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Mendeleev Commun., 2020, **30**, 714–716

Mendeleev Communications

4-Azidotetrahydroquinazoline derivatives in CuAAC reaction

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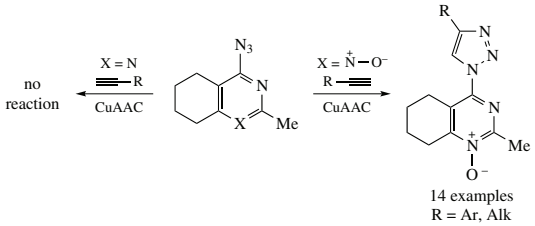
DOI: 10.1016/j.mencom.2020.11.008

4-Azido-2-methyltetrahydroquinazoline *N*-oxide cleanly undergoes the copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reaction with alkynes to give new conjugates with pyrimidine *N*-oxide and triazole moieties. Its deoxygenated analogue, 4-azido-2-methyltetrahydroquinazoline, is inert in CuACC process due to the shift of imidoyl azide–tetrazole equilibrium towards the tetrazole tautomer.



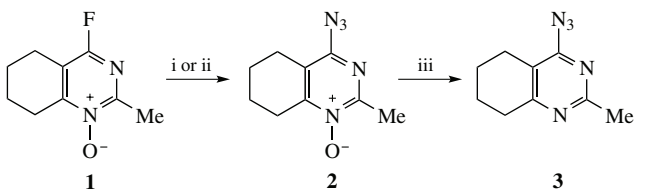
Keywords: pyrimidines, triazoles, CuAAC, *N*-oxides, tautomers, azidopyrimidine *N*-oxides, quantum chemical calculations.

Pyrimidine moiety is abundant in a number of natural compounds and is to be found among top-15 carbo- and heterocycles present in marketed medicinal drugs.[1–3] Azole heterocyclic scaffolds are also widely used in drug design,[4–8] in particular, as easily constructed linkers between pharmacophores.[9] The combination of pyrimidine and triazole heterocyclic moieties in the same molecule is not uncommon among compounds with various types of biological activity.[10–13]

The most general and effective construction of triazole core is the azide–alkyne cycloaddition under Cu^I catalysis.[14,15] A number of reports describe the influence of structural and electron factors on imidoyl azide–tetrazole equilibrium in 2/4-azidopyrimidines and their reactivity in CuAAC processes.[16–27]

Recently, we elaborated an effective preparative approach towards 4-halogenopyrimidine *N*-oxides and their synthetic derivatives based on three-component heterocyclization of *gem*-dihalogenocyclopropanes.[28–39] Taking into account that the effect of *N*-oxide group on tautomeric equilibrium and reactivity of azidopyrimidines have never been investigated previously, we aimed to obtain the first example of yet unknown 4-azidopyrimidine *N*-oxides and to compare it with the deoxygenated analogue.

4-Azido-2-methyl-5,6,7,8-tetrahydroquinazoline *N*-oxide **2** was obtained *via* the substitution of the fluorine atom in a readily available[29] 4-fluoro precursor **1** upon treatment with either trimethylsilyl azide or sodium azide (Scheme 1). The first method provided higher yield of compound **2** due to an easier isolation. Subsequent reduction of *N*-oxide **2** with PCl_3 under mild conditions[39] gave 4-azido-2-methyl-5,6,7,8-tetrahydroquinazoline **3**.



Scheme 1 *Reagents and conditions*: i, Me_3SiN_3, PhH, 25 °C, 15 h, 98%; ii, NaN_3, DMSO, 25 °C, 15 h, 65%; iii, PCl_3, CH_2Cl_2, 40 °C, 2 h, 65%.

According to the described regularities,[16] compound **3** containing three electron-donating groups in azidopyrimidine moiety should exist preferably as tetrazole **3**-**T** in non-polar medium, while the presence of the electron-withdrawing group in compound **2** may shift the equilibrium to the imidoyl azide form **2**-**A**. To verify this hypothesis, imidoyl azide–tetrazole equilibrium in compounds **2** and **3** was investigated.

Indeed, the IR spectra of *N*-oxide **2** both in thin film and in CH_2Cl_2 showed an intense band at 2134 cm^{-1} characteristic of azido group, while in the IR spectra of compound **3** the analogous band (2132 cm^{-1}) was very weak. ^1H NMR spectra of compounds **2** and **3** in $CDCl_3$ were significantly different: δ_H of 2.70 for Me group of compound **2** and δ_H of 3.07 for **3**, which is consistent with reported data for azidopyrimidines existing as open-chain or tetrazole forms, respectively.[22] The addition of TFA to compound **2** did not change the NMR spectra. On the contrary, after addition of TFA to the solution of compound **3** in $CDCl_3$, the expected shift of the equilibrium towards open-chain form

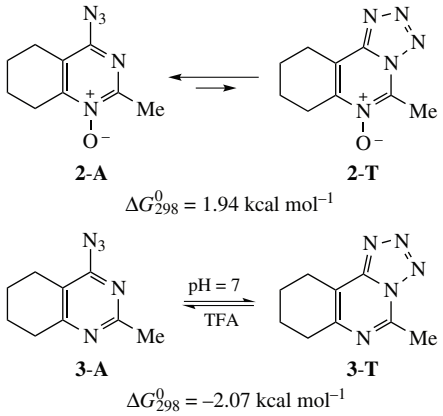


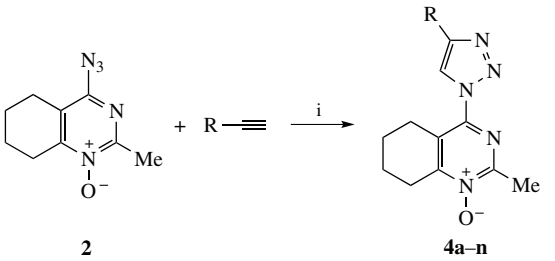
Figure 1 Imidoyl azide–tetrazole equilibrium in compounds **2** and **3**. Calculations were performed in ORCA 4.0 [B3LYP-D3/6-31G(d)/CH_2Cl_2(CPCM)].

