates[10]. *N*-acylation with the aid of sodium hydride, however, can be carried out utilizing weaker acylating reagents. For example, the synthesis of γ-lactam fused 1,3-diazaheterocyclic compound **16** has been accomplished by reacting **2** with dimethyl oxalate under basic conditions. The reaction has been proceeded by way of **15**, an intermediate resulting from *N*-acylation of **2**[11] (Scheme 4).

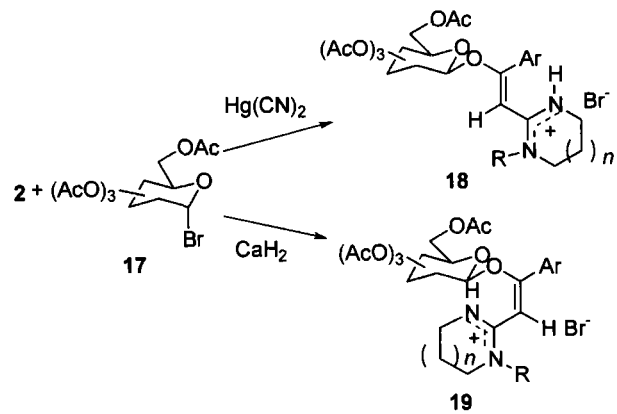


Scheme 4

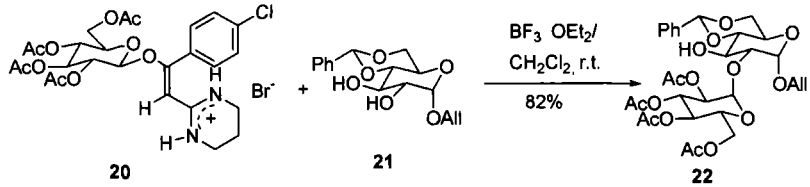
1.3 Regiospecific *O*-glycosidation

Promoted by a Lewis acid or a base, benzoyl-substituted heterocyclic ketene aminals **2** reacted readily with tetra-*O*-acetyl-α-*D*-glucopyranosyl and -galactopyranosyl bromide **17** to give exclusively β-anomers of *O*-glycosylated heterocyclic ketene aminals. Interestingly, the configuration of the double bond formed in products is controlled by the reagents employed. Lewis acid such as mercury (II) cyanide and silver trifluoromethanesulfonate give *E*-form product **18** while *Z*-isomer **19** was obtained with the use of calcium hydride[12,13] (Scheme 5).

It has been found that some of the *O*-glycopyranosyl heterocyclic ketene aminals are able to act as glycosyl donors in the synthesis of oligosaccharides. Illustrated in Scheme 6 is the preparation of disaccharide derivative **22** from the reaction of **20** and **21** catalyzed by boron trifluoride diethyl etherate[12].



