SHORT PAPER

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The reaction of heteroaroyl-substituted heterocyclic ketene aminals with arylhydroximic acid chloride: an efficient synthesis of polysubstituted isoxazoles[†]

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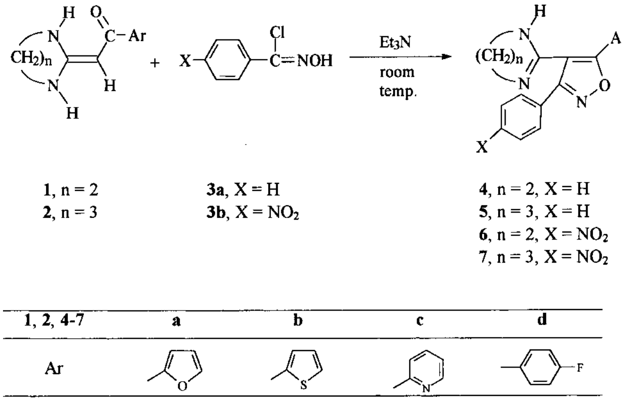
The heteroaroyl-substituted heterocyclic ketene aminals **1** or **2** reacted smoothly with arylhydroximic acid chlorides **3** to give the polysubstituted isoxazoles **4–7**.

Heterocyclic ketene aminals have shown great potential in the synthesis of a wide variety of new and/or fused heterocycles. The synthesis and reactions of heterocyclic ketene aminals have thus attracted much attention.[1] The reaction of aroyl-substituted heterocyclic ketene aminals with 1,3-dipolar reagents, such as azides, [2–7] nitrile imines, [8,9] benzonitrile oxide [10,11] or its precursor,[12] have been reported. As a continuation of our studies, we report here the reaction of heteroaroyl-substituted heterocyclic ketene aminals with arylhydroximic acid chlorides, the precursors of benzonitrile oxides.

The heteroaroyl groups used in this research were the furoyl, thiophenoyl and picolinoyl groups, as well as the *p*-fluorobenzoyl group. The heteroaroyl-substituted heterocyclic ketene aminals **1** or **2** were prepared by the heteroatom aroyl ketene-*S*,*S*-diacetals with diamines according to the literature procedure.[13]

1 or **2** reacted smoothly with arylhydroximic acid chlorides **3** in the presence of triethylamine to give the polysubstituted isoxazoles **4–7** in moderate to good yields. (Scheme 1)



Scheme 1

These results are similar to that of the base-promoted reaction of benzoyl-substituted heterocyclic ketene aminals with 4-nitrobenzhydroximic acid chloride. The polysubstituted isoxazoles are formed by the nucleophilic attack of α-carbon of ketene aminal to arylhydroximic acid chloride, then through the cyclocondensation and aromatizing elimination sequences.[12]

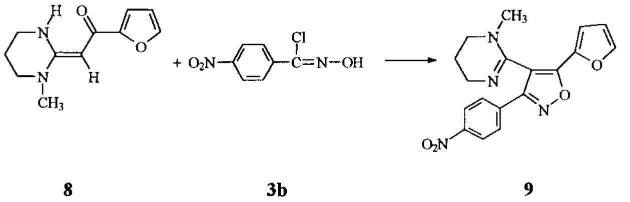
The reaction conditions and the yields of the products are listed in Table 1.

The constitution and structure of products **4–7** was confirmed by microanalytical data and mass, IR and ^{1}H NMR spectra.

Table 1 Reaction conditions and product yields

Reactacts	Time (h)	Product	Yield (%)
1a 3a	12	**4a**	59
1b 3a	12	**4b**	81
1c 3a	12	**4c**	85
1d 3a	12	**4d**	75
2a 3a	24	**5a**	40
2b 3a	24	**5b**	48
2c 3a	24	**5c**	55
2d 3a	24	**5d**	41
1a 3b	12	**6a**	53
1b 3b	12	**6b**	83
1c 3b	12	**6c**	83
1d 3b	12	**6d**	92
2b 3b	24	**7b**	45
2c 3b	24	**7c**	65

1-Methyl-2-[(2-furoyl)methylene]hexahydropyrimidine (**8**) also reacted with **3b** to afford the isoxazole **9** (Scheme 2) but, when both the protons of the heterocyclic ketene aminals were substituted by methyl groups, no product was isolated from the reaction with **3b**.