3-**A** due to the protonation of pyrimidine core[16] occurred, and the NMR spectrum displayed almost the same chemical shifts as observed for compound **2** (δ_H 2.78 for CH_3 group, see Online Supplementary Materials). Besides, calculation of the energy of the tautomeric forms showed that thermodynamic factors did not favor the intramolecular cyclization of *N*-oxide **2**, while the Gibbs free energy of cyclization for the compound **3** was negative (Figure 1).

4-Azidotetrahydroquinazoline *N*-oxide **2** and its deoxygenated analogue **3** were investigated as CuAAC reactants towards some alkynes. Optimization of the conditions was carried out for phenylacetylene as the model (for details, see Online Supplementary Materials). For compound **2**, the reflux of the reactants in CH_2Cl_2 in the presence of the catalytic system $Cu(OAc)_2$/AscNa/Et_3N was found optimal. A series of new triazolyltetrahydroquinazoline *N*-oxides **4a**–**n** with aromatic and aliphatic substituents was obtained under the optimal conditions, mainly, in good to high yields (Scheme 2).† The reaction proceeded smoothly with alkynes of diverse nature; a lower yield of amino substituted compound **4f** was a result of the difficulties during chromatographic isolation.

4-Azidotetrahydroquinazoline **3** turned out really inert under all the CuAAC conditions probed, that is expected for azidopyrimidine derivative existing in tetrazole form **3**-**T**.

To conclude, 4-azidotetrahydroquinazoline *N*-oxide **2** exists in open-chain form while its deoxygenated analogue **3** as a tetrazole tautomer. The CuACC reaction of 4-azidotetrahydroquinazoline *N*-oxide **2** with a variety of alkynes was accomplished to afford a series of new triazole tetrahydroquinazoline *N*-oxide conjugates promising for the search for novel biologically active compounds.



2 **4a–n**

a R = Ph, 89%
b R = 4-MeC_6H_4, 83%
c R = 4-$Bu^tC_6H_4$, 66%
d R = 2,4,6-$Me_3C_6H_2$, 65%
e R = 4-$Me_2NC_6H_4$, 77%
f R = 3-$H_2NC_6H_4$, 20%
g R = 4-$MeOC_6H_4$, 40%
h R = 3,4,5-$(MeO)_3C_6H_2$, 45%
i R = 4-FC_6H_4, 49%
j R = 4-$F_3CC_6H_4$, 75%
k R = 4-NCC_6H_4, 83%
l R = 4-$MeO_2CC_6H_4$, 72%
m R = Bu^t, 65%
n R = (1-indolyl)methyl, 40%

Scheme 2 *Reagents and conditions*: i, $Cu(OAc)_2 \cdot H_2O$, Na ascorbate, Et_3N, CH_2Cl_2, 40 °C.

† *Synthesis of 4-triazolyl-5,6,7,8-tetrahydroquinazoline* N-*oxides* **4a**–**n**. Compound **2** (0.25 g, 1.2 mmol), $Cu(OAc)_2 \cdot H_2O$ (24 mg, 0.12 mmol), Et_3N (13 mg, 0.24 mmol) and CH_2Cl_2 (4 ml) were mixed under argon. Corresponding alkyne (1.44 mmol) and sodium ascorbate (98 mg, 0.48 mmol) were added to the reaction mixture under stirring. The resulting mixture was refluxed for 24 h, cooled down to room temperature and quenched with saturated aqueous Trilon B (5 ml). Organic layer was separated; water layer was extracted with CH_2Cl_2 (3×5 ml). Combined organic layers were washed with saturated aqueous Trilon B (3×5 ml) and water (3×10 ml), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Product was isolated *via* preparative column chromatography (SiO_2).

Compound **4a**. Yield 0.33 g (89%). Yellow solid, R_f = 0.33 (light petroleum : ethyl acetate : MeOH, 3 : 1 : 0.5), mp 113–115 °C. ^{1}H NMR ($CDCl_3$) δ: 1.75–1.86 (m, 2H, CH_2), 1.92–2.02 (m, 2H, CH_2), 2.77 (s, 3H, Me), 3.02 (br.t, ^3J = 6.5 Hz, 2H, CH_2), 3.20 (br.t, ^3J = 6.1 Hz, 2H, CH_2), 7.35–7.41 (m, 1H, CH), 7.43–7.50 (m, 2H, 2CH), 7.90–7.95 (m, 2H, 2CH), 8.59 (s, 1H, CH, triazolyl). ^{13}C NMR ($CDCl_3$) δ: 19.8 (Me), 20.7 (CH_2), 21.3 (CH_2), 26.12 (CH_2), 26.17 (CH_2), 119.4 (CH, triazolyl), 123.0 [C(4a)], 126.1 (2CH), 128.8 (CH), 129.1 (2CH), 129.8 (C), 139.7 (C), 147.3 (C), 155.7 (C), 158.7 (C). HRMS (ESI) *m*/*z*: $[M + H]^+$ 308.1506 (calc. for $C_{17}H_{17}N_5O$, *m*/*z*: 308.1515).

We thank the Russian Foundation for Basic Research (project no. 18-03-00651-a) for financial support of this work. This study was fulfilled using an Agilent 400-MR NMR spectrometer purchased by the MSU Development Program.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.11.008.

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Received: 16th July 2020; Com. 20/6265