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Pericyclic reactions in the synthesis of new 5-aryl-5,6-dihydroquinolino[2,1-*b*]quinazolin-12-ones

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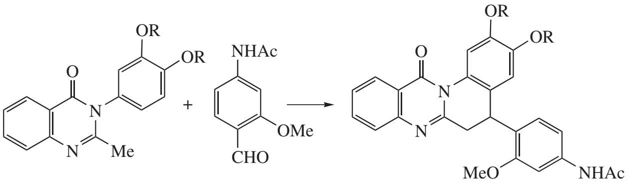
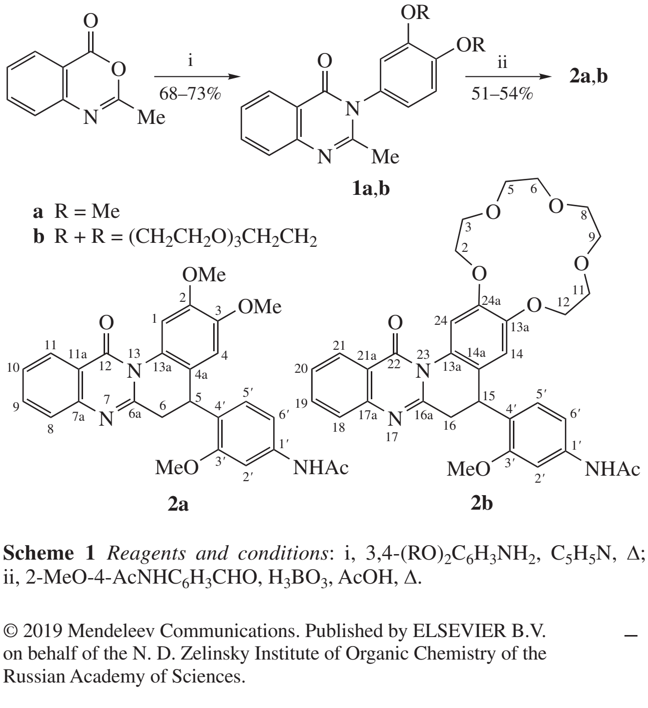
Novel tetracyclic 5-aryl-5,6-dihydroquinolino[2,1-*b*]quinazolin-12-ones bearing benzo-15-crown-5 ether and dimethoxyphenyl moieties were prepared by one-pot cascade synthesis involving the thermally allowed pericyclic transformations of (*E*)-2-(2-methoxystyryl)quinazolinones. The pseudocyclic transition state of six-electron electrocyclization has been located and the activation barrier has been estimated by RHF/3-21G and 6-311G* calculation methods. The crystal structure of *N*-[4-(2,3-dimethoxy-12-oxo-5,6-dihydroquinolino[2,1-*b*]quinazolin-5-yl)-3-methoxyphenyl]acetamide was determined by X-ray diffraction analysis.



A six-electron electrocyclization[1,2] of aryl polyenes with *cis*-1,3,5-triene moiety represents one of the most popular methods for the synthesis of polycyclic aromatic and heteroaromatic structures. Diarylethylenes (stilbenes,[3] distyrylbenzenes,[4,5] 2,2′-divinylbiphenyls,[6] *etc.*) and related heteroaromatic compounds[7–9] demonstrate a photochemical conrotatory electrocyclization. Natural[10] and biomimetic aryl-containing[11] hexatrienes are prone to thermal disrotatory electrocyclization. Usually, these transformations are carried out in tandem with subsequent reactions of oxidation,[3] elimination[12] or rearrangement.[11,13] Recently, we reported a convenient synthesis of (*E*)-2-(2-hydroxystyryl)quinazolinones.[14] Our research has shown that the incorporation of hydroxyl group in the styryl fragment of these compounds promotes a reversible photo/thermal *E–Z–E* isomerization in solutions. In the continuation of our studies on influence of various electron-donating substituents on luminescent properties of styrylquinazolinones, we explored the interaction of 2-methylquinazolin-4(3*H*)-ones **1a**,**b** with 4-acetamido-2-methoxybenzaldehyde in accordance with the earlier reported protocol[14] (Scheme 1).



