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The Aza-ene Reaction of Heterocyclic Ketene Aminals with Enones: An Unusual and Efficient Formation of Imidazo[1,2-*a*] pyridine and Imidazo[1,2,3-*ij*][1,8]naphthyridine Derivatives

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Abstract: Reaction of heterocyclic ketene animals with enones proceeds *via* an aza-ene addition followed by intramolecular cyclization to give imidazo[1,2-*a*]pyridine and imidazo[1,2,3-*ij*] [1,8]naphthyridine derivatives.

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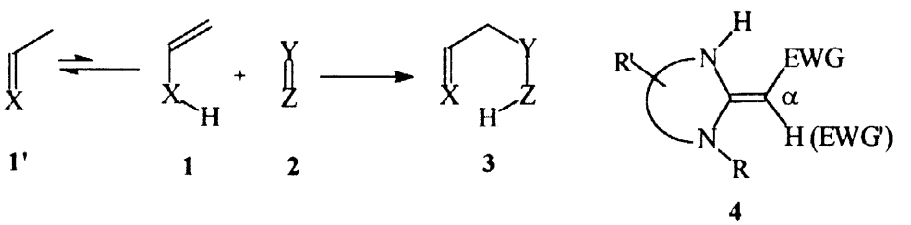
The ene reaction has received much attention because of its synthetic potential in organic chemistry and its interesting mechanistic aspects.[1] While ene reactions of an olefin bearing an allylic hydrogen atom (the "carba-ene") with activated alkenes and alkynes (the "carba-enophiles") and with hetero-enophiles including carbonyl, thio-carbonyl compounds, imines, nitroso and azo compounds are well documented,[1] little is known of ene reactions involving hetero-ene components.[2-4] This is particularly true for hetero-ene systems containing a heteroatom at the 2-position (X=heteroatom) (Scheme 1),[2,3] with the exception of enols, tautomerized from the corresponding ketones, which have been reported to undergo thermal intramolecular ene reactions (the Conia reaction).[1] This is not surprising, however, since hetero-ene components such as secondary enamines **1** [5] exist predominantly in the more stable tautomeric forms, as imines **1'**. Therefore they usually act as the hetero-enophiles rather than the hetero-ene components.[1] Nevertheless, we envisaged that hetero-ene reactions of secondary



1' 1 2 3 4

Scheme 1

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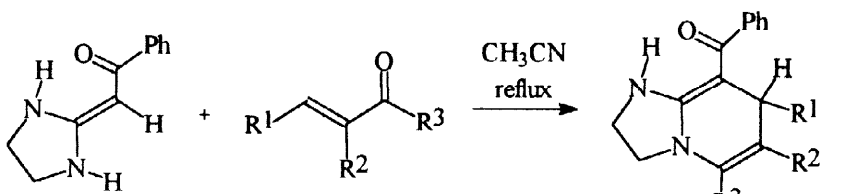
enamines would provide novel and valuable synthetic routes to imines **3** and to ketones, amines and *N*-heterocycles, respectively, upon hydrolysis, reduction and cyclization of **3**.

Heterocyclic ketene aminals **4**, also known as cyclic 1,1-enediamines, are powerful and versatile intermediates for the synthesis of various types of compounds which are hardly obtained by other synthetic methods.[6] 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.[7] Considerable effort has been made therefore during the past decade to investigate enaminic reactions such as nucleophilic additions[8] and substitutions[9] with a variety of electrophiles and even with 1,3-dipoles.[10] Most noticeably, however, heterocyclic ketene aminals bearing a secondary amino group have been shown recently to be a unique aza-ene component and the aza-ene reaction proceeded readily when ethyl propiolate[11] and 4-phenyl-1,2,4-triazoline-3,5-dione[12] were used as enophiles. To examine the scope and limitations of this novel aza-ene component in organic synthesis, we have extended aza-ene reactions of heterocyclic ketene aminals utilizing a range of carba- and hetero-enophiles. Herein we report an efficient and unexpected formation of imidazo[1,2-*a*]pyridine and imidazo[1,2,3-*ij*][1,8]naphthyridine derivatives *via* aza-ene addition of aroyl-substituted heterocyclic ketene aminals to enones followed by the intramolecular cyclization.



