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A variation of the Pictet–Spengler reaction via a sequential reduction–cyclization reaction of *N*-acylcarbamates: synthesis of 1-substituted tetrahydroisoquinoline derivatives

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Abstract—A new variation of the Pictet–Spengler reaction for the synthesis of 1-substituted tetrahydroisoquinoline derivatives has been developed. The reaction employs the reduction of *N*-acylcarbamates by DIBAL-H followed by simultaneous cyclization mediated by $BF_3{\cdot}OEt_2$. The synthetic potential of this method has been illustrated by the synthesis of the tetrahydroisoquinoline alkaloids, (±)-xylopinine, (±)-laudanosine, (±)-8-oxo-*O*-methylbharatamine, and (±)-isoindoloisoquinolone.

Isoquinoline alkaloids are a large family of natural products and display a broad variety of biological activities.[1a] Among the members of this class of compounds, tetrahydroisoquinoline derivatives constitute a major group. Many of them exhibit important biological activities, for example, anti-inflammatory, anti-microbial, anti-leukemic, and anti-tumor properties.[1b,c] Accordingly, these have encouraged the development of a number of synthetic methodologies for the construction of the tetrahydroisoquinoline core and have been a subject of several reviews.[2] The Pictet–Spengler reaction is one of the most effective methods and serves as a convenient method for the construction of racemic as well as asymmetric tetrahydroisoquinoline derivatives and related heterocyclic systems.[2b,3] The reaction involves the cyclization of imines or iminium ions derived from the condensation of β-arylethylamine derivatives with aldehydes or their synthetic equivalents. The reaction was traditionally carried out in a protic solvent with an acid catalyst.[4,5] However, the intrinsically poor electrophilicity of the protonated imine means that a variation involving the condensation of *N*-acyl or *N*-sulfonyl β-arylethylamine with aldehydes is often required.[6] The transformation proceeds by intramolecular electrophilic aromatic substitution by the activated iminium-type intermediate, formed from the aldehyde with an activated nitrogen moiety under Lewis acid promotion.

Recently, *N*,*O*-acetal TMS ethers have been demonstrated to be precursors for the in situ generation of *N*-acyliminium ions.[7a,b] *N*,*O*-Acetal TMS ethers can be easily prepared from *N*-acylcarbamates by sequential partial reduction of the amide carbonyl using DIBAL-H followed by TMSOTf trapping of the resulting hemiaminal. In the presence of a suitable Lewis acid, the *N*,*O*-acetal TMS ethers formed *N*-acyliminium intermediates, which could be trapped with nucleophiles. Synthetic applications of this methodology have also been demonstrated.[7c,d]

Our research group has long been interested in the development of efficient syntheses of tetrahydroisoquinoline-containing alkaloids.[8] We herein report an alternative strategy leading to the synthesis of (±)-xylopinine (**1**), (±)-laudanosine (**2**), (±)-8-oxo-*O*-methylbharatamine (**3**), and (±)-isoindoloisoquinolone (**4**) by means of a sequential reduction followed by Lewis acid promoted cyclization, in a new modification of the Pictet–Spengler type cyclization process (Scheme 1).

To begin the study, *N*-acylcarbamates **7** were conveniently prepared in two high-yielding steps from 2-(3,4-dimethoxyphenyl)ethylamine (**5**) as shown in Scheme 2. The starting 2-(3,4-dimethoxyphenyl)ethylamine (**5**) was treated with various acid chlorides under

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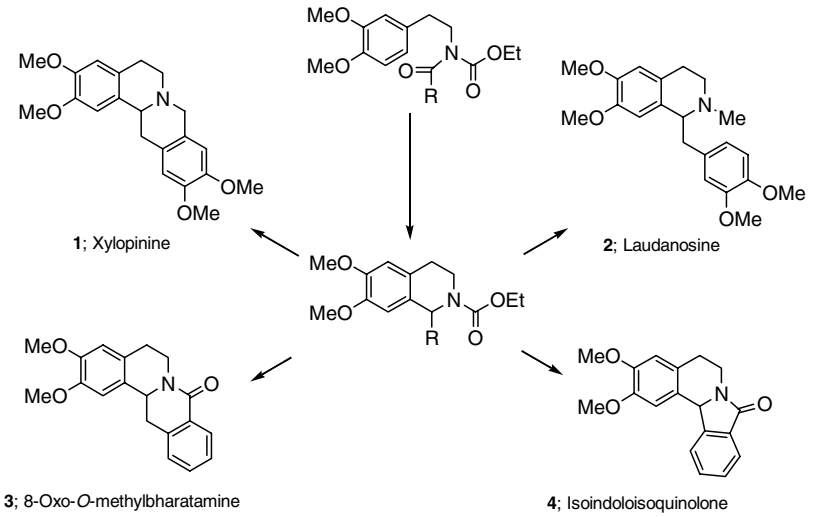
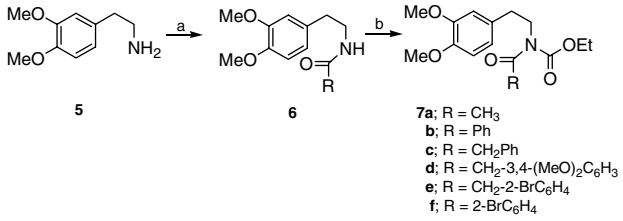


Scheme 1. Synthetic plan.



