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Reaction of aroyl-substituted heterocyclic ketene aminals with nitrile imines: an efficient synthesis of fully substituted pyrazoles and evidence of nucleophilic addition of enamines to 1,3-dipoles

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Abstract

The 1,3-cycloaddition reaction of aroyl-substituted heterocyclic ketene aminals with nitrile imines proceeded via a nucleophilic addition followed by intramolecular cyclocondensation to give fully substituted pyrazole derivatives.

Keywords: heterocyclic ketene aminal; nitrile imine; pyrazole; hydrazone.

The 1,3-dipolar cycloaddition reaction is a powerful method for the preparation of five-membered heterocyclic compounds.[1] Enamines, being electron-rich alkenes, are excellent 1,3-dipolarophiles and they react easily with both propargyl–allenyl and allyl types of 1,3-dipoles to give cycloaddition products.[2] Tertiary 1,1-enediamines have also been reported to undergo analogous 1,3-dipolar cycloaddition. For example, 1,1-dimorpholinoethene reacted readily with azides, nitrile oxides and nitrile imines to produce, after deaminative aromatization, amino-substituted triazoles, isoxazoles and pyrazoles, respectively.[3] In contrast, reaction of heterocyclic ketene aminals **1**,[4] which are the cyclic enediamine analogues bearing secondary amino group(s), with 1,3-dipoles proceeded in a totally different fashion. Thus, the reactions of **1** with aryl azides[5] and nitrile oxides[6] led to the formation of the corresponding triazoles **2** (abc=N=N-NAr) and isoxazoles **2** (abc=ArC=N-O), respectively. It should be noted that, instead of utilizing the enediamine double bond, heterocyclic ketene aminals **1** add to 1,3-dipolar reagents via the end alkene (Scheme 1). A stepwise mechanism, comprising nucleophilic addition of heterocyclic ketene aminals **1** to 1,3-dipoles, followed by intramolecular cyclocondensation has been proposed and evidence has been provided.[5,6] In view of the concerted mechanism proposed for the 1,3-cycloaddition of enamines,[1,2] heterocyclic ketene aminals **1** might tautomerise to their amidine-enol isomers **1′** prior to cycloaddition reaction.[7] Interest in this intriguing cycloaddition reaction and its application in organic synthesis has led us to undertake the current study. Here we wish to report the reaction between aroyl-substituted

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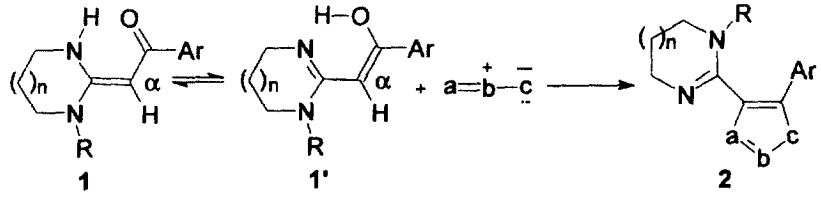
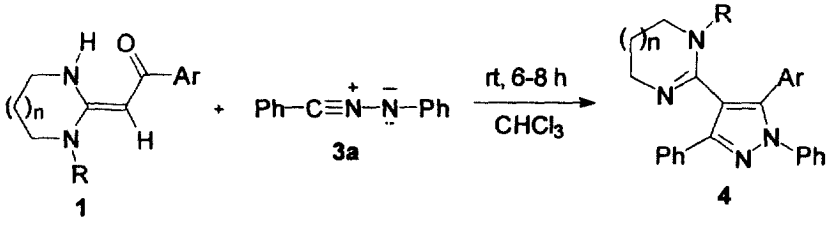
heterocyclic ketene aminals **1** and nitrile imines **3**, giving for the first time direct evidence of nucleophilic addition of enediamines to 1,3-dipoles. The reaction also appears very useful for the synthesis of fully substituted pyrazole compounds.



Scheme 1.

