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Acetylene-free synthesis of vinyloxy pyridine and quinoline

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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.

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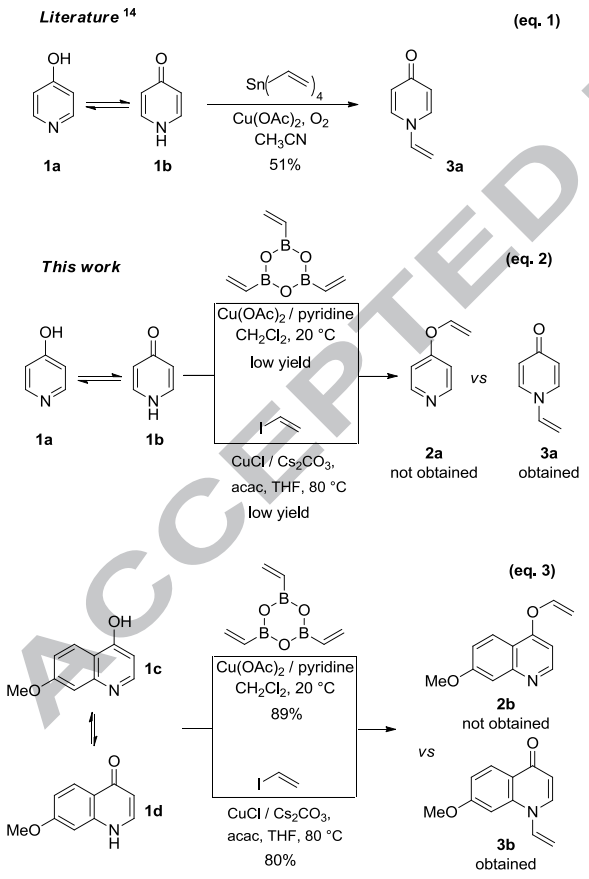
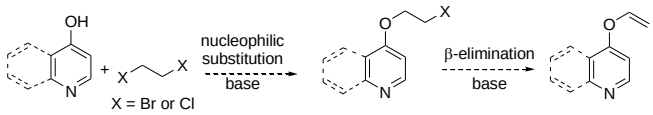
We thus started our study with 4-hydroxypyridine (**1a**) as a model substrate, with the aim to prepare 4-(vinyloxy)pyridine (**2a**). However, owing to the weak solubility of **1a** in some organic solvents (MeCN, THF) and to the volatility of the corresponding vinyl ether **2a** (that limit the yield), 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 4-hydroxyquinoline (**1c**) into 4-quinolinone (**1d**), and (ii) to the azaphilicity of copper towards **1b** and **1d**, respectively.



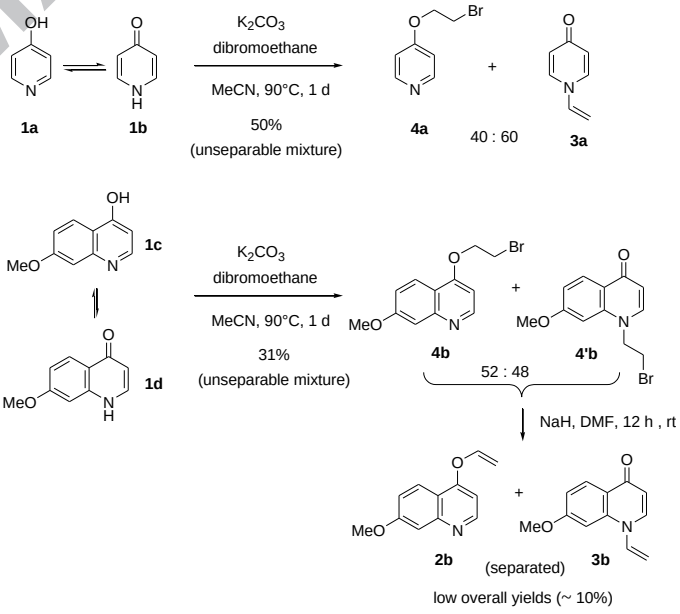
Scheme 1. Direct *N*-vinylation *vs O*-vinylation of 4-hydroxypyridine (**1a**) and 7-methoxy-4-hydroxyquinoline (**1c**).

