Chemical transformations of reaction products of 2-methyl-3-(4-tolyl)-4(3*H*)-quinazolone with benzil and its 4,4′-derivatives

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The reaction of 2-methyl-3-(4-tolyl)-4(3*H*)-quinazolone with benzil produces 2-[(*Z*)-3-oxo-2,3-diphenylprop-1-enyl]-3-(4-tolyl)-4(3*H*)-quinazolone, which is readily transformed into 2-(3,3-diphenylsuccinimido)-*N*-(4-tolyl)benzamide on dissolution in organic water-containing solvents. The rearrangement mechanism was suggested and investigated by the quantum chemical PM3 method.

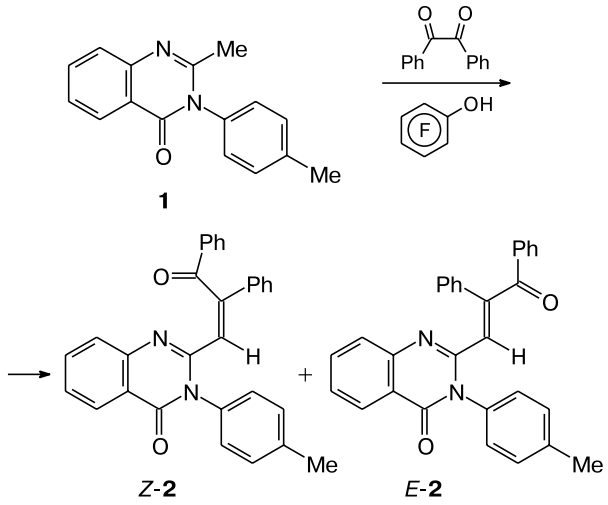
Key words: 3-aryl-2-methyl-4(3*H*)-quinazolones, α-diketones, 2-[(*Z*)-2,3-diaryl-3-oxoprop-1-enyl]-4(3*H*)-quinazolones, 2,2-diarylsuccinimides, quantum chemical calculations.

Quinazolone-based polymeric materials have attracted attention due to a combination of luminescent properties, high thermal stability, heat resistance, and wide possibilities of the molecular design.[1] In these objects, the optical properties occur not as a result of the presence of an additional dye, which is either bound to the polymer or introduced into the material, but are caused by the chromophoric system of the polymer. At the same time, it is necessary to search for new ways of modifying a chromophoric system and study in more detail the reactions for the construction of polymers with desired chemical structures with the use of model monomeric compounds.

Earlier, polyquinazolones containing arylenevinylene side groups have been synthesized[2] in pentafluorophenol (PFP), and a series of model compounds and polymers based on 3-amino-2-methylquinazolones and α-diketones have been prepared.[3] When synthesizing new model compounds, it was found that the reaction products of some 2-methylquinazolones with α-diketones have a property unusual for their structures, *i.e.*, their fluorescence is substantially increased in the presence of acids.[4] Because to this behavior, such compounds have attracted interest. In this connection, we decided to study these compounds more thoroughly.

One example is the reaction product of 2-methyl-3-(4-tolyl)-4(3*H*)-quinazolone (**1**) with benzil in PFP (Scheme 1). It was found that the reaction produces 2-[(*Z*)-3-oxo-2,3-diphenylprop-1-enyl]-3-(4-tolyl)-4(3*H*)-quinazolone (**2**) as the major product. We failed to unambiguously prove the presence of the possible *E* isomer in the reaction mixture. However, it is known[2] that these reactions can produce two isomers.

Scheme 1



The structure of compound *Z*-**2** was established by X-ray diffraction study of single crystals grown by vacuum sublimation (Fig. 1).

As mentioned above, the fluorescent properties of compound **2** and other reaction products of 2-alkylquinazolones with aromatic α-diketones are substantially changed in the presence of acids. This behavior could be attributed to certain changes in the three-dimensional molecular structures upon protonation, the electron density redistribution, and an increase in the degree of conjugation of the π system. With the aim of more reliably evaluating these changes, we performed an X-ray diffraction study of crystals of compound **2** grown in 85% formic acid. It appeared that the structure of crystalline 2-(3,3-di-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 146—151, January, 2007.

