Synthesis of 3,3-Spirocyclic 2-Phosphonoindolines via a Dearomative Addition of Phosphonyl Radicals to Indoles

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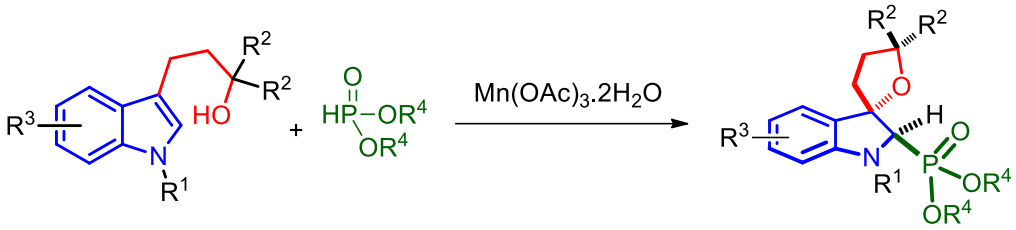
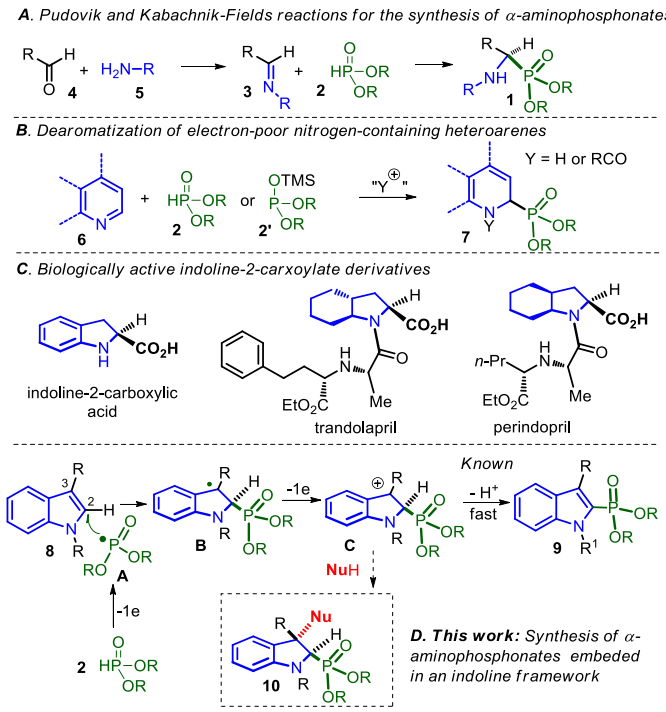
Supporting Information Placeholder



ABSTRACT: The diastereoselective synthesis of α-aminophosphonates derivatives embedded in spirocyclic indolines is reported. The present method proceeds via the dearomative addition of phosphonyl radicals at the C2-position of the indole nucleus in oxidative conditions followed by the intramolecular trapping of the resulting carbocation before rearomatization. *trans*-3,3-Spirocyclic-2-phosphono-indolines were thus obtained.

Dearomatization reactions of indoles[1] allow to generate three dimensional indoline structures which are of high interest to explore the chemical space and discover compounds of therapeutic potential.[2] This field has sparked our interest for few years.[3] We now wish to merge indole dearomatization with phosphorous chemistry and in particular the synthesis of alpha-amino-phosphonate derivatives **1** since the latters display a wide range of biological activities in the field of human health and crop-protection.[4] alpha-Amino-phosphonic acids are notably considered as bioisosters of the corresponding alpha-amino-carboxylic acids. The tetrahedral geometry of the phosphorous allows alpha-amino-phosphonate derivatives to mimic transition states involved in biological processes which gives unique biological properties to these compounds. Classically, alpha-amino-phosphonates are obtained through the nucleophilic addition of phosphites **2** to imines **3** via the Pudovik reaction or the Kabachnik-Fields reaction from amine **4** and aldehyde **5** (Scheme 1, A).[5] In few cases, the dearomative addition of phosphorous-containing nucleophiles to nitrogen-containing electron-poor heteroarenes **6** such as pyridines or quinolines has been reported towards cyclic amino-phosphonates **7** (Scheme 1, B).[6] In line with our research program towards indolines, we were interested to access original alpha-amino-phosphonates embedded in an indoline scaffold **10**.[7] These compounds would be analogues of indoline-2-carboxylic acid derivatives which are relevant in human medicine (Scheme 1, C).[8] For instance perindopril and trandolapril are commercial drugs to treat blood pressure.

Scheme 1. Radical-mediated dearomative synthesis of 2-phosphono-indolines.

