Organic LETTERS

Letter

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From Cyclic CF_3-ketimines to a Family of Trifluoromethylated Nazlinine and Trypargine Analogues

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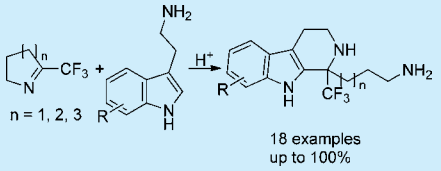
Supporting Information

ABSTRACT: An efficient (one- and two-step) synthesis of trifluoromethylated derivatives of the natural alkaloids nazlinine, trypargine, and homotrypargine was elaborated. Trifluoromethyl-substituted 5−7-membered cyclic imines were used as a masked carbonyl component in the Pictet−Spengler reaction with various tryptamines. As a result, this approach opens access to a family of alkaloid-like compounds bearing a CF_3 group at position 1 of tetrahydro-β-carboline.



Indole alkaloids are a large class of natural compounds often originating from the tryptophan metabolism in living organisms.[1] The indole fragment is a "privileged structure" in medicinal chemistry and one of the most important heterocycles in drug discovery.[2] β-Carboline alkaloids are one of the more important subtypes of indole alkaloid and are found in Nature very frequently. For example, these substances are important molecules in the life of plants, marine sponges, insects, and mammalians. Currently, natural and synthetic β-carbolines attract significant attention due to their diverse and sometimes very high biological activity.[3]

A subset of β-carboline alkaloids contain an additional ω-aminoalkyl chain at position 1 of the β-carboline core. For example, nazlinine (Figure 1) was isolated from the plant *Nitraria schoberi*.[4] Trypargine can be isolated from the African rhacophoridae frog *Kassina Senegalensis* and ascidian *Eudistona* sp.[5] 6-Hydroxy trypargine is a potent neurotoxin of the Brazilian web spider *Parawixia bistrata*.[6] Homotrypargines as well as some more complex natural compounds are other important alkaloids bearing an aminoalkyl group (Figure 1). These alkaloids exhibit a broad spectrum of biological activities: antimalarial, neurotoxic, antihelminthic, serotonergic, etc.[7] Moreover, nazlinine is a starting point for the biosynthesis of several important alkaloids such as indoloquinolizidine, scobericine, komaroidine, isokomarovine, etc.[8] As a result, these natural compounds and their derivatives attracts significant interest.

On the other hand, fluorinated organic compounds are of special importance for modern material science and drug design.[9] Incorporation of fluorine or the trifluoromethyl group in the target molecule is a useful modification in medicinal chemistry. Despite considerable progress in this area, methods for selective fluorination or installation of a fluorinated fragment in a molecule with atomic precision[10] have met with limited success.[11] An alternative strategy to achieve this aim utilizes fluorinated building blocks bearing a fluorinated fragment at a certain position. Several years ago, we introduced new fluorinated building blocks (α-perfluoroalkyl substituted cyclic imines[12]) and demonstrated their high synthetic potential.[13] Herein, we describe the use α-trifluoromethylated cyclic imines as valuable building blocks for the synthesis of derivatives of nazlinine, trypargine, and homotrypargine analogues having a trifluoromethyl group installed at the position 1.

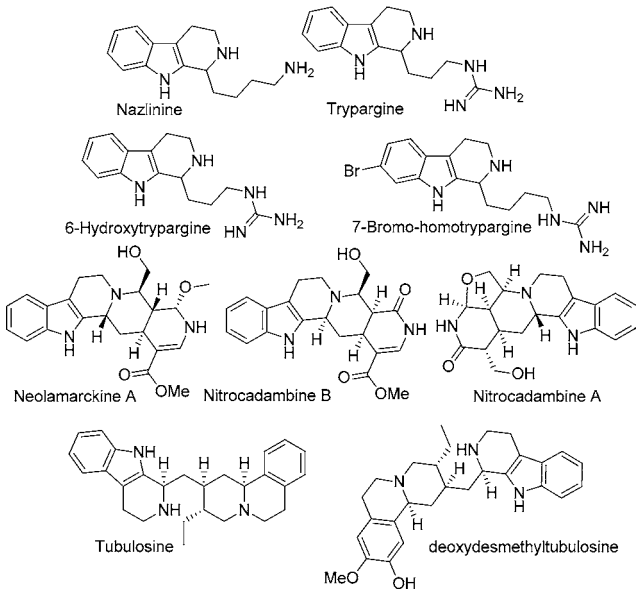


Figure 1. Some natural tetrahydro-β-carbolines bearing an aminoalkyl fragment.