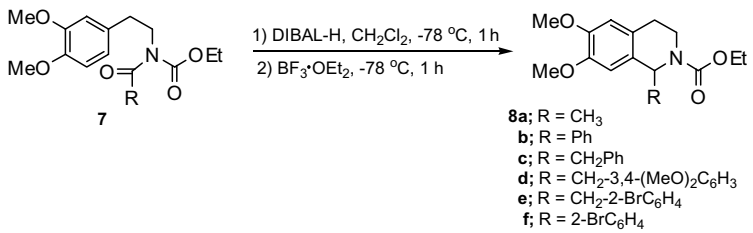
Scheme 2. Synthesis of *N*-acylcarbamate precursors **7**. Reagents and conditions: (a) RCOCl, Na_2CO_3, 1:1 v/v CH_2Cl_2/H_2O; (b) *n*-BuLi, THF, −78 °C then ethyl chloroformate.

biphasic conditions (80–96% yields), and the resulting amides were lithiated with *n*-BuLi followed by trapping with ethyl chloroformate to yield *N*-acylcarbamates **7a**–**f** with yields ranging from 72% to 98%.

As shown in Table 1, upon treatment of *N*-acylcarbamates **7** with 1.5 equiv of DIBAL-H in hexane followed by sequential addition of $BF_3{\cdot}OEt_2$, smooth production of the 1-substituted tetrahydroisoquinoline derivatives **8** was observed.[9] Yields were good to excellent and were generally higher than those previously recorded for acid catalyzed Pictet–Spengler condensation of *N*-acyl or *N*-sulfonyl β-arylethylamines with aldehydes.[6c,d] Attempts to prepare tetrahydroisoquinoline derivatives from precursors with no activating benzene ring substituents under similar conditions met with failure,[10] the oxygenated aromatic ring is essential for successful cyclization. In contrast to Suh's observations, attempts to trap the hemiaminal formed by the TMSOTf–pyridine system failed to provide the *N*,*O*-acetal TMS ether, and only fragmentation products were isolated, that is, the corresponding aldehyde and 2-(3,4-dimethoxyphenyl)ethylcarbamic acid ethyl ester. Furthermore, in a pairwise comparison, treatment of 2-(3,4-dimethoxyphenyl)ethylcarbamic acid ethyl ester with phenylacetaldehyde under acid catalyzed Pictet–Spengler conditions (HCO_2H, 110 °C, 7 h) gave **8c** in low yield (20%).

Having constructed the tetrahydroisoquinoline core, further elaborations of **8d** to (±)-xylopinine (**1**) and (±)-laudanosine (**2**); **8e** to (±)-8-oxo-*O*-methylbharatamine (**3**) and **8f** to (±)-isoindoloisoquinolone (**4**) were straightforward following the previously reported

Table 1. Sequential partial reduction-Lewis acid mediated cyclization of *N*-acylcarbamates **7**



Entry	**7**; R =	Product (% yield)
1	CH_3	**8a**; 76
2	Ph	**8b**; 80
3	CH_2Ph	**8c**; 98
4	CH_2–3,4$(MeO)_2C_6H_3$	**8d**; 83
5	CH_2–2-BrC_6H_4	**8e**; 83
6	2-BrC_6H_4	**8f**; 71

procedures. Treatment of **8d** with triflic anhydride/DMAP efficiently gave (±)-8-oxoxylopinine, which underwent reduction by $LiAlH_4$ to provide (±)-xylopinine (**1**) (75%, 2 steps).[11] Reduction of **8d** by $LiAlH_4$ afforded (±)-laudanosine (**2**) in 91% yield.[6d] The alkaloids (±)-8-oxo-*O*-methylbharatamine (**3**) and (±)-isoindoloisoquinolone (**4**) were obtained in 95% and 78% yields, respectively, by lithium–bromine exchange of **8e** and **8f** using *t*-BuLi, followed by cyclization.[6d]

In conclusion, we have developed a new variation of the Pictet–Spengler tetrahydroquinoline synthesis in which the *N*-acyliminium intermediates were formed by partial reduction of *N*-acylcarbamates by DIBAL-H followed by sequential addition of $BF_3{\cdot}OEt_2$. This procedure appears to be useful, in terms of synthetic efficiency, short reaction time, and mild conditions (−78 °C). Therefore, the *N*-acylcarbamates serve as convenient precursors for construction of 1-substituted tetrahydroisoquinolines, which can be further elaborated to the synthesis of tetrahydroisoquinoline-containing natural products. Application of this strategy to the diastereoselective synthesis is forthcoming.

Acknowledgments

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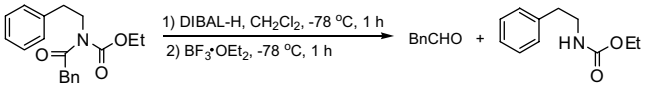
9. *General procedure*: To a solution of *N*-acylcarbamate (1.0 equiv) in dry CH_2Cl_2 (ca. 0.1 M) at −78 °C under an argon atmosphere, was added dropwise DIBAL-H (1.0 M solution in hexane, 1.5 equiv). After 1 h, the mixture was treated with $BF_3{\cdot}OEt_2$ (1.5 equiv) and was stirred at −78 °C for 1 h before being quenched with 15% aqueous sodium potassium tartrate (5 mL), and diluted with dichloromethane (5 mL). The mixture was warmed to room temperature and extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried (Na_2SO_4), filtered, and concentrated (aspirator then vacuo). The crude product was purified by column chromatography (SiO_2, ethyl acetate/hexanes as eluent) or crystallization.
10. Under similar conditions (DIBAL-H, −78 °C, 1 h then $BF_3{\cdot}OEt_2$, −78 °C, 1 h), the reaction of compound **9** yielded phenylacetaldehyde (60%) and phenethylcarbamic acid ethyl ester (**10**) (69%), implying that the reduction took place smoothly but that the cyclization was difficult.



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