Tetrahedron Letters 53 (2012) 4657–4660

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An alternative strategy to the Pictet–Spengler method for tetrahydroisoquinoline synthesis: a feasibility study

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ARTICLE INFO

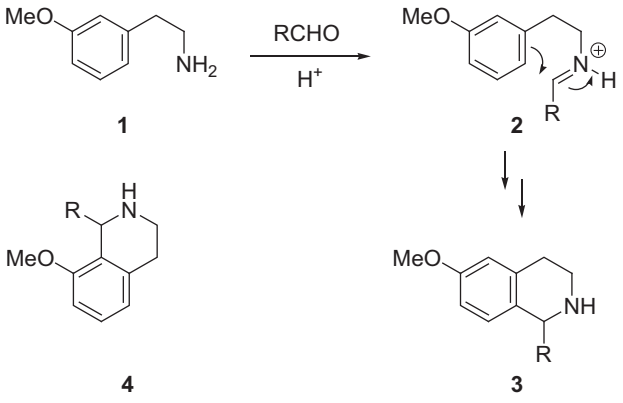
Article history:
Available online 26 June 2012

Keywords:
Pictet–Spengler
Alternative
Hydroamination
Acid-catalysed
Cyclisation

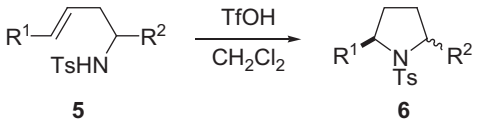
ABSTRACT

Acid-catalysed cyclisations of the 2-aminoethyl styrene derivatives **9** give good to excellent yields of the corresponding tetrahydroisoquinolines **7** by an intramolecular hydroamination reaction, which represents an alternative and potentially more flexible strategy to the classical Pictet–Spengler method for the syntheses of such heterocycles.

The Pictet–Spengler reaction[1] belongs to that venerable group of classical heterocyclic synthetic methods which have served their purpose extremely well over many years, despite some quite significant limitations. A generalised mechanism consists of an initial condensation between a phenethylamine **1** and an aldehyde, followed by activation of the resulting imine using a Brønsted or Lewis acid, and cyclisation of the resulting activated electrophilic species **2,** to arrive at the tetrahydroisoquinoline product **3** (Scheme 1).[2] Naturally, more recently there has been considerable interest and success in desymmetrizing the central cyclisation step to produce chiral, non-racemic products **3**, along with the related products derived from indole precursors, especially tryptophans.[3] It has been known for over 30 years that such chemistry is also used by Nature in the biosynthesis of many tetrahydroisoquinoline residues; in a notable development, the enzymes responsible for this transformation, the aptly named Pictet–Spenglerases, have been isolated and their structures determined.[4,5] There is, however, a significant limitation to the Pictet–Spengler reaction, in that it requires an activated, electron-rich aryl ring to complete the cyclisation. This has certainly not restricted its many applications in alkaloid synthesis, precisely because a very high proportion of these natural product targets possess exactly such an activated aryl ring, being either methoxylated or hydroxylated *para* to the desired reaction site. Even with such activating groups present, the formation of lesser amounts of the *ortho*-substituted product **4** can sometimes be an additional irritation. Thus, while this necessary condition usually does not affect the viability of the reaction



Scheme 1. The classical Pictet–Spengler reaction.



Scheme 2. An acid-catalysed pyrrolidine synthesis.

in such target synthesis, it can severely restrict its applications in the preparation of non-natural relatives. In view of the exceptionally important biological activities displayed by many of these alkaloids, this is obviously an area of great potential for the

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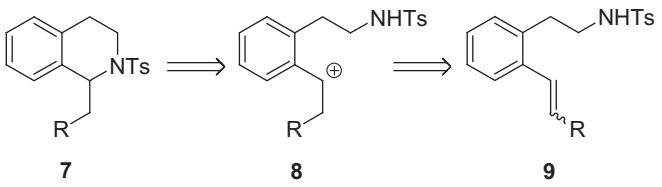
http://dx.doi.org/10.1016/j.tetlet.2012.06.091

