HETEROCYCLES, Vol. 82, No. 1, 2010, pp. 619 - 629. © The Japan Institute of Heterocyclic Chemistry
Received, 17th May, 2010, Accepted, 6th July, 2010, Published online, 7th July, 2010
DOI: 10.3987/COM-10-S(E)34

REACTIONS OF HETEROCYCLIC KETENE AMINALS WITH ACRYLONITRILE: AN EFFICIENT SYNTHESIS OF DIHYDROPYRIDINE-FUSED 1,3-DIAZAHETEROCYCLES

Hui Zhao,[1,3] Ai-Qun Zeng,[2] Wei-Lin Liao,[2] Yue-Mei Jia,[1] Li-Ben Wang,[1] Zhi-Tang Huang,[*1] and Chu-Yi Yu[*1]

[1]Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China; E-mail: yucy@iccas.ac.cn; [2]College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330046, China. [3]Graduate University of Chinese Academy of Sciences, Beijing 100049, China

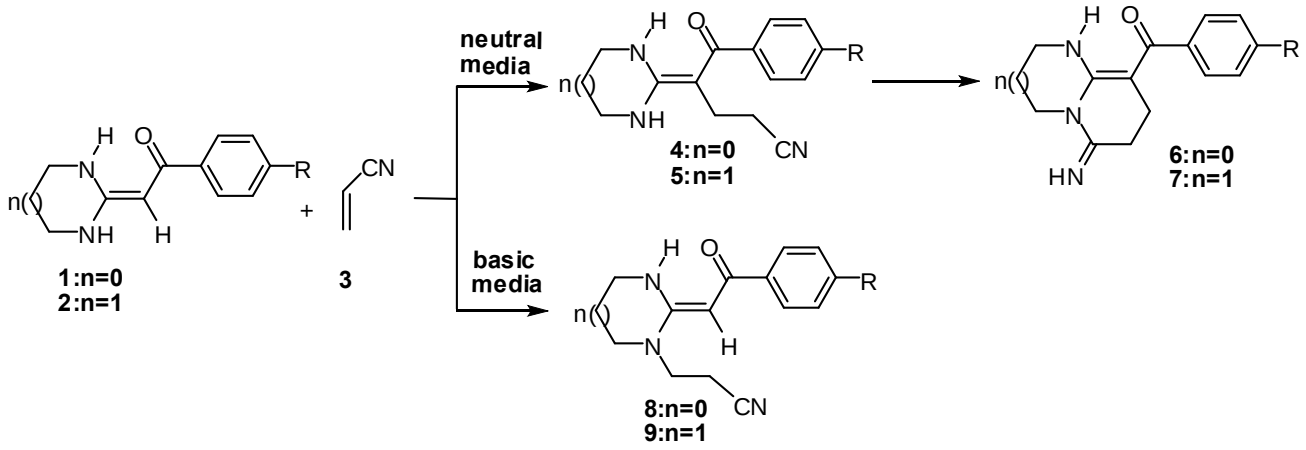
Abstract – A simple and efficient method for the synthesis of dihydropyridine-fused 1,3-diazaheterocycles has been developed *via* reactions of heterocyclic ketene aminals (HKAs) with acrylonitrile in good to excellent yields.

INTRODUCTION

Heterocyclic ketene aminals (HKAs) **1** or **2**, also referred to as cyclic 1,1-enediamines or cyclic ketene *N,N*-acetals, are an unique class of polyfunctionalized heterocyclic compounds which can serve as versatile intermediates for the syntheses of a wide variety of heterocycles and fused heterocycles that are difficult to obtain by other approaches.[1] The double bond of the enamine function is highly polarized and the electron density at the α-carbon increases considerably compared with normal olefins due to the extensive conjugation between electron-donating amino groups and electron-withdrawing substituents at α-carbon in HKAs.[2] As a result, both the α-carbon and the secondary amino group in the HKAs can be employed as nucleophiles in the reactions with various electrophiles. Therefore, HKAs have been used as bisnucleophiles to react with biselectrophiles for the construction of a number of structurally complex aza-heterocycles[3,4] and/or fused-ring heterocycles with potential therapeutic applications[5] by nucleophilic addition or substitution[6] with a variety of electrophiles including 1,3-diploles such as azides,[7] nitrile oxides,[8] and nitrile imines.[9] Furthermore, a number of HKAs and their derivatives have been found as pesticides,[10] antibacterial agents,[11] anti-anxiety agents,[12] antileishmanial agents[13] and anti-cancer agents.[14]

This paper is dedicated to Prof. Dr. Albert Eschenmoser on the occasion of his 85th birthday.

In the context of our efforts in developing efficient methods for the diversity-oriented rapid generation of novel heterocycles with potential biological activities based on the chemistry of HKAs, we have reported the reaction of HKAs with a number of α,β-unsaturated compounds for the synthesis of compound libraries of dihydro- or tetrahydropyridine fused 1,3-diazaheterocycles since these compounds might be valuable in drug discovery and in agrochemical development.[3,4] Herein, we report the reactions of HKAs with a simple biselectrophilic reagent, acrylonitrile. Because the –CN group can be converted into a variety of other functional groups, such as –COOH, =NH, –NHCOR etc., it can be envisaged that heterocyclic compounds containing an –CN group might be valuable intermediates for the diversity-oriented synthesis of heterocycles *via* reactions of the –CN group. It was expected that reactions of HKAs **1** or **2** with acrylonitrile would afford *C*-adducts **4** or **5**, and *N*-adducts **8** or **9**, under different neutral or strong basic reaction conditions, respectively. Subsequent intramolecular cyclization of compound **4** and **5** could form the polyfunctionalized dihydropyridine-fused 1,3-diazaheterocycles **6** or **7** (Scheme 1).



