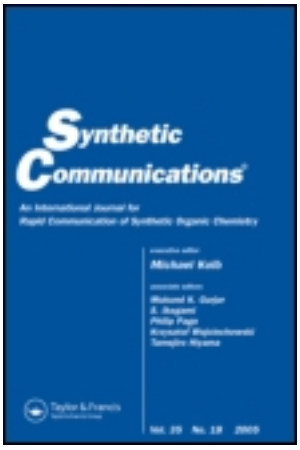

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Facile Synthesis of 2,3,6,11-Tetrahydro-1H, 5H-indolizino[8,7-*b*]indole-11*b*-Carboxylic Acid Methyl Ester via a 9-BBN-Mediated Tertiary Lactam Reduction

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Abstract: A facile synthesis of 2,3,6,11-tetrahydro-1H,5H-indolizino[8,7-*b*] indole-11*b*-carboxylic acid methyl ester, a versatile intermediate utilized in the synthesis of indole alkaloids, was achieved in two steps. Condensation of tryptamine with dimethyl α-ketoglutarate led to the formation of the corresponding indolizino[8,7-*b*]indolone ester, which subsequently underwent an efficient lactam reduction with 9-BBN to generate the tertiary amine ester in good yield.

Keywords: 9-BBN, Dimethyl α-ketoglutarate, lactam reduction, tryptamine

Indole alkaloids continue to be the target of scientific investigations because of their interesting physiological, biological, and structural properties.[1] They offer unique opportunities to explore a wide range of chemistry and biology space in the pursuit of new bioactive agents. In our search to design indole alkaloid-based screening libraries for drug discovery, we recently developed a strategy for the synthesis of structurally diverse 7-aryl-octahydroazonino[5,4-*b*]indoles via a three-component reaction utilizing indolizinoindoles, chloroformates, and aromatic nucleophiles.[2] Treatment of indolizinoindole **1** with chloroformate **2**, in the presence of an aromatic nucleophile **3**, resulted in the production of 7-aryl-octahydroazonino[5,4-*b*]indole **4** via a chloroformate-induced

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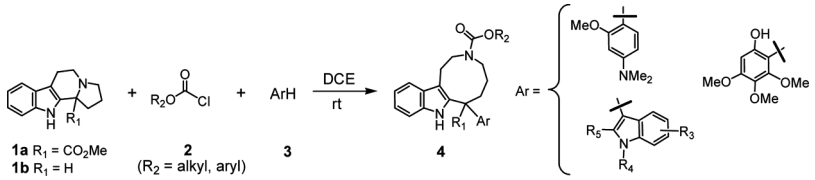
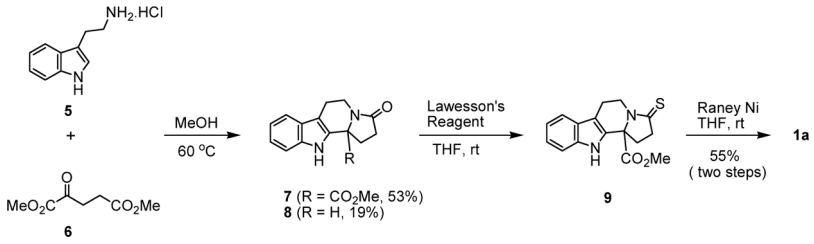


Scheme 1. 7-Aryl-octahydroazonino[5,4-*b*]indoles via a three-component reaction.

fragmentation of the β-tetrahydrocarboline (THC) ring, followed by insertion of the appropriate nucleophile to the azoninoindole nucleus (Scheme 1). Considering that a number of 7-substituted-azonino[5,4-*b*]indoles have exhibited a wide range of biological properties as central nervous system (CNS) stimulants, antidepressants, anti-inflammatories, diuretics, and anti-ulcer agents,[3] we surmised that access to libraries of structurally diverse azonino[5,4-*b*]indoles might facilitate the search for new bioactive agents.

