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THE REACTION OF BENZOYL SUBSTITUTED HETEROCYCLIC KETENE AMINALS WITH 2,4,6-TRIMETHYLBENZONITRILE OXIDE

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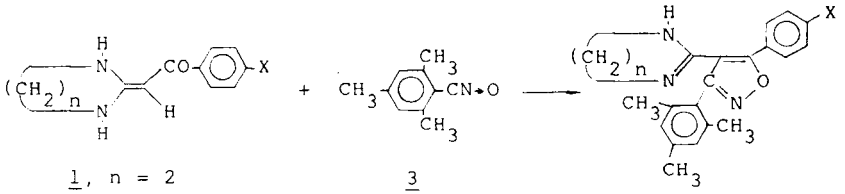
Abstract: Heterocyclic ketene aminals 1 or 2 reacted with 2,4,6-trimethylbenzonitrile oxide (3) to afford the 3,5-diaryl-4-(2-imidazolinyl)-isoxazoles 4 or 3,5-diaryl-4-(2-tetrahydropyrimidinyl)-isoxazoles 5. The mechanism of their formation was discussed.

Recently, we have reported the results of 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. However, the results indicated that heterocyclic ketene aminals are better nucleophile rather than 1,3-dipolarophile towards aryl azides.[1] In order to survey the other approach of 1,3-dipolar cycloaddition of heterocyclic ketene aminals, we try to react heterocyclic ketene aminals with 4-nitrobenzonitrile oxide, irrespectively direct or generated in situ, the most of ketene aminals were recovered after the reaction.[2] It is due to the easy dimerization of 4-nitrobenzonitrile oxide.[3] Consequently, we use 2,4,6-trimethylbenzonitrile oxide, which is hardly dimerized,[4,5] as the reagent to avoid the above obstacle.

Benzoyl substituted heterocyclic ketene aminals 1 or 2 were smoothly reacted at ambient temperature with 2,4,6-tri-

methylbenzonitrile oxide to give 3,5-diaryl-4-(2-imidazolinyl)-isoxazoles 4 or 3,5-diaryl-4-(2-tetrahydropyrimidinyl)-isoxazoles 5 in moderate to good yields.



1, n = 2
2, n = 3

3

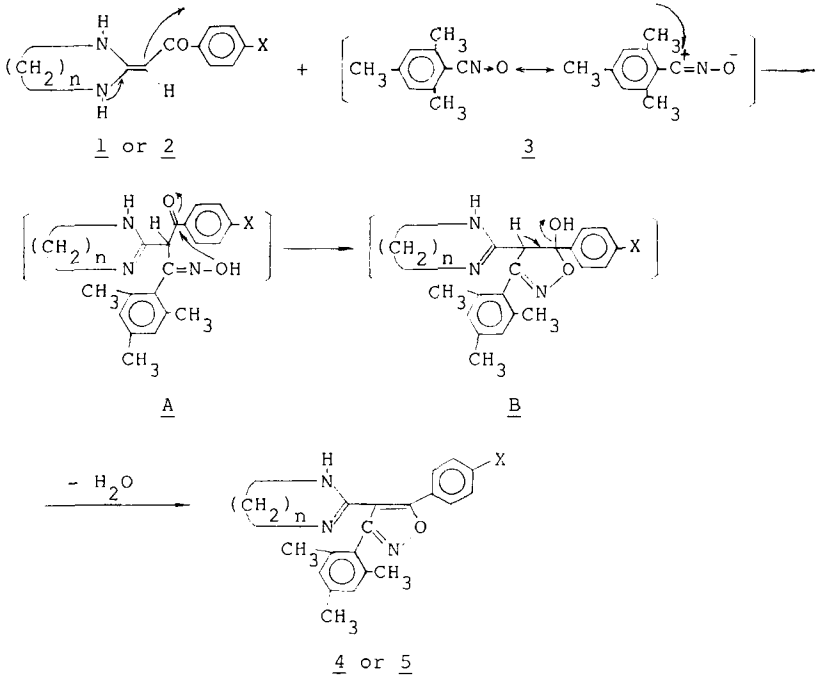
4, n = 2
5, n = 3

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

The constitution of 4 and 5 was confirmed by the mass spectra and elemental analyses, it 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. In the ^{1}H-NMR spectra of the products, except the aromatic proton signals, the deuterium exchangable proton signal (NH) and methyl proton signals, a singlet signal at 3.47-3.53 ppm corresponding to 4 protons or a triplet signal at 3.20-3.23 ppm corresponding to 4 protons and a quintet signal at 1.64-1.67 ppm corresponding to 2 protons were observed, respectively. This indicates that an 2-imidazolinyl or 2-tetrahydropyrimidinyl moiety is existed in the structure of the products. It excludes the another possible structure of the products of isoxazolo[5,4-e][1,4]-diazepines or isoxazolo[5,4-b][1,5]diazocines, which may be resulted by the 1,3-dipolar cycloaddition, cleavage of 1,3-diazaheterocyclic ring, and cyclocondensation reaction sequences. Therefore, the structure of the products may be as 4 or 5.