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



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

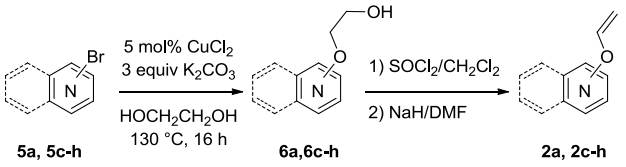
For the alkylation step, we have considered the conditions described by Harrowfield's group on 2,6-dicarboalkoxy-4-hydroxypyridine, which used excess dibromoethane and potassium carbonate in refluxing acetonitrile to afford the *O*-alkylated compound in good yield.[24] However, even after optimization 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.

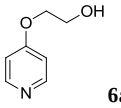
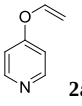
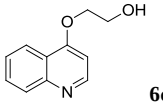
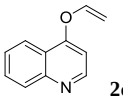
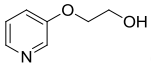
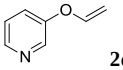
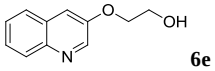
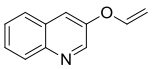
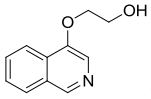
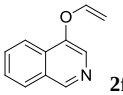
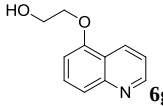
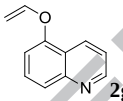
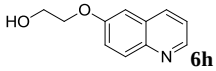
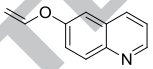


Scheme 3. Attempts of indirect vinylation of **1a** and **1c** *via O*-alkylation.

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

Table 1. 3-Step synthesis of *N*-heteroaryl vinyl ethers *via* Cu-catalyzed C–O coupling of bromides with ethylene glycol, β-chlorination and β-elimination reactions.



Entry	6	Yield	2	Yield
1	 **6a**	47%	 **2a**	50%
2	 **6c**	65%	 **2c**	68%
3	 **6d**	79%	 **2d**	31%
4	 **6e**	93%	 **2e**	61%
5	 **6f**	92%	 **2f**	65%
6	 **6g**	85%	 **2g**	75%
7	 **6h**	85%	 **2h**	67%

and co-workers.[27] Therefore, we chose to use 4-bromopyridine (**5a**) for the C-O cross coupling reaction with ethylene glycol under the catalytic effect of the Cu^{II} salt in the presence of K_2CO_3.

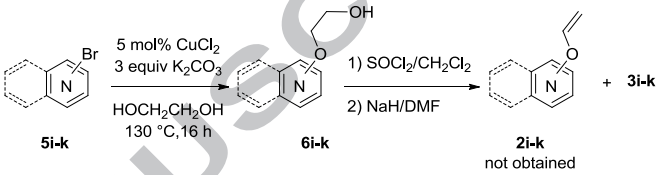
Fortunately, using Chea's conditions[27] (5 mol% $CuCl_2$, 3.0 equiv. K_2CO_3, 130 °C, 16 h), **6a** was obtained in moderate isolated yield (47%, Table 1, entry 1). The coupled product was easily chlorinated by $SOCl_2$ in CH_2Cl_2 under refluxing condition to give 4-(2-chloroethoxy)pyridine in quantitative yield which is pure enough to go to the next step without further purification. β-Elimination was smoothly carried out using 3.5 equiv. of NaH in anhydrous DMF under heating for 18 h to give the desired vinyl ether **2a** in 50% yield.

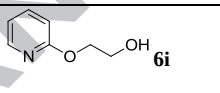
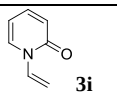
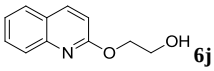
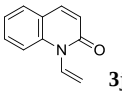
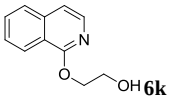
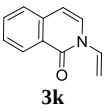
We then applied this 3-step procedure to various *N*-heteroaryl bromides **5c-k** possessing monocyclic and bicyclic rings with one nitrogen atom at different positions (Tables 1 and 2).

