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Reaction of *N*-Arylbenzamidines with Arenenitrile *N*-Oxides

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Looking for a method of 4-arylamino-4-aryl-3-aza-3-buten-2-one oximes preparation a reaction of *N*-arylbenzamidines with arenenitrile *N*-oxides (generated *in situ* form oximoyl chlorides) has been performed to produce unstable 5-amino-4,5-dihydro-1,2,4-oxadiazoles, which under aqueous acidic conditions hydrolyzed to acyclic *N*-benzoyloxy-*N'*-arylareneamidines. Structure of one of the latter compounds has been confirmed by X-ray analysis.

Key words: synthesis, oximoyl chlorides, amidines, nitrile *N*-oxides, X-ray

Recently 4-arylaminoquinazolines, due to their great potency as tyrosine kinase inhibitors [1], have been under intensive investigations. Despite this interest no substantial progress in syntheses of these quinazoline derivatives has been made in recent two decades. The most widely used method for synthesis of 4-arylaminoquinazolines is the reaction of 4-chloroquinazolines with aromatic amines [2]. Usually, yields of the synthesis do not exceed 50% [3].

For a few years we have been looking for a general method of quinazoline synthesis, a method that would not suffer from limitations typical for the known routes [4] and would be useful for preparation of 4-arylamino derivatives containing *e.g.* alkoxy groups. Particularly we would like to eliminate the strong acids in the reaction medium in the course of a synthesis to avoid a possible decomposition of acid-sensitive substituents. From this point of view the use of thermal pericyclic processes seems to be a very promising approach. We studied a method of synthesis of quinoline derivatives employing an electrocyclization of 4-phenyl-3-buten-2-one oxime acetate. This reaction consists of three following steps: disrotatory electrocyclization, inversion on the ring nitrogen atom in dihydro-intermediate and elimination of acetic acid [5]. Recently we have also shown [6] that 4,5-dihydro-3,5,5-triphenyl-1,2,4-oxadiazole (**1**), obtained by 1,3-dipolar cycloaddition of benzonitrile *N*-oxide to benzophenone imine, transforms thermally in the presence of acetic anhydride, probably *via* oxime acetate (**2**), into 2,4-diphenylquinazoline (**3**) (Scheme 1).

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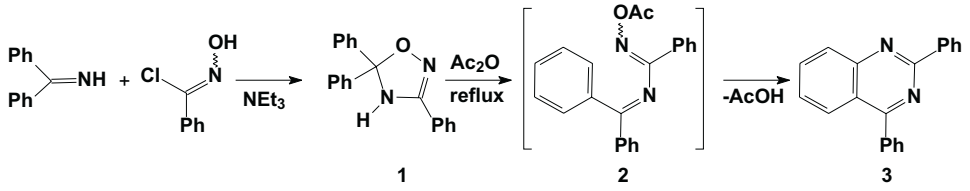
Scheme 1

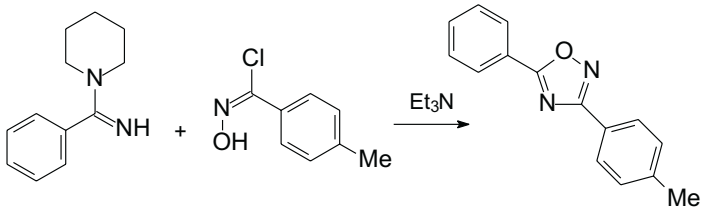


These results indicate that appropriate oximes or their esters should be convenient starting materials also for thermal formation of 4-arylaminoquinazolines. In the proposed thermal syntheses of 4-arylaminoquinazolines the main problem is connected with the preparation of appropriate starting materials. Here we present our unfortunately unsuccessful attempts of 4-arylamino-4-aryl-3-aza-3-buten-2-one oximes preparation in reaction of arenenitrile *N*-oxides with *N*-arylbenzamidines.

