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Dichotomy in the reactivity of 2-methyltetrahydroquinazoline 1-oxides towards aldehydes: an unprecedented condensation with simultaneous reduction of *N*-oxide fragment

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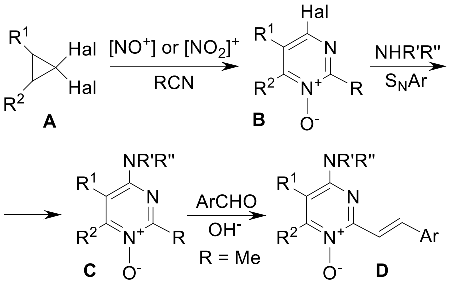
ABSTRACT

An unusual condensation reaction of 2-methyltetrahydroquinazoline *N*-oxides with aromatic aldehydes was found. The reaction of 4-cyano substituted heterocycles as well as the use of microwave irradiation for 4-morpholinyl substituted heterocycles resulted in the condensation engaging the methylene group of tetrahydroquinazoline fragment with simultaneous deoxygenation of the *N*-oxide. A preparative approach to previously unknown pyrimidine-containing conjugated molecules was developed based on this process.

1. Introduction

The pyrimidine core is prevalent in a number of important natural compounds, nucleobases and therapeutic agents,[1] as well as in other organic materials,[2] such as liquid crystals, light-emitting and nonlinear optical materials. Nevertheless, *N*-oxidized pyrimidines are not widely employed in the construction of compounds with useful properties, or as intermediates in organic synthesis, compared to their structurally related analogues. The main reason for such lack of attention to these compounds is their low synthetic availability. The only general approach to pyrimidine *N*-oxides, described until recently, was the oxidation of the pyrimidine ring, which is limited by the lack of regioselectivity and insufficient tolerance of functional groups to oxidative conditions.[3]

Previously, we have developed straightforward preparative approaches to a number of novel pyrimidine *N*-oxide derivatives on the basis of a three-component heterocyclization of 1,1-dihalogenocyclopropanes **A** upon treatment with nitrating or nitrosating reagents in the presence of an organic nitrile (Scheme 1).[4] 4-Amino-2-methylpyrimidine *N*-oxides **C** are readily available *via* a sequence of three-component heterocyclization and S$_N$Ar reactions. Recently, these pyrimidine derivatives have been studied in the reaction with aromatic aldehydes affording a series of π-conjugated molecules **D** possessing fluorescent properties (Scheme 1).[5] Although the condensation of methyl substituted electron-deficient heterocycles, acting as methylene components in the reactions with carbonyl compounds, is a well-described approach to conjugated structures,[6] only one such reaction has been reported for pyrimidine *N*-oxides.[7] However, their use for the construction of "push-pull" molecules with valuable photophysical characteristics was not described.

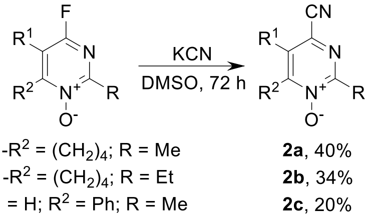


Scheme 1. Approaches to pyrimidine *N*-oxide derivatives based on the heterocyclization of 1,1-dihalogenocyclopropanes.

Herein, we report the reaction of 4-cyano-2-methylpyrimidine *N*-oxides with aromatic aldehydes, aiming to broaden the scope of this reaction, and to investigate the influence of electron-withdrawing substituents in position *4* of pyrimidine *N*-oxides on their reactivity in the condensation reactions. As a result, a novel reaction of 2-methylpyrimidine *N*-oxides with carbonyl compounds was discovered.

