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An efficient access to tetrahydropyrrolo[2,1-*a*]isoquinoline derivatives based on phosphoranylidene succinimide

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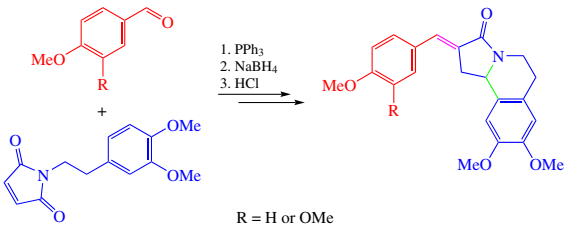
A simple and convenient synthesis of new isoquinolinone derivatives based on *N*-(homoveratryl)succinimide phosphorus ylide and natural aldehydes is suggested. The final formation of the tetrahydropyrrolo[2,1-*a*]isoquinoline framework occurs *via* the Pictet–Spengler cyclization.



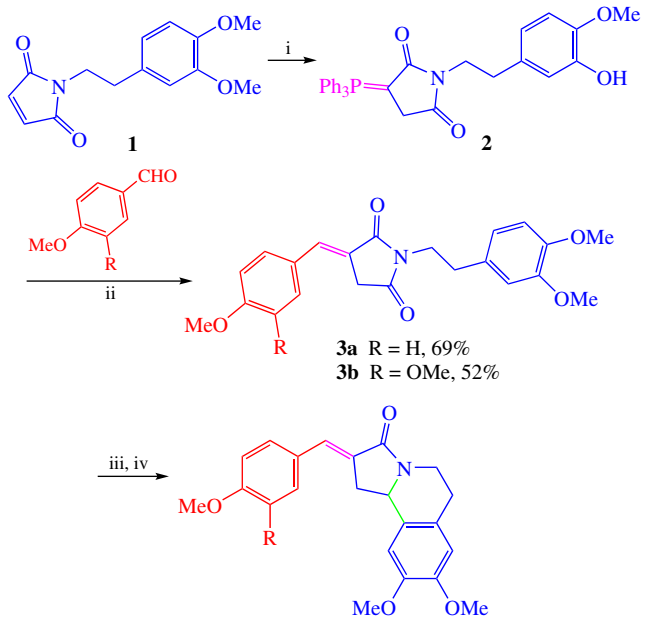
Keywords: isoquinoline, phosphorus ylide, *N*-(homoveratryl)maleimide, alkaloids, homoveratrylamine, tetrahydropyrrolo[2,1-*a*]isoquinoline, Pictet–Spengler reaction.

Naturally occurring isoquinoline alkaloids and their synthesized structural analogues are of pharmaceutical importance[1,2] due to their antitumour,[4–6] anti-inflammatory,[4,7] antidepressant,[4,8] antibacterial and antiviral properties.[9–11] Pyrrolo[2,1-*a*]isoquinoline is found among the most abundant nitrogen-containing heterocycles and forms the basis of natural alkaloids exhibiting a wide range of biological activity.[12]

Crispine and trolline are among the best known representatives of this class of compounds. The crispine alkaloid has long been used in folk medicine for the treatment of colds, stomach aches and rheumatism. It was isolated from an extract of *Carduus crispa* (curled thistle) that exhibits significant cytotoxic activity.[13] Trolline isolated from *Trollius chinensis Bunge* flowers exhibits antibacterial activity against strains of *Staphylococcus aureus*, pneumococcus and Friedlander's bacillus[14] and moderate antiviral activity against influenza A and B viruses. For this reason, the development of new methods for the synthesis of pyrrolo[2,1-*a*]isoquinolines and improvement of known ones have attracted much attention.[15–20] Therefore, the development of a new synthetic approach to unknown isoquinolines for broad pharmacological screening is an urgent task. In this study, we obtained isoquinolinone derivatives that are analogues of pharmacologically important alkaloids, such as crispine A and trolline, contributing a novel scheme for their preparation.

Homoveratrylamine[21,22] and *N*-homoveratrylmaleimide[23–25] **1** were synthesized using methods reported previously. Phosphorane **2** was synthesized by mixing equimolar amounts of triphenylphosphine with *N*-homoveratrylmaleimide **1** in dry acetone (Scheme 1). The Wittig reaction of phosphorane **2** with anisic aldehyde (R = H) in toluene under reflux afforded olefin **3a**. Importantly, the transformation occurs in the same way in the three-component reaction of maleimide **1** with triphenylphosphine and anisic aldehyde. After cooling the reaction mixture, the precipitated imide **3a** was filtered off and used without further purification in the reaction with $NaBH_4$ at 0–5 °C in methanol.[26–28] The subsequent synthesis of isoquinoline **4a** was carried out in methanol under reflux conditions in the presence of a small excess of HCl. The same reaction sequence involving veratric aldehyde (R = MeO) afforded imide **3b** whose intramolecular cyclization gave analogous pyrrolo[2,1-*a*]isoquinoline **4b** (see Scheme 1).