Scheme 2

Experimental

Melting points were uncorrected. ^{1}H NMR spectra were recorded on a Varian Unity 200 spectrometer. IR spectra were recorded on a Perkin-Elmer 782 spectrometer. Mass spectra were obtained on an AEI MS-50 instrument. Elemental Analyses were carried out by the Analytic Laboratory of the Institute.

General Procedure for the reaction of **1** *or* **2** *with* **3:** A mixture of **1** or **2** (1 mmol) and **3** (1.1 mmol) in chloroform (15 ml) was stirred at ambient temperature for some hours (see Table 1). After the reaction was finished (monitoring by TLC), the solid product was filtered out and suspended in chloroform. Triethylamine (0.2 ml) was added to the suspension. The solution was washed with brine (2 × 15 ml) and dried with anhydrous sodium sulfate. After removal of solvent, the residue was chromatographed on a basic aluminium oxide column and eluted with petroleum ether (60–90 °C)-etheyl acetate.

4a: m.p. 223–224 °C (Found: C, 68.56; H, 4.88; N, 14.95. $C_{16}H_{13}N_3O_2$ requires C, 68.81; H, 4.69; N, 15.05%); ν_{max}/cm^{-1} (KBr) 3210 (NH), 1662, 1617, 1610 and 1595; δ_H (DMSO-d_6) 4.10 (s, 4H), 6.88 (d, *J* = 5.4 Hz, 1H), 7.45 (d, *J* = 5.0 Hz, 1H), 7.58–7.72 (m, 5H), 8.15 (d, *J* = 3.0 Hz, 1H), 11.09 (S, 1H, NH); *m/z* (EI) 279 (M$^+$, 26), 278 (100) and 250 (7).

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[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

4b: m.p. 186–187 °C (Found: C, 65.05; H, 4.48; N, 13.98. $C_{16}H_{13}N_3OS$ requires C, 65.06; H, 4.44; N, 14.23%); ν_{max}/cm^{-1} (KBr) 3180 (NH), 1622, 1591 and 1578; δ_H (DMSO-d_6) 3.64 (s, 4H), 7.25–7.30 (m, 1H), 7.50–7.58 (m, 3H), 7.74–7.95 (m, 4H); *m/z* (EI) 295 (M^+, 32) and 294(100).

4c: Mp 133-134 ˚C (Found: C, 70.11; H, 4.97; N, 19.06. $C_{17}H_{14}N_4O$ requires C, 70.33; H, 4.86; N, 19.30%); υ_{max}/cm^{-1} (KBr) 3200 (NH), 1659, 1599 and 1490; δ_H (CDC1_3) 3.70 (s, 4H), 7.38–7.50 (m, 5H), 7.70–8.10 (m, 3H), 8.66–8.70 (m, 1H); *m/z* (EI) 290 (M^+, 29), 289 (100) and 260 (4).

4d: m.p. 177–178 ˚C (Found: C, 70.17; H, 4.83; N, 13.34. $C_{18}H_{14}FN_3O$ requires C, 70.35; H, 4.59; N, 13.67%); υ_{max}/cm^{-1} (KBr) 3210 (NH), 1648, 1610 and 1515; δ_H ($CDCl_3$) 3.71 (s, 4H), 7.16 (t, *J* = 8.5 Hz, 2H), 7.45–7.50 (m, 3H), 7.72–7.79 (m, 2H), 7.90–8.04 (m, 2H), 8.45 (br, 1Hm NH); *m/z* (EI) 307 (M^+, 31), 306 (100) and 288 (53).

5a: m.p. 265–266 ˚C (Found: C, 69.50; H, 5.51; N, 14.40. $C_{17}H_{15}N_3O_2$ requires C, 69.61; H, 5.15; N, 14.33%); υ_{max}/cm^{-1} (KBr) 3184 (NH), 1613, 1566 and 1440; δ_H (DMSO-d_6) 2.03 (quin, *J* = 6.0 Hz, 2H), 3.54 (t, *J* = 6.0 Hz, 5H), 6.80–6.85 (m, 1H), 7.34–7.39 (m, 1H), 7.57–7.72 (m, 2H), 8.08–8.12 (m, 1H), 10.73 (s, 1H, NH); *m/z* (EI) 293 (M^+, 100), 264 (18) and 225 (29).