Scheme 5



Scheme 6

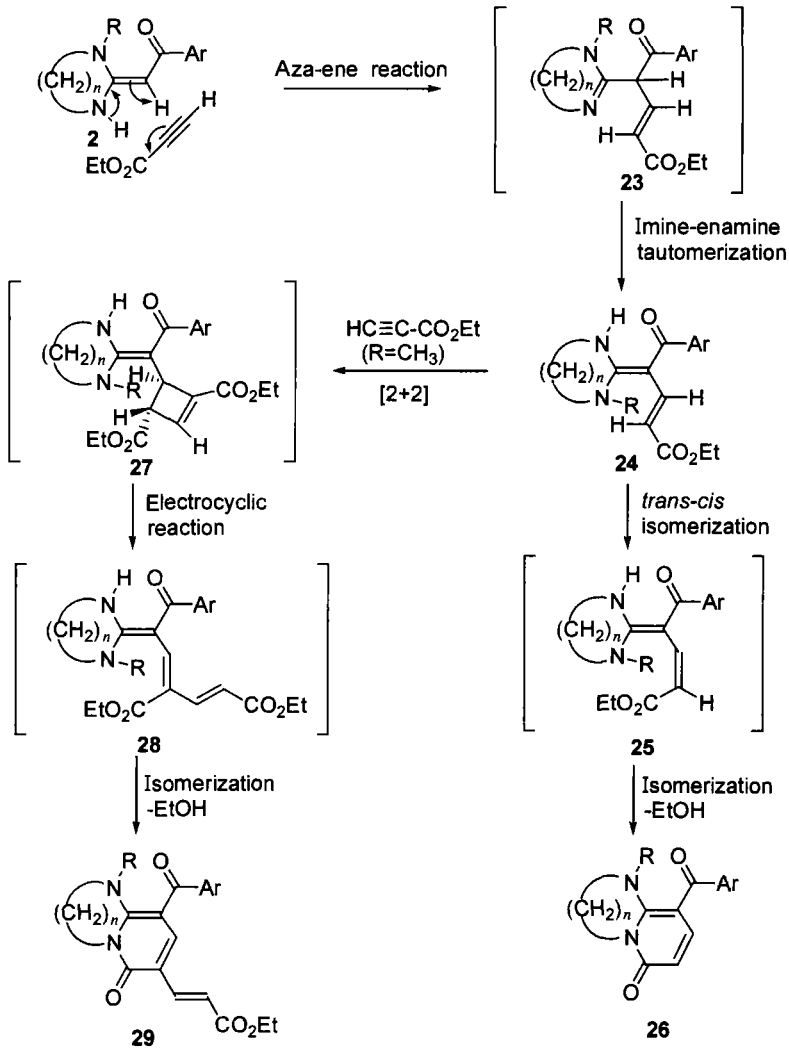
2 Aza-ene reaction of heterocyclic ketene aminals

Ene-reaction is one of the important carbon-carbon bond formation reactions in organic chemistry. Synthetic applications of the ene-reaction along with the reaction mechanisms have been extensively studied and well documented[14]. However, little is known of the hetero-ene reactions such as those involving secondary enamine moiety (H—N—C═C) as an ene-component. Heterocyclic ketene aminals, however, have been shown recently to be a unique aza-ene component. They undergo ready and often efficient aza-ene reactions with α, β-unsaturated compounds and with azo and carbonyl compounds.

2.1 Reaction with α, β-unsaturated compounds

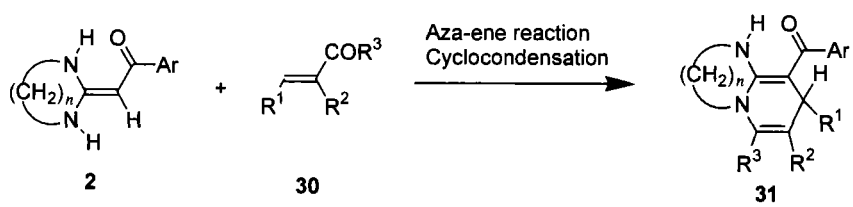
Reaction between heterocyclic ketene aminals and α, β-unsaturated carboxylic acid esters is a powerful synthetic route to δ-lactam fused 1, 3-diazaheterocyclic compounds[15~18]. In a recent study of the reaction pathways[19], results obtained from examination of the effect of heterocyclic ketene aminals' structures and from isolation of reaction intermediates

suggested that secondary enamine (H—N—C=C) in heterocyclic ketene aminals **2** is the reactive segment. It adds to the triple bond via an aza-ene reaction step. When an excess amount of ethyl propiolate was used, ethoxycarbonylvinyl substituted heterocyclic compounds **29** were produced from *N*-methylated heterocyclic ketene aminals through a pathway depicted in Scheme 7[19,20].



Scheme 7

Similar aza-ene reaction of heterocyclic ketene aminals **2** with α, β-unsaturated ketones has been reported very recently to furnish, after intramolecular cyclocondensation, dihydropyridine derivatives **31**[21] (Scheme 8).