The reaction[8] of **1** with diphenylnitrile imine **3a** in chloroform proceeded smoothly at room temperature to give the fully substituted pyrazole product **4**[9] in moderate yield (Scheme 2). *N*-Methylated heterocyclic ketene aminal **1f** reacted similarly to afford **4f** (Table 1). However, when *N*-(2,4-dinitrophenyl)-*C*-phenylnitrile imine **3b** was used under identical conditions, the reaction[8] took place rapidly and hydrazone derivatives **5**[10] were obtained as the sole product in good to excellent yield (Table 2). Prolonged reaction time at ambient temperature did not effect cyclization of **5**. Only under the forceful conditions of refluxing xylene, did the hydrazone intermediate cyclize to furnish pyrazole **4** (Scheme 3).



Scheme 2.

The outcomes shown above clearly indicate that 1,3-cycloaddition of aroyl-substituted heterocyclic ketene aminals **1** to nitrile imine **3** proceeds in a stepwise manner by way of addition intermediate **5**. In the case of diphenylnitrile imine **3a**, the resulting adducts underwent further intramolecular cyclization simultaneously to form the final heteroaromatic products **4**. On the other hand, because of the strong

Table 1
Reaction of **1** with diphenylnitrile imine **3a**

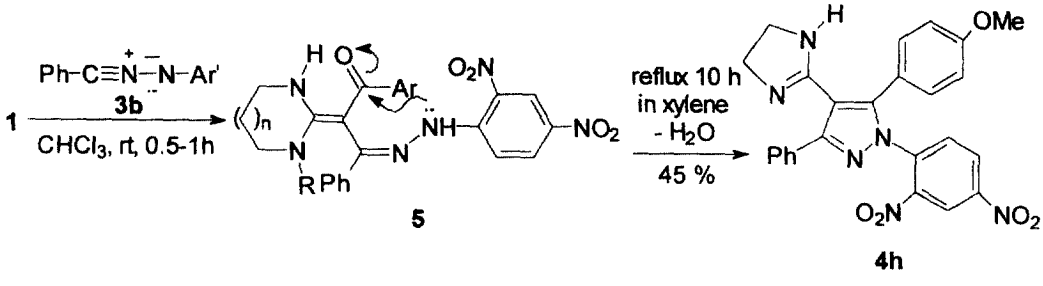
Entry	Ar	R	n	Reaction time (h)	Yield of 4 (%)[a]
a	Ph	H	1	6	53
b	4-MeO-C_6H_4	H	1	6	41
c	2-pyridyl	H	1	8	39
d	2-thienyl	H	1	8	47
e	2-furyl	H	1	8	60
f	2-furyl	Me	1	8	41
g	2-furyl	H	0	8	43

a: Isolated yield.

Table 2
Reaction of **1** with *N*-(2,4-dinitrophenyl)-*C*-phenylnitrile imine **3b**

Entry	Ar	R	n	Yield of 5 (%)[a]
a	Ph	H	1	94
b	4-F-C_6H_4	H	1	89
c	2-furyl	H	1	87
d	Ph	H	0	95
e	4-F-C_6H_4	H	0	93
f	2-furyl	H	0	83
g	2-furyl	Me	0	75
h	4-MeO-C_6H_4	H	0	87

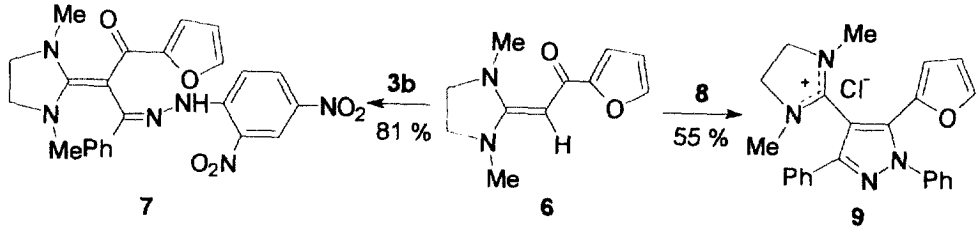
a: Isolated yield.