The structure of the resulting compounds was confirmed by IR, ^{1}H NMR, ^{13}C NMR spectroscopy, as well as by HSQC, HMBC, COSY, and NOESY 2D NMR experiments. For compound **4a**, the formation of an isoquinoline ring was confirmed by the disappearance of one keto group at C^6 and the appearance of a



Scheme 1 *Reagents and conditions*: i, PPh_3, acetone, room temperature, 2.5 h; ii, ArCHO, toluene, 110 °C; iii, $NaBH_4$, MeOH, $CHCl_3$, room temperature, 2 h; iv, HCl, MeOH, 65 °C, 3 h.

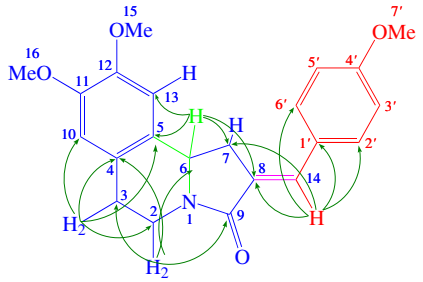
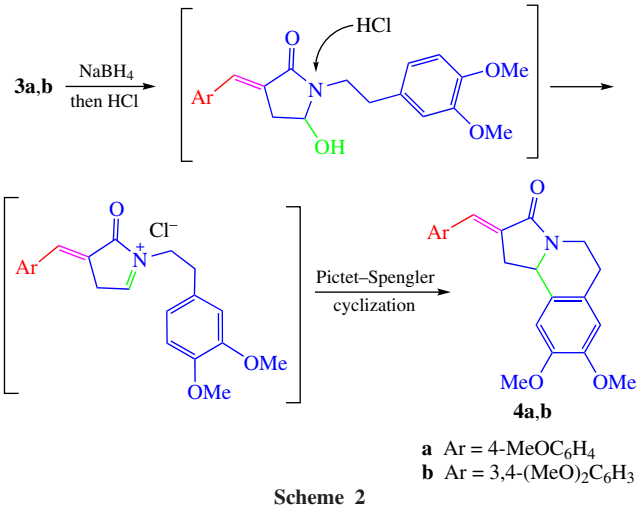


Figure 1 Principal correlations in the $^{1}H–^{13}C$ HMBC spectrum of compound **4a**. Atom numbering given for assignment differs from a systematic one.

methine moiety resonated at δ_C 54.47. We observed a distinct correlation of the proton at C^6 in the $^{1}H–^{13}C$ HMBC mode with carbon atoms of both the imide fragment, C^7 and C^8, and the aromatic ring at C^5 and C^{13} (Figure 1). Note the absence of interaction of the protons at the C^7 and C^{14} carbons in the $^{1}H–^{1}H$ NOESY spectrum, which confirms the formation of only one geometric isomer. Apparently, the cyclization occurs at the C^6 atom of the 3,4-dimethoxyphenyl substituent of homoveratryl moiety which is less sterically hindered than the C^2 one.

In HMBC spectrum of **4a**, cross-peaks for the methylene proton of isoquinoline at C^3 with the carbon atom of the benzene ring at δ_C 111.77 and 125.98 and with the newly formed quaternary carbon at δ_C 128.45, as well as with the neighbouring methylene moiety at δ_C 37.85 were observed. The correlations presented in Figure 1 unambiguously indicate that the double bond remains in the exocyclic position at the C^8 atom and intramolecular cyclization occurs at the carbonyl group distant from the double bond.

At first glance, the formation of isoquinoline **4a** resembles the intramolecular cyclization of acid β-phenylethylamides by the Bischler–Napieralski reaction (see Scheme 1), however we believe that the process may occur through the Pictet–Spengler reaction (Scheme 2).



Scheme 2

In conclusion, we herein presented a simple and efficient technique for the synthesis of new isoquinolinone derivatives available from *N*-(homoveratryl)succinimide phosphorus ylide and natural aldehydes. The suggested approach is very promising for synthesizing a number of new isoquinolinone derivatives that are analogues of biologically active alkaloids such as crispine A and trolline.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.02.036.

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