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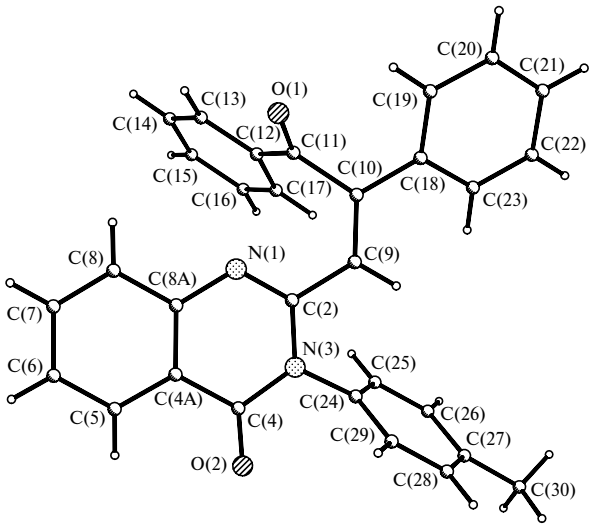
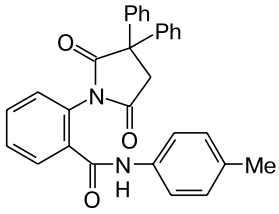


Fig. 1. Molecular structure of 2-[(*Z*)-3-oxo-2,3-diphenylprop-1-enyl]-3-(4-tolyl)-4(3*H*)-quinazolone (**2**).

phenylsuccinimido)-*N*-(4-tolyl)benzamide (**3**) is substantially different from that of the starting compound (Fig. 2).

The X-ray diffraction study showed that the quinazolone ring is absent in molecule **3**, but the latter contains the new five-membered succinimide fragment. In addition, the phenyl substituents, which are bound to different carbon atoms in the starting compound, are bound to the same carbon atom in compound **3**. Reaction product **3** was characterized by ^{1}H NMR spectroscopy, which additionally confirmed its chemical structure. Interestingly, the identical spectrum was obtained for a solution of the starting quinazolone **2** in DMSO-d_6. Compound **2** is poorly soluble in DMSO-d_6 at room temperature, whereas heating of compound **2** in a tube for the purpose of dissolving **2** led to its rearrangement. Since DMSO-d_6 generally contains water in an amount sufficient for hydrolysis of the quinazolone ring, compound **2** is finally completely transformed into product **3**. Therefore, it was impossible to record the ^{1}H NMR spectrum of compound **2**. It was found that this transformation also readily occurs in other organic solvents containing small amounts of water, for example, in ethanol.



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In addition to compound **2**, we studied the reaction products of 4,4′-disubstituted derivatives of benzil with 2-methyl-3-(4-tolyl)-4(3*H*)-quinazolone (**1**).

It appeared that dibromo-substituted compound **4** behaves similarly to unsubstituted analog **2** and is readily transformed into rearrangement product **6** on dissolution in DMSO-d_6 and heating (Scheme 2). As in the case of compound **2**, this substantially hinders the measurement of the ^{1}H NMR spectrum of unrearranged compound **4**.