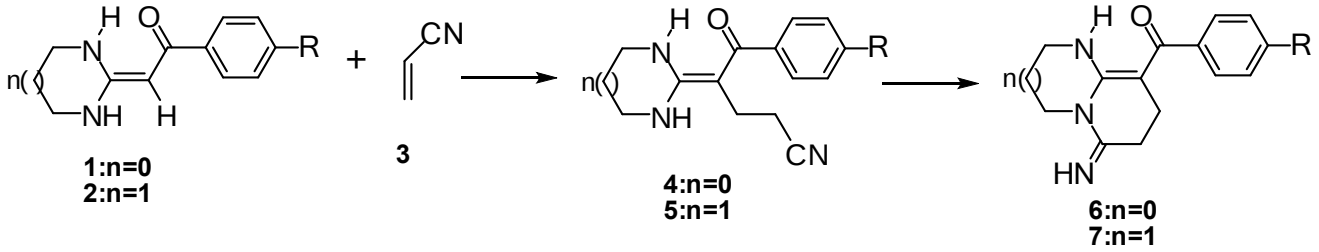
Scheme 1. Reactions of HKAs **1** or **2** with acrylonitrile

RESULTS AND DISCUSSION

HKAs **1** refluxed in acrylonitrile give products **4** while HKAs **2** refluxed in acetonitrile with just equivalent acrylonitrile (Scheme 1) afford compound **5**. The difference of the reactivities between HKAs **1** and HKAs **2** was ascribed to a better delocalization of the secondary amino groups into the carbon-carbon double bond of the six-membered HKAs **2** than that of the five-membered HKAs **1**. Due to the increased electron density of the double bond caused by electron-donating group, the HKAs **1** or **2** with electron-donating group on aroyl ring (Table 1, entries 2, 3, 6 and 7) gave a slightly better yield than that with electron-withdrawing group (Table 1, entries 4 and 8). The structure of the products **4** and **5** were determined by IR, ^{1}H NMR, and ^{13}C NMR and MS spectrometry and elemental analysis. The

disappearance of the signal of H-6 in ^{1}H NMR indicated that the products are compound **4** and **5** instead of **8** and **9**. Take **4a** for example, the signal of H-1, H-4 and H-6 of compound **1a** appeared at δ 9.20 (br, s), 7.32 (br, s), 5.20 (s) ppm respectively,[15] in product **4a** the singlet signal of H-6 was disappeared while the signal of H-1 (10.13ppm, br) and H-4 (5.35ppm, br) still existed, which identified the structure of compound **4a.**

Table 1. The aza-ene reaction of HKAs with acrylonitrile and subsequent cyclization reaction



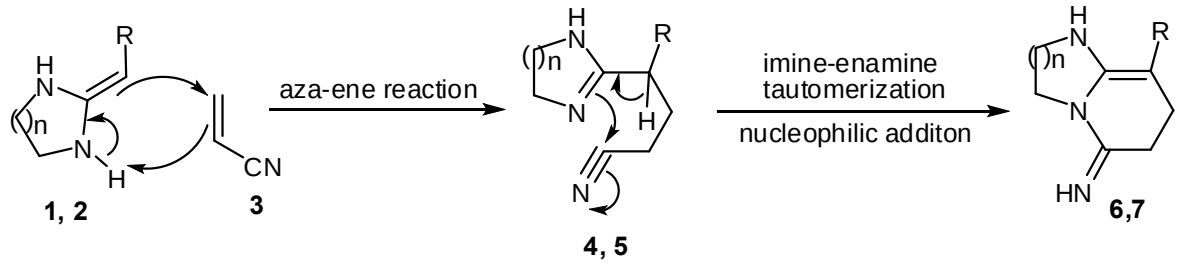
Entry	Substrate	R	Solvent	Temperature (°C)	Time (h)	Product	Yield (%)[a]
1	**1a**	H	CH_2=CHCN	reflux	12	**4a**	90
2	**1b**	Me	CH_2=CHCN	reflux	12	**4b**	95
3	**1c**	MeO	CH_2=CHCN	reflux	12	**4c**	97
4	**1d**	Cl	CH_2=CHCN	reflux	12	**4d**	88
5	**2a**	H	MeCN	reflux	6	**5a**	82
6	**2b**	Me	MeCN	reflux	6	**5b**	83
7	**2c**	MeO	MeCN	reflux	6	**5c**	84
8	**2d**	Cl	MeCN	reflux	6	**5d**	80
9	**4a**	H	DMF	0	0.75	**6a**	70
10	**4b**	Me	DMF	0	0.75	**6b**	73
11	**4c**	Cl	DMF	0	1	**6c**	74
12	**5a**	H	DMF	0	11	**7a**	72
13	**5b**	Me	xylene	reflux	13.5	**7b**	91[b]
14	**5c**	MeO	MeCN[c]	reflux	11	**7c**	77
15	**5d**	Cl	xylene	reflux	8	**7d**	86[b]

[a] Isolated yield by recrystallization or silica gel column chromatography.

