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Acetylene-free synthesis of vinyloxy pyridine and quinoline

Abdelrahman Hamdi [a], Amany S. Mostafa [a], Cedric Nana Watat [b], Mathieu Y. Laurent [b], Kawther Ben Ayed [b], Khalid B. Selim [a,*], Gilles Dujardin [b,*]

[a] Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt
[b] Université du Maine, IMMM-UMR 6283 CNRS, MSO Team, Faculté des Sciences, 72085 Le Mans Cedex 9, France

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ABSTRACT

Copper-catalyzed vinylation of 2- and 4-hydroxy pyridine and quinoline affords exclusively *N*-vinylation products. However, vinyl ethers of 4-hydroxy pyridine and quinoline can be prepared *via* a three-step sequence involving copper-catalyzed C-O cross coupling reaction of the corresponding *N*-heteroaryl bromides with ethylene glycol, chlorination of the terminal alcohol, and dehydrohalogenation of the β-chloro ethers. Although not efficient in 2-hydroxy series, this method can be conveniently applied to the preparation of various aza-aryl vinyl ethers in moderate to good overall yields.

Aryl vinyl ethers are promising key intermediates in a wide variety of reactions (e.g. cyclopropanation,[1] cycloaddition,[2] and metathesis processes[3]) as well as in the production of new polymeric materials[4] and biologically active molecules.[5] The synthesis of phenyl vinyl ethers is well documented either through one step vinylation or multistep protocols.[6] Among the former methods is the base-catalyzed reaction of phenols with acetylene which has wide scope but requires severe conditions (strong base, high pressure and temperature) and specific apparatus.[7] More practically, the utilization of iridium-based catalyst $(Ir(cod)Cl)_2$ allows vinyl transfer to phenols from vinyl acetate under thermal conditions in high yield.[8] *O*-Vinylation of alcohols conveniently occurred by several procedures of metal-based vinyl transfer, involving a vinyl ether as vinyl source. However, these procedures are reported to be inefficient (Pd^{II})[9] or poorly efficient (Au^{I}/Ag^{II}, Hg^{II})[10,11] when applied to phenol substrates. Interestingly, several copper-based cross-coupling reactions have been reported to proceed efficiently under mild basic conditions between phenols and different types of vinyl donors: vinyl halides (CuCl/acac, Cs_2CO_3, reflux),[12] trivinylcyclotriboroxanes ($Cu(OAc)_2$, Cs_2CO_3, rt),[13] or tetravinyl stannane ($Cu(OAc)_2$, O_2, rt).[14] On the other hand, an alternative and indirect way for preparing phenyl vinyl ethers relies on the base-mediated β-elimination of 2-bromo aryl ethers[15] or the oxidative β-elimination of 2-arylseleno aryl ethers,[16] whereas no reports regarded the regiocontrolled elimination from an unsymmetrical acetal[17] containing an aryloxy moiety.

While the preparation of phenol-derived vinyl ethers has been extensively studied, the preparation of aza-aryl vinyl ethers has been far less developed. To our knowledge, the *O*-vinylation of hydroxy aza-aromatic compounds by a direct vinylation transfer method is limited to two examples of 3-hydroxypyridines under copper-mediated conditions involving: (i) vinyl iodide, which allowed for *O*-vinylation of 3-hydroxy-6-methyl-pyridine in 51% yield,[18] (ii) trivinylcyclotriboroxane, which allowed for *O*-vinylation of 3-hydroxy-5-acetate-pyridine in 25% yield.[19] Importantly, the application of the Cu^{II}/O_2-procedure employing tetravinyl stannane was shown to exclusively lead to *N*-vinylated products in the case of 4-hydroxypyridine (Scheme 1, eq. 1) and 2-hydroxyquinoline,[14] both subjected to tautomerism with the pyridone form. As a consequence of these features, the only method available for the synthesis of 4-vinyloxy pyridines (and of the corresponding benzopyridine analogs) is the *O*-vinylation using the Reppe chemistry, a method that was extensively developed by the Russian group at Irkutsk Institute,[20] and which employs high pressure of acetylene and heavy metal salts.[21]

In connection with our research program on the development of 1,3-dipolar cycloaddition reaction between vinyl ethers and *C*-carboxynitrones,[22] we needed to prepare several *N*-aza-aryl vinyl ethers as dipolarophiles. We present in this letter our efforts to identify a general acetylene-free method, able to implement a vinyloxy group to pyridine or (iso)quinoline nucleus, especially at the γ-position.