The IR and UV spectral data shown in the experimental part are also consistant with the structure 4 or 5.

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 yield the open-chain 1,3-addition products A, and not the 1,3-dipolar cycloaddition products. The intermediate A is transformed to products 4 or 5 through the intermediate B by the cyclization, and then by the aromatized elimination.

From the above results, we could conclude that heterocyclic ketene aminals are only as a nucleophile rather than a 1,3-dipolarophile towards 2,4,6-trimethylbenzonitrile oxide. By the reaction of benzoyl substituted heterocyclic ketene aminals with 2,4,6-trimethylbenzonitrile oxide, we provide

another facile approach to synthesize 3,5-diaryl-4-(2-imidazolinyl)isoxazoles or 3,5-diaryl-4-(2-tetrahydropyrimidinyl)-isoxazoles in addition to the reaction with 4-nitrobenzhydroximic acid chloride.[2]

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 $CDCl_3$.

General Procedure for Synthesis of 4 and 5:

241 mg (1.5 mmol) of 3 was added portion-wise to a mixture of 1 mmol of 1 or 2 in 15 ml of chloroform under stirring during 5 minutes. The mixture was stirred at ambient temperature for 1-2 days. The reaction was monitored by TLC. After removal of solvent, the residue was recrystallized from acetone or petroleum ether (30-60°C)-ethyl acetate (1:1).

3-(2,4,6-Trimethylphenyl)-4-(2-imidazolinyl)-5-phenyl-isoxazole (4a):

Reaction time: 40 h. Yield: 66.4%, m.p. 184.5-186°C (ethyl acetate). MS: m/z = 331 (M^+, 16), 330 (45), 316 (100). UV: λ_{max} = 265 (lgε = 4.26), 220 nm (4.08). IR: ν = 3119 (NH), 1640, 1600, 1580, 1565, 1495 cm^{-1}. ^{1}H-NMR: δ = 7.33-8.23 (m, 5H), 6.90 (s, 2H), 4.20 (s, 1H), 3.49 (s, 4H), 2.30 (s, 3H), 2.13 ppm (s, 6H). Anal. calc. for $C_{21}H_{21}N_3O$: C, 76.10; H, 6.39; N, 12.68. Found C, 75.96; H, 6.34; N, 12.65.

3-(2,4,6-Trimethylphenyl)-4-(2-imidazolinyl)-5-(4-methylphenyl)-isoxazole (4b):

Reaction time: 40 h. Yield: 57.9%, m.p. 136.5-138°C (petroleum ether-ethyl acetate). MS: m/z = 345 (M^+, 36), 344 (100), 330 (74). UV: λ_{max} = 272 (lgε = 4.16), 221 nm (4.00). IR: $\tilde{\nu}$ = 3150 (NH), 1637, 1610, 1585, 1510 cm^{-1}. ^{1}H-NMR: δ = 7.98 (d, 2H), 7.18 (d, 2H), 6.87 (s, 2H), 3.77 (s, 1H), 3.47 (s, 4H), 2.37 (s, 3H), 2.30 (s, 3H), 2.13 ppm (s, 6H). Anal. calc. for $C_{22}H_{23}N_3O$: C, 76.49; H, 6.71; N, 12.16. Found C, 76.55; H, 7.05; N, 12.16.

3-(2,4,6-Trimethylphenyl)-4-(2-imidazolinyl)-5-(4-methoxyphenyl)-isoxazole (4c);

Reaction time: 40 h. Yield: 55.3%, m.p. 147.5-148°C (petroleum ether-ethyl acetate). MS: m/z = 361 (M^+, 12), 360 (29), 346 (100). UV: λ_{max} = 286 (lgε = 4.26), 220 nm (4.18). IR: $\tilde{\nu}$ = 3110 (NH), 1635, 1605, 1580,1510 cm^{-1}. ^{1}H-NMR: δ = 8.11 (d, 2H), 6.90 (d, 2H), 6.87 (s, 2H), 4.06 (s, 1H), 3.81 (s, 3H), 3.47 (s, 4H), 2.29 (s, 3H), 2.12 ppm (s, 6H). Anal. calc. for $C_{22}H_{23}N_3O_2$:C, 73.11; H, 6.41; N, 11.63. Found C, 72.66; H, 6.41; N, 11.32.

