

REACTION OF N-PHENYLBENZAMIDINE WITH O-ACETYL BENZENE OXIMOYL CHLORIDE

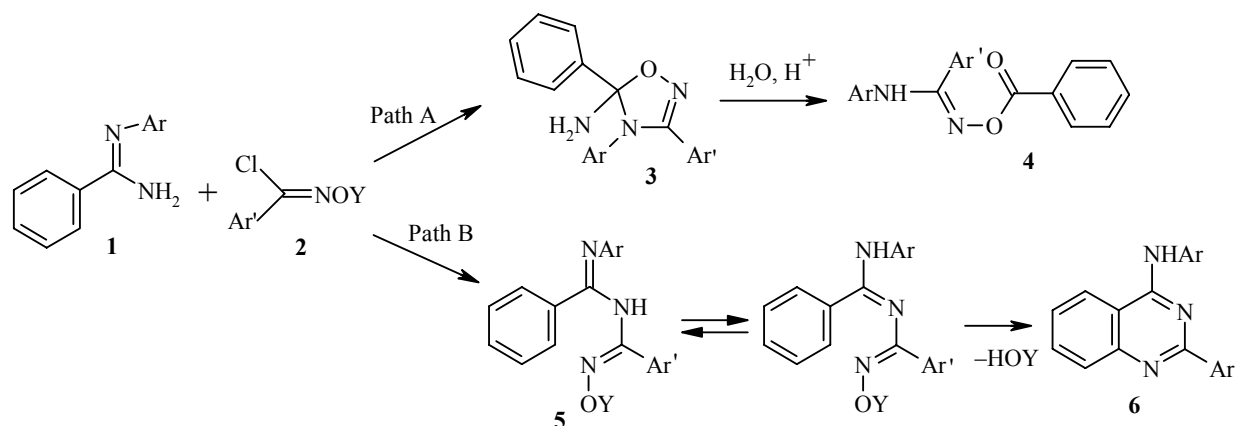
W. Szczepankiewicz¹, J. Suwinski¹, and Z. Karczmarzyk²

The reaction of N-phenylbenzamidine with O-acetylbenzeneoximoyl chloride in methanol solution gave unexpectedly 5-methoxy-3,4,5-triphenyl-4,5-dihydro-1,2,4-oxadiazole, which structure was confirmed by X-ray analysis. The last step of this reaction was simulated by the PM3 semiempirical method.

Keywords: amidines, nitrile N-oxides, oxadiazoles, oximoyl chlorides, X-ray analysis, semiempirical calculations, synthesis.

4-Arylaminoquinazolines are intensively investigated because of their potent antitumor properties [1, 2]. Recently, we have shown that these compounds can be obtained from 2-amino-N-arylbenzamidines and formic acid or aldehydes by formation of 2,3 and 3,4 bonds of the quinazoline system [3, 4]. Basing on results of semiempirical calculations and experimental data concerning the formation of similar systems, we believe that 4-arylaminoquinazolines can also be synthesized (Scheme 1) from 4-arylamino-1,3-diaza-1,3-butadienes **5**. The synthesis should occur as a tandem pericyclic process [5] including the formation of the 1,8a – quinazoline bond by thermal disrotatory electrocyclization of the starting material. We tried to obtain the latter compound from N-arylbenzamidines **1** and oximoyl chlorides **2**. However, this reaction afforded N-substituted amidoxime benzoates **4** instead of the expected **5** (Scheme 1, Path A, Y = H) [6]. The first step of the reaction is the formation of nitrile N-oxides from an oximoyl chloride in the presence of the basic

Scheme 1



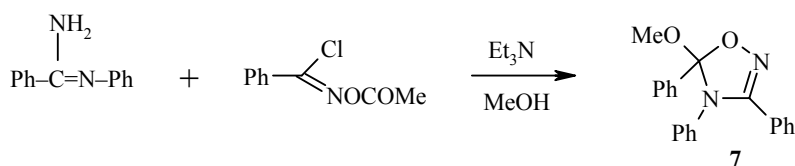
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N-arylbenzamidines. Nitrile oxide reacts then with an unconverted amidine to form 5-amino-4,5-dihydro-1,2,4-oxadiazole **3** by the 1,3-dipolar cycloaddition reaction. During acidic work-up of the reaction mixture the compound **3** transforms to **4**.