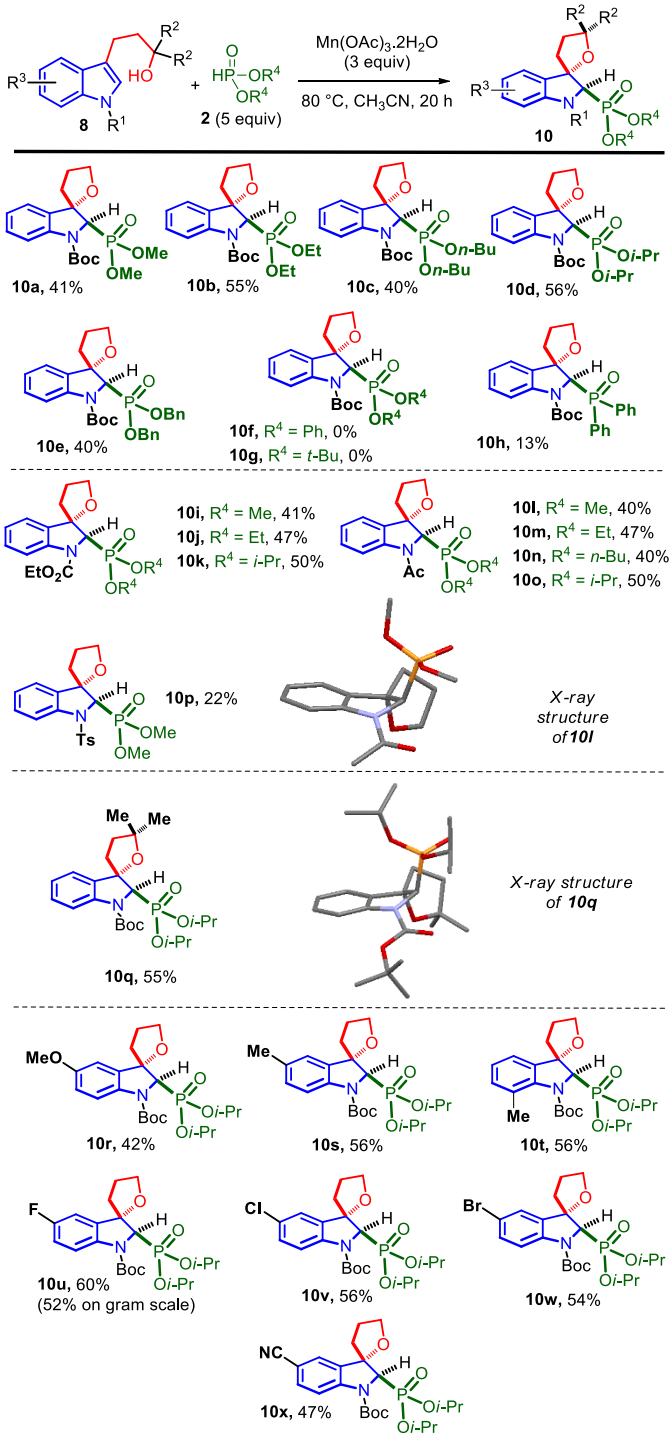


The deployment of a dearomative intermolecular addition of a phosphonyl radical **A**, resulting from oxidation of **2**, to the C2-position of indole nucleus **8** seems to be an appropriate strategy related to previous radical-mediated dearomatization of indoles.[9-11] Notably, we described the dearomative synthesis of 2-trifluromethyl-3,3-spiroindoline from the Langlois' reagent (sodium trifluoromethylsulfinate).[10]

Indeed, difunctionalizations of alkenes via the addition of a phosphoryl radical to the double bond are well described.[12] In the other hand, additions of phosphorus-centred radicals to indoles are known and lead to C-H functionalized products **9** after rearomatization of the indole nucleus from carbocation **C** resulting from the oxidation of the formed radical **B** at the C3 position.[13,14] After the addition of the radical to the indole at the C2 position, the proton in alpha of the introduced phosphorous atom is believed to be particularly acidic and therefore its elimination should be very fast. Consequently, the interception of the resulting carbocation by a nucleophile before the elimination of this proton and rearomatization of the indole should be especially challenging and is the subject of the present study.