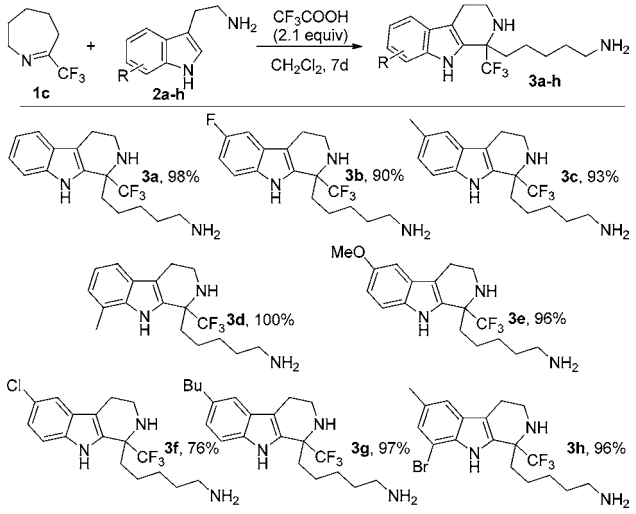
Received: July 12, 2016
Published: August 24, 2016

DOI: 10.1021/acs.orglett.6b02031
Org. Lett. 2016, 18, 4494−4497

We found in the literature only a few examples for the synthesis of nazlinine and trypargine[14] and nothing about synthetic preparations of homotrypargines. Moreover, to the best of our knowledge, no syntheses of nazlinine and trypargine derivatives bearing an additional substituent at the 1-position of the tetrahydro-β-carboline fragment have been reported. The incorporation of a CF_3 group could significantly improve metabolic stability, lipophilicity, and other physicochemical properties of target molecules. Also very important is the possibility of modulating basicity and nucleophilicity of the nitrogen atom at the 2-position to avoid the use of protective groups.[15] Moreover, the incorporation of a CF_3 group can change the preferred conformation of the piperidine ring due to its higher conformational energy (A value) as compared to an alkyl group (2.1 and 1.8 kcal/mol, respectively).

We started our investigation from 1-(trifluoromethyl)-tetrahydroazepine **1c**. In our previous reports,[16] it was shown that 7-membered cyclic imines react much easier with different nucleophiles due to the equilibrium between the cyclic form (imine) and the amino ketone being shifted to the open form under acidic conditions. The Pictet–Spengler reaction was performed at room temperature using CH_2Cl_2/CF_3COOH. We found that the expected transformation proceeded very smoothly for a broad range of substituted tryptamines to form target trifluoromethylated homonazlinines in high yield (Scheme 1). However, the reaction proceeded relatively slowly (up to 1 week reaction time), and all attempts to accelerate the reaction by heating resulted in lower yields and tarring.

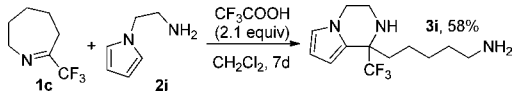
Scheme 1. Synthesis of 1-(Trifluoromethyl)homonazlinine Derivatives 3



The scope of the reaction is rather broad, and we found no restrictions with regard to the structure of starting tryptamines. Only in the case of tryptamines **2b** and **2f** bearing electron-withdrawing groups (Cl, F) at the 5-position were target compounds **3b** and **3f** coisolated with trace amounts of starting tryptamines. However, pure products were isolated as salts by crystallization with oxalic acid (**3b**, 90%; **3f**, 76%, see the SI).

Next, we decided to study this reaction with aminoalkyl-substituted benzenes and heterocycles. Gratifyingly, 2-(pyrrol-1-yl)ethanamine **2i** reacted cleanly with imine **1c** under the same reaction conditions, and the target amine **3i** was isolated in 58% yield after crystallization with oxalic acid (Scheme 2). However, other heteroaromatic and electron-rich aromatic

Scheme 2. Pictet–Spengler Reaction with 2i

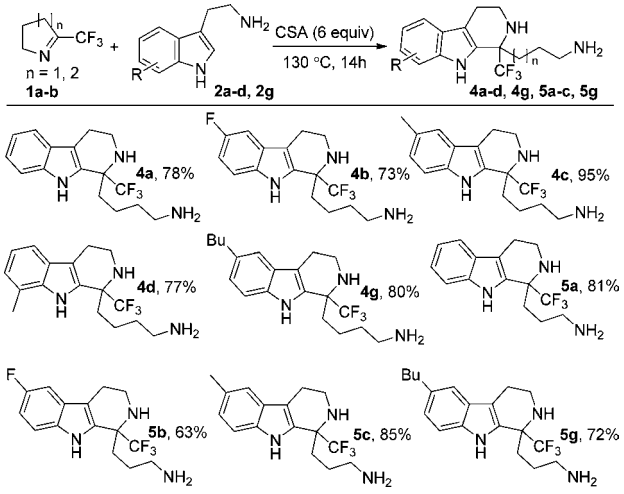


ethanamines (dimethoxyphenyl, hydroxyphenyl, imidazolyl) failed to provide the desired products under acidic conditions.

Tryptamine **2a** failed to react with 7-membered imines having a nonfluorinated substituent in the α-position such as 2-phenyl- or 2-butyltetrahydroazepine. The replacement of the trifluoromethyl group in imine **1c** with phenyl or butyl led to a significant reduction in imine electrophilicity. We failed to identify other acidic conditions that would allow us to overcome the difficulties with these nonfluorinated ketimines.