RESULTS AND DISCUSSION

Testing the reaction of 1-phenyl-1-piperidin-1-ylmethanimine (**4**) [7] with toluenenitrile *N*-oxide generated *in situ* from oximoyl chloride **5** [8], we obtained 3-(4'-methylphenyl)- 5-phenyl-1,2,4-oxadiazole (**6**) instead of the expected dihydrooxadiazole derivative (Scheme 2).

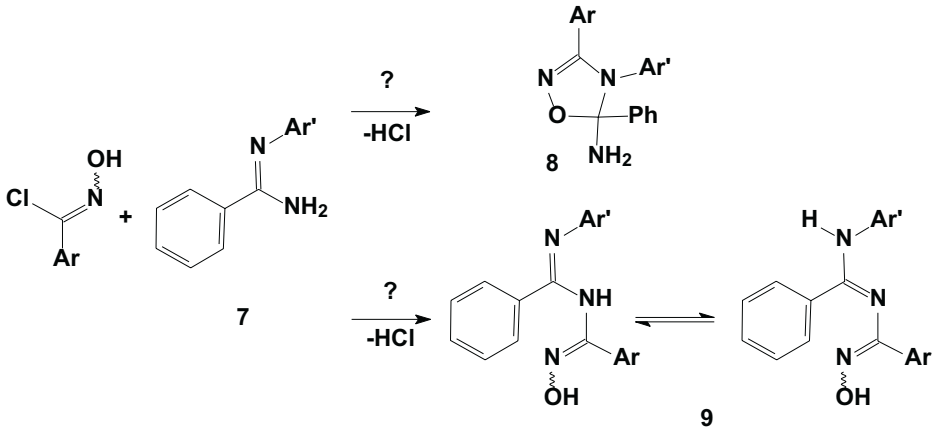
Scheme 2



1,3-Dipolar cycloaddition was followed by elimination of piperidine from the forming dihydrooxadiazole derivative. A similar elimination would be expected from 5-arylamino-3,5-diaryl-4,5-dihydro-1,2,4-oxadiazoles, being potential starting materials in syntheses of interesting us 4-arylamino-2-arylquinazolines. Therefore, we have not undertaken further attempts to obtain dihydro-oxadiazoles by this method. Instead, we paid attention to reactions of *N*-arylamidines with arenenitrile *N*-oxides.

El-Abdellah and co-workers have reported [9] that arenenitrile *N*-oxides react with hydrazones of aromatic aldehydes, affording respective oximes by a nucleophilic attack of the hydrazone primary amino group on carbon atom in nitrile *N*-oxide. Therefore, it was assumed that reaction of *N*-arylbenzamidine **7** with arenenitrile *N*-oxides would have led not only to oxadiazoles **8** but to the desired oximes **9** too (Scheme 3).

Scheme 3



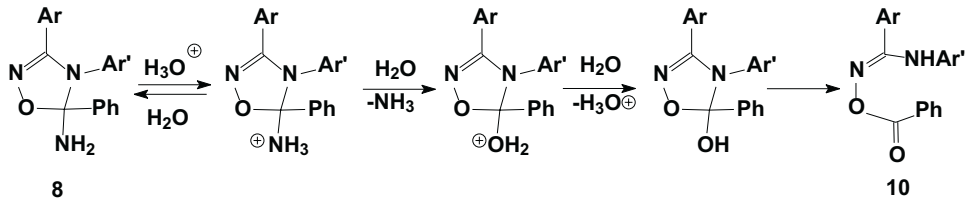
Unfortunately, the post-reaction mixtures obtained after a careful acidic work-up contained neither the oximes nor oxadiazole derivatives but other products. ^{1}H NMR spectra of these products indicated the presence of aromatic fragments derived from both starting materials and additionally one singlet signal near 9 ppm. In EI mass spectra molecular peaks were absent. For these products we assigned the structure of ester **10**. Three **10 a-c** were obtained in *circa* 50% yield each (Table).

Table. Yields of *N*-benzoyloxy-*N′*-arylareneamidines obtained from the reaction of *N*-arylbenzamidines with areneoximoyl chlorides.