Scheme 1 *Reagents and conditions*: i, 3,4-$(RO)_2C_6H_3NH_2$, C_5H_5N, Δ; ii, 2-MeO-4-$AcNHC_6H_3CHO$, H_3BO_3, AcOH, Δ.

When heating substrates **1a**/**1b** with the aldehyde for the first six hours, formation of *E*-styrylquinazolinone of type **A** (Scheme 2) was observed in the reaction mixture, according to UV-TLC monitoring. Moreover, ^{1}H NMR monitoring of the reaction mixture revealed doublets of vicinal protons of vinylene C=C bonds[14] in the range of ~7.96 and ~6.56 ppm with the spin–spin coupling constant of 15.6 Hz (see Online Supplementary Materials). In the case of substrate **1a**, the corresponding olefin **A** was isolated and characterized. Further refluxing of the reaction mixture (up to 180 h) afforded compounds **2a** and **2b**, whereas intermediate **A** disappeared almost completely. The polycyclic structures **2** were proven by ^{1}H and ^{13}C NMR signals assigned using 2D ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC, and HMBC experiments. In particular, the formation of the dihydropyridine ring was confirmed by typical ABX spin system of the H^{6A}/H^{16A}, H^{6B}/H^{16B} and H^5/H^{15} protons of compounds **2a**/**2b** in ^{1}H NMR spectra. Moreover, cross-peaks between H^5/H^{15} or H^4/H^{14} protons and C^4/C^{14} or C^5/C^{15} carbon atoms were observed in their 2D ^{1}H-^{13}C HMBC spectra, respectively (see Scheme 1). The structure of **2a** was ultimately proved by X-ray diffraction method (Figure 1).†

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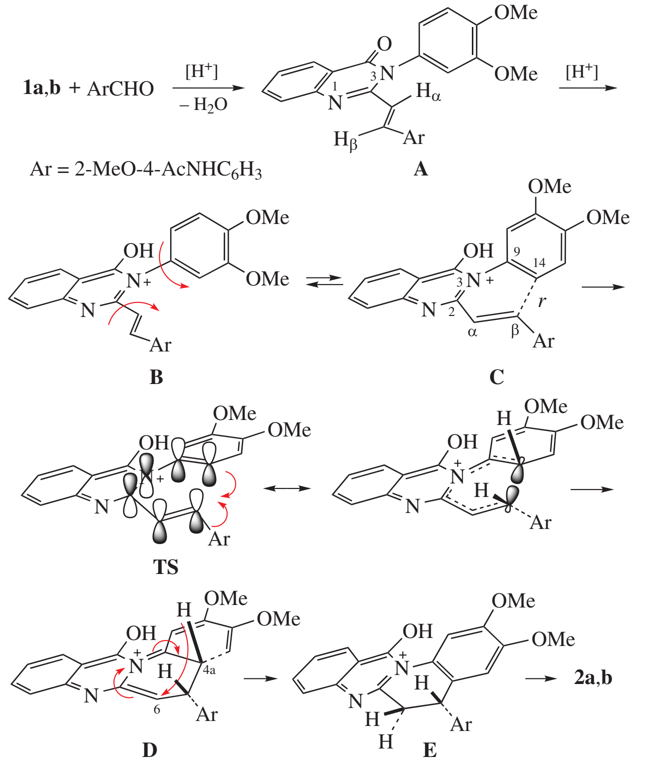
† *Crystal data for* **2a** *(solvate).* $C_{27}H_{25}N_3O_5 \cdot C_2H_3N$ (M = 512.55), triclinic, space group $P\bar{1}$, a = 9.441(6), b = 9.858(9) and c = 14.926(15) Å, α = 96.75(8)°, β = 106.55(7)°, γ = 103.20(7)°, V = 1271.3(19) Å^3, Z = 2, μ = 0.761 cm^{-1}, d_{calc} = 1.339 g cm^{-3}; 27546 reflections measured with an Xcalibur 3 automated diffractometer (MoKα radiation, λ = 0.71073 Å, graphite monochromator, ω-scan technique, with a 1° step) at 295(2) K