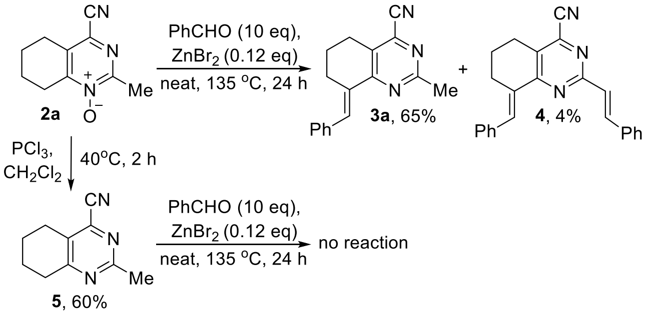
2. Results and Discussion

Pyrimidine *N*-oxides bearing a cyano group in position *4* were obtained from 4-fluoropyrimidine *N*-oxides **1a-c** *via* corresponding S$_N$Ar reactions (Scheme 2). Compound **1a** proved to be inert towards trimethylsilyl cyanide both at r.t. and at reflux in nitrobenzene, yet the treatment of *N*-oxides **1a-c** with potassium cyanide in DMSO afforded the target heterocycles **2a-c**, representing the first examples of previously not described 4-cyano substituted pyrimidine *N*-oxides.



Scheme 2. Synthesis of the starting 4-cyanopyrimidine *N*-oxides.

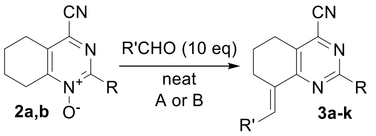
Heterocycle **2a** was investigated in the reaction with benzaldehyde under basic or acidic catalysis. The use of NaOH led to complete decomposition, and the Lewis acid was employed instead. In the presence of ZnBr$_2$, product **3a** was formed *via* condensation employing the methylene group accompanied by the deoxygenation of *N*-oxide; moreover, a small amount (4%) of the double condensation product **4** was obtained (Scheme 3). The configuration of the resulting double bond in **3a** was assigned by NMR ^{1}H NOE-experiments. For comparison, 4-cyanotetrahydroquinazoline **5** was obtained *via* the reduction of **2a** and proved to be inert under the condensation conditions.



Scheme 3. Reaction of heterocycles **2a** and **5** with benzaldehyde.

The series of heterocycles **3a-k** were obtained in moderate to good yields *via* the reaction of **2a,b** with aromatic or heteroaromatic aldehydes (Table 1). It should be noted that, in contrast to the reaction with 4-aminopyrimidine oxides[5], aldehydes containing EWG were readily involved in the reaction affording compounds **3h,i**. Overall, the condensation with 4-cyanotetrahydroquinazoline *N*-oxides proceeded in good yields, without significant amounts of by-products, according to NMR analysis of the reaction mixtures. When heterocycle **2b** bearing an ethyl substituent in position 2 was used as starting material, the reaction afforded only product **3b**, which was formed *via* the condensation employing the methylene group of the cyclohexane ring. Compound **2c** (Scheme 2), without the annelated cyclohexane ring, was inert under the developed reaction conditions.

Table 1. Condensation of heterocycles **2a,b** with aromatic aldehydes.



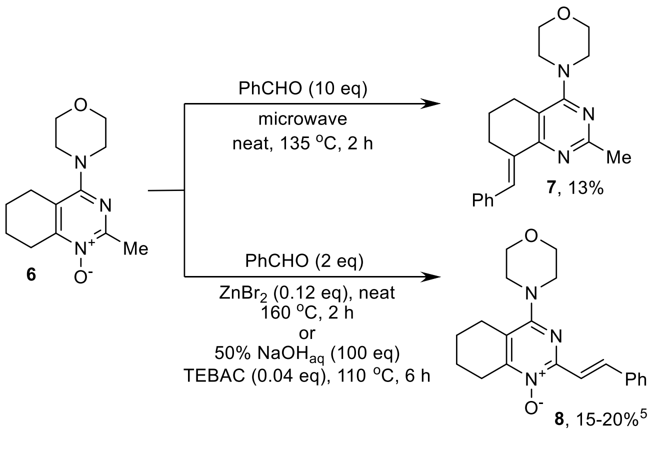
A: ZnBr$_2$ (0.12 eq), 135 °C, 24 h; B: microwave, 135 °C, 2 h

Product	R	R’	Yield **3** (%)[a]
3a	Me	Ph	65 (A); 70 (B)
3b	Et	Ph	58 (A); 67 (B)
3c	Me	2,6-Me$_2$-C$_6$H$_3$	61 (A)
3d	Me	4-OMe-C$_6$H$_4$	61 (A)
3e	Me	4-OEt-C$_6$H$_4$	54 (A)
3f	Me	3,4,5-(OMe)$_3$-C$_6$H$_4$	64 (A)
3g	Me	4-(CH=CHPh)-C$_6$H$_4$	43 (A)
3h	Me	4-NO$_2$-C$_6$H$_4$	70 (A)
3i	Me	4-F-C$_6$H$_4$	57 (A)
3j	Me	5-methylfur-2-yl	66 (A)
3k	Me	thien-2-yl	50 (A)