3-(2,4,6-Trimethylphenyl)-4-(2-imidazolinyl)-5-(4-chlorophenyl)-isoxazole (4d):

Reaction time: 40 h. Yield: 57.3%, m.p. 156-158°C (petroleum ether- ethyl acetate). MS: m/z = 366 (17), 365 (M^+, 21), 364 (42), 352 (35), 351 (25), 350 (100). UV: λ_{max} = 272 (lgε = 4.31), 223 nm (4.07). IR: $\tilde{\nu}$ = 3310 (NH), 1641, 1598, 1580, 1490 cm^{-1}. ^{1}H-NMR: δ = 8.27 (d, 2H), 7.48 (d, 2H), 6.98 (s, 2H), 4.13 (s, 1H), 3.53 (s, 4H), 2.33 (s, 3H), 2.14 ppm (s, 6H). Anal. calc. for $C_{21}H_{20}ClN_3O$: C, 68.94; H, 5.51; N, 11.49. Found C, 69.03; H, 5.59; N, 11.49.

3-(2,4,6-Trimethylphenyl)-4-(2-tetrahydropyrimidinyl)-5-phenyl-isoxazole (5a):

Reaction time: 24 h. Yield: 63.7%, m.p. 195.5-198°C (acetone). MS: m/z = 345 (M^+, 19), 344 (39), 330 (77), 77 (100). UV: λ_{max} = 267 (lgε = 4.23), 225 nm (4.07). IR: ν = 3180 (NH), 1630, 1604, 1590, 1530 cm^{-1}. ^{1}H-NMR: δ = 7.34-8.11 (m, 5H), 6.90 (s, 2H), 4.31 (s, 1H), 3.22 (t, 4H), 2.29 (s, 3H), 2.16 (s, 6H), 1.64 ppm (quin, 2H). Anal. calc. for $C_{22}H_{23}N_3O$: C, 76.49; H, 6.71; N, 12.16. Found C, 76.37; H, 6.80; N, 12.20.

3-(2,4,6-Trimethylphenyl)-4-(2-tetrahydropyrimidinyl)-5-(4-methylphenyl)-isoxazole (5b):

Reaction time: 24 h. Yield: 69.5%, m.p. 182-184°C (acetone). MS: m/z = 359 (M^+, 29), 358 (60), 344(100), 330 (14). UV: λ_{max} = 275 (lgε = 4.26), 226 nm (4.12). IR: ν = 3185 (NH), 1624, 1604, 1588, 1530 cm^{-1}. ^{1}H-NMR: δ = 7.87 (d, 2H), 7.18 (d, 2H), 6.86 (s, 2H), 4.31 (s, 1H), 3.21 (t, 4H), 2.37 (s, 3H), 2.29 (s, 3H), 2.15 (s, 6H), 1.65 ppm (quin, 2H). Anal. calc. for $C_{23}H_{25}N_3O$: C, 76.85; H, 7.01; N, 11.69. Found C, 76.88; H, 7.14; N, 11.59.

3-(2,4,6-Trimethylphenyl)-4-(2-tetrahydropyrimidinyl)-5-(4-methoxyphenyl)-isoxazole (5c):

Reaction time: 24 h. Yield: 71.9%, m.p. 169-171°C (acetone). MS: m/z = 375 (M^+, 23), 374 (41), 360 (100). UV: λ_{max} = 291 (lgε = 4.28), 224 nm (4.22). IR: ν = 3185 (NH), 1625, 1605, 1510 cm^{-1}. ^{1}H-NMR: δ = 7.99 (d, 2H), 6.95 (d, 2H), 6.90 (s, 2H), 4.37 (s, 1H), 3.83 (s, 3H), 3.23 (t, 4H), 2.30 (s, 3H), 2.16 (s, 6H), 1.67 ppm (quin, 2H). Anal. calc. for $C_{23}H_{25}N_3O_2$: C, 73.57; H, 6.71; N, 11.19. Found C, 73.58; H, 6.84; N, 11.02.

3-(2,4,6-Trimethylphenyl)-4-(2-tetrahydropyrimidinyl)-5-(4-chlorophenyl)-isoxazole (5d):

Reaction time: 24 h. Yield: 56.6%, m.p. 175-176°C (acetone). MS: m/z = 380 (20), 179 (M^+, 31), 378 (41), 366 (36), 365 (25), 364 (100). UV: λ_{max} = 273 (lgε = 4.43), 221 nm (4.35). IR: ν = 3190 (NH), 1631, 1602, 1585, 1532 cm^{-1}. ^{1}H-NMR: δ = 7.91 (d, 2H), 7.31 (d, 2H), 6.84 (s, 2H), 4.30 (s, 1H), 3.20 (t, 4H), 2.28 (s, 3H), 2.13 (s, 6H), 1.65 ppm (quin, 2H). Anal. calc. for $C_{22}H_{22}ClN_3O$: C, 69.55; H, 5.84; N, 11.06. Found C, 69.58; H, 5.62; N, 11.07.

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