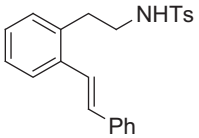
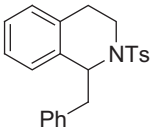
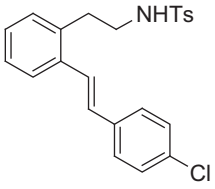
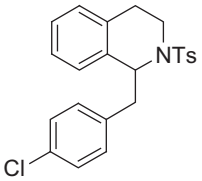
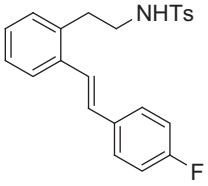
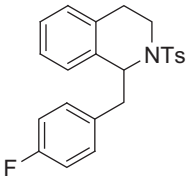
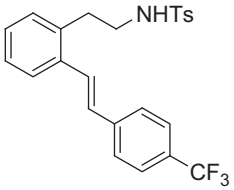
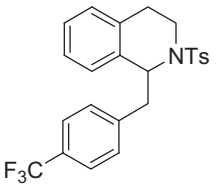
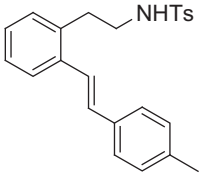
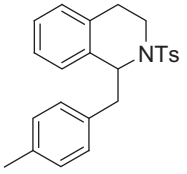
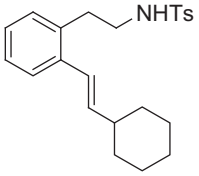
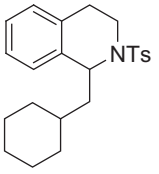
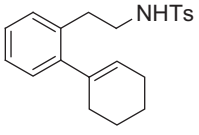
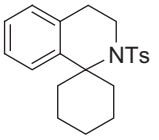
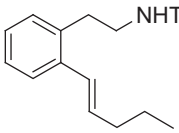
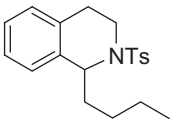


Scheme 3. Our proposed alternative to the Pictet–Spengler reaction.

discovery of novel pharmaceuticals which, in general, cannot therefore be accessed using the Pictet–Spengler method. Herein, we wish to report an alternative strategy which has the potential to overcome this limitation. While still based around a reactive and electron-deficient intermediate, this new approach to tetrahydroisoquinolines already has the two aryl substituents in place and hence cannot suffer from the foregoing limitations.

The idea arose from our discovery that alkenyl sulfonamides **5** could be induced to cyclise upon exposure to strong acid,

Table 1
Acid-catalysed cyclisations of styrenes **9** to give *N*-sulfonyl-tetrahydroisoquinolines **7**[a]

Entry	Precursor	Conditions	Product	Yield (%)
1		0.5 equiv TfOH, 0 °C, 24 h 0.4 equiv H_2SO_4, 20 °C, 48 h		100 99
2		0.5 equiv TfOH, 40 °C, 24 h		87
3		0.5 equiv TfOH, 40 °C, 24 h		72
4		0.5 equiv TfOH, 40 °C, 48 h 0.4 equiv 4, 40 °C, 48 h		75 56
5		0.5 equiv TfOH, 40 °C, 24 h 0.4 equiv H_2SO_4, 40 °C, 48 h		54 80
6		0.5 equiv TfOH, 40 °C, 24 h		90
7		0.5 equiv TfOH, 0 °C, 24 h 0.4 equiv H_2SO_4, 20 °C, 24 h		83 81
8		0.5 equiv TfOH, 0 °C, 24 h 0.4 equiv H_2SO_4, 40 °C, 24 h		92 89

[a] All reactions were carried out in stirred, anhydrous dichloromethane.

specifically catalytic trifluoromethanesulfonic (triflic) acid or concentrated sulfuric acid.[6] Although clearly a novel pyrrolidine synthesis, this type of transformation belongs to the burgeoning area of hydroamination methodologies, and should be especially suited to the synthesis of highly substituted and sterically crowded amine derivatives.[7]

The resulting pyrrolidines **6** were generally isolated in exceptionally high yields, but usually, where relevant, as mixtures of stereoisomers. (Scheme 2). We have more recently applied this methodology to a total synthesis of the pentacyclic alkaloid α-cyclopiazonic acid, in which a key transformation was a cascade cyclisation onto an initial benzylic carbenium ion, generated by exposure of a secondary benzylic alcohol to acid.[8] Having thus established that benzylic carbenium ions were able to participate in such cyclisations, we wondered if somewhat related chemistry could be successfully applied to the synthesis of tetrahydroisoquinolines; the basic idea is outlined in Scheme 3. Thus, if one imagines heterolytic cleavage of the C–N bond in a tetrahydroisoquinoline **7**, then the resulting carbenium ion intermediate **8** might be generated from the corresponding styrene **9** upon exposure to catalytic acid. Of course, protonation of the alkene function in precursors **9** could also lead to the isomeric carbenium ion, especially when R = Ar and thence to formation of a seven-membered ring. This possibility, along with determination of the exact conditions required to efficiently achieve the desired alkene protonation were our initial concerns, the successful resolution of which we report herein.

Very recently, a similar disconnection, but using carbamates rather than sulfonamides as the nucleophiles and carbenium ions generated by acidification of benzylic alcohols has been shown to be very useful for the synthesis of tetrahydroisoquinolines. However, all examples reported contained a 3,4-dimethoxyphenyl group, in which the presumed carbenium ion was in conjugation with one of the methoxy substituents and thus could suffer from exactly the same limitation as the original Pictet–Spengler reaction (see above).[9] 1-Vinyl-tetrahydroisoquinolines have also been obtained by formation of the same C–N bond by overall S_N2' mechanisms, again using nucleophilic attack by a carbamate group but in these cases onto a π-allylic palladium intermediate[10] or a bismuth-stabilized allylic carbenium ion.[11] Further, the former method delivers chiral, non-racemic products when a chiral phosphine is attached to the metal. In view of these reports, we wish to present our own preliminary results in this area, which feature largely successful outcomes to the idea shown in Scheme 3.