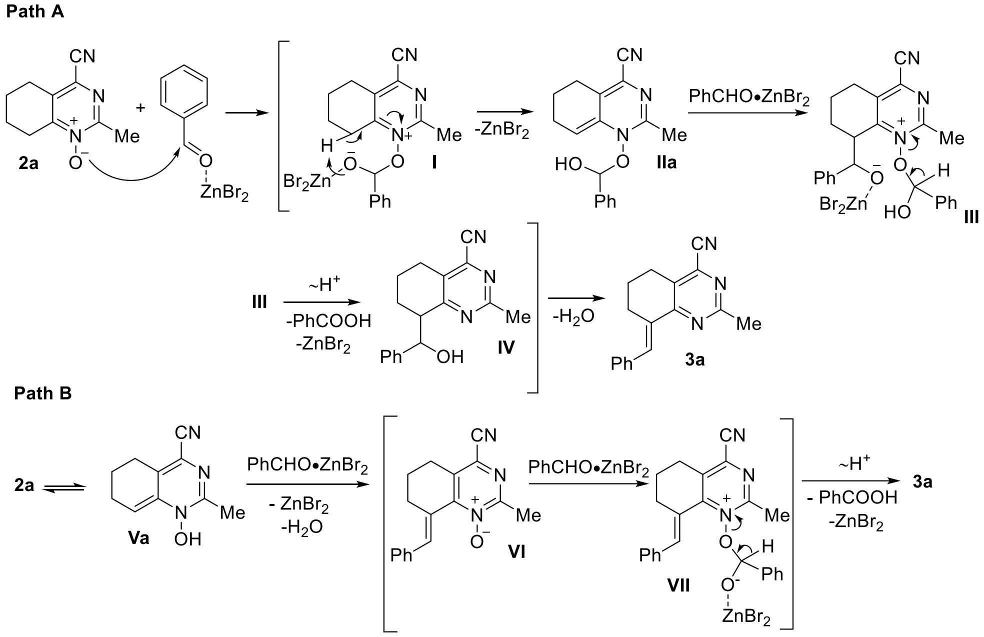
[a] Isolated yield

Microwave irradiation was also probed for the synthesis of compounds **3a,b** and gratifyingly represented a good alternative for the catalytic conditions (Table 1). Besides improving the yields, it also allowed for the condensation to proceed without a catalyst, reducing the reaction time, and simplifying the preparative procedure.

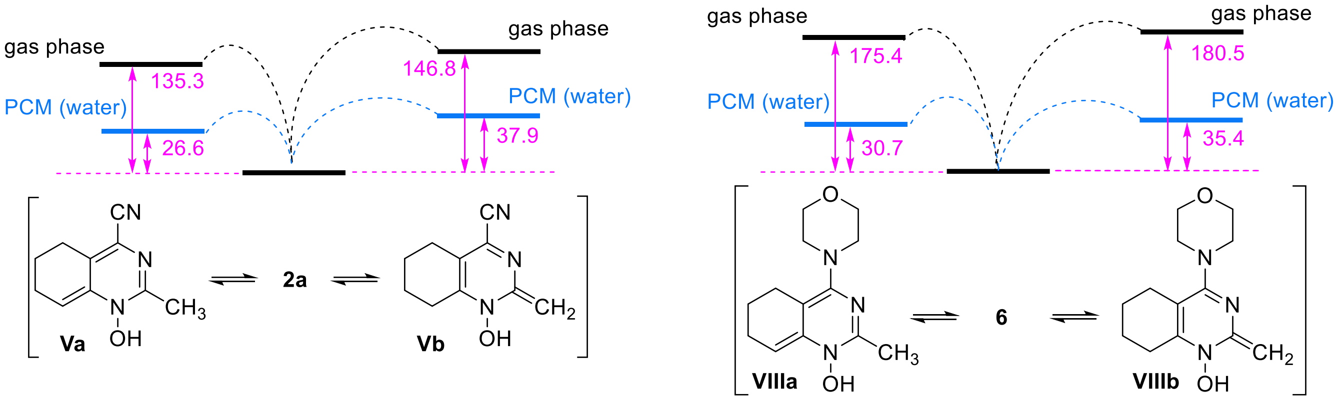
Hence, microwave irradiation was investigated as an alternative to the acid or basic catalysis utilised for the previously described[5] condensation of 4-aminotetrahydroquinazoline *N*- oxide **6** with benzaldehyde.