4-Bromoquinoline (**5c**) was converted to its respective coupled alcohol **6c** and then to the corresponding vinyl ether **2c** in good yield in both steps (Table 1, entry 2). This protocol was successfully applied to 3 examples of β-bromopyridine derivatives **5d-f** for the synthesis of pyridinyl and (iso)quinolinyl vinyl ethers **2d-f** in 25–60% yield for the three steps (Table 1, entries 3–5). It is noteworthy that the low yield of **2a** and **2d** is due to the high volatility of these ethers during vacuum evaporation process. Satisfied results were observed with 5- and 6-bromoquinolines (**5g** and **5h**) to give **2g** and **2h** (Table 1, entries 6,7).

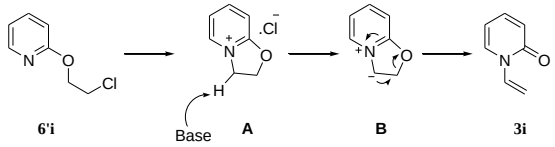
In contrast to these positive results, the present 3-step *O*-vinylation method was unsuccessful in the case of *α*-bromo pyridine derivatives **5i-k**. Indeed, applying the same conditions to 2-bromopyridine (**5i**) led to the formation of *N*-vinyl-2-pyridone (**3i**) (Table 2, entry 1). The same intriguing regiochemical outcome was observed when starting from 2-bromoquinoline (**5j**), and from 1-bromoisoquinoline (**5k**) (Table 2, entries 2, 3).

Table 2. *N*-Vinylation of α-bromo-*N*-heteroaromatics *via* 3-step method.



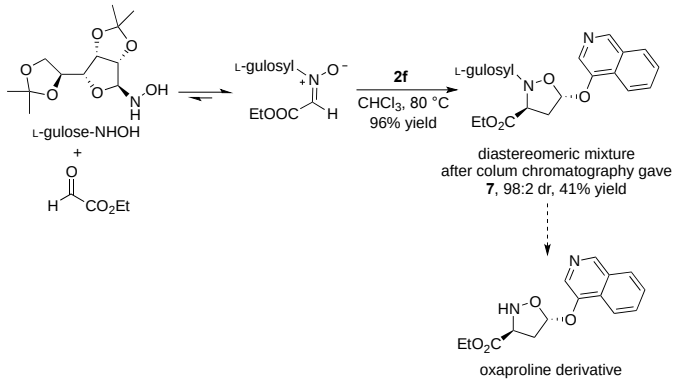
Entry	6	Yield	3	Yield
1	 **6i**	96%	 **3i**	63%
2	 **6j**	61%	 **3j**	24%
3	 **6k**	76%	 **3k**	75%

The copper-catalyzed coupling step clearly gave the *O*-alkylated compounds **6i-k** and this is confirmed by comparison of the ^{1}H NMR data of **6i** with the reported one of 2-hydroxyethoxypyridine[28] and *N*-hydroxyethylpyridone.[29] *O*-Alkylated pyridine **6i** is characterized with a typical deshielded proton at position 6 with a chemical shift of 8.12 ppm in comparison with a chemical shift of 7.56 ppm of the same proton in *N*-hydroxyethylpyridone. The formation of the *N*-vinyl compounds **3i-k** results therefore from an unexpected pathway occurring under the elimination conditions in the last step. Hypothesis on the possible mechanism of this "*O* to *N* migration" can involve a bicyclic pyridinium intermediate **A** (Scheme 4) obtained after neutralization and internal nucleophilic displacement. Further abstraction of the more acidic pseudo-benzylic proton gives intermediate **B** that evolves to **3i** by elimination.



Scheme 4. Proposed mechanism of *O*- to *N*- vinyl migration.

