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HAL Id: hal-03010593

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Submitted on 2 Dec 2020

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Dearomatization of a 3-Hydroxypyridine through an unexpected Oxidative Deformylation Process: an Entry to Aza-cyclohexadienones

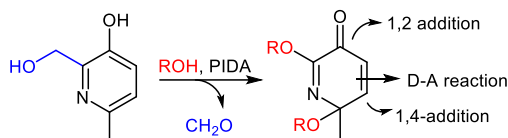
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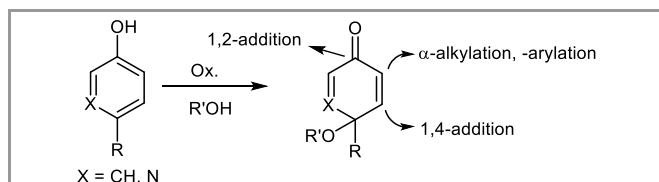


Received:
 Accepted:
 Published online:
 DOI:

Abstract Phenols are well-known precursors of cyclohexadienones, which have found useful widespread applications in organic synthesis. In contrast, their hydroxypyridine counterparts have not been explored yet. An unprecedented oxidative dearomatization of 3-hydroxypyridine involving an unexpected deformylation step, is reported. The chemical reactivity of the subsequent unreported aza-cyclohexadiene-type compound, was also explored.

Key words hydroxypyridine, oxidation, hypervalent iodine reagent, PIDA, aza-cyclohexadienone

The oxidative dearomatization of phenols offers a straightforward entry to a variety of 4-alkoxy-2,5-cyclohexadien-1-ones (also named *p*-quinol ethers) mostly from commercially or readily available starting materials.^{1, 2} This oxidation step notably increases the derivatization ability of phenols, as their cyclohexadienone derivatives can undergo subsequent nucleophilic 1,2 or 1,4 additions,^{3–5} α -alkylations or -arylations,⁶ Diels–Alder reactions,^{7, 8} photochemical ring contractions,⁹ or dienone-phenol rearrangements,^{6, 9} to cite a few (Scheme 1, X = CH).



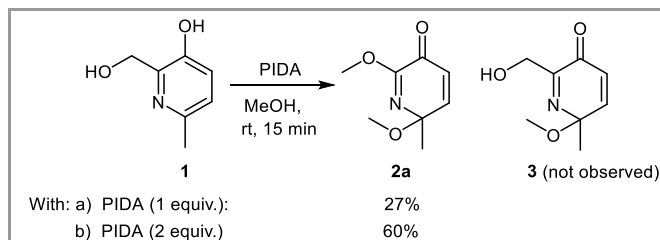
Scheme 1 Oxidative dearomatization of phenols and hydroxypyridines.

Whilst this strategy has extensively been studied and exploited through the expedient synthesis of natural products,^{10–14} on the other hand the oxidative dearomatization of their hydroxypyridine counterparts has not been reported yet, despite promising synthesis applications (Scheme 1, X = N).^{15–19}

Although the oxidative homocoupling of 3-hydroxypyridines was recently described,²⁰ the competitive oxidation of the pyridine nitrogen and hydroxyl group is a plausible issue²¹ which may have prevented further dearomatization studies and reports on hydroxypyridine systems.

Herein, as a proof-of-concept study, we report the unexpected formation of a 5-aza-2,5-cyclohexadien-1-one *via* an oxidative deformylation/1,3-alkoxy rearrangement process of commercially available 2,6-lutidine- α ,2,3-diol **1**. The chemical reactivity of the corresponding unreported dearomatized product was investigated.

Hypervalent iodine reagents, such as phenyliodine(III) diacetate (PIDA) $\text{PhI}(\text{OAc})_2$, are reagents of choice to promote phenols oxidation under mild and environmentally friendly conditions.^{22–27} Accordingly, the oxidation of commercially available 2,6-lutidine- α ,2,3-diol **1** was investigated under standard alcoholic conditions with the aim to provide the corresponding aza-*p*-quinol ether **3**. To this end, the oxidation was carried out in the presence of 1 equivalent of PIDA in MeOH at room temperature for 15 minutes (Scheme 2).