The chemistry described in Scheme 1 is amenable to high-throughput solution-phase parallel synthesis and could provide access to screening libraries of 7-aryl-octahydroazonino[5,4-*b*]indoles with general structure **4**. However, to be able to proceed with the library synthesis, we required large amounts of both indolizinoindoles **1a** and **1b**. There are several reports in the literature that describe the racemic[4] as well as the asymmetric[5] synthesis of indolizinoindole **1b**. Compound **1b** in large quantities can be obtained with the Corsano–Algieri protocol, which involves the condensation of tryptamine with α-ketoglutaric acid in AcOH followed by a $LiAlH_4$ reduction of the resulting tetracyclic lactam.[4a] The synthesis of optically active amine **1a** was first reported by Magnus et al.[6] in their studies directed toward the synthesis of vinblastine-vincristine models.[7] It was prepared in four steps in an overall yield of 30%, starting from either of the two antipodes of tryptophan *p*-toluenesulfonic acid salt and dimethyl α-ketoglutarate **6**. This route utilizes a Barton radical decarboxylation of the Pictet–Spengler tetracyclic adduct to yield lactam **7**, followed by a Raney nickel desulfurization of thiolactam **9**. Also, the synthesis of racemic amine **1a**, which was successfully utilized in the synthesis of strychnine, was reported to proceed in a similar fashion starting from tryptamine instead (Scheme 2).[8]

Before we embarked on the large-scale synthesis of **1a** according to Scheme 2, we wanted to test the feasibility of this route on a gram scale. When we attempted the Pictet–Spengler reaction of tryptamine hydrochloride **5** with dimethyl α-ketoglutarate **6** in MeOH, we observed the formation of tetracyclic lactam **7** in 53% yield and its decarboxylated byproduct **8** in 19% yield. Treatment of lactam **7** with Lawesson's reagent[9]



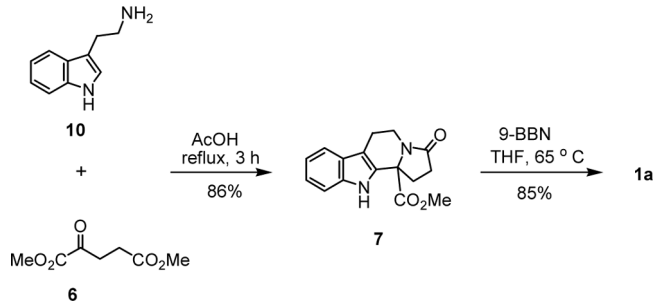
Scheme 2. Thiolactam reduction route to **1a**.

produced thiolactam **9**, which was then subjected, without purification, to a Raney nickel desulfurization to generate racemic **1a** in 55% yield for the two-step sequence (Scheme 2). Indeed, **1a** was prepared in three steps from tryptamine hydrochloride in an overall yield of 29%.

Although the thiolactam reduction route described in Scheme 2 could provide access to significant amounts of tetracyclic amine **1a**, the use of a large excess of the pyrophoric Raney nickel was deemed suboptimal. The Ni_2B/H_2 reagent system,[10] prepared in situ from $NiCl_2 \cdot 6H_2O$ and $NaBH_4$, could serve as a viable alternative to Raney nickel given its successful use in the desulfurization of similar indolic systems.[11] However, the need for a large excess of nickel chloride and $NaBH_4$ coupled with the problems associated with the handling and disposal of nickel salts, rendered this reduction protocol unattractive. Therefore, the search for a facile and user-friendly method of amide reduction, in the presence of the ester group, was deemed necessary. Furthermore, the chromatographic separation of lactam **7** from the decarboxylated by-product **8** would render the large-scale synthesis of amine **1a** cumbersome. Thus, optimization of the Pictet–Spengler step was required to eliminate the formation of the decarboxylated by-product **8**.