To show the importance of the prepared aza-aryl vinyl ethers **2**, unoptimized 1,3-dipolar cycloaddition reaction was performed between **2f** and the chiral nitrone formed *in situ* from reaction of L-gulose hydroxylamine[30] and ethyl glyoxalate (Scheme 5). The cycloadduct **7** was obtained as a mixture of 4 diastereomers in 96% yield, which gave a single stereoisomer (dr 98:2) in 41% yield after column chromatography. The relative and absolute configurations of **7** were tentatively assigned by analogy with adducts of known configuration[22c] obtained from D-mannosyl nitrone. Removal of the chiral auxiliary will be the next step to give enantiomerically pure isoxazolidines equipped with both an ester function and an aza-aryloxy side-chain as 5-aryloxy oxaproline unit, ready for use in our ingoing project.



Scheme 5. 1,3-DC reaction of chiral nitrone with vinyl ether **2f**.

In conclusion, a 3-step synthesis of vinyl ethers derived from *N*-heteroaromatic bromides was developed through a sequential Cu-catalyzed C-O coupling, chlorination and elimination process. Although not general, this reaction pattern allows a facile synthesis of *N*-heteroaryl vinyl ethers, including those derived from 4-hydroxypyridine and 4-hydroxyquinoline which are unavailable compounds by acetylene-free methods.

Acknowledgments

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Supplementary Material

Supplementary material is available for all experimental procedures and characterization data of compounds **2a-h**, **3a**,**b**,**i-k**, **4b**, **4'b**, **6a**,**c-k** and chlorinated intermediates **6'a**,**c-k**.