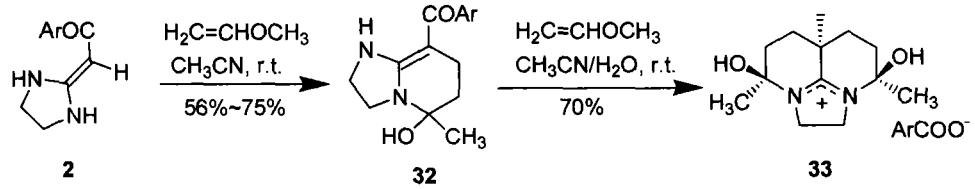


R^1, R^3 = Ar, R^2 = H; R^1 = Ph, R^2-R^3 = $(CH_2)_n$

Scheme 8

When methyl vinyl ketone (MVK) was used as an enophile, reaction appeared interesting. Hydroxy-substituted heterocyclic compounds **32** were yielded from the aza-ene reaction between **2** and MVK fol-

lowed by cyclization. In the presence of excess MVK, compounds **32** underwent further aza-ene addition and cyclization reactions with MVK. The reaction, which was facilitated by adding several drops of water, proceeded in a stereospecific manner with *cis*-dihydroxy imidazo[1, 2, 3-*ij*]- naphthyridine derivatives **33** being formed exclusively[21,22].

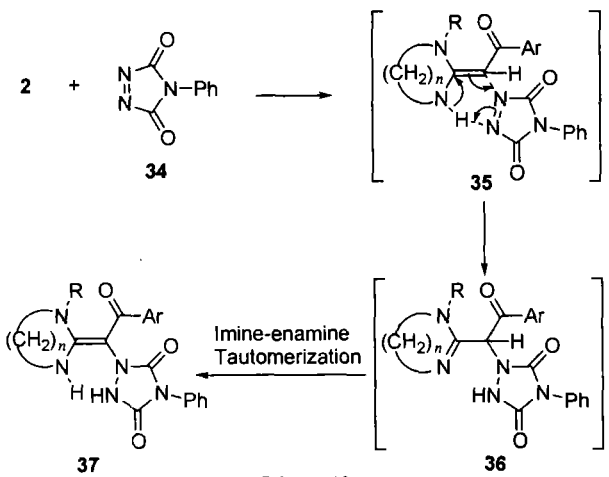


2 **32** **33**

Scheme 9

2.2 Reaction with azodicarboxylic acid diesters

It has been reported previously that the reaction of heterocyclic ketene aminals with diethyl azadicarboxylate proceeded rapidly to give the corresponding adducts[23,24]. Recently, a study of the reaction between **2** and 4-phenyl-1, 2, 4-triazoline-3, 5-dione **34** provided evidence supporting an aza-ene addition mechanism[25] (Scheme 10).