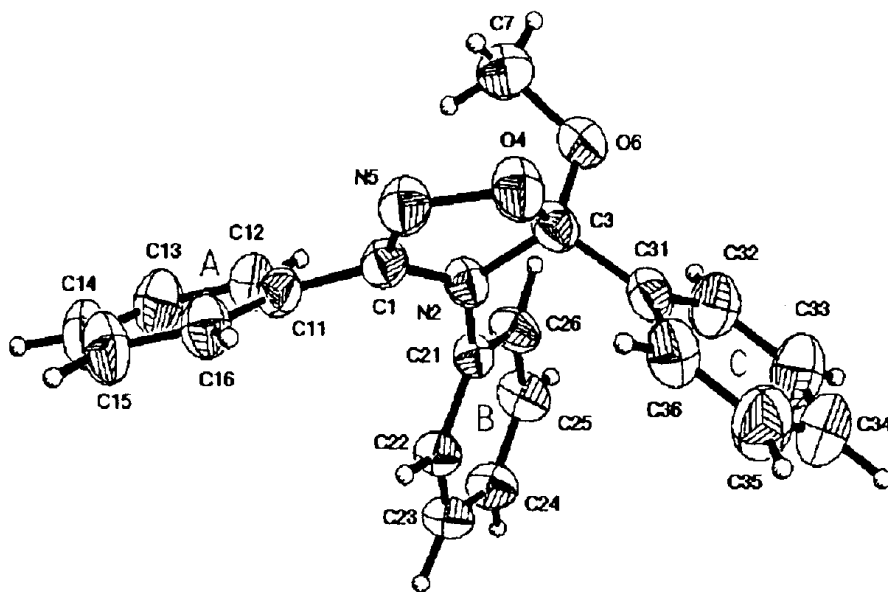
In this work we attempted to perform nucleophilic substitution of the chlorine atom in O-acetylbenzeneoximoyl chloride by the amino nitrogen atom of an amidine (Scheme 1, Path B, Y = Ac) assuming that O-acetylation of the oxime group would prevent formation of nitrile N-oxide.

Indeed, we found that the reaction of N-phenylbenzamidine with O-acetylbenzeneoximoyl chloride in methanol solution, in the presence of Et₃N, affords a crystalline precipitate straight from the reaction mixture. ¹H NMR spectrum of the precipitate showed the expected signals of aromatic protons and a singlet of the methyl group. Unexpectedly, the latter signal should be referred to protons of methoxy rather than of the acetyl group. X-Ray analysis confirmed this unexpected result, proving that the main reaction product was 5-methoxy-3,4,5-triphenyl-4,5-dihydro-1,2,4-oxadiazole (**7**) (Scheme 2, Fig. 1).

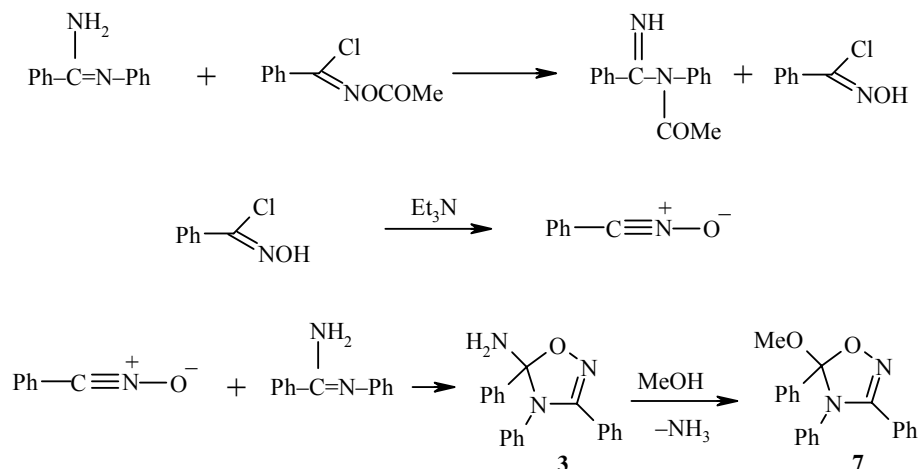
Scheme 2



Oxadiazole **7** probably arises from a preliminary attack of the amidine on the acetyl carbon atom in O-acetylbenzeneoximoyl chloride to produce N-acetylamidine and a free oximoyl chloride. The oximoyl chloride transforms to nitrile N-oxide which undergoes 1,3-dipolar cycloaddition to yet unconverted N-phenylbenzamidine giving 5-amino-3,4,5-triphenyl-4,5-dihydro-1,2,4-oxadiazole (**3**). Finally, **3** reacts with methanol used as a solvent to yield oxadiazole **7** (Scheme 3).