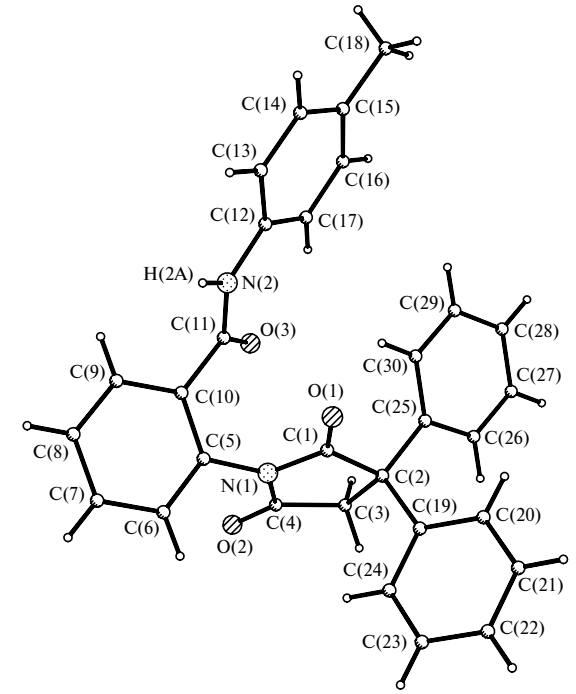
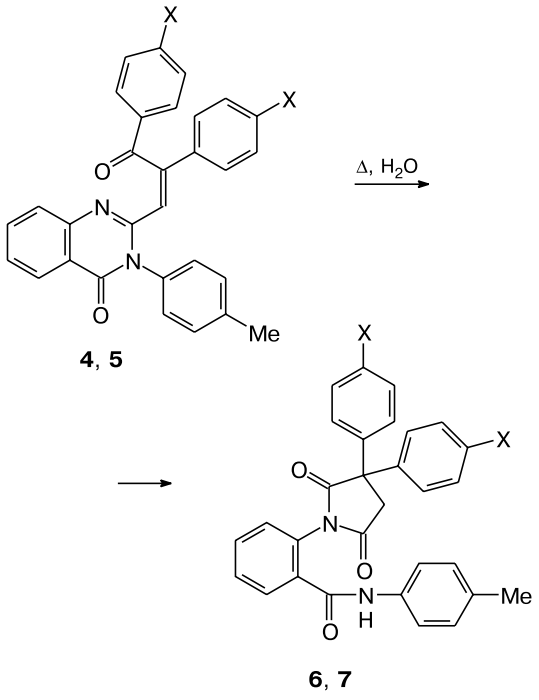


Fig. 2. Molecular structure of the rearrangement product, *N*-(4-tolyl)-2-(3,3-diphenylsuccinimido)benzamide (**3**).

Scheme 2



4, **5** **6**, **7**

X = Br (**4**, **6**), F (**5**, **7**)

The structure of difluoro-substituted compound **5** was established by X-ray diffraction study of crystals grown

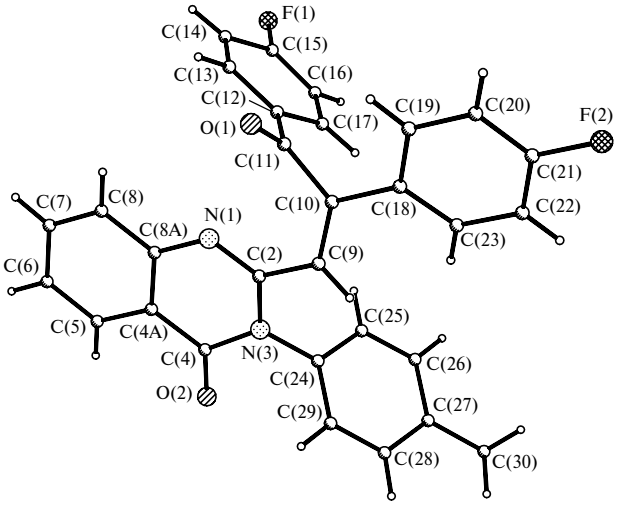


Fig. 3. Molecular structure of 2-[(*Z*)-3-oxo-2,3-bis(4-fluorophenyl)prop-1-enyl]-3-(4-tolyl)-4(3*H*)-quinazolone (**5**).

from dioxane (Fig. 3). It should be noted that this compound is more stable. We succeeded in measuring the ^{1}H NMR spectrum adequate for the chemical structure only for this compound (unlike related compounds **2** and **4**). The spectrum shows no signals of the CH_2 group of the succinimide fragment and the amide group, which are characteristic of the rearrangement products, and has a narrow singlet for the proton at the acyclic double bond. The rearrangement of compound **5** is hindered, but it can be performed under more drastic conditions (refluxing in 85% formic acid for ~100 h). The ^{1}H NMR spectrum of transformation product **7** is similar to that of compound **6**. Compounds **5** and **7** were additionally characterized by ^{19}F NMR spectroscopy.

The mechanism of the above-described transformations can be represented as follows (Scheme 3).