Compound	Ar	Ar′	Yield [%]
10a	Ph	Ph	49
10b	Ph	4-MeC_6H_4	51
10c	3,4-diMeC_6H_3	4-MeC_6H_4	52

X-ray analysis of **10c** mono-crystal proved that the isolated product was *N*-benzoyloxy-*N′*-(3,4-dimethylphenyl)-*p*-toluamidine (Figure). It formed by acidic hydrolysis of aminooxadiazole (**8**) during work-up of the reaction mixture (Scheme 4).

Scheme 4



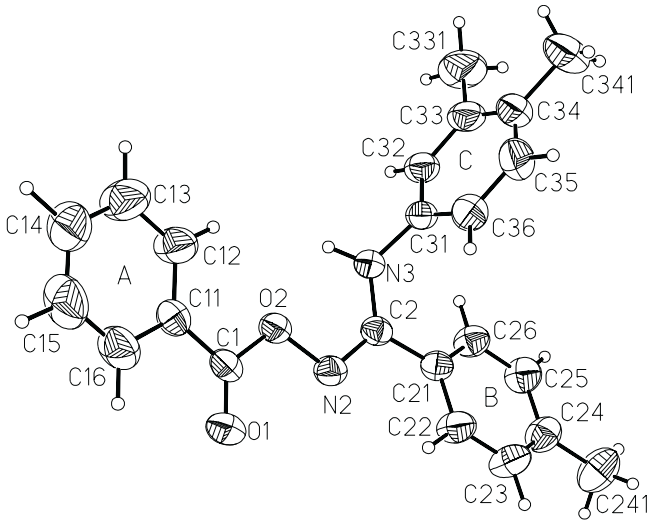


Figure. Crystal structure of **10c** showing 50% probability displacement ellipsoids. Selected bond lengths (Å) and angles (°): C1–N2 1.366(2), C3–N2 1.464(2), C3–O4 1.425(2), N5–O4 1.435(2), C1–N5 1.287(2), C3–O6 1.399(2), C31–C3–O6 106.91(12), N2–C3–O4 100.76(11), C1–N2–C3 107.90(11), C21–N2–C1–C11 –22.8(2), N5–C1–C11–C12 135.9(2).

CONCLUSIONS

N-Arylbenzamidines react with arenenitrile *N*-oxides (generated *in situ* form oximoyl chlorides) according to the 1,3-dipolar cycloaddition reaction mechanism. Forming 5-amino-4,5-dihydro-1,2,4-oxadiazoles under aqueous acidic conditions transform to acyclic *N*-benzoiloxy-*N'*-arylareneamidines. The problem of preparation of 4-arylamino-4-aryl-3-aza-3-buten-2-one oximes and their esters remains unsolved.

EXPERIMENTAL

Melting points (not corrected) were collected on Boetius HMK apparatus. EI-MS spectra were recorded on Shimadzu GCMS QP-2000 apparatus. ^{1}H NMR spectra were taken by Varian XL-300 in DMSO-d_6 with tetramethylsilane as an internal reference.

Crystallographic data (excluding structure factors) for compound 10c have been deposited with the Cambridge Crystallographic Data Centre as a supplementary publication number, CCDC 142820 (**10c**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Reactions of *N*-arylbenzamidines with oximoyl chlorides. Triethylamine (0.01 mole) solution in chloroform (20 ml) was dropped at 0°C to a freshly prepared solution of areneoximoyl chloride (prepared from 0.01 mole of a suitable oxime) in chloroform (30 ml). *N*-Arylbenzamidine (0.01 mole) solution in chloroform (20 ml) was added to the obtained nitrile *N*-oxide solution. The resulting mixture was stirred for 1 hour at 0°C, and then overnight at ambient temperature followed by extraction with hydrochloric acid (3 × 15 ml, 15%), with water (3 × 15 ml) and by drying over anhydrous magnesium sulphate. Chloroform was evaporated under reduced pressure, and the residue was crystallized from methanol. The following compounds were obtained:

10a (1.57 g, 49%), white crystals, m.p. 113–114°C; [Found: C, 75.90; H, 5.06; N, 8.73. $C_{20}H_{16}N_2O_2$ requires C, 75.93; H, 5.10; N, 8.85%]; δH 6.88–8.22 (15 H, m, aromatics), 9.30 (1 H, s, NH); *m/z* 316 (4, M+), 195 (47), 194 (100), 180 (29), 105 (72), 104 (11), 77 (33), 105 (34%).