Scheme 3.

electron-withdrawing effect of nitro groups, the nucleophilicity of the aniline moiety of hydrazones **5** decreased and therefore no further cyclocondensation occurred unless more severe conditions were applied. In other words, if 1,3-dipolar cycloaddition occurred between nitrile imines and the amidine-enol tautomers **1′**, pyrazoles would be the only products from identical conditions irrespective of the nature of substituents of nitrile imine.

To further eliminate the concerted cycloaddition pathway, the reaction of *N,N′*-dimethylated heterocyclic ketene aminals **6** with nitrile imines **3** was examined. Although being unable to tautomerize to the amidine-enol isomer, compound **6** reacted equally well with *N*-(2,4-dinitrophenyl)-*C*-phenylnitrile imine **3b** to give the corresponding adduct **7**, indicating again the stepwise nature of the reaction. Treatment of **6** with chlorodiphenylhydrazone **8**, the precursor of diphenylnitrile imine **3a**, led similarly to the formation of pyrazole derivative **9** (Scheme 4).



Scheme 4.

In conclusion, we have provided solid evidence supporting a stepwise reaction constituting enaminic addition and cyclocondensation between aroyl-substituted heterocyclic ketene aminals with 1,3-dipoles. We have also developed an efficient method for the preparation of fully substituted pyrazole compounds.

Acknowledgements

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8. General procedure for the reaction of heterocyclic ketene aminals with nitrile imines: To a suspension of **1** (1 mmol) in chloroform (15 ml) was added five drops of triethylamine and **2** (1.1 mmol). After stirring at room temperature for a period of time (Tables 1 and 2), the mixture was washed three times with saline. The organic layer was dried and concentrated, and products were obtained after chromatography.
9. Since pyrazole **4** was obtained from hydrazone intermediate **5**, the isomeric structure of 4-aryl-1,3-diphenyl-5-(3,4,5,6-tetrahydro-2-pyrimidinyl)-pyrazole was ruled out. Spectra data of **4b**: mp 286–289°C; IR (KBr) 3420 (NH), 1615, 1607, 1580, 1565; ^{1}H NMR ($CDCl_3$) 7.79 (d, 8.0 Hz, 2H), 7.12–7.31 (m, 10H), 6.69 (d, 8.0 Hz, 2H), 3.68 (s, 3H), 3.16 (t, 5.5 Hz, 4H), 1.62 (quin, 5.5 Hz, 2H); MS (EI): 408 (M^+, 31%), 407 (100). $C_{26}H_{24}N_4O$ requires: C, 76.44; H, 5.92; N, 13.72. Found: C, 75.95; H, 5.99; N, 13.53.
10. Hydrazone **5** was isolated as a single geometric isomer, which was indicated by one set of proton and carbon signals in ^{1}H NMR and ^{13}C NMR spectra, respectively. Spectra data of **5a**: mp 187–188°C; IR (KBr) 3420 (NH), 1618, 1585, 1515, 1335 (NO_2); ^{1}H NMR ($CDCl_3$) 12.15 (s, b, 1H), 11.61 (s, 1H), 9.11 (d, 2.5 Hz, 1H), 8.22 (dd, 9.6, 2.5 Hz, 1H), 7.89 (d, 9.6 Hz, 1H), 6.97–7.84 (m, 10H), 4.51 (s, b, 1H), 3.54 (s, b, 2H), 3.23 (s, b, 2H), 2.00 (quin, 5.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) 187.8, 158.1, 155.0, 144.9, 142.9, 138.7, 138.6, 131.1, 130.6, 130.4, 129.9, 129.6, 128.6, 128.3, 127.1, 124.5, 117.6, 83.9, 40.1, 39.1, 21.0; MS (FAB) 487 $(M+1)^+$; MS (EI) 468 (32), 467 (100), 437 (32). $C_{25}H_{22}N_6O_5$ requires: C, 61.72; H, 4.56; N, 17.28. Found: C, 61.49; H, 4.62; N, 17.56.