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Synthesis of 1,1-disubstituted tetrahydro-β-carbolines from 2-methyleneaziridines

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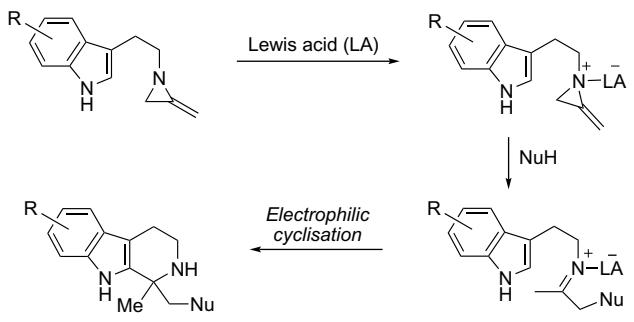
Abstract

Ring opening of indole functionalised methyleneaziridines (**3a**–**c**, **7**) with alcohols in the presence of boron trifluoride etherate leads to the formation of 1,1-disubstituted tetrahydro-β-carbolines in moderate to good yields (37–83%).

Keywords: Nitrogen heterocycles; Strained compounds; Ring opening; Pictet–Spengler; Aziridines

The tetrahydro-β-carboline (THBC) unit is a common constituent of many naturally occurring alkaloids, which display interesting biological activities.[1] Examples include harmicine,[2] fumitremorgin C[3] and haploscleridamine.[4] The THBC nucleus is also an important template in drug discovery,[5] and approved drugs such as tadalafil[6] possess this heterocyclic ring system. THBCs have also been found in many foods, and it is postulated that these compounds are important in the prevention of diseases associated with oxidative damage.[7]

The important biological effects of THBCs have made them key targets for chemical synthesis. The most commonly used approach to this ring system is based upon the Pictet–Spengler cyclisation.[8,9] The classical Pictet–Spengler reaction is a two-step process that involves the condensation of a β-arylethyl amine with a carbonyl compound to form an electrophilic iminium ion, which undergoes further ring closure by way of electrophilic aromatic substitution. The reaction works well with aldehydes and reactive ketones such as α-ketoesters but the reactions are often slow and low yielding with simple ketones. In the latter case, steric and electronic factors presumably slow down the rate of iminium ion formation, and make it less reactive towards further cyclisation. As a consequence, the preparation of 1,1-disubstituted tetrahydro-β-carbolines by this approach is generally rather inefficient. Recently, Lingam reported that molecular iodine can act as an effective catalyst for Pictet–Spengler reactions involving simple unactivated ketones.[10] Titanium (IV)



Scheme 1. New route to 1,1-disubstituted tetrahydro-β-carbolines.

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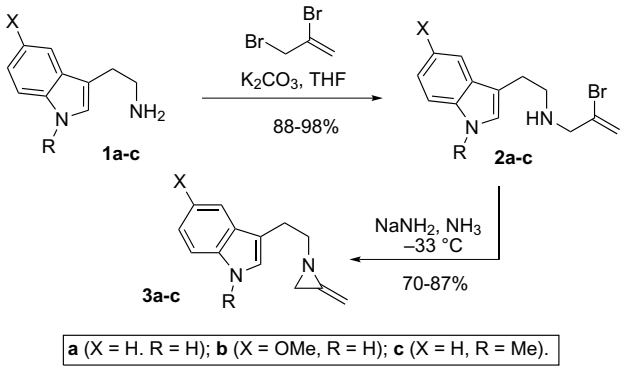
isopropoxide has also been used successfully as the iminating agent.[11]

As an alternative solution to the problems associated with slow iminium ion formation from ketones, we decided to explore a new route to 1,1-disubstituted tetrahydro-β-carbolines using a strategy based upon the ring opening of an indole substituted methyleneaziridinium ion with an appropriate nucleophile under Lewis acid catalysis (Scheme 1). By analogy with the Pictet–Spengler reaction, further cyclisation of the resultant iminium ion to the THBC nucleus was anticipated under the reaction conditions. By variation in the structure of the methyleneaziridine and nucleophile components, it was anticipated that a wide variety of 1,1-disubstituted THBCs could be produced using this approach. In this Letter, we establish the scope and limitations of this chemistry using alcohol-based nucleophiles.

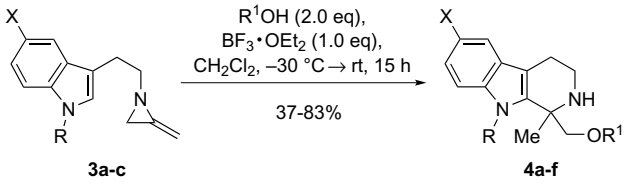
Initially, a series of methyleneaziridines containing an indole nucleus tethered to the aziridine nitrogen were prepared. The alkylation of 2,3-dibromopropene with 2.0 equiv of tryptamine (**1a**) afforded the monoalkylated derivative **2a** in 94% yield. Further ring closure[12] of **2a** using sodium amide in liquid ammonia gave methyleneaziridine **3a** in 87% yield after bulb-to-bulb distillation (Scheme 2). Methyleneaziridine **3b** was prepared from 5-methoxytryptamine (**1b**) in 85% overall yield using an identical sequence. Similarly, **3c** was made in 62% yield from *N*-2-(1-methyl-1*H*-indol-3-yl)ethylamine (**1c**).[13]