The rearrangement starts with reversible protonation of the starting compound **A** at the carbonyl oxygen atom at position 4 of the quinazolone ring (**B**-1), at the nitrogen atom at position 1 of the quinazolone ring (**B**-2), or at the carbonyl oxygen atom of the benzoyl fragment (**B**-3). In the protonated form **B**-3, the five-membered ring is reversibly closed to give the intermediate **C**. In our opinion, it is the presence of the intermediate product **C** that explains the characteristic increase in fluorescence of compounds **2**, **4**, and **5** in the presence of acids. The further transformation **C** → **D** can occur only through the transfer of the phenyl fragment, which was observed in rearrangements described in the literature.[5,6] The transformation **D** → **E** is apparently tautomeric, the proton being transferred from the carbonyl group to the =CH— fragment in the ring. Finally, the quinazolone ring undergoes hydrolysis to form the product **F**.

To describe the mechanism in more detail and confirm its validity, we performed the quantum chemical study of the structures of all possible intermediates **A**—**F** and the transition state of the key reaction step, *viz.*, the rearrangement **C** → **D**. The geometry calculations were carried out by the semiempirical PM3 method for the model compound with R = Me and X = H. The energies of the structures were estimated by the B3LYP/6-31G* method. The optimized geometry of the molecules **A** and **F** agrees well with the X-ray diffraction data for compounds **2** and **3**, respectively (the bond length deviations are at most 0.009 Å). This confirms the applicability of the PM3 calculation method and the validity of the replacement of R = Ar with R = Me.

Protonation of the starting molecule **A** can afford the following three cations: **B**-1, **B**-2, and **B**-3. However, it was demonstrated that the optimization leads to the

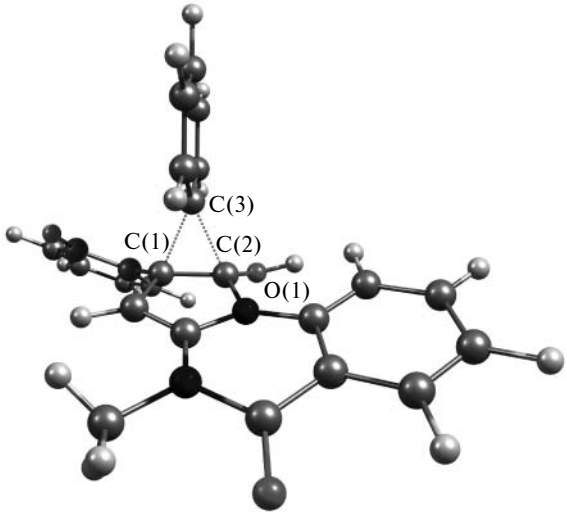


Fig. 4. Structure of the transition state of the rearrangement **C** → **D**. Bond lengths/Å: C(1)—C(2), 1.486; C(1)—C(3), 1.811; C(2)—C(3), 1.843; C(2)—O(1), 1.351.