* Corresponding authors.
E-mail addresses: khbselim@mans.edu.eg (K.B. Selim), gilles.dujardin@univ-lemans.fr (G. Dujardin).

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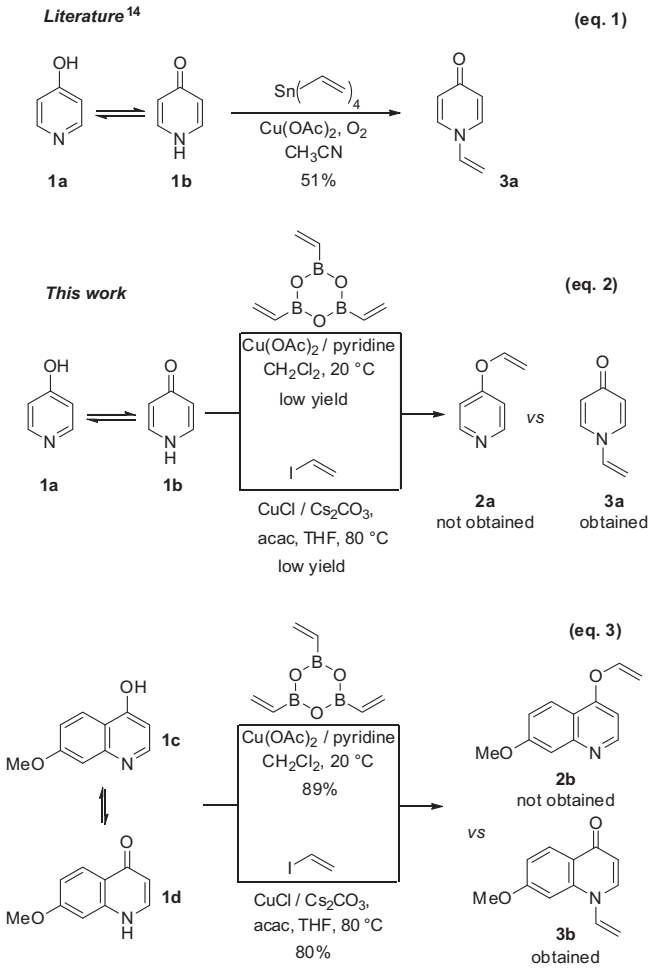
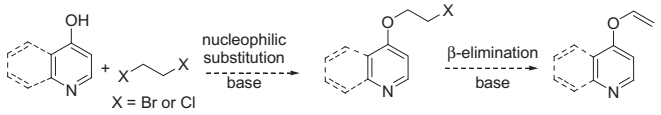


Scheme 1. Direct *N*-vinylation *vs* *O*-vinylation of 4-hydroxypyridine (**1a**) and 7-methoxy-4-hydroxyquinoline (**1c**).

We thus started our study with 4-hydroxypyridine (**1a**) as a model substrate, with the aim to prepare 4-(vinyloxy)pyridine (**2a**). However, owing to the weak solubility of **1a** in some organic solvents (MeCN, THF) and to the volatility of the corresponding vinyl ether **2a** (that limit the yield), we have explored the direct vinylation on 7-methoxy-4-hydroxy quinoline (**1c**) in most cases.

In a preliminary study, all our attempts to use iridium-based catalyst $(Ir(cod)Cl)_2$[8] for such vinyl transfer failed in our hands. Using direct vinylation reaction through copper-mediated vinyl transfer from trivinylcyclotriboroxanes[13] to 4-hydroxypyridine (**1a**) did not give the target vinyl ether **2a** but afforded instead the *N*-vinylated product **3a** (Scheme 1, eq. 2).[23] Applying the same conditions to 7-methoxy-4-hydroxyquinoline (**1c**) led again to the sole *N*-vinylated product **3b** (Scheme 1, eq. 3). Similar results were obtained when **1a** and **1c** were submitted to the conditions described by Ellman and coworkers with vinyl iodide.[18] Therefore, we concluded that the regiochemical outcome in favor of the *N*-vinylation previously reported with **1a**,[14] was not attributed to the conditions used by the authors (O_2 atmosphere, polar solvent) (Scheme 1, eq. 1) but should be considered as a general trend for any copper-based vinyl transfer procedure. This regioselectivity can be attributed (i) to the tautomerism of 4-hydroxypyridine (**1a**) into 4-pyridone (**1b**) and of 7-methoxy-4-hydroxyquinoline (**1c**) into 7-methoxy-4-quinolinone (**1d**), and (ii) to the azaphilicity of copper towards **1b** and **1d**, respectively.