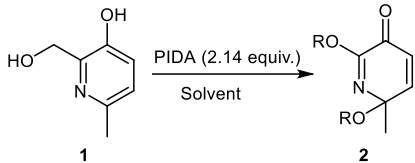
Scheme 2 Oxidative hydroxypyridine dearomatization

Surprisingly, the expected aza-*p*-quinol ether **3** was not formed, but instead, compound **2a** along with unreacted starting hydroxypyridine **1** in a ~2:3 ratio was observed by ¹H NMR analysis of the crude reaction mixture. Purification of the crude

mixture using flash column chromatography provided compound **2a** in 27% yield, whose structure was confirmed by spectroscopic and spectrometric data. Unexpectedly, the hydroxy-methyl group in **1** was replaced by a methoxy substituent in **2a**. Compound **2a** being two oxidation states higher than the parent compound **1**, 2.14 equivalents of PIDA were used in order to drive the reaction to completion and improve the overall efficiency of this transformation. As expected, under these optimized conditions, compound **2a** was isolated in 60% yield (Scheme 2b).

Following these preliminary results, the reaction was conducted in other low-boiling-point alcoholic solvents, and obtained results are presented in Table 1.²⁸

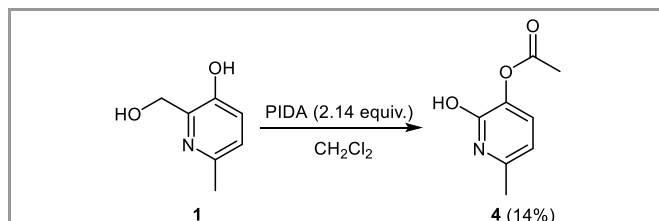
Table 1 Solvent-scope of the reaction



Entry	Solvent	R	Cmpds	Yield (%)
1	MeOH	Me	2a	60
2	EtOH	Et	2b	43
3	<i>i</i> PrOH	<i>i</i> Pr	2c	traces
4	TFE	CF ₂ CH ₃	2d	11
5	HFIP	(CF ₃) ₂ CH	2e	-

^a Reaction conditions: PIDA (2.14 equiv.), solvent, rt, 15 min.

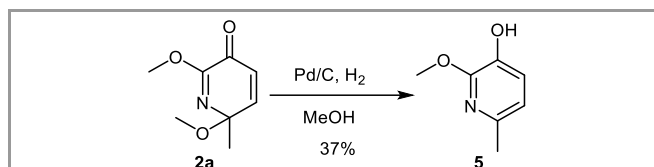
The yields of dearomatized 3-hydroxypyridines decreased as the bulkiness of the solvent increased. In fact, a moderate yield of 43% of **2b** was obtained in ethanol (entry 2), whereas only traces of product **2c** could be identified in *isopropanol* (entry 3). Besides, the use of electron-deficient alcohols such as 2,2,2-trifluoroethanol (TFE) markedly decreased the efficiency of the transformation with the isolation of 11% of dearomatized compound **2d**, while product **2b** was obtained in 43% in non-fluorinated analog, ethanol (entry 2 versus 4). Not surprisingly, no product was isolated when the reaction was conducted in 1,1,1,3,3,3-hexa-fluoroisopropanol (HFIP), a bulky and non-nucleophilic fluorinated alcohol. The reaction was also explored in the non-protic and chemically inert solvent, dichloromethane, in order to investigate whether the acetic acid released in the course of the reaction could trap the oxidized intermediates as alcoholic solvents did (Scheme 3).



Scheme 3 Oxidation of compound **1** in CH₂Cl₂

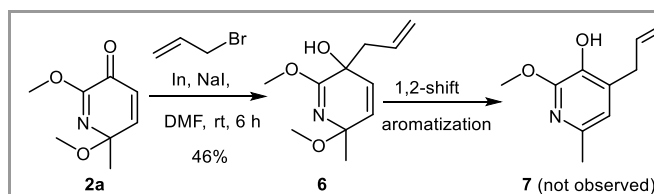
Under these conditions, only the deformedylated mono-oxidized compound **4** was obtained, albeit in a low 14% yield. In contrast to alcoholic solvents, the formation of this compound would involve a mono-oxidation process.

No example of such unfused aza-*p*-quinol ether systems having been reported yet, their reactivity was investigated using the representative compound **2a**. First, the direct reductive aromatization of **2a** to provide an electron-rich pyridine, was carried out by the action of Pd/C mediated hydrogenation, which delivered compound **5** in a low 37% yield. This volatile material possessed a pleasant fragrance (Scheme 4).