5b: m.p. 190–191 ˚C (Found: C, 65.92; H, 5.07; N, 13.47. $C_{17}H_{15}N_3OS$ requires C, 65.99; H, 4.89; N, 13.58%); υ_{max}/cm^{-1} (KBr) 3240 (NH), 1632, 1612 and 1560; δ_H (DMSO-d_6) 1.83 (quin, *J* = 6.0 Hz, 2H), 3.32 (t, *J* = 6.0 Hz, 2H), 3.32 (t, *J* = 6.0 Hz, 4H), 7.08–7.14 (m, 1H), 7.40-7.77 (m, 7H); *m/z* (EI) 309 (M^+, 47), 308 (100) and 280 (8).

5c: m.p. 173–174 ˚C (Found: C, 70.97; H, 5.23; N, 18.17. $C_{18}H_{16}N_4O$ requires C, 71.03; H, 5.30; N, 18.41%); υ_{max}/cm^{-1} (KBr) 3170 (NH), 1635, 1618, 1605, 1580 and 1550; δ_H (CDC1_3) 1.82 (quin, *J* = 6.0 Hz, 2H), 3.37 (t, *J* = 6.0 Hz, 4H), 7.31–7.50 (m, 5H), 7.80–8.02 (m, 3H), 8.67–8.71 (m, 1H); *m/z* (EI) 304 (M^+, 46), 303 (100) and 226 (40).

5d: m.p. 194–195 ˚C (Found: C, 71.13; H, 5.01; N, 13.05. $C_{19}H_{16}FN_3O$ requires C, 71.03; H, 5.02; N, 13.08%), υ_{max}/cm^{-1} (KBr) 3165 (NH), 1640, 1610, 1545 and 1510; δ_H ($CDCI_3$) 1.84 (quin, *J* = 5.6 Hz, 2H), 3.37 (t, *J* = 5.6 Hz, 4H), 7.14 (t, *J* = 8.8 Hz, 2H), 7.41–7.51 (m, 3H), 7.78–7.97 (m, 4H); *m/z* (EI) 321 (M^+, 50), 320 (100) and 292 (10).

6a: yellow cryst., m.p. 188–189 ˚C (Found: C, 59.31; H, 3.98; N, 17.33. $C_{16}H_{12}N_4O_4$ requires C, 59.26; H, 3.73; N, 17.28%); υ_{max}/cm^{-1} (KBr) 3120 (NH), 1628, 1600, 1560, 1518 and 1345 (NO_2); δ_H (DMSO-d_6) 3.63 (s, 4H), 6.76–6.79 (m, 1H), 7.32 (d, *J* = 4.0 Hz, 1H), 8.02 (d, *J* = 8.6 Hz, 2H), 8.02–8.04 (m, 1H), 8.38 (d, *J* = 8.6 Hz, 2H); *m/z* (EI) 324(M^+, 29), 323 (100) and 277 (18).

6b: m.p. 184–185 ˚C (Found: C, 56.63; H, 3.74; N, 16.20. $C_{16}H_{12}N_4O_3S$ requires C, 56.46; H, 3.56; N, 16.46%); υ_{max}cm^{-1} (KBr) 3175 (NH), 1610, 1592, 1520 and 1348 (NO_2); δ_H ($CDCI_3$) 3.81 (s, 4H), 4.60 (br, 1H, NH), 7.18–7.20 (m, 1H), 7.58 (d, *J* = 6.6 Hz, 1H), 7.87 (d, *J* = 4.5 Hz, 1H), 7.99 (d, *J* = 8.8 Hz, 2H), 8.33 (d, *J* = 8.8 Hz, 2H); *m/z* (EI) 340 (M^+, 29), 339 (100) and 293 (22).

6c: m.p. 175–176 ˚C (Found: C, 60.88; H, 4.02; N, 20.84. $C_{17}H_{13}N_5O_3$ requires C, 60.89; H, 3.91; N, 20.89%); υ_{max}/cm^{-1} 3190 (NH), 1655, 1605, 1595, 1521 and 1340 (NO_2); δ_H (DMSO-d_6) 3.62 (s, 4H), 7.55–7.63 (m, 1H), 8.03–8.07 (m, 2H), 8.06 (d, *J* = 8.8 Hz, 2H), 8.38 (d, *J* = 8.8 Hz, 2H), 8.78-8.80 (m, 1H); *m/z* (EI) 335 (M^+, 28), 334 (100) and 288 (21).