5 **6** **7**

Thus, 2-benzoylmethyleneimidazolidine **5** reacted smoothly in refluxing acetonitrile for 2 days with a number of enones **6** giving 1,2,3,7-tetrahydro-imidazo[1,2-a]pyridines **7** (Table 1). When enones derived from cyclohexanone (entry 7) and 5,5-dimethyl-1,3-cyclohexanedione (entry 8) were employed, the reaction afforded the corresponding tricyclic products. It should be noted that no reaction was observed when it was attempted at room temperature.

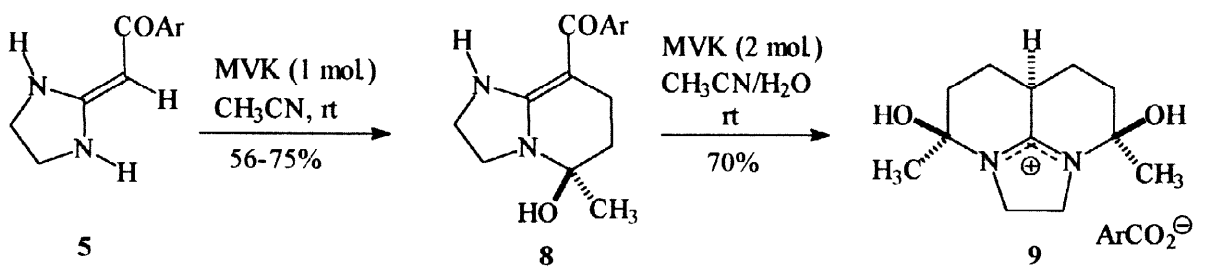
In contrast to the results illustrated in Table 1, reaction of aroyl-substituted heterocyclic ketene aminals with methyl vinyl ketone (MVK) in the molar ratio of 1:1 proceeded rapidly and efficiently at room temperature to give good yield of hydroxyl-containing imidazo[1,2-a]pyridine compounds **8**. Surprisingly, attempted dehydration of **8** by heating in acetonitrile with and without hydrochloric acid did not give **7**; only a small amount of the hydrochloric acid salt of the heterocyclic ketene aminal was obtained. Amazingly, a fused tricyclic compound **9** was isolated as the sole product from **5** or **8** when a large excess of MVK was used in the reaction. Most

Table 1. Reaction of Heterocyclic Ketene Aminals with Enones

Entry	R^1	R^2	R^3	Yield of 7 (%)[a]
1	Ph	H	CH_3	57
2	Ph	H	Ph	42
3	4-$CH_3OC_6H_4$	H	Ph	51
4	4-FC_6H_4	H	Ph	58
5	Ph	H	4-$CH_3OC_6H_4$	52
6	Ph	H	4-ClC_6H_4	54
7[b]	Ph	$CH_2CH_2CH_2CH_2$		47
8[c]	Ph	$COCH_2C(CH_3)_2CH_2$		61

a: isolated yield. b: refluxing for 72 h. c: refluxing for 15 h.

noticeably, this reaction was facilitated by adding several drops of water! It should also be noted that the reaction between **8** and methyl vinyl ketone took place in a stereospecific fashion, the *cis*-dihydroxy imidazo[1,2,3-*ij*][1,8]naphthyridine derivatives being formed exclusively.[13]



5 **8** **9**

Under identical conditions, however, no reaction occurred between enones **6** including MVK and 2-aroylmethylene-1,3-dimethyl-imidazolidine, the tertiary enamine analog of **5**. This demonstrated that the key step of the reactions involves the secondary enamine segment (H-N-C=C) of the heterocyclc ketene aminals. In other words, the addition of heterocyclic ketene aminals to enones most likely proceeds through an aza-ene reaction pathway.[11] As depicted in Scheme 2, the aza-ene reaction[14] of **5** with enones followed by tautomerization and cyclization can give bicyclic products **8**. In the case of MVK, compound **8** can undergo a second aza-ene reaction and cyclization to form the triheterocyclic intermediate which yielded **9** after dearoylization and protonation.

