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Novel 8-arylidenetetrahydroquinazoline *N*-oxides: synthesis, photophysical properties and biological evaluation

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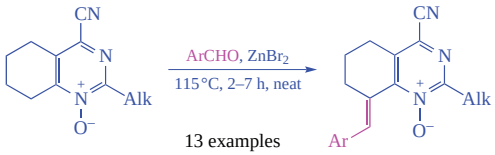
New 8-arylidene-4-cyanotetrahydroquinazoline *N*-oxides were obtained *via* the condensation of readily available 4-cyanotetrahydroquinazoline *N*-oxides with aromatic aldehydes. Some of the synthesized compounds revealed fluorescent properties and moderate cytotoxic activity.



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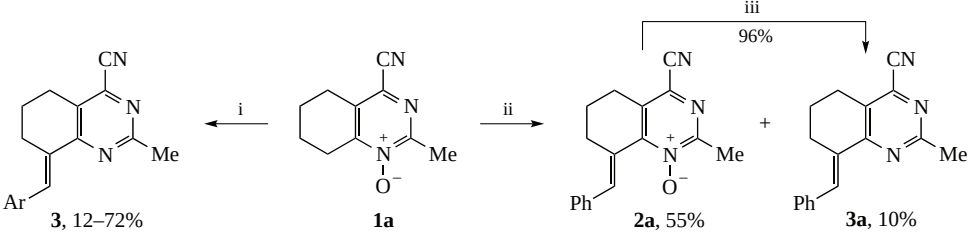
Quinazolines are privileged scaffolds featured in a number of natural compounds and widely used in drug design.[1–5] Quinazoline-containing marketed drugs are utilized in therapy of cancer, hypertension and prostatic hyperplasia; they reveal anti-inflammatory, sedative, antiviral, antibacterial and antifungal properties.[6,7] As for structurally related tetrahydro derivatives, 8-arylidenetetrahydroquinazolines possess antitumor,[8,9] antibacterial[10] and antitubercular/antidiabetic[11] activities. These compounds can also serve as building blocks for the synthesis of pyrimidine-containing polycyclic structures.[12]

The main synthetic access to 8-arylidenetetrahydroquinazolines is the construction of pyrimidine moiety *via* the reactions of urea derivatives with arylidenecyclohexanones, either preliminarily prepared[9–11,13,14] or generated *in situ*;[15,16] in some cases the synthetic scheme involving an additional aromatization step.[8,17] The functionalization of tetrahydroquinazolines *via* condensation with aromatic aldehydes was also reported,[18] nonetheless, regioselectivity of the reaction and substituents effects were never explored. None of these approaches has been previously employed to obtain the corresponding tetrahydroquinazoline *N*-oxides.

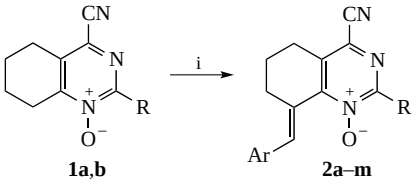
Recently, we elaborated the straightforward synthesis of pyrimidine and tetrahydroquinazoline *N*-oxides based on the heterocyclization of *gem*-dihalogenocyclopropanes into 4-halogenopyrimidine *N*-oxides upon the treatment with nitrating or nitrosating agents.[19–28] Thus obtained 4-cyano-2-methyltetrahydroquinazoline *N*-oxide **1a** (Scheme 1) was subjected to the condensation with aromatic aldehydes, which afforded unusual 8-benzylidenetetrahydroquinazolines **3**, the reaction having been accompanied by reduction of the *N*-oxide function.[29]

Here, we report the preparation of new relative 8-arylidenetetrahydroquinazolines **2** with retained *N*-oxide functions (see Scheme 1) and comparison of their photophysical properties and biological activity with those of deoxygenated analogues **3**. Presuming that formation of products **3** involved the sequence of condensation and *N*-oxide reduction,[29] an optimization of the reaction conditions was carried out for the model 4-cyanotetrahydroquinazoline *N*-oxide **1a** and benzaldehyde in order to stop the process at the step of *N*-oxide **2a** formation (see Scheme 1, Table S1 of the Online Supplementary Materials). The optimal conditions were found to be heating of neat mixture of compound **1a** and 10 equiv. benzaldehyde at 115 °C for 3 h. Lowering either temperature or excess of aldehyde reduced the conversion of reactant **1a**, while prolongation of the process reduced the preparative yield due to its decomposition. In all cases, small amounts of deoxygenated analogue **3a** were also formed. Mild reduction of *N*-oxide **2a** with PCl_3[30] gave compound **3a**, which additionally confirmed the structure of **2a** (see Scheme 1).

To verify the scope of the procedure, tetrahydroquinazoline *N*-oxides **1a**,**b** were condensed with the series of aromatic and



Scheme 1 *Reagents and conditions*: i, ArCHO (10 equiv.), $ZnBr_2$, neat, 135 °C, 24 h; ii, PhCHO (10 equiv.), $ZnBr_2$ (0.12 equiv.), neat, 115 °C, 3 h; iii, PCl_3 (4 equiv.), CH_2Cl_2, 20 °C, 5 h.