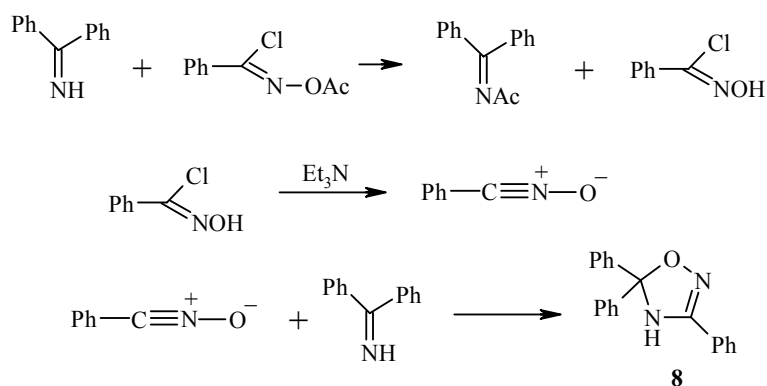


Scheme 3



The use of chloroform instead of methanol in the reaction of N-phenylbenzamidine with O-acetylbenzeneoximoyl chloride led to formation of O-benzoylamidoxime (**4**, Ar = Ar' = Ph). This result confirms the formation of nitrile N-oxide, followed by its cycloaddition to the amidine. An additional confirmation of this postulate was the reaction of O-acetylbenzeneoximoyl chloride with benzophenone imine which gave the well-known 3,5,5-triphenyl-4,5-dihydro-1,2,4-oxadiazole (**8**) [7, 8]. The latter result supports the assumption that the first reaction stage is an attack of the imine nitrogen atom on the acetyl group with the formation of oximoyl chloride followed by its transformation in the presence of a base into nitrile N-oxide further reacting as the dipolar reagent with the C=N bond of the imine to form **8** (Scheme 4).

Scheme 4



These results show that the amidine rather attacks the C=O carbon atom than the imidoyl one despite their formal similarity. It was interesting to estimate how polar is the C-Cl bond in O-acetylbenzeneoximoyl chloride. Treating its 1 molar solution in acetonitrile with equimolar amount of silver nitrate (the mixture obtained was left in the dark at room temperature for two weeks) produced only traces of silver chloride. In contrast to that, imidoyl chlorides produced silver chloride precipitate in nearly quantitative amount almost immediately, under similar conditions [9]. A comparison of these results might indicate that the C-Cl bond in the investigated O-acetylbenzeneoximoyl chloride is much more similar to the chlorovinyl bond than to the chloroacyl one.

We had doubts about a pathway of substitution of the amino group by methanol in the transformation of **3** to **7**. Results of quantum-chemical semiempirical calculations [10], accomplished by PM3 [11] and a modified [12] COSMO procedure [13], show that the protonation of substrate **3** plays the main role in this transformation. It was necessary to make the assumption that methanol is a donor of protons. Oxadiazoles are not too strong bases but even a slight concentration of the protonated form should initiate the reaction, especially taking into account that the basicity of oxygen and nitrogen organic bases increases in methanol solution [14].

Initially, we have simulated S_N1 and S_N2 mechanisms of substitution of the protonated amino group by the methoxide anion, but the path with the less energy profile is initiated by the protonation of the cyclic oxygen atom in **SS** to form oxonium ion **SS1** (Scheme 5). This cation is unstable and decomposes spontaneously to acyclic amidineamidoxime **SSII**, which is attacked by the methoxide anion and transforms *via* the transition state **TSSNC** to the aminoamidoxime **TIN**. Transprotonation of **TIN** gives the betaine **TINI**. The structure **TINI** would transform directly by an intramolecular cyclization of the S_N2 type to the final products, but we have found a path with less energy profile. **TINI** can decompose through the transition state **TSD** to betaine **IZI** with lose of the ammonia moiety. **IZI** cyclizes to products **PP** *via* the transition state **TSIZI**. Estimated heats of formation of ground and transition states show that the slowest step in this reaction is the decomposition of **TINI** to **IZI** and ammonia (Table 1). Finally, the investigated transformation belongs to the ANRORC type mechanism (addition of nucleophile, ring opening, ring closure) promoted by the initial protonation.