[b] Isolated only by removing the solvent.

[c] TsOH was added to catalyze the reaction.

Although the compound **4** and **5** was obtained smoothly with high yield, the attempts to prepare pyridine-fused 1,3-diazaheterocycles **6** and **7** from compound **4** and **5** *in situ* were failed. Except compound **7c**, which was made directly from the reaction of **2c** with equilibrium acrylonitrile in refluxing acetonitrile catalyzed by TsOH, pyridine-fused 1, 3-diazaheterocycles **6** or **7** can not be obtained either by the extension of reaction time or by addition of acid (Lewis or proton acid) and/or organic base such as Et_3N, DBU. To our delight, pyridine-fused 1, 3-diazaheterocycles **6** and **7** were made from the isolated **4** and **5** in DMF under strong basic condition (NaH) in ice-water bath (Table 1, entry 9-12) or in refluxing xylene (Table 1, entry 13,15). A plausible mechanism of the reaction was depicted in Scheme **2**. Firstly, the ene-component HKAs **1** or **2** and the enophile acrylonitrile **3** underwent an aza-ene reaction to give the compound **4** or **5**, which successively underwent imine-enamine tautomerization under strong basic condition, followed by nucleophilic addition of the secondary amino group to the cyano group, resulting in the formation of dihydropyridine-fused 1,3-diazaheterocycles **6** or **7**.



Scheme 2. Proposed mechanism for the aza-ene reaction between HKAs and acrylonitrile

It is worth noting that the imine group of compounds **7** was easy to undergo hydrolysis under acidic conditions to give the pyridone derivatives (for example **7e**,[3] Figure 1), which made compound **7** difficult to purify by column chromatography.

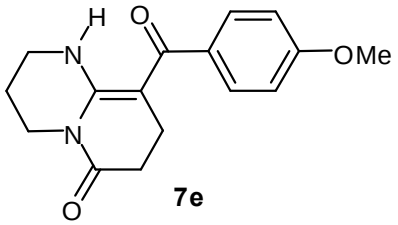


Figure 1. The hydrolyzed product **7e**

When HKAs **1** reacted with acrylonitrile in DMF under strong basic condition (NaH) at 0 °C Michael addition products **8a**–**8d** were obtained in excellent yields. However, the attempts to get dihydropyridine-fused 1,3-diazaheterocycles by intramolecular cyclization of **8a**–**8d** failed. The hydrogen bond existed in compound **8** make the secondary amino group difficult to be attacked by the base to give cyclization products (Figure 2). In ^{1}H NMR of HKAs **1**, **2** and **8**, compared with the signal of H-4 (7.32

ppm), the downfield shift of the H-1 signal (9.20ppm) identified the existing of the intramolecular hydrogen bond between secondary amino group and the carbonyl group of benzoyl. All the structures of the products **8a**–**8d** were determined by the IR, ^{1}H NMR, ^{13}C NMR and MS. Similarly, in ^{1}H NMR the disappearance of the signal of H-4 (7.32 ppm, brs) and the existing of the signal of H-6 (5.22 ppm, singlet) indicated that the reaction was occurred at the secondary amino group. The attempts to make compound **9** from six-membered HKAs **2** failed, i.e., no reaction occurred between **2** and **3** under the same reaction conditions.

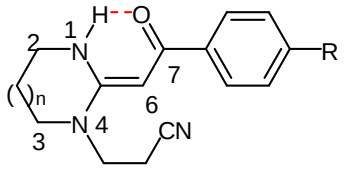
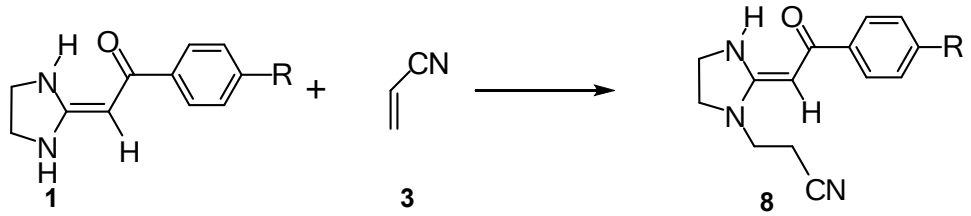


Figure 2. The hydrogen bond existed in the HKAs

Table 2. Aza-Michael addition of HKAs **1** with acrylonitrile **3**



Entry	Substrate	R	Product	Yield(%)[a]
1	**1a**	H	**8a**	94
2	**1b**	Me	**8b**	94
3	**1c**	MeO	**8c**	96
4	**1d**	Cl	**8d**	91

[a] Isolated yield by recrystallization or silica gel column chromatography.

In conclusion, a simple method for synthesis of dihydropyridine-fused 1,3-diazaheterocycles has been developed via the reaction of HKAs with acrylonitrile. Further work upon the reactions of compounds **6,7** and **8** is undergoing.