Indeed, we found that treatment of tryptamine-free base **10** with α-ketoester **6** in AcOH resulted in the clean formation of tetracyclic lactam **7** in 86% yield. The use of a borane reagent for the chemoselective reduction of the tertiary lactam **7** seemed a viable alternative. For example, 9-borabicyclo[3.3.1]nonane (9-BBN) was reported to efficiently reduce tertiary amides and appeared to be an attractive candidate for this transformation.[12] Indeed, when lactam **7** was treated with 9-BBN (3.2 equiv), the desired amine **1a** was formed cleanly in 85% yield. Compound **1a** was prepared in two steps from tryptamine-free base in an overall yield of 73% (Scheme 3).

The method in Scheme 3 represents a facile synthesis of tetracyclic amine **1a**, a versatile intermediate that could be utilized in the synthesis of indole alkaloids as well as several biologically interesting azonino



Scheme 3. Entry to **1a** via a 9-BBN-mediated reduction of a tertiary lactam.

[5,4-*b*]indoles. It involves an efficient reduction of a tertiary lactam with 9-BBN in the presence of an ester group. Although the described synthesis is racemic, the combination of Magnus' Pictet–Spengler/radical decarboxylation protocol with the 9-BBN reduction of the intermediate indolizino[8,7-*b*]indolone ester would enhance the synthesis of large quantities of optically active **1a**.

EXPERIMENTAL

Improved Synthesis of Tetracyclic Lactam 7

A solution of tryptamine **10** (16.2 g, 0.10 mol) and dimethyl α-ketoglutarate **6** (19.4 g, 0.11 mol) in AcOH (300 mL) was stirred at 120 °C under reflux for 3 h. The reaction mixture was cooled to room temperature, and the solvent was then evaporated in vacuo. The resulting residue was dissolved in $CHCl_3$ (300 mL), and the chloroform solution was washed with water (2×150 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo to give the crude amide **7**, which was then treated with hot *t*-butyl methyl ether under stirring. The resulting suspension was cooled and then filtered to give a solid, which was subsequently washed with cold *t*-butyl methyl ether and dried under vacuum to afford 24.4 g (86%) of lactam **7** as a pale brown solid. Compound **7** exhibited ^{1}H NMR (300 MHz, $CDCl_3$) spectral data identical with the data reported in the literature.[6]

Reduction of 7 to Tetracyclic Amine 1a

A solution of lactam **7** (8.53 g, 0.030 mol) and 9-BBN dimer (11.7 g, 0.048 mol) in THF (100 mL) was stirred at 65 °C for 1 h. The reaction

mixture was cooled to room temperature and then treated with MeOH (30 mL) and 2 M HCl in Et_2O (30 mL). The mixture was stirred at room temperature for 1 h and then concentrated in vacuo. The resulting residue was partitioned between EtOAc (200 mL) and 3 M aqueous HCl (100 mL). The aqueous phase was separated, and the organic phase was washed with 3 M aqueous HCl (2×50 mL). The combined aqueous phase was neutralized with solid $NaHCO_3$ and then extracted with EtOAc (2×100 mL). The combined organic phase was dried over Na_2SO_4 and concentrated in vacuo to afford 6.9 g (85%) of amine **1a** as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1 H), 7.50 (d, 1 H, $J = 7.5$ Hz), 7.35 (d, 1 H, $J = 7.8$ Hz), 7.18 (t, 1 H, $J = 7.0$ Hz), 7.10 (t, 1 H, $J = 7.0$ Hz), 3.78 (s, 3 H), 3.40–3.33 (m, 2 H), 3.15 (m, 1 H), 3.02–2.88 (m, 2 H), 2.59–2.45 (m, 2 H), 2.35–2.22 (m, 1 H), 1.95 (m, 1 H), 1.72 (m, 1 H). MS (ES^+) m/z for $C_{16}H_{18}N_2O_2$: calcd. 270.14; found 271.05 (M + H). We have noticed that the authors in Ref. 6 missed two multiplet peaks: one at 2.59–2.35 ppm and the other at 2.35–2.22 ppm, corresponding to two and one aliphatic proton, respectively. The remainder of the spectral data is identical with the data reported therein.

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