Scheme 5

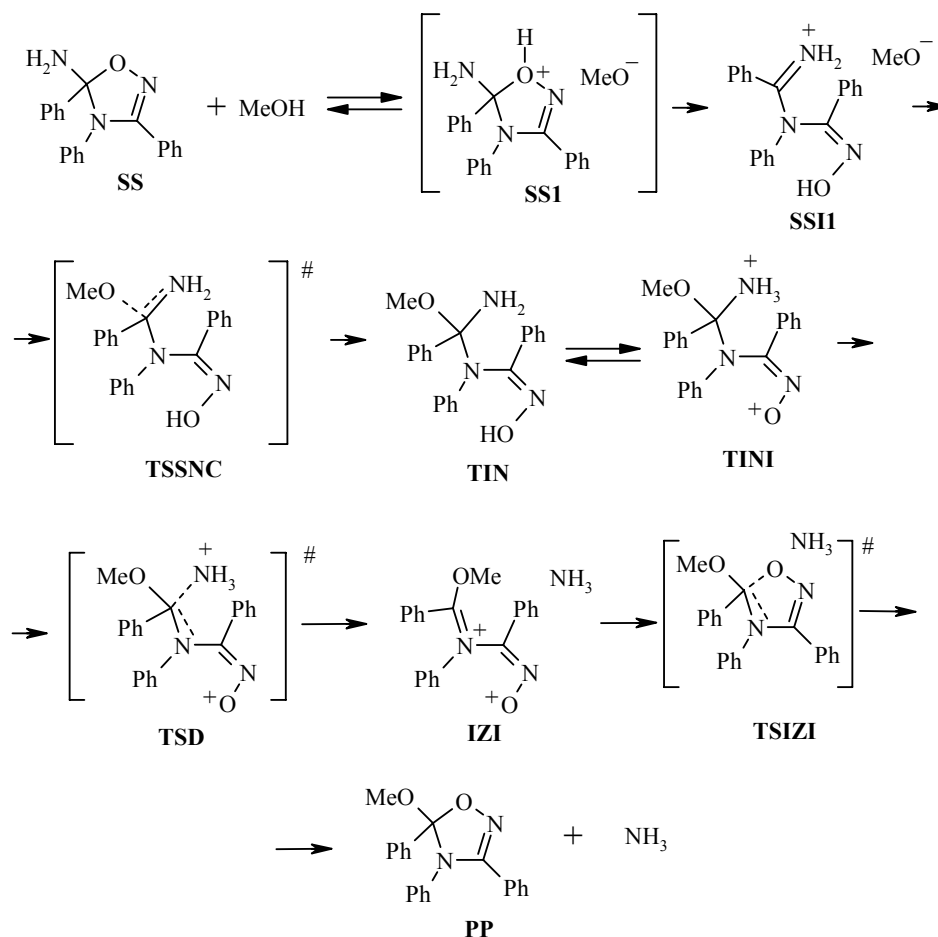


TABLE 1. Heats of Formation of Ground and Transition States Calculated by the PM3/COSMO Method for Transformation of 3 to 7 at 25°C in Methanol Solution

State	Heat of formation, kcal/mol	State	Heat of formation, kcal/mol
SS	27.8	TINI	36.9
SSI	—	TSD	71.2
SSII	41.2	IZI	53.4
TSSNC	68.7	TSIZI	69.1
TIN	44.7	PP	36.1

The investigated reaction of N-phenylbenzamidine with O-acetylbenzene-oximoyl chloride in methanol solution leads to 5-methoxy-3,4,5-triphenyl-4,5-dihydro-1,2,4-oxadiazole. Unfortunately, the facts rule out this approach to the synthesis of 1-acetoxy-4-aryl amino-4-phenyl-1,3-diaza-1,3-butadienes **5**. However, the results do not exclude our assumption that blocking of the hydroxy group of oximoyl chloride by its alkylation or arylation would be a convenient route to formation of the desired diazabutadienes, promising potential starting materials in the thermal synthesis of quinazolines. The latter hypothesis is under investigation.

