Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

The Reaction of Benzoyl Substituted Heterocyclic Ketene Aminals with 4-Nitrobenzhydroximic Acid Chloride

Zhi-Tang Huang [a] & Mei-Xiang Wang [a]
[a] Institute of Chemistry, Academia Sinica, Beijing, People's Republic of China
Published online: 16 Feb 2007.

To cite this article: Zhi-Tang Huang & Mei-Xiang Wang (1991): The Reaction of Benzoyl Substituted Heterocyclic Ketene Aminals with 4-Nitrobenzhydroximic Acid Chloride, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 21:10-11, 1167-1176

To link to this article: http://dx.doi.org/10.1080/00397919108021036

SYNTHETIC COMMUNICATIONS, 21(10&11), 1167-1176 (1991)

THE REACTION OF BENZOYL SUBSTITUTED HETEROCYCLIC KETENE AMINALS WITH 4-NITROBENZHYDROXIMIC ACID CHLORIDE

Zhi-Tang Huang* and Mei-Xiang Wang

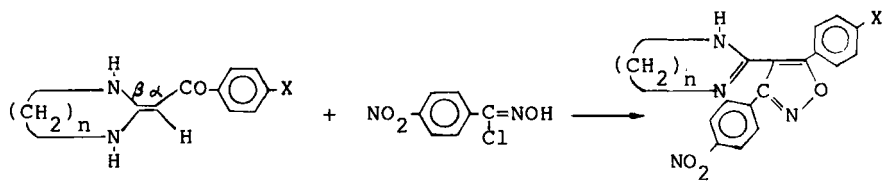
Institute of Chemistry, Academia Sinica
Beijing, People's Republic of China

Abstract: Heterocyclic ketene aminals 1 or 2 reacted with 4-nitrobenzhydroximic acid chloride (3) to give the 3,5-diaryl-4-(2-imidazolinyl)-isoxazoles 4 or 3,5-diaryl-4-(2-tetrahydropyrimidinyl)-isoxazoles 5. The mechanism of their formation were also discussed.

Heterocyclic ketene aminals are versatile starting materials for the synthesis of a wide variety of fused heterocycles. The synthesis and reactions of heterocyclic ketene aminals have been aroused much attention.[1-23] Due to the conjugation of two nitrogen atoms with the double bond, their α-carbon possesses much higher electronic density, therefore, they may be used as nucleophile and more attention has been given to their nucleophilic addition and substitution reactions with electron deficient compounds, and various fused or spiro heterocycles were obtained.[10,12-17,23] However, to our knowledge, the reactions concerned the gem-enediamine carbon (β-carbon) of ketene aminals were only reported in a few cases.[24-27] Recently, we have reported the reaction of benzoyl substituted heterocyclic ketene aminals with aryl

azides and intend to explore the possibility of 1,3-dipolar cycloaddition of heterocyclic ketene aminals. The results indicated that heterocyclic ketene aminals are better nucleophile rather than 1,3-polarophile towards aryl azides.[32] Here, we report the results of reaction of benzoyl substituted heterocyclic ketene aminals 1 or 2 with another 1,3-dipolar reagent, 4-nitrobenzhydroximic acid chloride.

At first, heterocyclic ketene aminals 1 or 2 were reacted directly with 4-nitrobenzonitrile oxide, the result indicated that the conversion of 1 or 2 was very low traced by TLC, and the most of 1 or 2 were recovered after the reaction. Then, the precursor 4-nitrobenzhydroximic acid chloride (3) with triethylamine was used instead of 4-nitrobenzonitrile oxide, we intend that the 4-nitrobenzonitrile oxide generated in situ may reacted with 1 or 2, but the situation is same as above. The reason why 1 or 2 can not be reacted is that 4-nitrobenzonitrile oxide dimerized easily,[33] and the rate of dimerization may be far fast than that of the reaction with 1 or 2. However, 1 or 2 reacted smoothly with 3 itself at ambient temperature, and crystalline products were obtained by work-up of the reaction mixture with sodium carbonate solution in moderate yields.