References and notes

1. (a) Maligres, P. E.; Waters, M. M.; Lee, J.; Reamer, R. A.; Askin, D.; Ashwood, M. S.; Cameron, M. *J. Org. Chem*. **2002**, *67*, 1093–1101. (b) Wenkert, E.; Alonso, M. E.; Buckwalter, B. L.; Sanchez, E. L. *J. Am. Chem. Soc*. **1983**, *105*, 2021–2029.
2. (a) Martin, J. G.; Hill, R. K. *Chem. Rev*. **1961**, *61*, 537–562. (b) Pindur, U.; Gundula, L.; Otto, C. *Chem. Rev*. **1993**, *93*, 741–761. (c) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost B. M.; Fleming I., Eds.; Pergamon: Oxford, **1991**; Vol. 5, Part 4.1, pp 315. (d) Nguyen, T. B.; Martel, A.; Gaulon, C.; Dhal, R.; Dujardin, G. *Org. Prep. Proc. Int.* **2010**, *42*, 387–431.
3. Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029–4031.
4. Kojima, K.; Sawamoto, M.; Higashimura, T. *Macromolecules* **1989**, *22*, 1552–1557.
5. Gopal, D.; Rajagopalan, Z. *Tetrahedron Lett*. **1987**, *28*, 5327–5330.
6. Winternheimer, D. J.; Shade, R. E.; Merlic, C. A. *Synthesis* **2010**, *15*, 2497–2511.
7. (a) Shostakovsky, M. F.; Bogdanova, A, V. *J. Gen. Chem.* **1947**, *17*, 565-574; **1950**, *20*, 1315. (b) Reppe, W. *Ann*. **1956**, *601*, 84–111.
8. (a) Okimoto, Y.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2002**, *124*, 1590–1591. (b) Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *Org. Synth.* **2005**, *82*, 55–58.
9. Bosch, M.; Schlaf, M. *J. Org. Chem.* **2003**, *68*, 5225–5227.
10. Nakamura, A.; Tokunaga, M. *Tetrahedron Lett.* **2008**, *49*, 3729–3732.
11. (a) Adelman, R. L. *US Patent* **1951** 2579411 19511218. (b) Watanabe, W.H.; Conlon, L. E. *J. Amer. Chem. Soc.* **1957**, *79*, 2828–2833.
12. (a) Wan, Z.; Jones, C. D.; Koenig, T. M.; Pu, Y. J.; Mitchell, D. *Tetrahedron Lett.* **2003**, *49*, 8257–8259. (b) Taillefer, M.; Ouali, A.; Renard, B.; Spindler, J.-F. *Chem. Eur. J.* **2006**, *12*, 5301–5313. (c) Ouali, A.; Laurent, R.; Caminade, A.-M.; Majoral, J.-P.; Taillefer, M. *J. Am. Chem. Soc.* **2006**, *128*, 15990–15991.
13. McKinley, N. F.; O'Shea, D. F. *J. Org. Chem.* **2004**, *69*, 5087–5092.
14. Blouin, M.; Frenette, R. *J. Org. Chem.* **2001**, *66*, 9043–9045.
15. (a) Nerdel, F.; Buddrus, J.; Brodowski, W.; Hentschel, P.; Klamann, D.; Weyerstahl, P. *Justus Liebigs Ann. Chem.* **1967**, *710*, 36-58. (b) Mizuno, K.; Kimura, Y.; Otsuji, Y. *Synthesis* **1979**, *9*, 688-689.
16. (a) Fu, G-Y.;Yu, L-M.;Mao, X-C.; Wu, D. *J. Chem. Res*. **2008**, 597–599. (b) Zhang, J-L., Sheng, S-R.; Lin, S-Y. *J. Chem. Res.* **2009**, 287–289. (c) Yu, L-M.; Tang, N.; Sheng, S.;Chen, R.; Liu, X.; Cai, M.; *Chin. J. Chem.* **2012**, *30*, 1027–1030.
17. Dujardin, G.; Rossignol, S.; Brown, E. *Tetrahedron Lett.*, **1995**, *36*, 1653–1656.
18. Yotphan, S.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2010**, *12*, 2978–2981.
19. Andrews, M. D. et al., *PCT Int Appl.*, 2012137089, 11-10-2012.
20. (a) Skvortsova, G. G.; Tirina, S. M.; *Khim. Geterotsikl. Soedin*. **1968**, 1132–1133. (b) Skvortsova, G. G.; Tirina, S. M.; Voronov, V. K. *Khim. Geterotsikl.Soedin*. **1971**, 798-800; (c) Shostakoskii, M. F.; Skvortsova, G. G.; Tirina, S. M.; *Khim. Geterotsikl.Soedin*. **1971**, 917–920; (d) Skvortsova, G. G.; Andriyankov, M. A.; Stepanova Z. V.; Kashik T. V.; Ponomareva, S. V.; Kim, D. G. *Khim. Geterotsikl. Soedin*. **1976**, 375.
21. This unique preparation was reported to afford the target *O*-vinyl compounds as sole or main products, combined in this last case with minor *N*-vinyl compounds (42 and 15% yields respectively for 2-hydroxypyridine[20a]).
22. (a) Nguyen, T. B.; Martel, A.; Dhal, R.; Dujardin, G. *Org. Lett*. **2008**, *10*, 4493**–**4496. (b) Nguyen, T. B.; Beauseigneur, A.; Martel, A.; Dhal, R.; Laurent, M. Y.; Dujardin, G. *J. Org. Chem.* **2010**, *75*, 611**–**620. (c) Zhang, X. ; Cividino, P.; Poisson, J.-F.; Shpak-Kraievskyi, P.; Laurent, M. Y.; Martel, A.; Dujardin, G.; Py, S. *Org. Lett.* **2014**, *16*, 1936**–**1939. (d) Ben Ayed, K.; Beauchard, A.; Poisson, J.-F.; Py, S.; Laurent, M. Y.; Martel, A.; Ammar, H.; Abid, S.; Dujardin, G.; *Eur. J. Org. Chem.* **2014**, 2924**–**2932. (e) Shpak-Kraievskyi, P.; Mankou Makaya, A.; Beauchard, A.; Martel, A.; Laurent, M. Y.; Dujardin, G. *Eur. J. Org. Chem.* **2015**, 2924**–**2932.
23. Structures of vinyl ethers obtained in our study (*O*-vinyl *vs N*-vinyl) were unambiguously attributed by comparison of ^{1}H and ^{13}C NMR data with those described by the Russian group cited before[20] for a wide range of *O*-vinyl and *N*-vinyl derivatives of hydroxypyridines and quinolines: (a) Afonin, A. V.; Andriyankova, L. K.; Pertsikov, B. Z.; Voronov, V. K. *Zhur.. Organich. Khim*. **1976**, *11*, 2451–2454; (b) Afonin, A. V.; Andriyankova, L. K.; Pertsikov, B. Z.; Voronov, V. K. *Russ. J. Org. Chem.* **1997**, *33*, 1427–1433. (c) Afonin, A. V.; Ushakov, I. A.; Kuznetsova, S. Yu.; Andriyankova, L. V. *Magn. Reson. Chem.* **2003**, *41*, 557–566 and references cited therein.
24. Froidevaux, P.; Harrowfield, J. M.; Sobolev, A. N. *Inorg. Chem*. **2000**, *39*, 4678–4687.
25. The crude product contained also significant amounts of dimers resulting from the coupling of one equivalent of dibromoethane to two equivalents of the substrate.
26. Nielsen, S. F.; Nielsen, E. O.; Olsen, G. M.; Liljefors, T.; Peters, D. *J. Med. Chem.* **2000**, *43*, 2217–2226.
27. Metal-catalyzed coupling with ethylene glycol (a) Liu, Y.; Park, S. K.; Xiao, Y.; Chae, J. *Org. Biomol. Chem.* **2014**, *12*, 4747–4753. Base-mediated coupling with ethylene glycol (b) Katritzky, A. R.; Murugan, R. *J. Chem. Soc. Perkin Trans II*, **1987**, 1867–1869. (c) Albrecht, B. K. et al. *U. S. Pat. Appl. Publ*. 20150065522 A1.
28. Newkome, G. R.; Nayak, A.; McClure, G. L.; Danesh-Khoshboo, F.; Broussard-Simpson, J. *J. Org. Chem*. **1977**, *42*, 1500–1508.
29. Somekawa, K.; Okuhira, H.; Sendayama, M.; Suishu, T.; Shimo, T. *J. Org. Chem*. **1992**, *57*, 5708–5712.
30. (a) Juarez-Garcia, M. E.; Yu, S.; Bode, J. W. *Tetrahedron* **2010**, *66*, 4841–4853. (b) Pattabiraman, V. R.; Ogunkoya, A. O.; Bode, J. W. *Angew. Chem. Int. Ed*. **2012**, *51*, 5114–5118.