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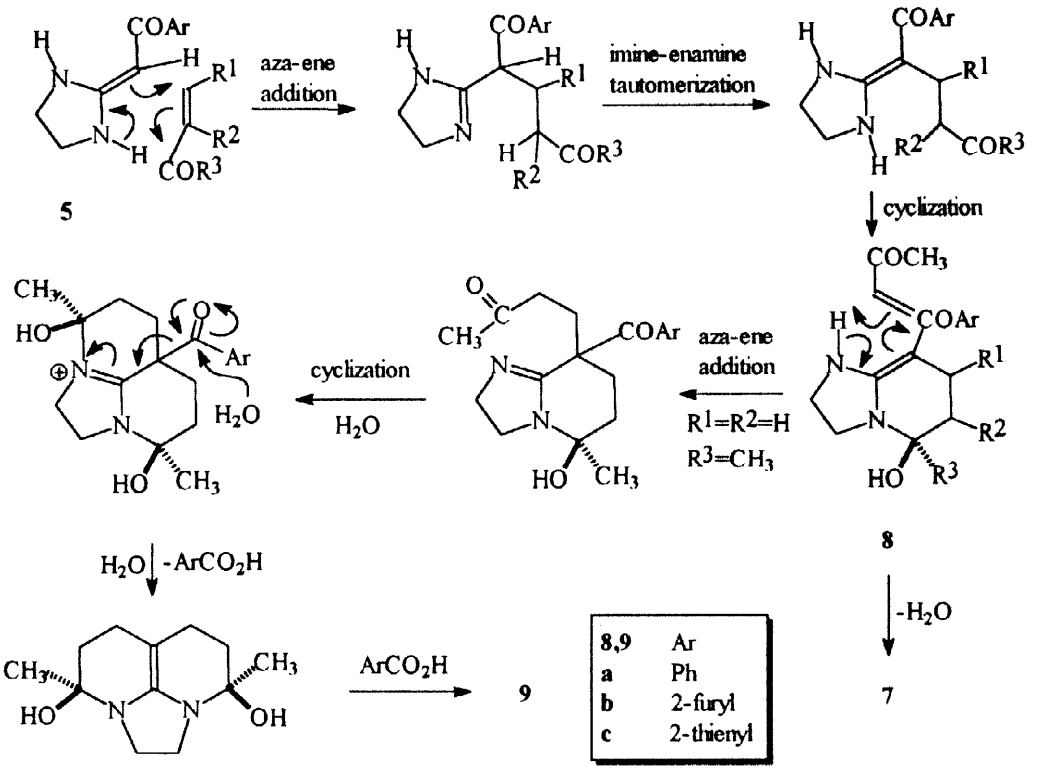

Scheme 2

References and notes

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13. X-Ray Determination: $C_{12}H_{21}N_2O_2^+.C_7H_5O_2^-$ (9, Ar = Ph), monoclinic, $P2_1/n$, a = 13.210(3)Å, b =9.801(3)Å, c = 13.968(3)Å, β = 91.728(12)°, V = 1807.7(7)Å^3, Z = 4, Dc = 1.273 Mg m^{-3}, R = 0.044, wR = 0.111.
14. Although a concerted aza-ene mechanism is proposed, a non-concerted two-step pathway is also possible. For examples of two-stage mechanism of ene reaction see Snider BB. *Acc. Chem. Res.*, 1980; **13**: 426.