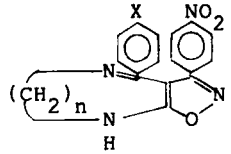
1, n = 2
2, n = 3

3

4, n = 2
5, n = 3

1,2,4,5,6	a	b	c	d
X	OCH_3	CH_3	H	Cl

The constitutions of 4 and 5 were confirmed by the mass spectra and elemental analyses, which indicated that in fact a reaction took place between 1 or 2 with 3 in 1:1 molar ratio accompanied with the loss of one mole of water. From these experimental results, the structure of the products may be 4 and 5 or isoxazolo[5,4-e][1,4]diazepines and isoxazolo-[5,4-b][1,5]diazocines (A),which may be resulted by the 1,3-dipolar cycloaddition, cleavage of 1,3-diazaheterocyclic ring and cyclocondensation reaction sequences. In the ^{1}H-NMR

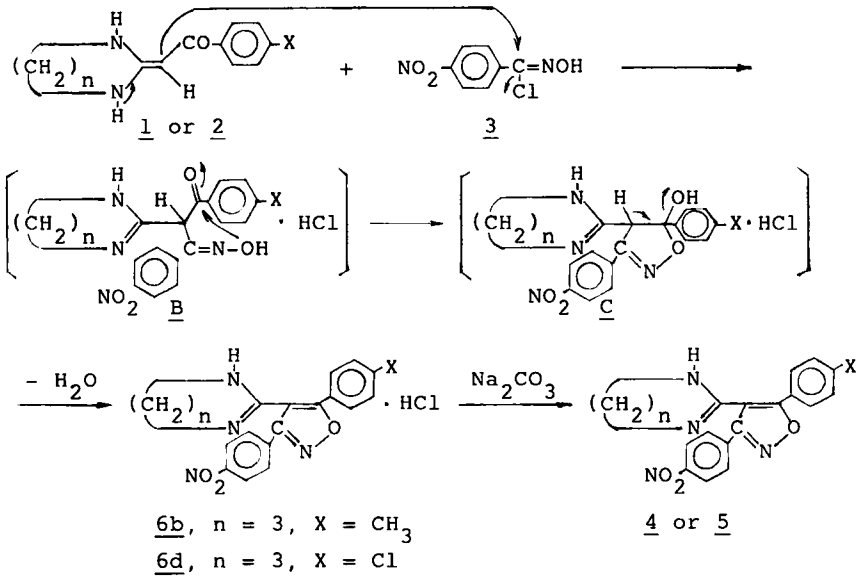


A

spectra of the products, except the aromatic proton signals and the deuterium exchangable proton signal (NH), only a singlet signal at 3.68-3.70 ppm corresponding to 4 protons or a triplet signal at 3.35-3.41 ppm corresponding to 4 protons and a quintet signal at 1.82-1.87 ppm corresponding to 2 protons were observed, respectively. It indicates that an 2-imidazolinyl or 2-tetrahydropyrimidinyl moiety is existed in the structure of the products, therefore the structure A is excluded. The IR and UV spectral data are also consistant with the structure 4 or 5.

When the reaction mixture did not treated with sodium carbonate solution, the hydrochloride 6b and 6d of 5b and 5d could be obtained.

The mechanism of formation of 4 or 5 from 1 or 2 with 3 may be as follows:



By this mechanism, 1 or 2 are as nucleophile to react with 3 to form the intermediate B, which are transformed to 6 through the intermediate C by the cyclization and aromatized elimination sequences. The final products 4 or 5 are formed by work-up of the hydrochloride 6 with sodium carbonate.

From the above results, we could conclude that heterocyclic ketene aminals are only a nucleophile rather than a 1,3-dipolarophile towards 4-nitrobenzhydroximic acid chloride. By the reaction of benzoyl substituted heterocyclic ketene aminals with 4-nitrobenzhydroximic acid chloride, we provide

a facile approach to synthesize 3,5-diaryl-4-(2-imidazolinyl)-isoxazoles or 3,5-diaryl-4-(2-tetrahydropyrimidinyl)-isoxazoles.

EXPERIMENTAL

Melting points are uncorrected. Microanalyses were carried out by the Analytical Laboratory of the Institute. Mass spectra were obtained on a AEI MS-50 instrument. IR spectra were recorded on a Perkin-Elmer 782 spectrometer for KBr tablets. UV spectra were measured by a Hitachi 340 spectrometer in ethanol solution. ^{1}H-NMR spectra were recorded on Varian EM-360L and Jeol FX-100 instrument in $CDCl_3$-DMSO-d_6 (4:1).