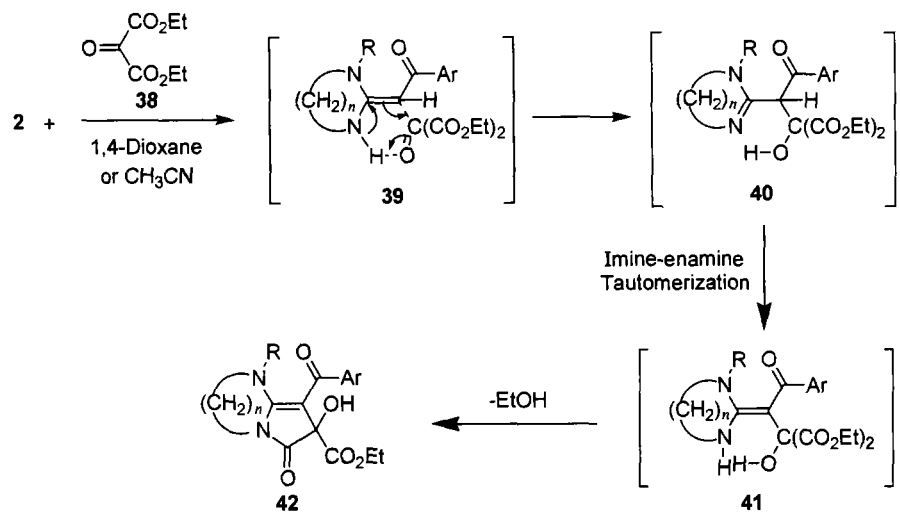


34 **35** **36** **37**

Scheme 10

2.3 Reaction with carbonyl compounds

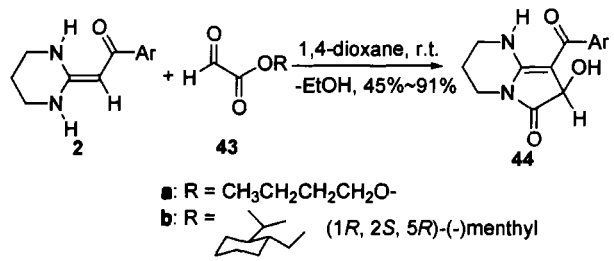
In both a polar and a nonpolar solvent such as acetonitrile and 1, 4-dioxane, respectively, heterocyclic ketene aminals **2** interacted with diethyl oxomalonate **38** at ambient temperature leading to condensed heterocyclic compounds **42**. Being a weaker enophile compared to ethyl propiolate, **38** reacted only with active heterocyclic ketene aminals. In other words, the reaction between **2** and **38** is strongly influenced by the structure of **2**. For example, six-membered heterocyclic ketene aminals reacted rapidly with **38** and the reaction went completion within several hours while it took two days for the five-membered analogues to react with **38**. No reaction occurred when *N*, *N*′-dimethylated heterocyclic ketene aminals were applied. A hetero-ene reaction mechanism has been proposed to account for all experimental facts (Scheme 11).



39 **40** **41** **42**

Scheme 11

Only when the most active six-membered heterocyclic ketene aminals were used, did the aza-ene reaction with *n*-butyl glyoxylate **43a** take place, leading to γ-lactam fused pyrimidine derivatives **44**. Since a chiral center was created during the aza-ene addition, attempts have been made to prepare optically active products **44** utilizing (1*R*, 2*S*, 5*R*)-(-)menthyl glyoxylate **43b** as a chiral substrate. Unfortunately, however, no asymmetric induction was observed. Glyoxylate **43b** is probably not a good chiral reagent in this case as the chiral center of (-)-menthyl group is remote from the aza-ene reaction site (Scheme 12).



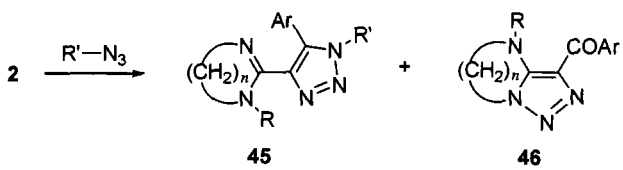
Scheme 12

3 Reaction of heterocyclic ketene aminals with 1, 3-dipolar reagents

Early studies have shown that benzoyl-substituted heterocyclic ketene aminals act as nucleophiles rather than 1, 3-dipolarophiles when being treated with 1, 3-dipolar reagents[26~29]. Only in the case of unfavorable electronic factors may heterocyclic ketene aminals behave as 1, 3-dipolarophiles[29]. It has also been reported that products derived from the reaction with 1, 3-dipolar reagents possess interesting bioactivities. To explore the scope of the reactions of heterocyclic ketene aminals with 1, 3-dipolar reagents, and also to prepare various types of compounds for bioassay, studies of the reactions of aroyl- and heteroaroyl-substituted heterocyclic ketene aminals with different 1, 3-dipolar reagents have been conducted.

3.1 Reaction with azides

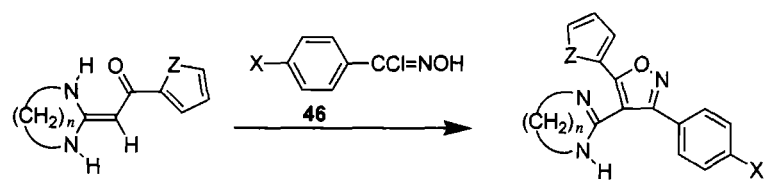
Consistent with our previously reported results, heterocyclic ketene aminals bearing a heteroaroyl group reacted easily with aryl azides to give polysubstituted triazoles **45** as the major product in high yield. A number of triazoles with a sugar substituent has been prepared analogously when the reaction started with an azido sugar. In some cases, condensed triazoles **46** were isolated in low yield[30,31] (Scheme 13).