EXPERIMENTAL

General procedure for the reactions of HKAs 1 with acrylonitrile (3): A stirred solution of heterocyclic ketene aminals **1** (1.0 mmol) in acrylonitrile **3** (5 mL) was refluxed for 12 h. The reactions were monitored by TLC. When TLC indicated the disappearance of the starting materials, solvents were

removed by distillation under vacuum and the resulting residue was purified by recrystallization (EtOAc) or column chromatography on silica gel (EtOAc : MeOH = 100 : 1) to afford the products. Compound **4a**: white solid. mp 161–163 °C. IR (KBr): 3104, 2241, 1597, 1534 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.13 (br s, 1H, N–H), 7.38–7.28 (m, 5H, Ph–H), 5.53 (br s, 1H, N–H), 3.73 (s, 2H, CH_2), 3.45 (s, 2H, CH_2), 2.50 (t, *J* = 8.0 Hz, 2H, CH_2), 2.21 (t, *J* = 7.2 Hz, 2H, CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 190.6, 165.5, 142.9, 128.3, 128.1, 125.9, 120.0, 85.4, 44.0, 42.5, 24.7, 18.4. ESI-MS: *m/z* 242.26 $[M+H]^+$. Anal. Calcd (%) for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C 69.51, H 6.22, N 17.11. Compound **4b**: white solid. mp: 198–201 °C. IR (KBr): 3147, 2246, 1596, 1534cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.1 (s, 1H, N–H), 7.16 (s, 4H, Ph–H), 3.50 (s, 1H, N–H), 3.72 (s, 2H, CH_2), 3.42 (s, 2H, CH_2), 2.52 (t, *J* = 8.0 Hz, 2H, CH_2), 2.20 (t, *J* = 7.0 Hz. 2H, CH_2), 2.4 (s, 3H, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 190.2, 165.5, 140.1, 137.9, 128.9, 125.9, 120.1, 85.6, 44.0, 42.5, 24.8, 21.2, 18.3. ESI-MS: *m/z* 256.33 $[M+H]^+$. Anal. Calcd (%) for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.80; H, 6.67; N, 16.69. Compound **4c**: white solid. mp 168–170 °C. IR (KBr): 3147, 2246, 1599, 1531cm^{-1}. ^{1}H-NMR (300 MHz,$CDCl_3$): δ = 10.1 (s, 1H, N–H), 7.23–7.27 (d, *J* = 10.0 Hz, 2H, Ph–H), 6.87–6.93 (d, *J* = 10.0 Hz, 2H, Ph–H), 5.30 (s, 1H, =N–H), 3.82 (s, 3H, CH_3), 3.74 (t, *J* = 8.5 Hz, 2H, CH_2), 3.48 (t, *J* = 8.5 Hz, 2H, CH_2), 2.56 (t, *J* = 8.0 Hz, 2H, CH_2), 2.21 (d, *J* = 7.0 Hz, 2H, CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 190.0, 185.5, 159.6, 135.5, 127.7, 120.2, 113.7, 85.6, 55.3, 44.0, 42.7, 24.9, 18.3. ESI–MS: *m/z* 272.33 $[M+H]^+$. Anal. Calcd (%) for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.69; H, 6.40; N, 15.34. Compound **4d**: white solid. mp 168–171 °C. IR (KBr): 3157, 2241, 1592, 1532cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.99 (s, 1H, N–H), 7.20–7.38 (m, 4H, Ph–H), 6.35 (s, 1H, N–H), 3.69 (s, 2H, CH_2), 3.32 (s, 2H, CH_2), 2.46 (t, *J* = 8.0 Hz, 2H, CH_2), 2.18 (t, *J* = 7.5 Hz, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.3, 167.3, 142.8, 134.9, 129.4, 129.3, 129.1, 120.6, 87.5, 44.2, 25.0, 18.5. ESI–MS: *m/z* 276.28 $[M+H]^+$. Anal. Calcd (%) $C_{14}H_{16}ClN_3O$: C, 60.98; H, 5.12; N, 15.24. Found: C, 61.25; H, 5.07; N, 15.06.

General procedure for the reactions of HKAs 2 with acrylonitrile (3) in neutral condition: A stirred solution of of heterocyclic ketene aminals **2 (**1.0 mmol**)** and acrylonitrile **3** (1.0 mmol) in MeCN (5 mL) was refluxed for 6 h. The reactions were monitored by TLC. When TLC indicated the disappearance of the starting materials, solvents were removed by distillation under vacuum and the resulting residue was purified by recrystallization (EtOAc) or column chromatography on silica gel (EtOAc : MeOH = 5 : 1) to afford the products. Compound **5a**: white solid. mp 184–186 °C. IR (KBr): 3225, 2241, 1622, 1575 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 12.34 (br s, 1H , N–H), 7.38–7.22 (m, 5H, Ph–H), 5.45 (br s, 1H, N–H), 3.35 (s, 4H, $2CH_2$), 2.46–2.41 (m, 2H, CH_2), 2.21–2.16 (m, 2H, CH_2), 1.96–1.89 (m, 2H, CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 187.3, 159.2, 143.5, 128.2, 127.6, 125.9, 119.1, 86.7, 38.5, 38.5, 23.7, 20.1, 18.2. ESI–MS: *m/z* 256.31 $[M+H]^+$. Anal. Calcd (%) for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.62; H, 6.65; N, 16.62. Compound **5b:** white solid. mp 170–172 °C. IR (KBr): 3269, 2241, 1602, 1509

cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 12.3 (s, 1H, N–H), 7.10–7.13 (m, 4H, Ph–H), 5.3 (s, 1H, N–H), 3.3 (s, 4H, CH_2), 2.41–2.44 (m, 2H, CH_2), 2.15–2.20 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 1.82–1.89 (m, 2H, CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 187.1, 159.2, 140.7, 137.2, 128.8, 125.9, 120.0, 87.1, 38.4, 38.4, 23.8, 21.1, 20.0, 18.0. ESI-MS: *m/z* 270.31 $[M+H]^+$. Anal. Calcd (%) for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11; N, 15.60. Found: C, 71.47; H, 7.20; N, 15.57. Compound **5c**: white solid. mp 158–160 °C. IR (KBr): 3263, 2241, 1603, 1513 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 12.10 (s, 1H, N–H), 7.17–7.21 (d, *J* = 10.0 Hz, 2H, Ph–H), 6.89–6.90 (d, *J* = 9.0 Hz, 2H, Ph–H), 5.29 (s, 1H, N–H), 3.82 (s, 3H, CH_3)3.70 (s, 2H, CH_2), 3.46 (s, 2H, CH_2), 2.47–2.50 (m, 2H, CH_2), 2.15–2.19 (m, 2H, CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 186.7, 159.2, 159.1 136.2, 131.3, 127.5, 120.0, 113.6, 87.1, 55.2, 38.4, 23.8, 20.0, 18.1. ESI–MS: *m/z* 286.32 $[M+H]^+$. Anal. Calcd (%) for $C_{16}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.19; H, 6.75; N, 14.67. Compound **5d**: yellow solid. mp 110–112 °C. IR (KBr): = 3157, 2242, 1593 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 12.84 (br s, 1H, NH), 7.32–7.28 (m, 4H, Ph–H), 5.29 (br s, 1H, NH), 3.91 (s, 4H, $2CH_2$), 3.43–3.45 (m, 2H, CH_2), 2.53–2.48 (m, 2H, CH_2), 2.43–2.39 (m, 2H, CH_2), 2.07–2.01 (m, 2H, CH_2). ^{13}C-NMR(75 MHz, $CDCl_3$): δ = 185.6, 159.2, 141.8, 133.4, 128.5, 127.5, 119.7, 86.9, 38.5, 23.6, 20.0, 18.2. ESI–MS: *m/z* 290.21 $[M+H]^+$. Anal. Calcd (%) for $C_{15}H_{16}ClN_3O$: C, 62.18; H, 5.57; N, 14.50. Found: C, 62.06; H, 5.78; N, 15.94.

The procedure for the pyridine-fused 1, 3-diazaheterocycles products 6 and 7a: To an anhydrous solution of **4** or **5a** (0.4mmol) in DMF (5 mL) at 0 °C was added NaH (0.7 mmol). The reactions were monitored by TLC. When TLC indicated the disappearance of the starting materials, transfer the solution into 10 mL water, then extracted with CH_2Cl_2 (3×3mL). The combined organic phase was washed with water, dried (anhydrous Na_2SO_4). After removing of the solvent under reduced pressure, the residue was purified by recrystallization (anhydrous EtOAc). Compound **6a:** yellow crystals. mp 171–173 °C. IR (KBr): 3269, 1675, 1636 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.55 (s, 1H, N–H), 7.35–7.46 (m, 5H, Ph–H; s, 1H, =N–H), 3.98–4.04 (m, 2H, CH_2), 3.81 (m, 2H, CH_2), 2.59–2.63 (m, 2H, CH_2), 2.50–258 (m, 2H, CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 189.9, 161.3, 158.1, 141.7, 129.0, 128.0, 126.9, 84.6, 43.3, 42.5, 33.0, 22.5. ESI–FAB: *m/z* 242.26 $[M+H]^+$. HRMS-FAB: *m/z* for $C_{14}H_{15}N_3O$ $[M+H]^+$: 242.1304; found: 242.1293. Compound **6b**: yellow crystals. mp 175–177 °C. IR (KBr): 3295, 1633, 1620cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.53 (br s, 1H, NH), 7.36–7.33 (d, *J* = 5.3 Hz, 2H, CH_2), 7.18–7.16 (d, *J* = 8.0 Hz, 2H, CH_2), 6.90 (br s,1H, =NH), 3.96–4.02 (m, 2H, CH_2), 3.79–3.85 (m, 2H, CH_2), 2.59–2.95 (m, 2H, CH_2), 2.49–2.54 (m, 2H, CH_2), 2.36 (s, 3H, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 190.0, 161.3, 158.0, 139.0, 138.8, 128.5, 127.0, 84.6, 43.3, 42.5, 33.0, 22.7, 21.2. ESI–MS: *m/z* 256.28 $[M+H]^+$. HRMS-FAB: *m/z* for $C_{15}H_{17}N_3O$ $[M+H]^+$: 256.1450; found: 256.1441. Compound **6c**: yellow crystals. mp 144–146 °C. IR (KBr): 3246, 1647, 1618 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.54 (s, 1H, N–H), 7.32–7.40 (m, 4H, Ph–H; s, 1H, =N–H), 3.94–4.04 (m, 2H, CH_2), 3.82–3.88 (m, 2H, CH_2), 2.50–2.68 (m,

