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Chemistry of pyrrolizidine alkaloids revisited—semi-synthetic microwave and continuous-flow approaches toward *Crotalaria*-alkaloids

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ABSTRACT

Efficient and rapid syntheses of various pyrrolizidine alkaloids via microwave synthetic protocols using monocrotaline from a natural source (*Crotalaria spectabilis*) are reported. Retronecine, hydroxydanaidal, and acetylated hydroxydanaidal (utilized in the chemical communication system of various insect species) were obtained. In addition, a continuous flow hydrogenolysis/hydrogenation approach to directly access platynecine, retronecanol, and desoxyretronecine was realized.

Introduction

Pyrrolizidine alkaloids (PAs)[1,2] are a class of alkaloids scattered in several plant families. Notably, in some *Crotalaria*-species, the seeds can often contain up to 5% dry weight of PAs.[3] Pyrrolizidine alkaloids contain predominantly a pyrrolizidine amino alcohol nucleus (necine base, which can be saturated or possesses a double bond in the 1,2-position, Fig. 1) esterified with branched-chain mono- or di-carboxylic acids containing four to six carbon atoms (necic acid) to give monoesters, non-macrocyclic diesters, or macrocyclic diesters, for example, monocrotaline (Fig. 1, **1**). These alkaloids are considered to be exemplary secondary metabolites that serve as defensive mechanism in the plant–herbivore interactions.[4] PAs with plant origin are accumulated and utilized by various insects either in the defense against predators and parasitoids[4] or in the production of male pheromones.[5] The pyrrolizidine alkaloids are among the most common poisonous compounds found in plants. Of nearly 700 known PAs more than the halves are connected with distinctive hepatotoxic activity.[6] Nevertheless, polyhydroxylated PAs have revealed potential antibacterial, antiviral, antitumor, antidiabetic, immunostimulators, or anti-inflammatory activities.[1d] The necine bases alone can be utilized as natural insecticides.[1f] These small bicyclic ring systems of biological relevance and containing few stereocenters are attractive but demanding targets for synthetic chemists. This has led to many elegant approaches toward their total synthesis.[2] Many pyrrolizidine alkaloids, though isolated in the beginning of the last century, did not succumb to total synthesis until many years later, for example, platynecine, whose first synthesis was achieved by Visconti and Buzek in 1972[7] or the total synthesis of monocrotaline (retronecine as necine base) achieved by Vedejs et al. in 1987.[8] Therefore, a semi-synthetic approach using PAs with natural origin (e.g., monocrotaline from *Crotalaria spectabilis*) is apparently plausible. Monocrotaline can be subjected to various synthetic transformations, based on the adoption of modern synthetic technologies—microwave heating and continuous-flow processing—in order to gain rapid and easy access to various necine bases as

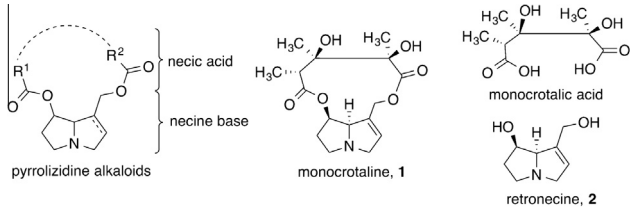

Figure 1. General structure of pyrrolizidine alkaloids with monocrotaline and the corresponding incorporated necic acid and necine base (retronecine).

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starting materials for extended biological studies as well as for forthcoming synthetic efforts.

In microwave promoted chemistry reaction times can be often reduced from hours to minutes by efficient and rapid dielectric heating of the reaction mixture in a sealed vessel to temperatures even above the boiling point of the solvent.[9] On the other side, continuous flow processes—already established in the production of commercial chemicals—are nowadays increasingly implemented in the synthesis of fine chemicals and active pharmaceutical ingredients.[10] In this context, continuous flow hydrogenation technology presents a safe and attractive alternative to batch processing. The utilization of the H-Cube®, a continuous-flow hydrogenation device that incorporates in situ hydrogen generation and prepacked catalyst cartridges, provides a safe and reliable method for performing hydrogenation reactions under pressure.[10] Herein, we describe robust and improved synthetic protocols for the preparation of various pyrrolizidine alkaloids based on monocrotaline with a plant origin as a starting material and involving the implementation of commercially available continuous-flow hydrogenation and microwave heating device.