Scheme 13

3.2 Reaction with nitrile oxides

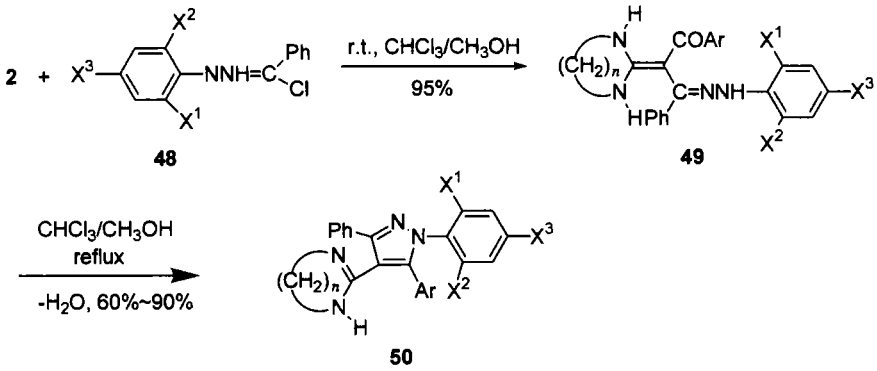
Heteroaroyl substituted heterocyclic ketene aminals **2** underwent nucleophilic substitution and consecutive cyclocondensation reaction with 4-substituted benzohydroximic acid chloride, precursor of nitrile oxide to produce isoxazole compounds **47** (Scheme 14).



Scheme 14

3.3 Reaction with nitrilimines

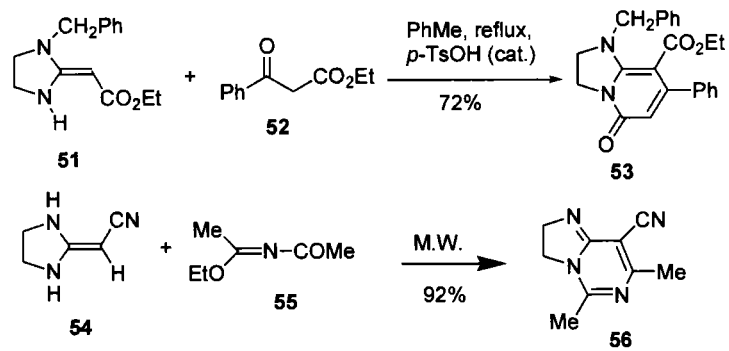
Heterocyclic ketene aminals **2** can react with phenylhydrazidoyl chloride **48**, precursor of nitrilimine in the presence or absence of triethylamine. By the action of **2** with **48** that bears one or more electron-withdrawing substituents such as nitro group on the phenyl ring (X^1, X^2 or $X^3 = NO_2$), the reaction proceeded very rapidly at room temperature to furnish excellent yields of intermediate **49**. Cyclization of **49** at elevated temperature afforded pyrazoles **50**. Reaction of **2** with **49** having no electron-withdrawing group(s) attached to the phenyl ring generally required heating and resulted in direct formation of pyrazoles **50**. These results demonstrate again that benzoyl-substituted heterocyclic ketene aminals act as nucleophiles to react with 1,3-dipolar reagents to produce, after cyclocondensation, polysubstituted five-membered heterocycles (Scheme 15).