General Procedure for Synthesis of 4 and 5:

301 mg (1.5 mmol) of 4-nitrobenzhydroximic acid chloride was added portion-wise to a mixture of 1.5 mmol of 1 or 2 in 20 ml of chloroform under stirring. The mixture was stirred at ambient temperature for 12 hours. The solid products was filtered out and dissolved in the mixture solvent of chloroform and acetonitrile (3:1). The solution was worked-up with saturated solution of sodium carbonate (2 x 15 ml), then washed with sodium chloride solution (2 x 15 ml). The organic layer was dried with anhydrous sodium sulfate. After removal of solvent, the residue was recrystallized from ethyl acetate-methanol (1:1) to give pure 4. In order to obtain the pure 5, the residue was chromatographed on a basic aluminium oxide column and eluted with petroleum ether (30-60°C)-ethyl acetate (1:1), and then recrystallized from ethyl acetate.

3-(4-Nitrophenyl)-4-(2-imidazolinyl)-5-(4-methoxyphenyl)-isoxazole (4a):

Yield: 49.5 %, m.p. 208.5-210°C. MS: m/z = 364 (M^+, 30), 363 (100), 317 (14). UV: λ_{max} = 286 (lgε = 4.47), 226 nm (4.05). IR: ν = 3140 (NH), 1518, 1331 (NO_2), 1249 (C-O-C), 1637, 1604 cm^{-1}. ^{1}H-NMR: δ = 8.24 (d, 2H), 7.97 (d, 2H), 7.79 (d, 2H), 6.93 (d, 2H), 4.32 (s, 1H), 3.82 (s, 3H), 3.70 ppm (s, 4H). Anal. calc. for $C_{19}H_{16}N_4O_4$: C, 62.63; H, 4.43; N, 15.38. Found C, 62.78; H, 4.25; N,15.44.

3-(4-Nitrophenyl)-4-(2-imidazolinyl)-5-(4-methylphenyl)-isoxazole (4b):

Yield: 61.3%, m.p. 222.5-223.5°C. MS: m/z = 348 (M^+, 22), 347 (75), 301 (100). UV: λ_{max} = 281 (lgε = 4.32), 223 nm (3.98). IR: ν = 3120 (NH), 1510, 1333 (NO_2), 1631, 1598 cm^{-1}. ^{1}H-NMR: δ = 8.22 (d, 2H), 7.96 (d, 2H), 7.72 (d, 2H), 7.21 (d, 2H), 4.05 (s, 1H), 3.70 (s, 4H), 2.37 ppm (s, 3H). Anal. calc. for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found C, 65.73; H, 4.72; N, 16.05.

3-(4-Nitrophenyl)-4-(2-imidazolinyl)-5-phenyl-isoxazole (4c):

Yield: 63.5%, m.p. 220.5-221.5°C. MS: m/z = 334 (M^+, 35), 333 (100), 287 (21). UV: λ_{max} = 275 (lgε = 4.36), 222 nm (3.94). IR: ν = 3141 (NH), 1518, 1341 (NO_2), 1635, 1600 cm^{-1}. ^{1}H-NMR: δ = 8.27 (d, 2H), 8.01 (d, 2H), 7.44-7.93 (m, 5H), 3.93 (s, 1H), 3.73ppm (s, 4H). Anal. calc. for $C_{18}H_{14}N_4O_3$: C, 64.66; H, 4.22; N, 16.76. Found C, 64.67; H, 4.22; N, 16.55.

3-(4-Nitrophenyl)-4-(2-imidazolinyl)-5-(4-chlorophenyl)-isoxazole (4d):

Yield: 59.7%, m.p. 258-260°C. MS: m/z = 369 (36), 368 (M^+, 32), 367 (100), 321 (11). UV: λ_{max} = 282 (lgε = 4.45),

221 nm (4.02). IR: ν = 3120 (NH), 1511, 1341 (NO_2), 1633, 1600 cm^{-1}. ^{1}H-NMR: δ = 8.29 (d, 2H), 8.00 (d, 2H), 7.90 (d, 2H), 7.46 (d, 2H), 4.10 (s, 1H), 3.68 ppm (s, 4H). Anal. calc. for $C_{18}H_{13}ClN_4O_3$: C, 58.62; H, 3.55; N, 15.19. Found C, 58.56; H, 3.64; N, 15.13.