At this stage, we turned our attention to indirect methods. As shown in Scheme 2, the synthesis of **2a** and **2b** could be carried

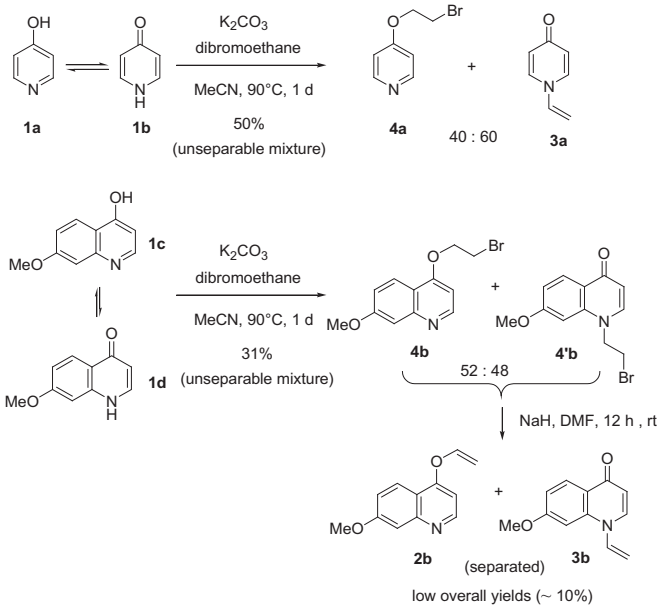


Scheme 2. Proposal of indirect *O*-vinylation *via* *O*-alkylation.

out by indirect vinylation of **1a** and **1c** through *O*-nucleophilic substitution with 1,2-dihaloethane to furnish 4-(2-haloethoxy)pyridine/quinoline which would undergo β-elimination reaction under basic conditions.

For the alkylation step, we have considered the conditions described by Harrowfield's group on 2,6-dicarboalkoxy-4-hydroxypyridine, which used excess dibromoethane and potassium carbonate in refluxing acetonitrile to afford the *O*-alkylated compound in good yield.[24] However, even after optimization of these reaction conditions, the competition between *O*- and *N*-alkylation was found to remain a problematic issue in order to give **2a** or **2b** as a sole product in a good yield after dehalogenation step (Scheme 3). Indeed, in the case of **1a**, the *O*-alkylated product **4a** was obtained in an unseparable mixture (40:60) with the *N*-vinyl product **3a**, which resulted from the competitive *N*-alkylation and subsequent *in situ* dehydrobromination under basic thermal conditions.[25] In the case of **1c**, **3b** was produced in minor amount and the main by-product was the *N*-bromoethyl compound **4′b**.[25] Treatment of the unseparable mixture **4b**/**4′b**/**3b** by NaH in DMF led to the *O*- and *N*-vinyl products **2b** and **3b** in low overall yield (~10%) for the two steps.

To overcome this problem, we finally decided to use 4-halopyridine instead of **1a** as a starting material based on the work of Liljefors's group[26] who reported the mono dechloro-vinyloxylation of 3,5-dichloropyridine by a three-step sequence: (i) mono nucleophilic substitution with ethylene glycol, (ii) chlorination of the terminal alcohol with thionyl chloride, (iii) β-elimination of the 2-chloro ether with potassium hydroxide. The yield of the first step was not given and the 3-chloro-5-(vinyloxy)pyridine was obtained in 11% yield for the last two steps. The copper-catalyzed coupling of ethylene glycol with 3-bromopyridine (**5d**) was recently described in high yield by Chae and co-workers.[27] Therefore, we



Scheme 3. Attempts of indirect vinylation of **1a** and **1c** *via* *O*-alkylation.