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An unexpected reaction pathway in the synthesis of the ABCE framework of strychnine-type alkaloids – A multidisciplinary study

Michal Šoral [a, *], Jozef Markus [b], Jana Doháňošová [a], Stanislava Šoralová [c], Dana Dvoranová [d], Andrej Chyba [e], Ján Moncol [f], Dušan Berkeš [b], Tibor Liptaj [a]

[a] Central Laboratories, Faculty of Chemical and Food Technology, Slovak University of Technology in Bratislava, Radlinského 9, SK-81237, Bratislava, Slovak Republic
[b] Institute of Organic Chemistry, Catalysis and Petrochemistry, Faculty of Chemical and Food Technology, Slovak University of Technology in Bratislava, Radlinského 9, SK-81237, Bratislava, Slovak Republic
[c] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Comenius University in Bratislava, Odbojárov 10, SK-83232, Bratislava, Slovak Republic
[d] Institute of Physical Chemistry and Chemical Physics, Faculty of Chemical and Food Technology, Slovak University of Technology in Bratislava, Radlinského 9, SK-81237, Bratislava, Slovak Republic
[e] Analytical Department, Institute of Chemistry, Slovak Academy of Sciences, Dúbravská Cesta 9, SK-84538, Bratislava, Slovak Republic
[f] Institute of Inorganic Chemistry, Technology and Materials, Faculty of Chemical and Food Technology, Slovak University of Technology in Bratislava, Radlinského 9, SK-81237, Bratislava, Slovak Republic

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ABSTRACT

Acid-catalyzed cyclization of spirocyclic 1′-benzyl-2′-(prop-2-en-1-yl)spiro[indole-3,3′-pyrrolidine]-5′-one (**1**) was performed. The pentacyclic product of Povarov-like imino-Diels-Alder reaction was isolated in high yield instead of expected tetracyclic *aza*-Prins intermediate. The unusual exotic alkaloid-type structure of the resulting molecule **2** was unambiguously confirmed by a detailed NMR analysis using a set of 2D NMR spectra including an INADEQUATE experiment. The relative configuration of **2** was predicted from the synthesis mechanism and DFT geometry calculations and independently confirmed using NOESY and residual dipolar coupling (RDC) assisted NMR analysis in stretched crosslinked polystyrene gels. The reversibility of the cycloaddition in aprotic solvents was observed. A new reaction pathway yielding a rare 6-5-5-5 tetracyclic spiroindoline **3** was suggested. The relative configuration within the tetracyclic framework was ultimately proved using Single-crystal X-ray diffraction analysis of compound **4**.

1. Introduction

The 3,3′-pyrrolidinyl-spiroindole unit is a privileged heterocyclic motif that forms the core of a large family of the Aspidosperma and Strychnos alkaloids with strong bioactivity profiles and interesting structural properties. These alkaloids share the same tetracyclic core, known as the Büchís ketone [1,2], from which their complex structures could be elaborated. Only a few studies are devoted to the formation of the cycle E from a spirocyclic ABC derivative [3,4]. In the course of our research of spiroindole derivatives [5] we have tested the known *aza*-Prins protocols [6,7] treating the starting spiroderivative **1** with both Brønsted (trifluoric acid (TFA)) and Lewis (ethylaluminium dichloride ($EtAlCl_2$)) acids. The reaction was straightforward; sole product was isolated in high yield. However, instead of the desired tetracyclic structure, the formation of a complex polyheterocycle **2** was observed (see Scheme 1). We have found that the starting indolenine **1** treated with acid undergoes Povarov-type imino-Diels-Alder cyclization [8–10], and it forms a new heterocyclic structure. Only one precedens was found in the literature on a structurally similar derivative [11]. So we decided to study of this unexpected transformation in detail.

Due to the structure complexity and improbability of **2**, reason dictated that a detailed structural analysis is necessary to avoid speculative structural interpretations. For this purpose, NMR

* Corresponding author.
E-mail addresses: michal.soral@stuba.sk (M. Šoral), jozef.markus@stuba.sk (J. Markus), jana.dohanosova@stuba.sk (J. Doháňošová), stanislava.soralova@gmail.com (S. Šoralová), dana.dvoranova@stuba.sk (D. Dvoranová), andrej.chyba@savba.sk (A. Chyba), jan.moncol@stuba.sk (J. Moncol), dusan.berkes@stuba.sk (D. Berkeš), tibor.liptaj@stuba.sk (T. Liptaj).

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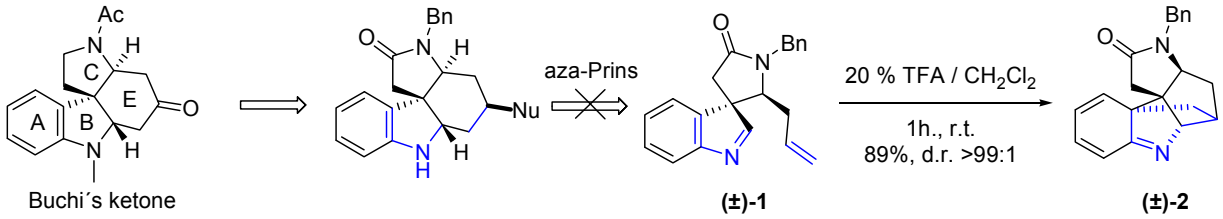