Graphical Abstract

Vinyl ethers of hydroxy pyridine and quinoline, not accessible by direct copper-catalyzed *O*-vinylation, are prepared *via* a three-step sequence from the corresponding *N*-heteroaryl bromides.

Acetylene-free synthesis of vinyloxy pyridine and quinoline

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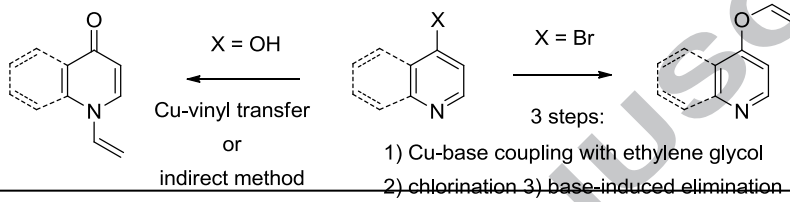
Abdelrahman Hamdi[a], Amany S. Mostafa[a], Cedric Nana Watat[b], Mathieu Y. Laurent[b], Kawther Ben Ayed[b], Khalid B. Selim[a,*] and Gilles Dujardin[b,*]



Acetylene-free synthesis of vinyloxy pyridine and quinoline

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Research highlights

Bullet 1

► State of art reviewed on vinylation methods of hydroxy pyridines / quinolines

Bullet 2

► 2- & 4-Hydroxy pyridines / quinolines : *N*-vinylation with known copper-based methods

Bullet 3

► First synthesis of 4-vinyloxy pyridine & 4-vinyloxy quinoline from bromides