EXPERIMENTAL

Melting points were measured on Boetius HMK apparatus. EI-MS spectra were recorded on Shimadzu QP-2000 apparatus. ¹H NMR was scanned on Varian XL-300 (300 MHz) with TMS as an internal reference. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre as a supplementary publication number CCDC 157269. 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.

Quantum-chemical calculation were performed using MOPAC 2000 package [10], on a PC computer (Intel Pentium III, 767 MHz). The eigenvector following (EF) optimization procedure (GNORM = 0.5) was applied to estimation of ground states and transition states (as TS variant of EF). The solvation effect of methanol was calculated with the COSMO model (EPS = 32.63, NSPA = 90, DISEX = 4) [12].

Synthesis of 5-Methoxy-3,4,5-triphenyl-4,5-dihydro-1,2,4-oxadiazole (7). To a freshly prepared benzeneoximoyl chloride [16] solution in chloroform an equimolar amount of acetic anhydride was added at 0°C. The reaction mixture was stirred overnight at ambient temperature. The solvent was removed under reduced pressure and the resulting amber oil was left for crystallization at 0°C. The colorless crystals were filtered off, washed with hexane, air-dried, and used in the next step without additional purification. To a solution of N-phenylbenzamidine (1.96 g, 10 mmol) and O-acetylbenzeneoximoyl chloride (1.98 g, 10 mmol) in methanol (20 ml) triethylamine (1.01 g, 10 mmol) was added and the resulting solution was stirred for 2 h at ambient temperature. The white crystalline precipitate formed upon stirring was filtered off, washed with cold methanol, air-dried, and recrystallized from methanol. Crystals suitable for X-ray diffraction analysis were grown by slow evaporation of hexane solution. Yield of **7** as colorless prisms was 1.39 g (42%); mp 125-127°C. ¹H NMR (DMSO-*d*₆): 3.6 (3H, s, OCH₃); 6.8-7.5 (15H, m, H-aromatics). *m/z* 330 [M]⁺ (2), 299 (2), 288 (1), 297 (2), 210 (1), 195 (15), 194 (100), 193 (12), 105 (36), 103 (10), 91 (14), 77(45), 52 (22).

Crystallographic Data for 7. C₂₁H₁₈N₂O₂, M = 330.37, orthorhombic, space group *Pbca*; *a* = 8.1642(6), *b* = 12.3137(9), *c* = 34.292(3) Å; *V* = 3447(4) Å³; *Z* = 8; *d*_{calc} = 1.273 g cm⁻³; *F*(000) = 1392; *μ* = 0.662 mm⁻¹; crystal size 0.40 × 0.20 × 0.15 mm. X-Ray data were collected on a KUMA KM4 four-circle diffractometer at room temperature. Lattice parameters were obtained from least-squares refinement of setting angles of 64 reflections (θ range 14.46-16.92°) using the KM4 program system [17]. Intensity data were collected

using graphite-filtered $\text{CuK}\alpha$ ($\lambda = 1.54178 \text{ \AA}$) radiation and applying the ω - 2θ scan technique; number of measured reflections 4167 (θ range 2.58 - 80.15° , index ranges $-1 \leq h \leq 10$, $-15 \leq k \leq 1$, $-43 \leq l \leq 1$), number of independent reflection 3234 ($R_{\text{int}} = 0.262$), data reduction was performed with the DATAPROC program package [18]. The structure was solved by direct methods using SHELXS86 [19] and refined by full-matrix least squares with anisotropic temperature factors for non-hydrogen atoms with SHELXL93 [20]. All hydrogen atoms were placed in calculated positions and their coordinates were refined using a riding model with isotropic displacement parameters taken as 1.5 times those of the respective parent atoms. The programs supplied atomic scattering factors. The final $R = 0.0438$, $wR = 0.1195$ $\{w = [\sigma^2(F_o)^2 + 0.0704P^2 + 0.7554P]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3\}$ for 3232 reflections [$I > 2\sigma(I)$] and 227 parameters, goodness of fit on $F^2S = 1.045$, $(\Delta/\sigma)_{\text{max}} = 0.000$, $(\Delta\rho)_{\text{max}} = 0.258$ and $(\Delta\rho)_{\text{min}} = -0.215 \text{ e\AA}^{-3}$. Empirical isotropic extinction parameter $x = 0.0025(2)$ were also applied with $F_c' = kF_c[1 + 0.001F_c^2\lambda^3/\sin(2\theta)]^{-1/4}$.

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