6d: Pale yellow cryst., m.p. 214–215 ˚C (Found: C, 61.38; H, 3.96; N, 15.90. $C_{18}H_{13}FN_4O_3$ requires C, 61.36; H, 3.72; N, 15.90%); υ_{max}cm^{-1} (KBr) 3150 (NH), 1645, 1610, 1522 and 1340 (NO_2); δ_H ($CDCI_3$) 3.77 (s 4H), 7.20 (t, *J* = 9.0 Hz, 2H), 7.90–8.00 (m, 2H), 8.02 (d, *J* = 8.6 Hz, 2H), 8.32 (d, *J* = 8.6 Hz, 2H); *m/z* (EI) 352 (M^+, 28), 351 (100) and 305 (30).

7b: Pale yellow cryst., m.p. 212–213 ˚C (Found: C, 57.77; H, 4.02; N, 15.75. $C_{17}H_{14}N_4O_3S$ requires C, 57.61; H, 3.98; N, 15.81%); υ_{max}cm^{-1} (KBr) 3155 (NH), 1630, 1607, 1518 and 1340 (NO_2); δ_H (DMSO-d_6) 1.81 (quin, *J* = 5.6 Hz, 2H), 3.33 (t, *J* = 5.6 Hz, 4H), 7.25–7.29 (m, 1H), 7.76–7.79 (m, 1H), 7.86–7.90 (m, 1H), 8.08 (d, *J* =8.6 Hz, 2H), 8.40 (d, *J* = 8.6 Hz, 2H); *m/z* (EI) 354 (M^+, 42), 353 (100) and 307 (14).

7c: Pale yellow cryst., m.p. 197–198 ˚C (Found: C, 61.60; H, 4.46; N, 19.78. $C_{18}H_{15}N_5O_3$ requires C, 61.88; H, 4.33; N, 20.05%); υ_{max}cm^{-1} (KBr) 3210 (NH), 1630, 1610, 1522 and 1348 (NO_2); δ_H (DMSO-d_6) 1.78 (quin, *J* = 5.6 Hz, 2H), 3.30 (t, *J* = 5.6 Hz, 4H), 7.50–7.60 (m, 1H), 8.01–8.04 (m, 2H), 8.13 (d, *J* = 8.6 Hz, 2H), 8.41 (d, *J* = 8.6 Hz, 2H), 8.76–8.77 (m, 1H); *m/z* (EI) 349 (M^+, 32), 348 (100) and 302 (15).

9: Yellow cryst., yield: 45%, m.p. 140–142 ˚C (Found: C, 61.29; H, 4.61; N, 15.64. $C_{18}H_{16}N_4O_4$ requires C, 61.36; H, 4.58; N, 15.90%); υ_{max}/cm^{-1} (KBr) 1615, 1600, 1520 and 1345 (NO_2); δ_H (DMSO-d_6) 1.91 (quin, *J* = 5.8 Hz, 2H), 2.58 (s, 3H), 3.28–3.40 (m, 4H), 6.77–6.80 (m, 1H), 7.11–7.15 (m, 1H), 8.02–8.07 (m, 1H), 8.05 (d, *J* = 9.4 Hz, 2H), 8.41 (d, *J* = 9.4 Hz, 2H); *m/z* (EI) 352 (M^+, 78), 323 (21), 311 (17), 298 (22) and 95 (100).

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References

1 Z.-T. Huang and M.-X. Wang, *Heterocycles*, 1994, **37**, 1233.
2 G. Bolis, D. Pocar, R. Stradi, and P. Trimarco, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2365.
3 N.I. Viswanathan and V. Balakrishnan, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2361.
4 S. Fioravanti, M.A. Loreto, L. Pellacini and P.A. Tardella, *Heterocycles*, 1987, **25**, 433.
5 R.T. Chakrasali, H. Ila, and H. Junjappa, *Synthesis*, 1988, 851.
6 Z.-T. Huang and M.-X. Wang, *Chin. Chem. Lett.*, 1990, **1**, 5.
7 Z.-T. Huang and M.-X. Wang, *J. Org. Chem.*, 1992, **57**, 184.
8 D. Pocar, L. M. Rossi and R. Stradi, *Synthesis*, 1976, 684.
9 B. Liu, M.-X. Wang and Z.-T. Huang, *Tetrahedon Lett.*, 1999, **40**, 7399.
10 S. Rajappa, B. G. Advani and R. Sreenivasan, *Synthesis*, 1974, 656.
11 Z.-T. Huang and M.-X. Wang, *Synth. Commun.*, 1991, **21**, 1909.
12 Z.-T. Huang and M.-X. Wang, *Synth. Commun.*, 1991, **21**, 1167.
13 Z.-T. Huang and Z.-R. Liu, *Synth. Commun.*, 1989, **19**, 943.