Scheme 4. Condensation of 4-aminotetrahydroquinazoline *N*-oxide **6** with benzaldehyde.



Scheme 5. Proposed mechanism for the condensation-reduction process.



Scheme 6. Equilibrium between the tautomeric forms of 2-methyltetrahydroquinazoline *N*-oxides (energies are given in kcal/mol).

Unexpectedly, the direction of the process was changed: the methylene group was involved in the condensation to give exclusively the condensation-reduction product **7** instead of compound **8**, which was formed under the catalytic conditions (Scheme 4).

Two possible pathways for the formation of **3a** in the presence of $ZnBr_2$ are given in Scheme 5. The principal steps of this process are (i) the reduction of the *N*-oxide group *via* nucleophilic addition to the carbonyl group (giving **I** or **VII**), followed by deacylation; and (ii) the condensation of tetrahydroquinazoline in the tautomeric form **IIa** or **Va** with benzaldehyde by the assistance of a Lewis acid.

The hypothesis that the benzaldehyde acts as a reducing agent is supported by the presence of benzoic acid in the reaction mixture, in ratio close to equimolar with the product **3a**. It is unclear in which step the deoxygenation takes place; either alongside (Scheme 5, Path A) or after the condensation (Scheme 5, Path B). However, it is certain that the reduction does not occur *before* the condensation because the deoxygenated heterocycle **5** (Scheme 3) is inert towards benzaldehyde under the reaction conditions. The scheme requires two equivalents of aldehyde for the reaction to proceed, and in practice at least a five-fold excess of the carbonyl component is necessary to obtain a good yield of the condensation product. There are no literature analogues for a similar reduction of pyridimine *N*-oxides, but it has been observed that deoxygenation may occur as a rare by-process in the reactions of pyridine *N*-oxides with carbonyl compounds under acidic conditions.[8]

As for the condensation step, it should be noted that the described direction of the reaction of **2a,b** and **6** with benzaldehyde is quite unexpected, and represents the first example of the condensation of polyalkyl substituted pyrimidine, employing a methylene group in the presence of an inert methyl group.[9] Previously, only acceptor-substituted methylene groups have been described to participate in the condensations in the presence of CH_3 group as an alternative.[10] Such an experimental outcome is reminiscent of the two competing pathways of aldol condensation in methyl-alkyl ketones, where under basic conditions the methyl-derived enolate predominates, giving a kinetic product, while under acidic catalysis, the thermodynamic product is formed from the more substituted enol. In our case, the more reactive 4-cyanotetrahydroquinazoline *N*-oxide **2a** readily gives the thermodynamic product **3a** under both acidic and microwave conditions (basic conditions are not applicable). However, more inert 4-amino derivative **6** gives kinetic product **8** under basic or acidic conditions, and only microwave irradiation activates the system enough to shift the reaction path to the formation of methylene-derived compound **7**. Unfortunately, it is impossible to evaluate the kinetic parameters of the proton transfer steps using DFT calculations. However, regarding the thermodynamics, we offer the following.

DFT calculations using the Gaussian 09 package[11] show that species **Va** and **VIIIa**, which lost a proton from the cyclohexyl moiety, are lower in energy than species **Vb** and **VIIIb**, which lost a proton from the methyl group, accounting for the observed reactivity (Scheme 6, ZPE-corrected B3LYP/6-311+G(d,p) relative energies in kcal/mol are shown). Intermediate **IIa** (Scheme 5) is also predicted to favour the alternative species by 11.9 (gas phase) to 12.9 kcal/mol (PCM, water; see ESI). For the cyano substituted intermediates, the gaps between the **a** and **b** tautomeric forms are significantly higher than that of the 4-amino substituted ones; to some extent, this correlates with the unchanged direction for the condensation of 4-cyanotetrahydroquinazoline *N*-oxides under different conditions. The inertness of compound **2c**, containing only a methyl group which could participate in the condensation, also evidences that a loss of a proton from the methyl group is a high-energy process.