4H, $–CH_2–CH_2–$). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 188.3, 161.2, 158.4, 140.0, 134.9, 128.5, 128.2, 84.5, 43.4, 42.6, 33.0, 22.6. ESI-MS: *m/z* 276.25 $[M+H]^+$. HRMS-FAB: *m/z* for $C_{14}H_{14}N_3OCl$ $[M+H]^+$: 276.0900; found: 276.0904. Compound **7a:** yellow solid. mp 134–136 °C. IR (KBr): 3300, 1635, 1605cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 12.90 (s, 1H, N–H), 7.31–7.41 (m, 5H, Ph–H), 7.27 (s, 1H, =N–H), 3.92 (t, *J* = 5.5Hz, 2H, CH_2), 3.45–3.47 (d, *J* = 5.5Hz, 2H, CH_2), 2.42–2.52 (m, 4H, $–CH_2–CH_2–$), 2.03–2.08 (m, 2H, CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 187.3, 163.6, 157.2, 142.5, 128.3, 127.9, 126.8, 87.1, 40.8, 38.3, 34.3, 22.5, 20.9. ESI-MS: *m/z* 256.31 $[M+H]^+$. Anal. Calcd (%) for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.62; H, 6.65; N, 16.62.

The procedure for the pyridine-fused 1,3-diazaheterocycles products 7c and 7e: A stirred solution of **5c (**1.0mmol) and TsOH (10mg) in anhydrous MeCN (5 mL) was refluxed for 5 h. the reactions were monitored by TLC. When TLC indicated the disappearance of the starting materials, stop the reaction, and washed the solution with water (3×3 mL). Then solvent was removed by distillation under vacuum and the resulting residue was purified by recrystallization to give **7c**, or by column chromatography on silica gel (EtOAc : MeOH = 5 : 1) to give **7e**. Compound **7c**: yellow solid. mp 171–172 °C. IR (KBr): 3290, 1642, 1601 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 12.92 (s, 1H, –N–H) , 7.33–7.38 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 2H, Ph–H), 6.85–6.90 (dd, J_1 = 8.5 Hz, J_2 = 3.0 Hz, 2H, Ph–H), 7.16 (s, 1H, =N–H), 3.86–3.93 (d, 2H, CH_2, *J* = 10.0Hz), 3.82 (s, 3H, CH_3), 3.42–3.46 (m, 2H, CH_2), 2.50–2.52 (d, 4H, $–CH_2–CH_2–$, *J* = 3.0Hz), 2.00–2.07 (m, 2H, CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 186.9, 163.6, 159.8, 157.1, 135.1, 128.6, 113.2, 87.1, 55.2, 40.8, 38.3, 34.4, 22.8, 20.9. ESI-MS: *m/z* = 286.28 $[M+H]^+$. HRMS-FAB: *m/z* for $C_{14}H_{14}N_3OCl$ $[M+H]^+$: 286.1556; found: 286.1547. Compound **7e**: white solid. mp 167–169 °C. IR (KBr): 2961, 1697, 1604 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 12.76 (s, 1H, N–H), 6.86–6.91, 7.34–7.40 (m, 4H, Ph–H), 3.82 (s, 3H, CH_3), 3.43–3.48 (m, 4H, CH_2), 2.57–2.63 (m, 2H, CH_2), 2.49–2.53 (m, 2H, CH_2), 2.01–2.04 (m, 2H, CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 188.6, 170.6, 160.1, 156.5, 134.6, 128.6, 113.2, 87.4, 55.3, 39.1, 38.6, 32.8, 21.9, 20.7. ESI-MS: *m/z* = 287.29 $[M+H]^+$ (litr,[3] mp 173–175 °C. IR (KBr): 1685, 1610 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$): δ = 12.73 (s, 1H), 7.40 (d, 2H), 6.91 (d, 2H), 3.83 (t, 2H), 3.81 (s, 3H), 3.43 (dt, 2H), 2.53 (t, 4H), 2.00 (quin, 4H). ^{13}C-NMR (15 MHz, $CDCl_3$): δ = 188.5, 170.9, 160.2, 156.8, 134.7, 128.9, 113.4, 87.6, 55.5, 39.4, 38.8, 33.0, 22.2, 20.9. ESI-MS: *m/z* = 287.29 $[M+H]^+$. Anal. Calcd (%) for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.79. Found: C, 69.95; H, 6.41; N, 10.05).

The procedure for the pyridine–fused 1,3–diazaheterocycles products 7b and 7d: A stirred solution of **5b** or **5d** (1 mmol) in anhydrous xylene (5 mL) was refluxed for 13.5 or 8 h. The reaction was monitored by TLC. When TLC indicated the disappearance of the starting materials, solvents were removed by distillation under vacuum and the resulting residue was products **7b** and **7d**. Compound **7b**: yellow semi–solid. IR (KBr): 3293, 1599, 1636cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 12.91 (s, 1H,