In order to favor the trapping of carbocation **C** over the elimination of the proton, we decided to use an intramolecular nucleophile that would lead to 3,3-spiroindolines which are a framework encountered in a large number of biologically relevant molecules.[15] We evaluated several oxidants which are known to oxidize phosphites into phosphonyl radicals. No reaction was observed with $K_2S_2O_8$ while $AgNO_3$ with $K_2S_2O_8$ resulted in the formation of a mixture of unidentified products. The outcome was similar with CAN, which was the optimal oxidant of our previous dearomative trifluoromethylation of indoles.[10] Only manganese triacetate[16] proved to be a competent oxidant to produce the desired 3,3-spirocyclic-2-phosphono-indolines **10** as the major product and in each cases, only the *trans* diastereoisomer was observed. The optimal conditions required to perform the reaction at 80 °C in acetonitrile during 20 h with 3 equivalents of $Mn(OAc)_3$ and 5 equivalents of phosphites. The scope of this reaction was then investigated (Scheme 2). The nature of the phosphonyl radical that could be added to N-Boc-3-(3-hydroxypropyl)-indole **8a** was first evaluated. We were pleased to note, that dimethyl, diethyl and di-nbutyl phosphites could be employed to synthesize **10a-c** in reasonable yields (41%, 55% and 40%). Remarkably, di-isopropyl phosphite was the optimal phosphorous-containing reagent and delivered 56% of **10d**. In general less than 15% of rearomatized compounds **9** were observed.[17] Dibenzyl phosphite was also competent to produce **10e** in 40% yield, while more hindered di-tertbutyl and diphenyl phosphites could not allow to isolate the dearomatized product **10f,g**. Interestingly, when we employed diphenyl phosphine oxide instead of a phosphite, indoline **10h** was obtained in a 13% yield. The influence of the electron-withdrawing substituent on the indole nitrogen, beside the Boc group (**10a-h**) was then scrutinized. Indeed, the ethoxycarbonyl group allow to introduce methyl, ethyl and isopropyl phosphonates in **10i-k** (40%, 47%, 50%). This dearomatization also permits the acetyl group to lead to 2-phosphono-indolines **10l-o** from dimethyl, diethyl, di-nbutyl and di-isopropyl phosphites in respectively 41%, 47%, 40% and 50%. The *trans* relationship between the phosphorous and the oxygen was ascertained through X-ray crystallographic analysis of compound **10l**. A moderate yield of 22% of **10p** was obtained in presence of the tosyl substituent. The use of a tertiary alcohol in lieu of a primary one as an intramolecular nucleophile efficiently gave rise to spirocyclic indoline **10q**, whose *trans* structure was solved by X-ray diffraction of a crystal.[18]

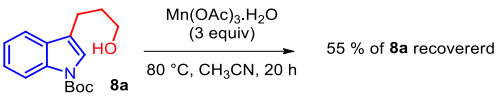
Scheme 2. Synthesis of 3,3-spirocyclic-2-phosphino-indolines.



The substitution of the benzene part of the indole was the last point to be studied. The reaction tolerates electron-donating groups such as methoxy at C5 (**10r**, 42%) and methyl at C5 (**10s**, 56%) and C7 (**10t**, 56%). Halogens could be present during this dearomatization process: 5-fluoro, 5-chloro and 5-bromo spirocyclic indolines **10u-w** were obtained in 60%, 56% and 54% yield. The electron-withdrawing cyano group at the C5 position led to phosphono-indoline **10x** in 47% yield.

As a control experiment, we heated starting indole **8a** in presence of 3 equivalents of manganese triacetate during 20 h, without any phosphites and we were able to recover 55% of **8a** (Scheme 3). The relative stability of **8a** towards the oxidant seems to exclude a mechanism in which the indole is oxidized into a radical cation followed by the nucleophilic attack of the phosphite and the mechanism depicted in Scheme 1 seems the more plausible.[19]

Scheme 3. Radical-mediated dearomative synthesis of 2-phosphono-indolines.



In conclusion, the oxidative coupling between adequately substituted indoles and phosphites in presence of manganese triactate results in the diastereoselective synthesis of *trans*-3,3-spirocyclic-2-phosphono-indolines via the dearomative addition of a phosphoryl radical to the indole nucleus. Remarkably, the carbocation generated at the C3-position of the indole nucleus could be intramolecularly intercepted in a *trans* fashion before rearomatization of the indole.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization and NMR spectra of new compounds, copies of NMR spectra. (PDF)

X-ray crystallography analysis data. (cif)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no conflict of interest.

ACKNOWLEDGMENT

We thank Prof. Isabelle Chataigner, Dr. Michael De Paolis (Univ. Rouen) and Dr. Xavier Moreau (Univ. Versailles) for helpful discussions. DR thanks the Ministère de l'Enseignement Supérieur, de la Recherche et de l'Innovation (MESRI) for a PhD fellowship. We also gratefully acknowledge the ANR (ANR-17-CE07-0050; "ArDCo"), Université Paris Sud and the CNRS for financial support.

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(17) In general, we also observed products arising from the addition of radical **A** onto the benzene part of compounds **9**.

(18) Replacing the terminal alcohol on the C3-side chain by a tosyl amide (NHTs) or using di-N,N'-Ac-tryptamine only led to rearomatized products of type **9** after the addition of the phosphonyl radical.

(19) To operate in the absence of an intramolecular nucleophile, we used N-Boc-3-methylindole in the classical reaction conditions of scheme 2 with di-isopropyl phosphite. We observed the formation of compound **9y** as well as products arising from the addition of radical **A** onto the benzene part of compounds **9y** (see footnote 17). We did not observed a Ritter type reaction with the trapping of carbocation **C** by acetonitrile.