1a,**b** **2a**–**m**

a R = Me
b R = Et

a R = Me, Ar = Ph, 55%
b R = Et, Ar = Ph, 42%
c R = Me, Ar = 2,6-$Me_2C_6H_3$, 36%
d R = Me, Ar = 4-$MeOC_6H_4$, 64%
e R = Me, Ar = 4-$EtOC_6H_4$, 56%
f R = Me, Ar = 3,4,5-$(MeO)_3C_6H_2$, 56%
g R = Me, Ar = 4-$Me_2NC_6H_4$, 18%
h R = Me, Ar = 4-FC_6H_4, 65%
i R = Me, Ar = 4-$O_2NC_6H_4$, 48%
j R = Me, Ar = 4-(PhCH=CH)C_6H_4, 40%
k R = Me, Ar = 2-naphthyl, 54%
l R = Me, Ar = 5-methylfuran-2-yl, 34%
m R = Me, Ar = 2-thienyl, 5%

Scheme 2 *Reagents and conditions*: i, ArCHO (10 equiv.), $ZnBr_2$ (0.12 equiv.), 115 °C, 2–7 h, neat.

heteroaromatic aldehydes under optimal conditions to afford new 8-substituted 4-cyanotetrahydroquinazoline *N*-oxides **2a**–**m** in reasonable isolated yields (Scheme 2).† The reaction proceeded regioselectively involving methylene group of the carbocyclic moiety while no condensation involving methyl or ethyl group occurred. Also, benzaldehydes with either electron-withdrawing or electron-donating groups as well as aldehydes containing naphthyl, styryl or furyl substituents gave similar results. Only product **2m** was obtained in lower yield because of the decomposition of thiophene ring under the reaction conditions.

The study of photophysical properties of compounds **2a**,**c**–**m** revealed the absorption maxima at 328–421 nm. Generally, *N*-oxides **2a**,**c**–**m** exhibited weaker fluorescence and lower Stokes shifts than deoxygenated analogues **3**, while compounds **2a**,**c**–**e**,**h**, in contrast to the corresponding tetrahydroquinazolines **3**,[29] did not possess fluorescent properties (see Online Supplementary Materials). Such tendencies may be explained by the structural factors: according to the computations, in fluorescent molecule **3a** the dihedral angle between the double bond and phenyl ring is 24°, whereas in non-fluorescent molecule **2a** it is 33° that evidences a lack of conjugation through the π-bond system (Figure 1).

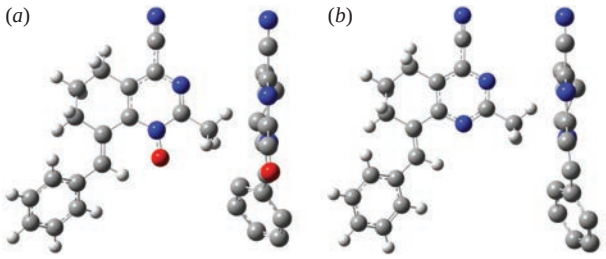


Figure 1 Molecular structures of compounds (*a*) **2a** and (*b*) **3a** according to DFT calculation (B3LYP-D3/def2-TZVP) using ORCA 4.0.1.[31] On the side projections, hydrogen atoms are omitted for clarity.

† *Condensation of 4-cyanotetrahydroquinazoline* N*-oxides* **1a**,**b** *with aldehydes (general procedure).* The mixture of a 4-cyanotetrahydroquinazoline *N*-oxide **1** (0.5 mmol), corresponding aldehyde (5 mmol) and $ZnBr_2$ (0.06 mmol, 14 mg) was stirred at 115 °C for 2–7 h under argon. The resulting hot mixture was poured into a saturated solution of $NaHCO_3$ (5 ml) and extracted with EtOAc (3×5 ml). The combined organic extracts were washed with saturated solution of $NaHCO_3$ (3×5 ml) and water (5 ml) and dried over $MgSO_4$. The solvent was evaporated *in vacuo*. When possible, the residual aldehyde was pumped-off *in vacuo*, and the product was isolated by column chromatography (SiO_2). Unreacted starting compound **1** was also isolated and re-used.

Screening the activity of the synthesized substances towards three human cancer (MCF-7, HCT116, A549) and one normal (WI38) cells lines showed that compounds **2a**,**c**,**e**,**f**,**j**,**k** reveal cytotoxicity in micromolar concentrations towards cancer and normal cells (see Online Supplementary Materials). Compounds **2a**,**f** exhibited the most prospective activity and compound **2f** revealed appreciable selectivity towards cancer cells (IC_{50} = 29 μM for HCT-116 and IC_{50} = 54 μM for WI38). Introduction of *N*-oxide function led to twofold increase in the activity for **2a** compared to **3a**,[29] whereas for **2e** the effect was controversial for different cell lines, and **2f** was less active than the corresponding tetrahydroquinazoline.

To conclude, the one-step synthetic approach to previously unknown 8-arylidenetetrahydroquinazoline *N*-oxides **2** from readily available 4-cyanotetrahydroquinazoline *N*-oxides **1** has been elaborated. Their comparison with deoxygenated analogues **3** has demonstrated that introduction of *N*-oxide function into the structure leads to decrease in fluorescent properties and has controversial impact on anticancer activity.

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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.2021.01.011.

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