N–H), 7.26–7.29 (d, *J* = 8.0 Hz, 2H, CH_2), 7.14–7.17 (d, *J* = 8.0 Hz, 2H, Ph–H; s, 1H, =N–H), 3.92 (t, *J* = 6.0 Hz, 2H, CH_2), 3.44–3.47 (t, *J* = 6.0 Hz, 2H, CH_2), 2.49 (s, 4H, –CH_2–CH_2–), 2.36 (s, 3H, CH_3), 2.01–2.17 (m, 2H, CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 187.4, 163.7, 157.1 139.7, 138.2, 128.5, 126.9, 87.2, 40.8, 38.3, 34.4, 22.6, 21.3, 20.9. ESI–MS: *m/z* = 270.31 $[M+H]^+$. HRMS-FAB: *m/z* for $C_{16}H_{19}N_3O$ $[M+H]^+$: 270.1599; found: 270.1606. Compound **7d**: yellow semi–solid. IR (KBr): 3293, 1638, 1601 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 12.85 (s, 1H, N–H), 7.28–7.35 (m, 4H, Ph–H; s, 1H, =N–H), 3.93 (t, *J* = 6.0 Hz, 2H, CH_2), 3.44–3.49 (m, 2H, CH_2), 2.42–2.46 (m, 2H, CH_2), 2.04–2.09 (m, 2H, CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.6, 163.4, 157.4, 140.8, 134.2, 128.7, 128.3, 128.1, 87.1, 40.8, 38.3, 34.3, 22.5, 20.7. ESI–MS: *m/z* 290.24 $[M+H]^+$.

General procedure for the reactions of HKAs 2 with acrylonitrile (3) in basic condition. To an anhydrous solution of heterocyclic ketene aminals **1** (0.4mmol) and acrylonitrile (0.26 mL) in DMF (5 mL) at 0 °C was added NaH (0.7 mmol). The reactions were monitored by TLC. When TLC indicated the disappearance of the starting materials, transfer the solution into 10 mL water, then extracted them with CH_2Cl_2 (3×3mL) followed by washed with water. After drying and filtering, the residue was purified by recrystallization (EtOAc). Compound **8a**: yellow solid. mp 101–103 °C. IR (KBr): 3254, 2249, 1601cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.68 (s, 1H, N–H), 7.80–7.84 (m, 2H, Ph–H), 7.36–7.41 (m, 3H, Ph–H), 5.22 (s, 1H, =C–H), 3.68–3.73 (m, 2H, CH_2), 3.60–3.67 (m, 2H, CH_2), 3.52–3.59 (m, 2H, CH_2), 2.64 (t, *J* = 6.5 Hz, 2H, CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 186.2, 163.6, 141.2, 130.0, 128.0, 126.7, 117.5, 72.4, 48.2, 42.5, 41.8, 16.6. ESI–MS: *m/z* 242.31 $[M+H]^+$. Anal. Calcd (%) for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.78; H, 6.93; N, 17.67. Compound **8b**: yellow solid. mp 100–103 °C. IR (KBr): = 3318, 2246, 1598 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.65 (s, 1H, N–H), 7.71–7.74 (d, *J* = 8.0 Hz, 2H, Ph–H), 7.18–7.20 (d, *J* = 8.0 Hz, 2H, Ph–H), 5.21 (s, 1H, =C–H), 3.62–3.70 (m, 2H, CH_2), 3.57–3.63 (m, 2H, CH_2), 3.52–3.56 (m, 2H, CH_2), 2.61–2.67 (m, 2H, CH_2), 2.37 (s, 3H, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 186.2, 163.5, 140.2, 138.4, 128.7, 126.7, 117.5, 72.2, 48.2, 42.2, 41.9, 21.3, 16.5. ESI–MS: *m/z* 256.32 $[M+H]^+$. Anal. Calcd (%) for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.34; H, 6.70; N, 16.39. Compound **8c**: yellow solid. mp 72–74 °C. IR (KBr): 3177, 2245 1598 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.62 (s, 1H, N–H), 7.79–7.83 (d, *J* = 9.0Hz, 2H, Ph–H) , 6.88–6.91 (d, *J* = 9.0Hz, 2H, Ph–H) 5.19 (s, 1H, =C–H), 3.83 (s, 3H, CH_3), 3.66–3.73 (m, 2H, CH_2), 3.57–3.63 (m, 2H, CH_2), 3.53–3.57 (m, 2H, CH_2), 2.65 (t, *J* = 6.5 Hz, 2H, CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 185.5, 163.4, 161.3, 133.7, 128.4, 117.6, 113.3, 71.8, 55.3, 48.2, 42.2, 41.9, 16.5; ESI–MS: *m/z* 272.33 $[M+H]^+$. HRMS–FAB: *m/z* for $C_{15}H_{17}N_3O_2$ $[M+H]^+$: 272.1400; found: 272.1399. Compound **8d**: yellow solid. mp 143–145 °C. IR (KBr): 3303, 2249, 1535 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.66 (s, 1H, N–H), 7.74–7.78 (d, *J* = 9.5 Hz, 2H, Ph–H), 7.33–7.37 (d, *J* = 8.5 Hz, 2H, Ph–H), 5.177 (s, 1H, =C–H), 3.69–3.74 (m, 2H, CH_2), 3.61–3.66 (m, 2H, CH_2), 3.54–3.59 (m, 2H, CH_2), 2.66 (t, *J* = 6.5 Hz, 2H, CH_2).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 184.7, 163.7, 139.5, 136.0, 128.2, 128.1, 117.4, 72.2, 48.2, 42.2, 41.8, 16.6; ESI-MS: *m/z*: 276.29 $[M+H]^+$. Anal. Calcd (%) for $C_{14}H_{14}ClN_3O$: C, 60.98; H, 5.12; N, 15.24. Found: C, 60.87; H, 5.31; N, 14.96.