As described in the foregoing paper,[12] the necessary precursors **9** are readily accessible from optimised Suzuki–Miyaura couplings between vinylboronic acids and *N*-tosyl-2-bromophenethylamine, using microwave activation, in company with a pre-mixed catalyst system. We were delighted to find that exposure of the precursors **9** to sub-stoichiometric quantities of either triflic acid or concentrated sulfuric acid in dichloromethane resulted in slow but smooth cyclisation, as anticipated in Scheme 3, to give generally good to outstanding yields of the desired tetrahydroisoquinolines. The results are collected in Table 1.[13]

In general, the cyclisations were slow but clean when using around half an equivalent of the acid catalyst.[13] In the first five examples, there is a distinct possibility of formation of the isomeric benzylic carbenium ion, trapping of which by the sulfonamide would lead to the corresponding seven-membered azepine products. This is presumably especially true in the case of the relatively electron-rich aryl substituents present in entries 1 and 5. However, in none of these examples were any traces of such seven membered products identified by ^{1}H NMR analysis of the crude products. Although not fully optimised, there was little difference found in the conditions necessary to drive the cyclisations to completion in the case of these aryl substituted (stilbene) examples. In general, concentrated sulfuric acid was less reactive than triflic acid, not surprisingly, but this still gave quite similar yields of the cyclised products. The alkenyl substituted precursors (entries 6–8) reacted somewhat more rapidly but equally cleanly, with the exception of the cyclohexenyl-substituted precursor in entry 7, which understandably reacted more rapidly, presumably because the reactive intermediate is a tertiary benzylic carbenium ion. The lack of very rapid cyclisation is presumably a reflection of the considerable degree of steric hindrance present in this example, which is of considerable significance as it demonstrates that this methodology can be used to obtain such *spiro*-derivatives which would be difficult to prepare using alternative methods. It should be noted that the reaction times reported in Table 1 have not been optimised.

We therefore suggest that this methodology should form the basis of a viable alternative to the classical Pictet–Spengler reaction. Further studies aimed at more fully defining its scope, stereochemical features and applicability to other (hetero)aromatic frameworks are underway.

Acknowledgement

We are grateful to Eli Lilly and Co Ltd and the EPSRC for financial support.

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13. *A typical procedure is as follows:*- 1-benzyl-2-(4-toluenesulfonyl)-1,2,3,4,-tetrahydroisoquinoline (entry 1, Table 1): (*E*)-4-methyl-*N*-[2-(2-phenylethenyl)phenethyl]benzenesulfonamide (97 mg, 0.257 mmol) was dissolved in dry dichloromethane (10 ml) to which was added concentrated sulfuric acid (ca. 35 mg, two drops). The resulting heterogeneous mixture was stirred at ambient temperature for 48 h then basified using a slight excess of 2 M aqueous potassium carbonate. The separated aqueous layer was extracted

with dichloromethane (2 × 10 ml) and the combined organic solutions dried over potassium carbonate and filtered through a pad of silica gel. Evaporation of the filtrate and washings left the *isoquinoline* (96 mg, 99%) as a pale yellow oil which showed δ_H ($CDCl_3$, 400 MHz) 7.37 (d, 2H, *J* 8.3 Hz), 7.13–6.85 (m, 10H), 6.75–6.71 (m, 1H), 5.12 (app. t, 1H, *J* 6.6 Hz, CHN), 3.48–3.42 (m, 1H, CH_aH_b), 3.36–3.28 (m, 1H, CH_aH_b), 3.07–3.02 (m, 2H), 2.64–2.55 (m, 1H), 2.42–2.34 (m, 1H), 2.23 (s, 3H, TsMe); δ_C ($CDCl_3$, 100 MHz) 143.0 (C), 137.7 (C), 136.9 (C), 135.6 (C), 133.5 (C), 129.9 (2 × CH), 129.5 (2 × CH), 128.7 (CH), 128.3 (2 × CH and CH), 127.3 (CH), 127.2 (2 × CH), 126.9 (CH), 125.0 (CH), 57.9 (CHN), 44.5 (CH_2N), 40.0 (CH_2), 27.2 (CH_2), 21.5 (TsMe); ν_{max}/cm^{-1} (film) 3290, 3060, 3027, 1652, 1598, 1448, 1274, 990, 815; HRMS (ES) *m*/*z* calcd for $C_{23}H_{24}NO_2S$, $[M+H]^+$, 378.1528; found 378.1539.