Scheme 2

The formation of compounds **2a**,**b** can be explained by thermally allowed pericyclic transformations of *E*-styrylquinazolinone **A** generated *in situ* in the reaction medium (see Scheme 2). The protonation of the keto group of the pyrimidinone ring in AcOH solution is able to initiate both the formation of the enol form **B** and the involvement of the *n*-orbital[2] of the atom N(3) to the π-electron conjugated system of this heterocycle. As a result, the C=N bond of the aromatic pyrimidinium tautomer **C** together with the two spatially approaching C=C bonds of the terminal vinylene and aryl groups provide suitable pre-requisites for the emergence of six-electron pseudocyclic transition state **TS** in accordance with the Woodward–Hoffmann rules.[1] Quantum mechanical calculations of distance (*r*) between the terminal carbon atoms in such pseudocycles[15] is estimated at ~2.24 Å. Considering the *m*-symmetry[1] of highest occupied molecular orbital (HOMO) for 6π electron system of intermediate **TS**, the disrotatory electrocyclization of *E*-isomer is to produce the *syn* configuration of the hydrogen atoms in intermediate **D**. The following [1,5]-hydrogen suprafacial shift allowed by symmetry leads to intermediate **E** (see Scheme 2).

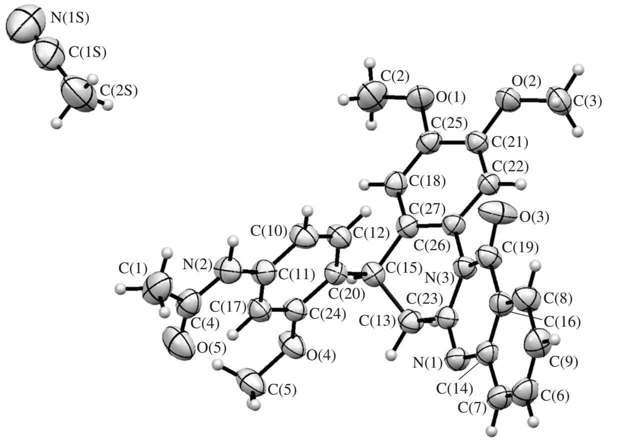


Figure 1 Molecular structure of *rac*-(15)*R**-isomer **2a** based on the X-ray analysis. Thermal ellipsoids are given with 50% probability.