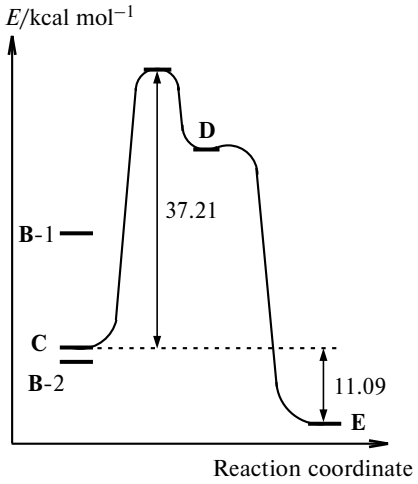
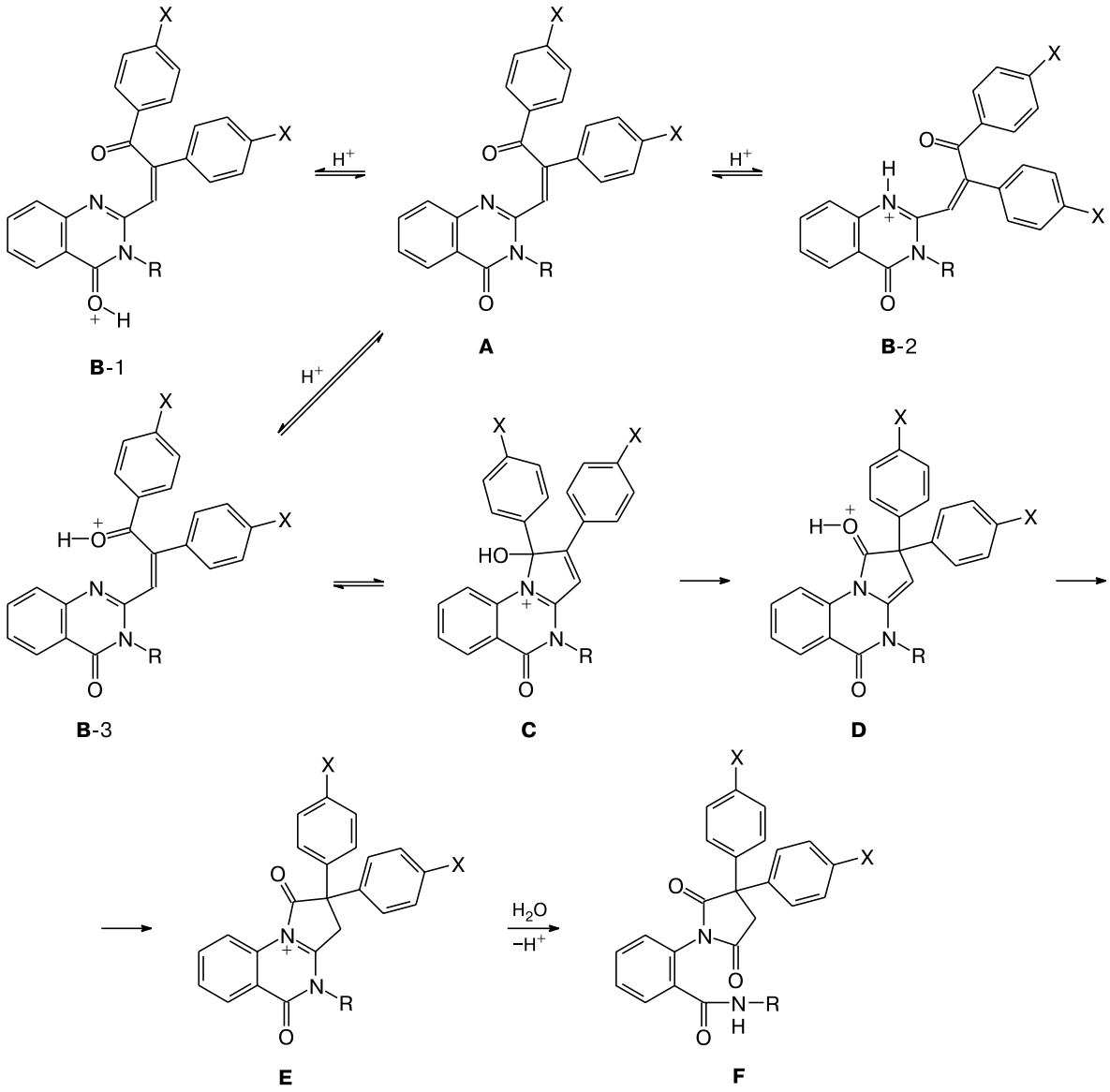


Fig. 5. Energy profile of the transformation **C** → **E** for the reaction **A** + H_2O → **F**.

Scheme 3



barrierless transformation of the structure **B**-3 into the cyclic form **C**, which is substantially more stable than **B**-1 (by 15.64 kcal mol^{-1}) and is only slightly less stable than **B**-2 (by 3.75 kcal mol^{-1}). The further rearrangement **C** → **D** proceeds through the *ipso*-type transition state (Fig. 4), whose energy is 37.21 kcal mol^{-1} higher than that of the structure **C**, and this transition state determines the overall reaction rate. The rather high activation energy is apparently attributed to the fact that the calculations ignore the solvation effects, which can substantially influence stability of cationic species in a polar medium.