3-(4-Nitrophenyl)-4-(2-tetrahydropyrimidinyl)-5-(4-methoxyphenyl)-isoxazole (5a):

Yield: 52.9%, m.p. 156.5-158°C. MS: m/z = 378 (M^+, 44), 377 (100), 331 (10). UV: λ_{max} = 290 (lgε = 4.45), 226 nm (4.12). IR: ν = 3190, 3140 (NH), 1519, 1341 (NO_2), 1260 (C-O-C), 1623, 1607, 1597, 1548 cm^{-1}. ^{1}H-NMR: δ = 8.24 (d, 2H), 8.03 (d, 2H), 7.79 (d, 2H), 6.95 (d, 2H), 4.14 (s, 1H), 3.83 (s, 3H), 3.37 (t, 4H), 1.82 ppm (quin, 2H). Anal. calc. for $C_{20}H_{18}N_4O_4$: C, 63.48; H, 4.79; N, 14.81. Found C, 63.38; H, 4.79; N, 14.68.

3-(4-Nitrophenyl)-4-(2-tetrahydropyrimidinyl)-5-(4-methylphenyl)-isoxazole (5b):

Yield: 58.9%, m.p. 167-169°C. MS: m/z = 362 (M^+, 37), 361 (100), 315 (13). UV: λ_{max} = 280 (lgε = 4.40), 224 nm (4.04). IR: ν = 3198, 3147 (NH), 1516, 1331 (NO_2), 1629, 1607, 1597 cm^{-1}. ^{1}H-NMR: δ = 8.17 (d, 2H), 7.93 (d, 2H), 7.67 (d, 2H), 7.22 (d, 2H), 4.67 (s, 1H), 3.35 (t, 4H), 2.37 (s, 3H), 1.83 ppm (quin, 2H). Anal. calc. for $C_{20}H_{18}N_4O_3$: C, 66.29; H, 5.01; N, 15.46. Found C, 66.50; H, 5.63; N, 15.52.

3-(4-Nitrophenyl)-4-(2-tetrahydropyrimidinyl)-5-phenyl-isoxazole (5c):

Yield: 57.5%, m.p. 228.5-230°C. MS: m/z = 348 (M^+, 35), 347 (100), 301 (19). UV: λ_{max} = 274 (lgε = 4.41), 222 nm

(4.01). IR: ν = 3185, 3150 (NH), 1517, 1336 (NO_2), 1630, 1604, 1590 cm^{-1}. ^{1}H-NMR: δ = 8.21 (d, 2H), 7.98 (d, 2H), 7.39-7.91 (m, 5H), 4.41 (s, 1H), 3.39 (t, 4H), 1.86 ppm (quin, 2H), Anal. calc. for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found C, 65.62; H, 4.40; N, 15.99.

3-(4-Nitrophenyl)-4-(2-tetrahydropyrimidinyl)-5-(4-chlorophenyl)-isoxazole (5d):

Yield: 52.2%, m.p. 275-276°C. MS: m/z = 383 (38), 382 (M^+, 38), 381 (100), 335 (12). UV: λ_{max} = 276 (lgε = 4.48), 219 nm (4.05). IR: ν = 3190, 3130 (NH), 1518, 1340 (NO_2), 1631, 1610, 1584 cm^{-1}. ^{1}H-NMR: δ = 8.23 (d, 2H), 7.97 (d, 2H), 7.78 (d, 2H), 7.38 (d, 2H), 4.24 (s, 1H), 3.41 (t, 4H), 1.87 ppm (quin, 2H). Anal. calc. for $C_{19}H_{15}ClN_4O_3$: C, 59.61; H, 3.95; N, 14.64. Found C, 59.77; H, 4.07; N, 14.71.

General Procedure for Synthesis of 6:

216 mg (1 mmol) of 3 was added portion-wise to a mixture of 1 mmol of 2 in 20 ml of chloroform under stirring. The mixture was stirred at ambient temperature for 12 hours. The solid product was filtered and recrystallized from ethyl acetate-methanol (1:1).

3-(4-Nitrophenyl)-4-(2-tetrahydropyrimidinyl)-5-(4-methylphenyl)-isoxazole Hydrochloride (6b):

Yield: 52.7%, m.p. >300°C. MS: m/z = 362 (M - HCl, 28), 361 (100), 315 (12). UV: λ_{max} = 280 (lgε = 4.37), 224 nm (4.04). IR: ν = 3100, 2856, 2754, 2700 (NH_2^+), 1513, 1335 (NO_2), 1638, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 10.88 (s), 8.48 (d, 2H), 8.05 (d, 2H), 7.78 (d, 2H), 7.54 (d, 2H), 3.60 (t, 4H), 2.50 (s, 3H), 2.08 ppm (quin, 2H). Anal. calc. for

$C_{20}H_{19}ClN_4O_3$: C, 60.23; H, 4.80; N, 14.05. Found C, 60.26; H, 4.62; N, 13.99.