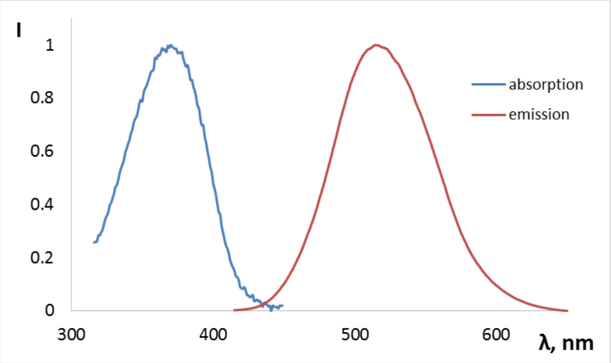


Figure 1. Normalized absorption and emission spectra of **3f** in CH_2Cl_2 solution, c = 1.0 × 10^{-5} M, r.t.

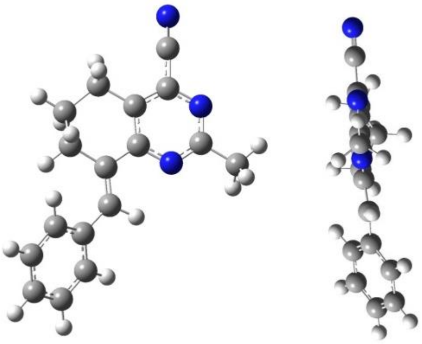


Figure 2. Molecular structure of **3a** according to DFT calculation (B3LYP 6-311+G(d,p)).

For comparison the energies of the compound **3a** and its tautomer are given in SI.

Taking into account that the products of the condensation-reduction step represent previously not described conjugated π-systems, we studied the photophysical properties of condensation products **3a-j** (Fig. 1, S1-2, Table S1). The styryl derivatives **3a-j** revealed absorption maxima at 324–399 nm. Compounds **3a,b,i** revealed weak fluorescence (λ^{max}_{em} 426–432 nm) while the insertion of electron-donating groups (**3d-f,j**) or an additional styryl moiety (**3g**) led to the increase of quantum yields and the batofluoric shift of emission maxima (λ^{max}_{em} 464–518 nm). When the phenyl ring contained a nitro group (**3h**) or the substituents in *ortho*-position (**3c**), the complete quenching of fluorescence was observed. The visible fluorescence in the blue-green region and large Stokes shifts (4600–7700 cm^{-1}), presumably, is an indication of ICT in the organic fluorophores. Low quantum yields (<1.5%) should be due to the lack of effective conjugation in a distorted structure, where the aromatic and heteroaromatic rings lay in different planes (Fig. 2).

Due to 8-(arylidene)tetrahydroquinazoline representing a known structural motif in compounds with anticancer activity,[12] we carried out a brief screening on the activity of synthesized heterocycles towards two human cancer cells lines (see ESI). Compound **3f** showed cytotoxic activity against both cancer cell line, IC_{50} values being 17 µM (colon carcinoma HCT-116) and 35 µM (human lung carcinoma A549). Taking into account the possibility to transform the cyano group into a variety of pharmacophores, the synthesized heterocycles are of interest for further functionalization in the search for promising candidates for anticancer agents.

3. Conclusion

To conclude, it was found that the condensation of 2-methyltetrahydroquinazoline *N*-oxides and aldehydes could be directed by the substituents' electronic nature and reaction conditions. The insertion of an electron-withdrawing cyano group at position 4 of the heterocycle or the use of microwave irradiation, in the case of 4-aminotetrahydroquinazoline *N*-oxide, shifted the reaction pathway from the previously described condensation employing the methyl group to condensation with the cyclohexane ring accompanied by the simultaneous deoxygenation of the *N*-oxide. Such a reaction represents a peculiar example when both structure and conditions controll the reactivity of an unsymmetrical methylene component in the condensation with carbonyl compounds. Furthermore, this reaction represents a preparative approach to previously unknown pyrimidine-containing conjugated molecules that may reveal promising biological activity.

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