Next, we investigated the Pictet–Spengler reaction with 2-(trifluoromethyl)pyrroline **1a** and 2-(trifluoromethyl)-tetrahydropyridine **1b** (Scheme 3). It is known that 5- and 6-

Scheme 3. Synthesis of 4 and 5



membered ketimines preferentially populate the cyclic ketimine. We were therefore not surprised that the reaction conditions (CH_2Cl_2/CF_3COOH) employed for 7-membered imine **1c** did not yield the desired trifluoromethylated carbolines with imines **1a**,**b**.

Various reaction conditions (TfOH/different solvents, $BF_3\cdot Et_2O/CH_2Cl_2$, CF_3COOH, CSA/H_2O, CF_3COOH/H_2O, CSA/H_2O–microwave heating, HCl, AcOH) proved ineffective, and only starting compounds were detected in the reaction mixture. The use of some acids (CF_3COOH, TfOH, AcOH/$MeSO_3H$) without solvents under heating led to tarring of the starting materials. However, encouraging results were obtained in the case of heating the reactants without solvents with sulfonic acids such as $MeSO_3H$, TsOH, and CSA. The best yields were achieved when unsubstituted tryptamine **2a** was heated with an excess of CSA (6 equiv), leading to the corresponding tetrahydro-β-carbolines **4a** and **5a** in 78% and 81% isolated yields, respectively. The corresponding reaction with substituted tryptamines led in some cases to trace amounts of contaminating starting materials. Nevertheless, a number of pure carbolines **4** and **5** were isolated in good yield (up to 95%) after crystallization with oxalic acid (Scheme 3).

The structure of product **5b** was unambiguously confirmed by X-ray crystallography (Figure 2). Careful analysis of the structure shows that the piperidine ring adopts a *sofa*

DOI: 10.1021/acs.orglett.6b02031
Org. Lett. 2016, 18, 4494–4497

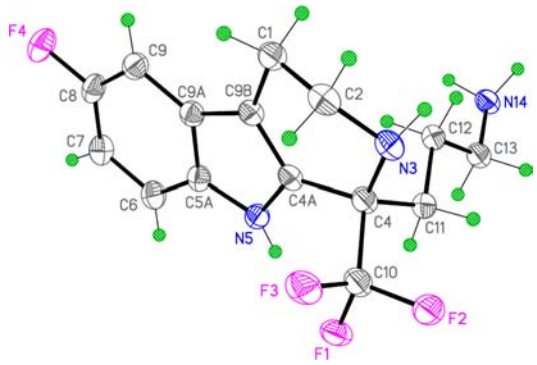
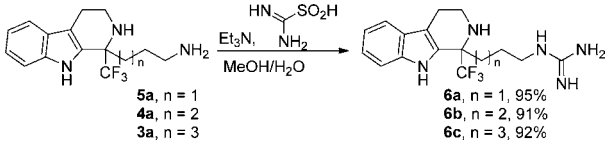


Figure 2. Molecular structure of **5b**.

conformation with the N3−C4−C4a−C9b−C1 basal plane (rms deviation is 0.017 Å). The dihedral angles for the trifluoromethyl group (C10−C4−C4a−C9b) and the aminopropyl fragment (C11−C4−C4a−C9b) are 123.29(13) and −118.48(13)°, respectively. These results confirmed that the preferable conformation was significantly influenced by incorporation of a CF_3 group as compared to the natural alkaloid congeners.

Since trypargine and homotrypargine contain a guanidinylated alkyl chain, we decided to synthesize trifluoromethylated analogues of these natural alkaloids. The reaction of starting amines **3a**, **4a**, and **5a** with formamidinesulfinic acid (1.1 equiv) was carried out in a MeOH/H_2O mixture in the presence of Et_3N. This transformation proceeded highly selectively due to differences in the nucleophilicity between the two amino groups; as a result, trifluoromethylated analogues **6a−c** of natural guanidinylated alkaloids were isolated in excellent yield (91−95%) (Scheme 4).

Scheme 4. Synthesis of Guanidine Derivatives



In conclusion, we have established a very efficient one- and two-step synthesis of CF_3 derivatives of the naturally occurring alkaloids nazlinine, trypargine, and homotrypargine in good to excellent yields. We also demonstrated that the reactivity of trifluoromethylated cyclic imines **1a−c** in this Pictet−Spengler reaction depends significantly on its ring size.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02031.

Crystallographic data for **5b** (CIF)
Synthetic procedure, ^1H, ^{13}C, and ^{19}F NMR spectra for **3a−i**, **4a−d,g**, and **5a−c,g** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This study was funded by RFBR, according to the research project No. 16-33-60012 mol_a_dk. We also thank N. G. Voznesenskaya, V. M. Muzalevskiy, and N. E. Shevchenko (Department of Chemistry, Lomonosov Moscow State University) for helpful discussions and assistance in data treatment and P. V. Dorovatovskii and Y. V. Zubavichus (National Research Center "Kurchatov Institute") for assistance in the X-ray diffraction study on the "BELOK" beamline.

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DOI: 10.1021/acs.orglett.6b02031
Org. Lett. 2016, 18, 4494−4497