3-(4-Nitrophenyl)-4-(2-tetrahydropyrimidinyl)-5-(4-chlorophenyl)-isoxazole Hydrochloride (6d):

Yield: 50.1%, m.p. >300°C. MS: m/z = 383 (35), 382 (M - HCl, 28), 381 (100), 335 (12). UV: λ_{max} = 278 ($lg\varepsilon$ = 4.42), 224 nm (3.89). IR: ν = 3120, 2860, 2760, 2700 (NH_2^+), 1512, 1341 (NO_2), 1640, 1598 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 10.99 (s), 8.48 (d, 2H), 8.06 (d, 2H), 7.92 (d, 2H), 7.79 (d, 2H), 3.60 (t, 4H), 2.08 ppm (quin, 2H). Anal. calc. for $C_{19}H_{16}Cl_2N_4O_3$: C, 54.43; H, 3.85; N, 13.36. Found C, 54.42; H, 3.76; N, 13.23.

This work was supported by the National Natural Science Foundation of China.

References

1. Gompper, R., Schaefer, H., Chem. Ber. 1967, 100, 591.
2. Rajappa, S., Sreenivasan, R., Advani, B.G., Summerville, R.H., Hoffmann, R., Indian J. Chem. 1977, 15B, 297.
3. Rudorf, W.-D., Augustin, M., J. Prakt. Chem. 1977, 319, 545.
4. Augustin, M., Groth, C., J. Prakt. Chem. 1979, 321, 205.
5. Augustin, M., Groth, C., J. Prakt. Chem. 1979, 321, 215.
6. Augustin, M., Jahreis, G., J. Prakt. Chem. 1979, 321, 699.
7. Augustin, M., Doelling, W., J. Prakt. Chem. 1982, 324, 3.
8. Nair, M.D., Rajappa, S., Desai, J.A., Indian J. Chem. 1982, 21B, 1.
9. Nair, M.D., Desai, J.A., Indian J. Chem. 1982, 21B, 4.

10. Rajappa, S., Nair, M.D., Sreenivasan, R., Advani, B.G., Tetrahedron, 1982, 38, 1673.
11. Huang, Z.-T., Wamhoff, H., Chem. Ber. 1984, 117, 622.
12. Huang, Z.-T., Wamhoff, H., Chem. Ber. 1984, 117, 1856.
13. Huang, Z.-T., Wamhoff, H., Chem. Ber. 1984, 117, 1926.
14. Huang, Z.-T., Tzai, L.-H., Chem. Ber. 1986, 119, 2208.
15. Huang, Z.-T., Liu, Z.-R., Heterocycles, 1986, 24, 2247.
16. Huang, Z.-T., Wang, X.-J., Tetrahedron Lett. 1987, 28, 1527.
17. Huang, Z.-T., Wang, X.-J., Chem. Ber. 1987, 120, 1803.
18. Huang, Z.-T., Liu, Z.-R., Synthesis, 1987, 357.
19. Huang, Z.-T., Gan, W.-X., Wang, X.-J., J. Prakt. Chem. 1988, 330, 724.
20. Wang, X.-J., Huang, Z.-T., Acta Chim. Sin. 1989, 47, 890.
21. Huang, Z.-T., Liu, Z-R., Chem. Ber. 1989, 122, 95.
22. Huang, Z.-T., Liu, Z.-R., Synth. Commun. 1989, 19, 943.
23. Huang, Z.-T., Liu, Z.-R., Synth. Commun. 1989, 19, 1801.
24. Rajappa, S., Advani, B.G., Indian J. Chem. 1977, 15B, 890.
25. Viswanathan, N.I., Balakrishnan, V., J. Chem. Soc. Perkin I, 1979, 2361.
26. Bolis, G., Pocar, D., Stradi, R., Trimarco, P., J. Chem. Soc. Perkin I, 1977, 2365.
27. Fioravanti, S., Loreto, M.A., Pellacani, L., Tardella, P.A., Heterocycles, 1987, 25, 433.
28. Huang, Z.-T., Wang, M.-X., Chinese Chem. Lett. 1990, 1, 5.
29. Barbaro, G., Batlaglia, A., Dondoni, A., J. Chem. Soc. (B) 1970, 588.

(Received in UK 28 February, 1991)