To identify the geometry of the transition state and to assess the activation barrier (E_a/kcal mol^{-1}), we carried out a study of the disrotatory electrocyclization mechanism for the triethoxy-substituted *E*-styrylquinazolinone. The stationary points on the chemical reaction energy curve have been located using Orca 4.0.1 program complex with Restricted Hartree–Fock theory calculations and the 3-21G and 6-311G* basis sets.[16–19] The optimized structures were proved by the absence of imaginary frequencies in Hessian, and the **TS** – by the presence of one imaginary frequency. The optimized structures of located intermediates **B**, **C**, **D**, **E** and transition states **TS**, **TS-D/E** and their relative energy values are given in Table S1 (see Online Supplementary Materials). Two possible original conformations of *E*-styrylquinazolinone are represented by structures **B** and **C** (see Table S1). The conformer **C** is 7.39 kcal mol^{-1} higher in energy than the conformer **B**. However, the higher-energy conformer **C** is characterized by a closer distance (*r*) between the reaction centers C(β) and C(14), 3.4 Å, and can be considered as the initial coordinate of the electrocyclization reaction (Figure 2, see Table S1). The transition state **TS** was determined through analysis of the reaction pathway points **C→D** obtained by the above methods. It was established that the pseudocyclic 6π electron system becomes more planar with the reaction coordinate (*r*) decreasing due to the disrotatory movement of the terminal bonds C(α)=C(β) and C(9)=C(14), which is expressed by changing the values of torsion angles (see Scheme 2, Figure 2, Table S1). The disrotatory transition structure **TS** has a boat-like conformation of the forming six-membered ring and a close interaction distance *r* equal to 2.09 Å. A boat-like conformation is characterized by lower steric repulsions between the inward hydrogen atoms and provides almost perfect eclipsing between the atoms C(β) and C(14). However, the inclusion of (hetero)aromatic rings in the π-system of **TS**, along with a bulky substituent, leads to the more significant geometric deformations of pseudocyclic conformation and subsequently to an increase in the activation energy.[15] The energy barrier required for the formation of the calculated intermediate **D** through the transition state **TS** is 66.39–68.36 kcal mol^{-1}. A somewhat larger value of the computed activation barrier at the highest level of theory employed for conformer **C** compared to that for the substituted 1,3,5-hexatrienes is generally consistent with the previously published quantum chemical studies.[15] It should be noted that the RHF/3-21G and RHF/6-311G* methods that we applied give the overestimated values of the relative energies E_a (kcal mol^{-1}) of the transition structures.[15] On the contrary, a significant shortening of the distance *r* to 2.09 Å against the postulated 2.24 Å[15] can be explained by the involvement of the π-conjugated system of both (hetero)aromatic rings in the transition state formation process. The HOMO of intermediates $\mathbf{C}_{1-2}$ and **TS** shows the localization of the electron density on these fragments (Table S2). In other words, the pseudocyclic transition state can be viewed as an 18-electron π-conjugated system. Moreover, the transition state is additionally stabilized by π-stacking interaction (~3.4 Å) between closely spaced phenyl moieties (see Tables S1, S2). Cyclization is not accompanied by a decrease in electron density from intermediates $\mathbf{C}_{1-2}$ to **TS**, according to the quantum chemical calculations (see Table S2). This fact may also be an evidence in favor of stereospecific electrocyclization. In

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($3.15 < \theta < 66.88°$), 4448 unique reflections [$R_{int} = 0.0631$], $R_1 = 0.0486$, $wR_2 = 0.1284$ for 2841 reflections with $I > 2\sigma(I)$, $R_1 = 0.0661$, $wR_2 = 0.1326$ for all reflections. All calculations were performed using SHELXS-97 and SHELXL-97.[20]

CCDC 1890210 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

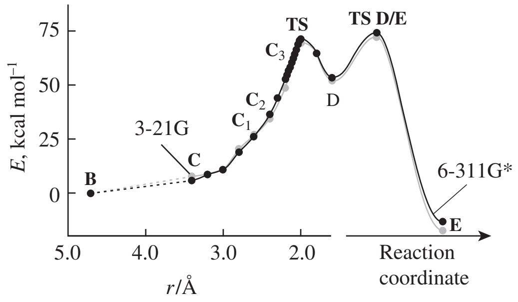

Figure 2 Intermediate and transition state structures **B**, **C**, $\mathbf{C_{1-3}}$, **TS**, **D**, **TS-D/E** and **E** (see Scheme 2 and Table S1) and their relative energies on the chemical reaction energy curve for the disrotatory electrocyclization of *E*-styrylquinazolinone and the following [1,5]-hydrogen shift, which were obtained using RHF/3-21G and 6-311G*.

addition, the calculated **TS-D/E** transition state for the following [1,5]-hydrogen suprafacial shift is characterized by a distance of 1.35 and 1.62 Å between the C(4a)/C(6) and H(4a) atoms. The energy barrier for the formation of the calculated intermediate E_a is 70.49–73.41 kcal mol^{-1} (see Figure 2, Table S1).

In conclusion, the one-pot cascade synthesis of novel polycyclic 5-aryl-5,6-dihydroquinolino[2,1-*b*]quinazolin-12-ones bearing benzo-15-crown-5 ether and dimethoxyphenyl moieties was developed. The domino process includes the condensation reaction, electrocyclization and sigmatropic shift. The pyrimidone ring protonation proved to be the determining pre-requisite for the passage of six-electron disrotatory cyclization of *E*-styrylquinazolinones forming *in situ* in the reaction medium. A rare case of thermally allowed electrocyclization of hetarylethylenes was found.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.03.004.

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