10b (1.68 g, 51%), white crystals, m.p. 159–161°C; [Found: C, 76.39; H, 5.40; N, 8.49. $C_{21}H_{18}N_2O_2$ requires C, 76.34; H, 5.49; N, 8.48%]; δH 2.32 (3 H, s, Me), 6.85–8.04 (14 H, m, aromatics), 9.21 (1H, s, NH); *m/z* 330 (1, M+), 210 (15), 209 (51), 208 (96), 207 (25), 193 (31), 122 (24), 118 (16), 117 (16), 116 (14), 105 (100), 104 (12), 93 (16), 92 (15), 91 (29), 90 (13), 78 (13), 77 (73), 65 (29), 63 (13), 52 (35), 51 (17), 41 (20%).

10c (1.86 g, 52%), white crystals, m.p. 148–150°C; δH 2.07 (3 H, s, *p*-Me), 2.09 (3 H, s, *m*-Me), 2.32 (3 H, s, *p*-Me), 9.04 (1 H, s, NH); *m/z* 238 (10), 237 (12), 236 (24), 195 (12), 194 (69), 193 (13), 136 (14), 122 (19), 121 (15), 120 (14), 117 (14), 106 (20), 105 (100), 104 (11), 103 (31), 91 (18), 90 (11), 78 (11), 77 (98), 76 (19), 65 (12), 64 (11), 63 (13), 53 (11), 52 (43), 51 (129), 41 (17%).

Crystallographic data for 10c: $C_{23}H_{22}N_2O$, $M = 358.43$, orthorhombic, $a = 11.489(2)$, $b = 11.212(2)$, $c = 30.264(4)$ Å, $V = 3898.3(4)$ Å^3, $Z = 8$, $D_{calc} = 1.22$ g cm^{-3}, space group *Pbca*, $\mu = 0.08$ mm^{-1}, $F(000) = 1520$, crystal size = 0.45 × 0.2 × 0.15 mm, θ range = 2–50(^{0}), *hkl* range; $-13 \le h \le 13$, $-9 \le k \le 13$, $-35 \le l \le 35$; Reflections: collected 23357, unique(R_{int}) = 3418 (0.03), observed ($I > 2\sigma(I)$) 2430; Number of parameters 333, $R(F) = 0.049$, $wR(F^2) = 0.105$, Goodness of fit = 1.33, max/min $\Delta\rho = 0.17/-0.15$ e·Å^{-3}. X-ray diffraction data were collected on a KUMA KM4CCD κ-geometry diffractometer with CCD detector [10] at 296 K, using graphite-filtered MoKα (λ = 0.71073 Å) radiation. The unit cell dimensions were calculated from the least-squares fit of 2400 well-defined reflections. The ω scan method was used for 6 runs (752 frames). Intensity data were corrected for Lorentz and polarization effects; the determination of the unit cell parameters and the data reduction were performed with CrysAlis program system [11]. The structure was solved by direct methods, using the SHELXS86 program [12]. Full-matrix least-squares refinement was done with the SHELXL93 program [13]. Scattering factors incorporated in SHELXL93 were used. The function $\Sigma w(|F_o|^2 - |F_c|^2)^2$ was minimized, with $w^{-1} = [\sigma^2(F_o)^2 + 0.03 \cdot P^2 + 0.9 \cdot P]$, where $P = [Max(F_o^2, 0) + 2]/3$). Empirical extinction corrections were also applied according to the formula [13] $F_c' = kF_c[1 + 0.001 \times F_c^2\lambda^3/sin(2\theta)]^{-1/4}$, the x value converged at 0.0025(3). At the final stages of refinement four reflections were excluded from the reflection files due to their large $|F_o|^2 - |F_c|^2$ differences. The non-hydrogen atoms were refined anisotropically, all hydrogen atoms were found in subsequent difference Fourier maps and isotropically refined.

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