The intermediate **D** is 25.79 kcal mol^{-1} less stable than **C**. However, it can undergo a tautomeric transformation into the cation **E**, which is 11.09 kcal mol^{-1} more stable than **C**. In a polar medium, the activation barrier for this tautomerization is insignificant (presumably, is lower than 5 kcal mol^{-1}). The resulting overall reaction profile is shown in Fig. 5.

The calculated total thermal effect of the reaction **A** + H_2O → **F** is 24.66 kcal mol^{-1}.

Therefore, the experimental data and the results of quantum chemical calculations obtained in the present study suggest that the observed rearrangement can occur by the above-described mechanism. It remains unclear how the substituents X influence the rearrangement rate. Presumably, in the case of X = F, protonation of the carbonyl oxygen atom of the benzoyl fragment (**A** → **B**-3) is less favorable, which hinders further transformations.

Experimental and calculation procedure

The melting points were determined on a Boetius hot-stage apparatus and are uncorrected. The ^{1}H and ^{19}F NMR spectra were recorded on Bruker AMX-400 (400.13 MHz) and Bruker AV-300 (282.40 MHz) instruments in DMSO-d_6; δ were calculated relative to the residual signals for the protons of the deuterated solvent as the internal standard (^{1}H) and $CFCl_3$ as the external standard (^{19}F). The course of the reactions was monitored and the purities of the reaction products were checked by TLC on Silufol UV-254 plates (toluene—acetone, 2 : 1, as the eluent). Compounds **2**, **4**, and **5** were visualized by placing the eluted and dried chromatograms in a vessel with CF_3COOH vapor, after which an increase in the fluorescence intensity of their spots was observed in UV light (λ = 365 nm). Pentafluorophenol and anthranilic acid (Aldrich) were used without additional purification.

2-Methyl-4*H*-3,1-benzoxazin-4-one. Anthranilic acid (8 g, 58 mmol) was refluxed in Ac_2O (20 mL) for 4 h using a calcium chloride tube. Excess Ac_2O was distilled off, and the resulting crystals were sublimed at 75—100 °C (0.01 Torr). The yield was 8.30 g (88%), m.p. 80—82 °C (*cf.* lit. data[7]: m.p. 86—87 °C).

2-Methyl-3-(4-tolyl)-4(3*H*)-quinazolone (1). 2-Methyl-4*H*-3,1-benzoxazin-4-one (1.61 g, 10 mmol) and *p*-toluidine (1.07 g, 10 mmol) were stirred in Et_2O (20 mL) for 8 h. The white precipitate of the acetamidinium salt that formed was filtered off, dried in air, and added with stirring to a 0.5% aqueous NaOH solution (20 mL). The suspension was stirred for 4 h. The precipitate was filtered off, washed with water to neutral pH, and dried. The yield was 1.75 g (70%), m.p. 151—152 °C (*cf.* lit. data[8]: m.p. 151—152 °C), R_f 0.6. ^{1}H NMR, δ: 2.13 and 2.40 (both s, 3 H each, $C_6H_4\underline{Me}$, 2-Me); 7.29 and 7.36 (both d, 2 H each, C_6H_4, J = 8.0 Hz); 7.49 (t, 1 H, H(4), J = 7.5 Hz); 7.65 (d, 1 H, H(3), J = 8.1 Hz); 7.82 (t, 1 H, H(2), J = 7.4 Hz); 8.09 (d, 1 H, H(1), J = 7.8 Hz).

2-[(*Z*)-3-Oxo-2,3-diphenylprop-1-enyl]-3-(4-tolyl)-4(3*H*)-quinazolone (2). Compound **1** (0.25 g, 1 mmol) and benzil (0.21 g, 1 mmol) were heated in PFP (0.5 g) at 140 °C for 40 h. The reaction mixture was precipitated with ethanol (10 mL). The yellow precipitate that formed was filtered off and washed with cold ethanol. The yield was 0.18 g (40%), m.p. 200—210 °C, R_f 0.7 (fluorescent spot). Found (%): C, 81.39; H, 5.11; N, 6.28. $C_{30}H_{22}N_2O_2$. Calculated (%): C, 81.43; H, 5.01; N, 6.33.