ACKNOWLEDGEMENTS

This work is supported by The Ministry of Science and Technology and the Ministry of Health of the P.R. China (No. 2009ZX09501-006), and The Chinese Academy of Sciences.

.

REFERENCES

1. Z.-T. Huang and H. Wamhoff, *Chem. Ber.*, 1984, **117**, 622; A. Basheer and Z. Rappoport, *J. Org. Chem.*, 2006, **71**, 9743; For reviews, see: Z.-T. Huang and M.-X. Wang, *Heterocycles*, 1994, **37**, 1233; M.-X. Wang and Z.-T. Huang, *Prog. Nat. Sci.*, 2002, **12**, 249.
2. R. Destro, U. Cosentino, G. Moro, E. Ortoleva, and T. Pilati, *J. Mol. Struct.*, 1989, **212**, 97; M. W. Anderson, M. J. Begley, and R. C. F. Jones, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2599; R. C. F. Jones, P. Patel, S. C. Hirst, and I. Turner, *Tetrahedron*, 1997, **53**, 11781; R. C. F. Jones, P. Patel, S. C. Hirst, and M. J. Smallridge, *Tetrahedron*, 1998, **54**, 6191.
3. Z.-T. Huang and Z.-R. Liu, *Synth. Commu.*, 1989, **19**, 1801.
4. C.-Y. Yu , P.-H. Yang, M.-X. Zhao, and Z.-T. Huang, *Synlett*, 2006, 1835; J.-P. Liao, T. Zhang, C.-Y. Yu, and Z.-T. Huang, *Synlett*, 2007, 761; M. Yaqub, C.-Y. Yu, Y.-M. Jia, and Z.-T. Huang, *Synlett*, 2008, 1357; S.-J. Yan, C. Huang, C.-X. Sun, Y.-F. Ni, and J. Lin, *J. Comb. Chem.*, 2010**, 12**, 91; R. Pratap, A. Sharon, P. R. Maulik, and V. J. Ram, *Tetrahedron Lett.*, 2005, **46**, 85.
5. H. Kondo, M. Taguchi, Y. Inoue, F. Sakamoto, and G. Tsukamoto, *J. Med. Chem.*, 1990, **33**, 2012; H. Wamhoff and L. Lambers, *Synthesis*, 1993, 111; B. E. Maryanoff, W. Ho, D. F. McComsey, A. B. Reitz, P. P. Grous, S. O. Nortey, R. P. Shank, B. Dubinsky, R. J. Jr. Taylor, and J. F. Gardocki, *J. Med. Chem.*, 1995, **38**, 16; B. E. Maryanoff, S. O. Nortey, J. J. McNally, P. J. Sanfilippo, D. F. McComsey, B. Dubinsky, R. P. Shank, and A. B. Reitz, *Biomed. Chem. Lett.*, 1999, **9**, 1547; V. J. Ram, A. Goel, S. Sarkhel, and P. R. Maulik, *Bioorg. Med. Chem.*, 2002, **10**, 1275; A. D. Jordan, A. H.Vaidya, D. I. Rosenthal, B. Dubinsky, C. P. Kordik, P. J. Sanfilippo, W.-N. Wu, and A. B. Reitz, *Biomed. Chem. Lett.*, 2002, **12**, 2381; M. M. Abdelhalim, M. M. T. El-Saidib, S. T. Rabie, and G. A. Elmegeeda, *Steroids*, 2007, **72**, 459; S. N. Suryawanshi, S. Pandey, Rashmirathi, B. A. Bhatt, and S. Gupta, *Eur. J. Med. Chem.*, 2007, **42**, 511.
6. M.-X. Wang, J.-M. Liang, and Z.-T. Huang, *J. Chem. Res.*, *Synop*., 1994, 166; *J. Chem. Res., Miniprint*, 1994, 1001.
7. Z.-T. Huang and M.-X. Wang, *J. Org. Chem.*, 1992, **57**, 184 and references cited therein.

8. Z.-T. Huang and M.-X. Wang, *Synth. Commun.*, 1991, **21**, 1167; Z.-T. Huang and M.-X. Wang, *Synth. Commun*., 1991, **21**, 1909.
9. B. Liu, M.-X. Wang, and Z.-T. Huang, *Tetrahedron lett.*, 1999, **40**, 7399.
10. X.-S. Shao, H. Fu, X.-Y. Xu, X.-L. Xu, Z.-W. Liu, Z. Li, and X.-H. Qian, *J. Agric. Food Chem.*, 2010, **58**, 2696.
11. M. M. Abdelhalim, M. M. T. El-Saidib, S. T. Rabie, and G. A. Elmegeeda, *Steroids,* 2007, **72**, 459.
12. A. D. Jordan, A. H. Vaidya, D. I. Rosenthal, B. Dubinsky, C. P. Kordik, P. J. Sanfilippo, W. N. Wu, and A. B. Reitz, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2381.
13. S. N. Suryawanshi, S. Pandey, Rashmirathi, B. A. Bhatt, and S. Gupta, *Eur. J. Med. Chem.*, 2007, **42**, 511.
14. S.-J. Yan, C. Huang, X.-H. Zeng, R. Huang, and J. Lin, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 48.
15. Z.-T. Huang and Z.-R. Liu, *Synthesis*, 1987, 357.