Scheme 1. The originally planned cyclization of **1** and its unexpected outcome.

spectroscopy is the method of choice for its high informational value in structural analysis and usually easy sample preparation. The combined progress in the development of high field NMR spectrometers, coldprobes and sophisticated pulse sequences in the last decade helped to overcome sensitivity and resolution issues resulting from the fundamental principles of NMR. When supported by data from other analytical methods (especially mass spectrometry and infrared spectroscopy), an unambiguous constitutional analysis of organic molecules often becomes a simple task. The NMR-based configurational analysis commonly relies on the examination of NOESY enhancements and *J*-couplings (especially for cyclic or non-saturated fragments in the structure), both being reliable and generally accepted methods. The diversity in the methods of organic synthesis and the elaborate natural processes in living organisms occasionally result in molecules where the analysis of conventional NMR spectra generates only tentative structural proposals (e. g. structural fragments sparse on protons or with five-membered rings).

The desire for additional independent NMR data containing structural information led to the development of weak orienting media for the application of a residual dipolar coupling assisted NMR analysis of small organic molecules. The residual dipolar coupling (RDC) assisted analysis of small molecules had been mostly used in special issues when conventional methods failed to provide unambiguous results [12–14]. Illustrative examples of solved structures using RDCs are demonstrated in Fig. 1 – most of them containing an exotic structural motif [15–17]. Thiele [18] showed a simple possibility of a simultaneous assignment of all diastereotopic CH_2-protons in a molecule of Strychnine using RDCs – as will be demonstrated later in the text, this will be the case in this paper as well.

2. Experimental

The chloroacetyl derivative **6** (Scheme 2) was synthesized according to [4] with a good agreement of NMR data within. The

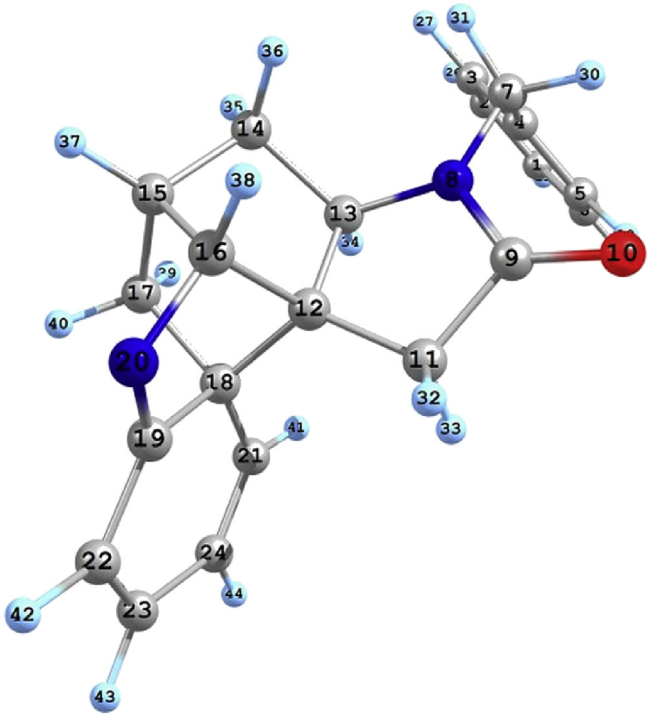

Fig. 2. Calculated structure of **2** by DFT *in vacuo* (colors of atoms: carbon (grey), hydrogen (cyan), nitrogen (blue), oxygen (red)). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

spiroindolenine **1** was recently prepared by AgOTf catalyzed spirocyclization [4]. In our hands a base-mediated spirocyclization using NaH/THF system was more convenient, proceeded with comparable stereoselectivity, and produced crystalline spiroderivative **2** with good yield in gram scale.

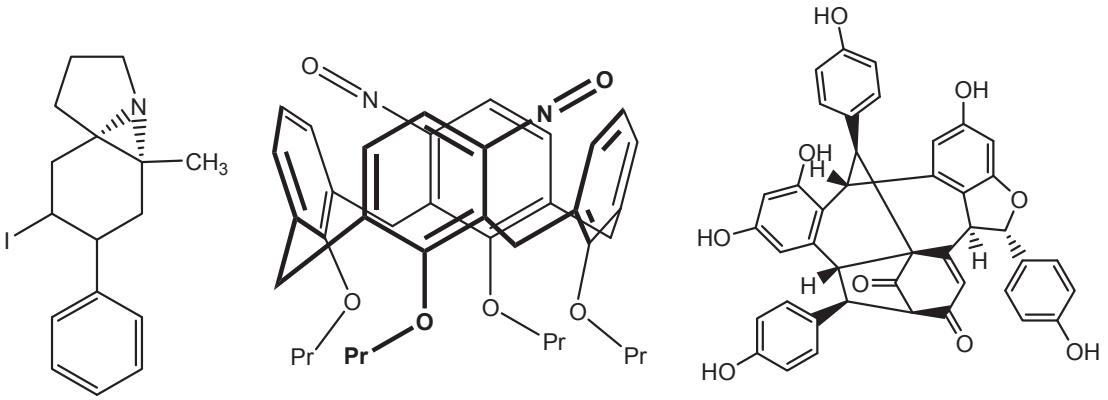

Fig. 1. Examples of molecules whose identity (constitutional, conformational or configurational) was obtained through an RDC assisted structural analysis [15–17].