2-(3,3-Diphenylsuccinimido)-*N*-(4-tolyl)benzamide (3). Compound **2** (0.10 g, 0.218 mmol) was refluxed in a water—ethanol mixture (1 : 1, v/v, 10 mL) for 2 h and then cooled. The white precipitate that formed was filtered off. The yield was 0.09 g (86%), m.p. 220—225 °C, R_f 0.6 (the spot shows no fluorescence). Found (%): C, 78.26; H, 5.23; N, 6.10. $C_{30}H_{24}N_2O_3$. Calculated (%): C, 78.24; H, 5.25; N, 6.08. ^{1}H NMR, δ: 2.30 (s,

Table 1. Crystallographic data and the refinement statistics for compounds **2**, **3**, and **5**

Parameter	**2**	**3**	**5**
Molecular formula	$C_{30}H_{22}N_2O_2$	$C_{30}H_{24}N_2O_3$	$C_{30}H_{20}F_2N_2O_2$
M	442.50	460.51	478.48
Space group	$P2_1/n$	$P2_1/c$	$P2_1/c$
T/K	120	173	193
a/Å	10.609(1)	19.076(6)	11.704(2)
b/Å	10.824(1)	7.392(3)	18.497(4)
c/Å	20.603(3)	16.974(6)	11.040(2)
β/deg	104.847(3)	104.45(3)	106.06(3)
V/Å^3	2286.9(5)	2318(1)	2296.7(8)
Z	4	4	4
d_{calc}/g cm^{-3}	1.285	1.320	1.384
Crystal color and shape	Colorless prisms	Colorless plates	
Crystal dimensions/mm	0.35×0.30×0.25	0.50×0.45×0.30	0.25×0.20×0.15
Diffractometer	«SMART Bruker»	«Syntex P21»	
μ/cm^{-1}	0.81	0.86	0.98
Scanning mode	φ/ω	θ/2θ	ω
$2\theta_{max}$/deg	58.0	52.0	48.0
Number of reflections	17051	4388	3707
Number of independent reflections (R_{int})	5942 (0.0489)	4108 (0.0326)	3516 (0.129)
R_1 (based on F for reflections with $I > 2\sigma(I)$)	0.0562 (2934)	0.0615 (2831)	0.0829 (1165)
wR_2 (based on F^2 for all reflections)	0.1134	0.1319	0.1537
Number of parameters in refinement	307	316	290
Weighting scheme		$w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$	
P		$1/3(F_o^2 + 2F_c^2)$	
a	0.0259	0.0137	0.0000
b	0.5000	4.4615	0.0000
GOOF	1.005	1.001	0.867
F(000)	928	968	992

3 H, C_6H_4Me); 3.50 and 3.86 (both d, 1 H each, CH_2 of the succinimide fragment, J = 18.6 Hz); 7.14—7.82 (m, 18 H, H arom.); 10.47 (s, 1 H, NH).

2-[(*Z*)-2,3-Bis(4-bromophenyl)-3-oxoprop-1-enyl]-3-(4-tolyl)-4(3*H*)-quinazolone (4). Compound **1** (0.25 g, 1 mmol) and 4,4′-dibromobenzil (0.37 g, 1 mmol) were heated in PFP (0.6 g) at 140 °C for 40 h. The reaction mixture was precipitated with ethanol (20 mL), unconsumed 4,4′-dibromobenzil (0.26 g) was filtered off, the mother liquor was concentrated, isopropanol (10 mL) was added, and the precipitate was filtered off. The yield was 0.12 g (20%), m.p. 185—210 °C, R_f 0.7 (fluorescent spot). Found (%): C, 59.97; H, 3.37; Br, 26.55; N, 4.62. $C_{30}H_{20}Br_2N_2O_2$. Calculated (%): C, 60.02; H, 3.36; Br, 26.62; N, 4.67.