Results and discussion

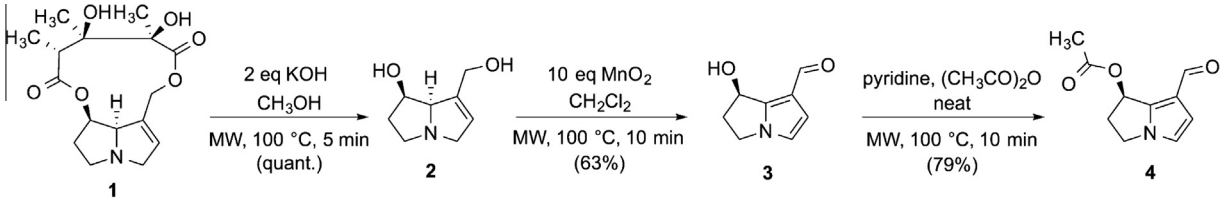
To initiate our studies, monocrotaline **1** in pure form for synthetic applications had to be obtained. The pyrrolizidine alkaloid occurs in several *Crotalaria* species including *Crotalaria spectabilis*. Although highly sophisticated extractive procedures based on supercritical carbon dioxide as a solvent exist,[11] a simple but effective procedure (Soxhlet extraction)[12] proved suitable for our purpose to access alkaloid **1** in feasible amounts (40 g kg^{-1} plant material) with more than 95% purity (NMR analysis). With the monocrotaline at hand a straightforward approach toward retronecine **2** was envisaged. The necic base can be traditionally obtained by a simple hydrolysis of monocrotaline with aqueous NaOH or $Ba(OH)_2$ after refluxing for one hour and extensive acid-base extractive work-up.[13] Using organic bases such as triethylamine or diisopropylethylamine (Hünig's base) in water, acetonitrile or methanol resulted in only trace amounts of product. The low solubility of NaOH and KOH in acetonitrile was found to be the reason for rather sluggish hydrolysis. Using water as a solvent helped to achieve full conversion, however the good water solubility of the product made it difficult to obtain more than 85% of pure retronecine even after multiple extractions. Finally, a methanolic KOH solution (~1.2%) provided the most satisfactory results. Full conversion could be achieved while the overall reaction required only 5 min at 100 °C under microwave heating to provide a quantitative yield of retronecine after solvent removal and chromatographic work-up of the residue (Scheme 1).[14]

Retronecine-PAs acquired during larval and adult feeding on plants are biosynthetically oxidized into hydroxydanaidal (Scheme 1, **3**) which is used as male pheromone in a wide spectrum of adapted *Lepidoptera*-insects.[15] Culvenor et al. explored this oxidative transformation by employing manganese dioxide (MnO_2) at room temperature within 6 h reaction time.[16] Manganese dioxide is a cheap and useful reagent, whose oxidative properties for the mild conversion of the hydroxyl-group into carbonyl functionality have been successfully utilized since the late 1940s.[17] Recently, a microwave protocol has been also demonstrated where the microwave heating greatly enhanced the reaction progress, shortening the reaction time to 1 min.[18] Stimulated by these results, our attention was next focused on the direct microwave oxidation/aromatization of retronecine **2** into hydroxydanaidal **3** using MnO_2 as a mild oxidant. After a short optimization study we have found that full conversion in this process can be achieved in an elevated temperature regime. Employing dichloromethane (CH_2Cl_2) as a solvent high conversion levels could readily be achieved at 100 °C within only 10 min. Fine-tuning of reaction conditions and manganese dioxide stoichiometry ultimately led to the final reaction conditions (10 equiv MnO_2, 100 °C, 10 min) that provided full conversion and a high selectivity for the desired oxidized product **3** (Scheme 1). Isolation of hydroxydanaidal **3** by flash chromatography furnished 63% yield of the pure yellow oil. As a subsequent step, we evaluated the possibility to protect the remaining hydroxyl-moiety in product **3**.

Obtaining acetylated hydroxydanaidal opens new ways to further extend the synthesis in the PAs pheromone series by undisturbed chemical modifications of the aldehyde moiety and the pyrrole ring. Using the previously synthesized hydroxydanaidal as a starting material, optimization experiments quickly delivered optimal conditions for the desired acetylation. Using 11 equiv of pyridine instead of triethylamine as a base and neat acetic acid as a reagent/solvent (neat reaction) instead of combinations of other solvents (acetonitrile, toluene) and acidic acid, clean and complete conversion of the free hydroxyl group was achieved at 100 °C within 10 min, providing a 79% isolated yield of acetylated hydroxydanaidal **4** (Scheme 1). Variation of the optimal reaction temperature/time and/or the reagent stoichiometry led to rather unsatisfactory results.

In a further attempt to extend the synthetic opportunities starting with **1** or **2**, we turned our attention to hydrogenation and hydrogenolysis of the two readily available starting pyrrolizidines (**1** and **2**). For safety and convenience reasons, not requiring a special hydrogenation room and equipment for a batch process, we opted for the employment of a continuous-flow hydrogenation instrument (H-Cube®), able to in situ generate hydrogen and directly apply it in a hydrogenation process.[10] As a starting point in our investigations we evaluated the hydrogenolysis of monocrotaline **1**. As already demonstrated by Adams et al., this type of substrate can be readily hydrogenolyzed over PtO_2,[13,19a,b] Raney-Ni,[19a] or $Pd/SrCO_3$[19c] in a batch mode (e.g., PtO_2, 3 bar of H_2, and acetic acid as a solvent at rt for 5 h)[13] with variable success. Depending on the reaction conditions, mainly on the catalyst/solvent system, two main products can be obtained—desoxyretronecine **5** and/or retronecanol **6** (Table 1).

Our initial flow experiments involved ethanol as the solvent and PtO_2 as the catalyst of choice, available as a pre-packed cartridge (10% w/w). Full conversion was achieved with 0.03 M monocrotaline solution at 60 °C by employing a flow rate of 1 mL min^{-1} (30 bar H_2). The obtained product using these conditions was a 1:1 mixture of desoxyretronecine and retronecanol (Table 1, entry



Scheme 1. Microwave-assisted transformations of monocrotaline into retronecine **2**, hydroxydanaidal **3**, and acetylated hydroxydanaidal **4**.