Scheme 4 Direct aromatization of aza-*p*-quinol ether **2a**

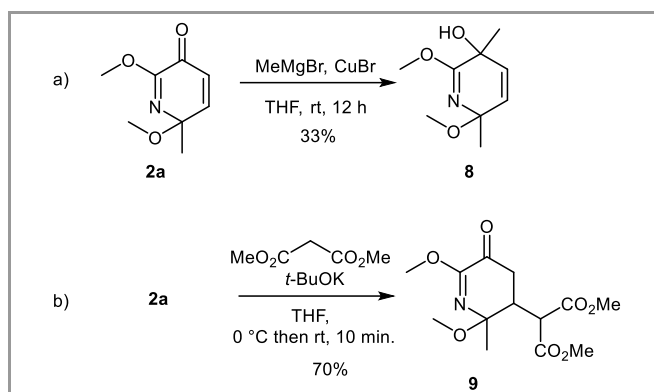
Then, compound **2a** was subject to 1,2-nucleophilic addition conditions. In view of the operational simplicity associated with the use of non toxic allyl indium reagents, compound **2a** was treated with indium (In) in the presence of allyl bromide to produce the corresponding allylic alcohol **6** in 46% yield as a mixture of inseparable diastereoisomers in a 1:1 ratio (Scheme 5).



Scheme 5 Allylindium-mediated 1,2-alkylation of **2a**

It is worth mentioning that, in contrast to what was reported with *p*-quinol ether systems,²⁹ no further anionic vinylogous semipinacol type rearrangement of **6** into **7** was observed in the present case.

The conjugate addition of *in situ* generated organocuprate reagent to the α,β-unsaturated system of **2a** was not observed (Scheme 6a). In fact, the reaction of methyl magnesium bromide in the presence of copper (I) bromide favored the formation of carbonyl addition product **8**, which was isolated in 33% yield as a ~3:1 mixture of inseparable isomers.

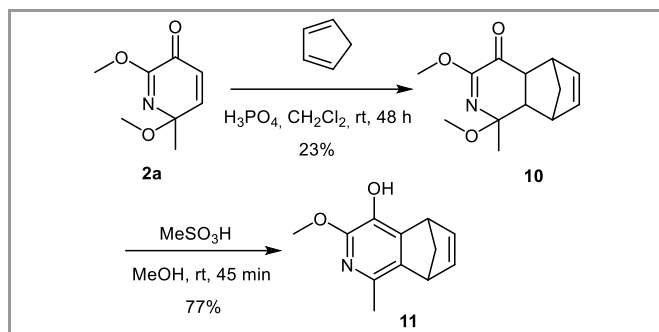


Scheme 6 Investigation of conjugate additions with dimethyl malonate

Thus, the reaction was next investigated with the Michael donor dimethyl malonate, which enabled this time the formation

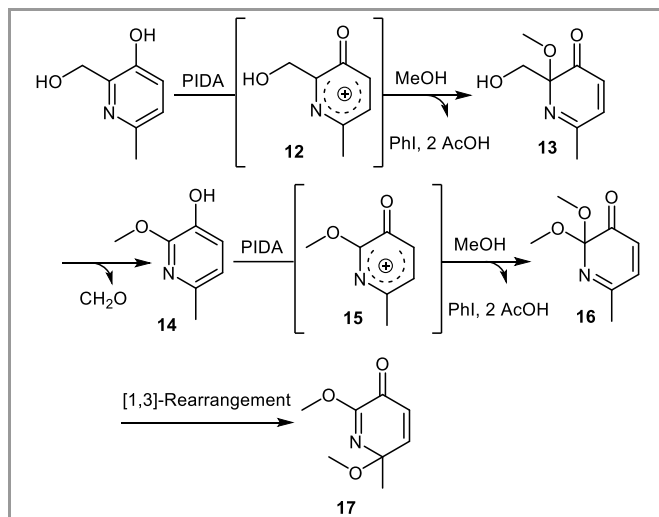
of the 1,4-addition product **9**, isolated in 70% yield as a single diastereoisomer (Scheme 6b).

Next, the reactivity of aza-*p*-quinol ether as a diene in a Diels-Alder reaction was investigated. To this end, compound **2a** was reacted with freshly distilled cyclopentadiene in the presence of phosphoric acid as the catalyst (Scheme 7).³⁰ The corresponding cycloadduct **10** was formed in 23% isolated yield. This low yield may partly be ascribed to the formation of fused bicyclic pyridine **11**, which can be formed cleanly in 77% yield from isolated compound **10**, in the presence of methanesulfonic acid in methanol.