2-[(*Z*)-3-Oxo-2,3-bis(4-fluorophenyl)prop-1-enyl]-3-(4-tolyl)-4(3*H*)-quinazolone (5). Compound **1** (0.25 g, 1 mmol) and 4,4′-difluorobenzil (0.25 g, 1 mmol) were heated in PFP (0.5 g) at 140 °C for 40 h. The reaction mixture was precipitated with ethanol (10 mL), and the yellow precipitate that formed was filtered off. The yield was 0.24 g (50%), m.p. 230—232 °C, R_f 0.7 (fluorescent spot). ^{1}H NMR, δ: 2.43 (s, 3 H, C_6H_4Me); 6.39 (s, 1 H, —CH=); 6.99 (d, 1 H, J = 8.0 Hz); 7.21—7.49 (m, 11 H); 7.73 (t, 1 H, J = 7.5 Hz); 7.98—8.05 (m, 3 H). ^{19}F NMR, δ: −105.66 and −110.53 (both s, 1 F each).

2-[3,3-Bis(4-bromophenyl)succinimido]-*N*-(4-tolyl)benzamide (6). Compound **4** (0.02 g, 0.0323 mmol) was dissolved in DMSO-d_6 (1 mL) on heating. R_f 0.6 (the spot shows no fluorescence). ^{1}H NMR, δ: 2.30 (s, 3 H, Me); 3.58 and 3.78 (both d, 1 H each, CH_2 of the succinimide fragment, J = 18.4 Hz); 7.13—7.90 (m, 16 H, H arom.); 10.45 (s, 1 H, NH).

2-[3,3-Bis(4-fluorophenyl)succinimido]-*N*-(4-tolyl)benzamide (7). Compound **5** (0.1 g, 0.201 mmol) was refluxed in 85% aqueous formic acid (5 mL) for two weeks. The solution was cooled. The brown crystals (m.p. 210—223 °C) that precipitated were separated from the mother liquor and dissolved on heating in DMSO-d_6 (2 mL). R_f 0.6 (the spot shows no fluorescence). Found (%): C, 72.62; H, 4.45; F, 76.90; N, 5.68. $C_{30}H_{22}F_2N_2O_3$. Calculated (%): C, 72.57; H, 4.47; F, 76.50; N, 5.64. ^{1}H NMR, δ: 2.30 (s, 3 H, Me); 3.56 and 3.81 (both d, 1 H each, CH_2 of the succinimide fragment, J = 18.4 Hz); 6.99—7.81 (m, 16 H, H arom.); 10.43 (s, 1 H, NH). ^{19}F NMR, δ: −114.84 and −115.26 (both s, 1 F each).

X-ray diffraction study of compounds 2, 3, and 5. A single crystal of compound **2** was grown by vacuum sublimation (200 °C, the residual pressure was 0.01 Torr); a single crystal of **3**, by dissolution of compound **2** in refluxing formic acid followed by evaporation of the solvent at ~20 °C for two weeks; a single crystal of compound **5**, by slow evaporation of a solution of compound **5** in dioxane. The experimental data sets were collected on Bruker SMART CCD Area Detector (at 120 K for **2**) and Syntex P21 (at 173 K for **3** and 193 K for **5**) diffractometers. The crystallographic data and the X-ray data collection and refinement statistics are given in Table 1.

The structures were solved by direct methods. All non-hydrogen atoms were located in difference electron density maps and refined anisotropically against F^2_{hkl}. The hydrogen atoms were placed in geometrically calculated positions and refined using a riding model with U(H) = nU(C) (n = 1.2 and 1.5 for the sp^2- and sp^3-hybridized carbon atoms, respectively; U(C) are the equivalent thermal parameters of the C atoms to which the corresponding H atoms are bound). All calculations were carried out using the SHELXTL PLUS 5 program package.[9]

Quantum chemical calculations were performed with the use of the Gaussian 98 program package (version A.7).[10] The geometry of the species **A**—**F** was calculated by the semiempirical PM3 method. The transition state of the rearrangement **C** → **D** was found using the QST2 algorithm according to the same method. The energies of the structures were evaluated by the B3LYP/6-31G* method. The results of calculations were visualized using the ChemCraft program, version 1.5 (*www.chemcraftprog.com*).

We thank E. I. Goryunov for continuous support and valuable advice.

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Received July 20, 2006;
in revised form October 3, 2006