Earlier work on the ring opening reactions of methyleneaziridines had established that $BF_3{\cdot}OEt_2$ promotes nucleophilic attack at C-3 with carbon-based nucleophiles such as RMgCl.[14] Thus, we reasoned that this Lewis acid might induce the required ring opening/Pictet–Spengler cyclisation (Scheme 1). The treatment of **3a** (1.0 equiv) in CH_2Cl_2, at −30 °C with an equimolar quantity of $BF_3{\cdot}OEt_2$ then benzyl alcohol as nucleophile (2 equiv) and the subsequent warming of the reaction mixture to room temperature overnight afforded **4a** in an optimised 73% yield after column chromatography (Scheme 3 and Table 1, entry 1). Lower yields were observed when the reaction was conducted in chloroform (32%), toluene (38%), dichloroethane (39%), or MeCN (52%). By using just 1.1 equiv of benzyl alcohol in CH_2Cl_2, the yield of **4a** was reduced to 54%. Having optimised the conditions for the reaction, a range of alcohol-based nucleophiles were examined in order to evaluate its scope. These reactions proceeded in moderate to good yields, and a small set of tetrahydro-β-carbolines **4a**–**i** were produced (Scheme 3 and Table 1). It is notable that the substitution of the indole nitrogen leads to lower product yields (Table 1, entry 1, cf. entry 8). Preliminary results indicate that the reaction tolerates additional functionality contained within the alcohol or attached indole nucleus.

As the reaction generates a new quaternary asymmetric centre, we sought to ascertain if any asymmetric induction could be achieved. As an initial test, (±)-α-methyl-tryptamine (**5**) was converted into methyleneaziridine **7** via vinyl bromide **6** in 92% yield over the two steps (Scheme 4). The reaction of this aziridine with benzyl alcohol in the presence of $BF_3{\cdot}OEt_2$ led to the isolation of **8** in 63% yield as a single diastereomer. The analysis of the crude reaction



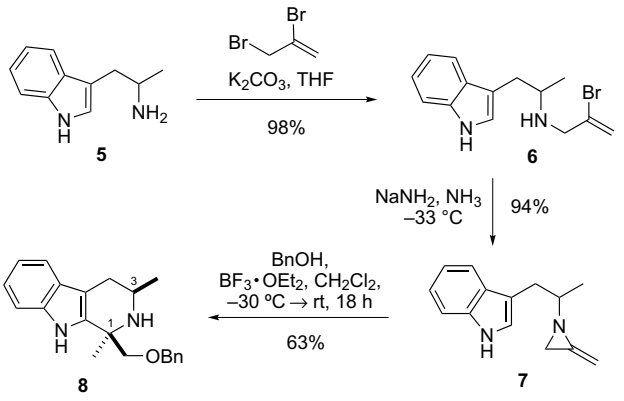
Scheme 2. Synthesis of indole substituted 2-methyleneaziridines **3a**–**c**.



Scheme 3. Synthesis of 1,1-disubstituted tetrahydro-β-carbolines **4a**–**i**.

Table 1
Synthesis of 1,1-disubstituted tetrahydro-β-carbolines

Entry	Aziridine	R	X	R^1OH	Product	Yield (%)
1	**3a**	H	H	$PhCH_2OH$	**4a**	73
2	**3a**	H	H	^{n}PrOH	**4b**	83
3	**3a**	H	H	*c*-HexOH	**4c**	63
4	**3a**	H	H	^{t}BuOH	**4d**	58
5	**3a**	H	H	$H_2C{=}CHCH_2OH$	**4e**	80
6	**3a**	H	H	$HC{\equiv}C(CH_2)_3OH$	**4f**	71
7	**3b**	H	OMe	$PhCH_2OH$	**4g**	66
8	**3c**	Me	H	$PhCH_2OH$	**4h**	43
9	**3c**	Me	H	$H_2C{=}CHCH_2OH$	**4i**	37



Scheme 4. Stereoselective cyclisation to 1,1,3-trisubstituted-β-carbolines.

mixture by ^{1}H NMR indicated the presence of a second component tentatively assigned as the minor diastereomer (dr = 8:1) which was not isolated. The relative stereochemistry of **8** was deduced by NOESY experiments.[15]

In summary, a new approach to 1,1-disubstituted tetrahydro-β-carbolines has been devised based upon the ring opening of indole substituted methyleneaziridines. Studies to extend this reaction to other types of nucleophiles are ongoing in our laboratories and will be disclosed in due course.

Acknowledgements

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Supplementary data

Supplementary data (experimental procedures and characterisation data for **2a–c**, **3a–c**, **4a–i** and **6–8**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.095.

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