Scheme 15

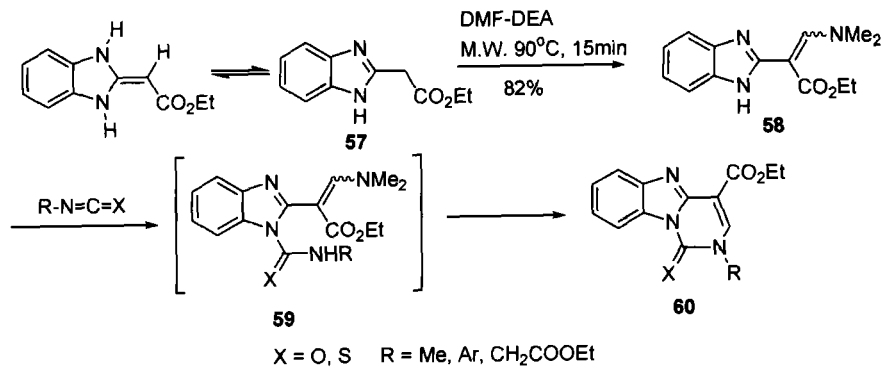
4 Miscellaneous reactions

In addition to the reactions discussed above, other reactions of heterocyclic ketene aminals have also been investigated and they have been applied in the synthesis of fused heterocycles. For example, annulation of *N*-benzylated heterocyclic ketene aminals **51** with ethyl benzoylacetate, catalyzed by *p*-toluenesulphonic acid, yielded products **53**[32] while the reaction between cyano-substituted heterocyclic ketene aminals **54** and **55** under microwave (M. W.) irradiation led to 2,3-dihydro-imidazo [1,2-*c*] pyrimidine **56**[33] (Scheme 16).



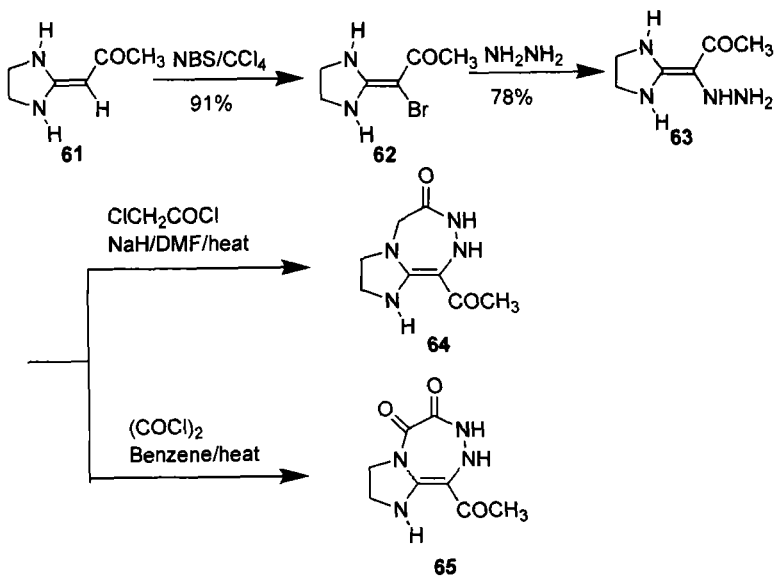
Scheme 16

Reaction with isothiocyanate and isocyanate reagents has been one of the important acylation methods for heterocyclic ketene aminals[9,10]. More examples have been reported recently[34]. It is noteworthy that formylation of heterocyclic ketene aminals **57** using the Vilsmeier reagent under microwave irradiation conditions furnished enaminoester **58** in good yield. Treatment of **58** with isothiocyanate and isocyanate led to products **60**[35] (Scheme 17).



Scheme 17

Reaction of bromo-substituted heterocyclic ketene aminals **62**, derived from the bromination of **61** with NBS, with hydrazine resulted in hydrazino-substituted heterocyclic ketene aminals **63**. It has been converted readily into medium-sized heterocyclic compounds **64** and **65** when treated by chloroacetyl chloride and oxalyl chloride, respectively[36] (Scheme 18).



Scheme 18

5 Outlook

As polyfunctionalized synthetic intermediates, heterocyclic ketene aminals have exhibited intriguing and diverse reaction properties. Having three nucleophilic sites including α-carbon, nitrogen and oxygen within one molecule, heterocyclic ketene aminals render uniqueness in organic chemistry research. Therefore it is always important to study selective reactions of heterocyclic ketene aminals in order to achieve the regiocontrol. Additionally, the synthesis of chiral heterocyclic ketene aminals and their asymmetric reactions are of great interest and they will surely draw the attention from chemists. Synthesis of novel heterocyclic compounds, particularly those that are hardly obtainable by other methods, using heterocyclic ketene aminals protocol will also be actively pursued and fruitful results can be anticipated. The challenge both organic and medicinal chemists are facing, however, is to explore application of heterocyclic ketene aminals in the preparation of bioactive compounds of pharmaceutical and agrochemical importance.

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