Scheme 7 Diels-Alder reaction of aza-*p*-quinol ether **2a**

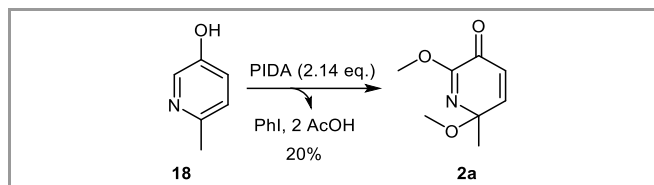
Finally, a plausible reaction mechanism for the oxidative deformylation process of 3-hydroxypyridine **1** can be proposed in Scheme 8. The oxidation of the aromatic hydroxyl function promoted by the first equivalent of hypervalent iodine reagent would lead to the formation of the phenoxonium intermediate **12**, which would subsequently be trapped by methanol to furnish the transient intermediate **13**.



Scheme 8 Proposed reaction mechanism

Then, compound **13** would undergo a retroaldolization-driven aromatization process to provide the 2-methoxy-3-hydroxy-pyridine **14**. This reaction would occur with the concomitant release of formaldehyde. It is worth noting that the putative intermediate **14** has not been isolated, even in the presence of sub-stoichiometric amounts of PIDA, presumably because this electron-rich pyridine is more readily oxidized than the starting 3-hydroxypyridine **1**. Then, the second equivalent of PIDA would oxidize **14** to generate the aza-*o*-quinone monoketal

16 through the regioselective addition of methanol to the methoxy-stabilized carbocation at the α -position of the carbonyl of the intermediate **15**.³¹ This compound would be converted into enone **17** through a 1,3-methoxy rearrangement process, similarly to what was reported with *o*-quinone monoketals under Lewis acid catalysis.³² Accordingly, the presence of the temporary hydroxy-methyl group at the position 2 of the pyridine ring system of **1** would play an important role in favoring the methanol addition to occur at this position due to the enhanced stability of this tertiary carbocation. To investigate this point, the 3-hydroxypyridine **18**, unsubstituted at position 2, was oxidized under identical optimized PIDA conditions (Scheme 9).



Scheme 9 Oxidation of 2-unsubstituted-3-hydroxypyridine **18**

This reaction provided **2a** in only 20% yield, instead of 60% when the position 2 was functionalized by the hydroxy-methyl substituent. This result shows that the presence of a removable hydroxy-methyl group, was required to ensure effective formation of aza-*p*-quinol ethers **2**.

In conclusion, the first oxidative dearomatization of a hydroxypyridine system leading to the formation of aza-*p*-quinol ethers, is reported. This reaction proceeded under mild conditions, and involved a deformylation/1,3-migration process favoring the formation of aza-*p*-quinol ethers. Subsequent modifications of this particular cyclohexadienone through 1,2-, 1,4-addition, and Diels-Alder reaction were investigated.

Funding Information

This work was funded by the Centre National de la Recherche Scientifique (CNRS), INSA Rouen, Normandie Rouen University, Région Normandie and the Labex SynOrg (ANR-11-LABX-0029).

Acknowledgment

We thank Albert Marcual (CNRS) for HRMS analyses.

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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Typical procedure
To a stirred solution of 2,6-lutidine-  2,3-diol (100 mg, 0.719 mmol) in 1.5 ml of solvent (MeOH, EtOH or TFE), phenyliodine(III) diacetate (PIDA) PhI(OAc)₂ (500 mg, 1.538 mmol, 2.14 equiv) in 1.5 ml of solvent (MeOH, EtOH or TFE) was added dropwise (using pipette) under air atmosphere at room temperature. After stirring for 15 min, the reaction which came yellow and was completed by TLC analysis, was concentrated under reduced pressure. The crude product was purified by flash-column chromatography on silica gel using cyclohexane and ethyl acetate (7:3) as eluent to give a yellow oil product (73 mg, 60%).
¹H NMR (300 MHz, CDCl₃)    (ppm) = 7.34 (d, *J* = 10.30 Hz, 1H), 6.44 (d, *J* = 10.12 Hz, 1H), 3.87 (s, 3H), 3.21 (s, 3H), 1.55 (s, 3H). ¹³C NMR (75 MHz, CDCl₃)    = 171.1, 159.0, 155.4, 129.0, 86.2, 53.8, 51.7, 28.7. IR (cm⁻¹)    = 2990, 2948, 2829, 1750, 1696, 1646, 1443, 1328, 1204. HRMS (ESI): *m/z* Calculated. For C₈H₁₂NO₃:170.0817, found: 170.0813.
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