Thioorthoesters in the activated Pictet–Spengler cyclization. Synthesis of 1-thiosubstituted tetrahydroisoquinolines and carbon–carbon bond formation via sulfonyl iminium ions generated from N,S-sulfonyl acetals

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Received 8 April 2003; revised 6 June 2003; accepted 6 June 2003

Abstract—The elaboration of 1-alkylthio- and 1-arylthio-tetrahydroisoquinolines by means of the activated Pictet–Spengler reaction of N-sulfonyl-β-phenethylamines with thioorthoesters as electrophiles, and their use as sulfonyl iminium ion precursors for carbon–carbon bond formation, leading to 1-substituted tetrahydroisoquinoline derivatives, is reported.

The controlled formation of new carbon–carbon bonds is of great importance in organic chemistry and thus it constitutes a major area of research. In this respect, the generation of N-acyliminium and N-sulfonyliminium ions from suitable precursors, as reactive intermediates towards carbon nucleophiles, has become an attractive approach to this problem. This is amply documented by the unusually high number of natural product syntheses reported involving such strategy, which allows building structural complexity under mild and convenient conditions.

The condensation of N-acyl or N-sulfonyl β-phenethylamines with aldehydes, known as the activated Pictet–Spengler reaction, is a well established procedure for the elaboration of tetrahydroisoquinolines. In spite of the fact that alternative mechanisms may account for its outcome, the transformation probably proceeds by intramolecular nucleophilic attack of the aromatic ring to an iminium-type intermediate, formed by reaction of the aldehyde with the activated nitrogen moiety, under Lewis acid promotion.

The original strategy has been modified and recently extended to the use of masked aldehydes and aldehyde equivalents, such as acetics and enol ethers, chloro(methylthio)acetate and various α-chloro-α-phenylchalcogeno carboxyls, as electrophilic components.

The participation of thioorthoester derivatives as nucleophiles is well documented in the chemical literature; they are valuable synthetic tools for the introduction of masked carbonyl functions. On the contrary, the use of thioorthoesters as precursors of electrophilic species has only few and scattered precedents.

Keywords: thioorthoesters; 1-substituted tetrahydroisoquinolines; sulfonyl iminium ions; activated Pictet–Spengler.

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0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01452-7
Here, we wish to report the synthesis of 1-arylthio- and 1-alkylthio-tetrahydroisoquinoline derivatives (2) by reaction of N-sulfonyl-β-phenethylamines (1) with thioorthoesters as electrophiles, under Lewis acid promotion, in a new modification of the activated Pictet–Spengler type cyclization process. We also disclose the use of the resulting 1-heterosubstituted tetrahydroisoquinoline intermediates as sulfonyliminium ion precursors for the elaboration of 1-substituted tetrahydroisoquinolines (3) upon the reaction of 2 with suitable carbon nucleophiles (Scheme 1), under Lewis acid assistance.

Thioorthoester-stabilized carbocations have not been explored to date as electrophilic partners in the activated Pictet–Spengler reaction. A close analogy to this is the use of ethyl orthoformate under tosic acid catalysis for the synthesis of quinazolino-tetrahydro-β-carbolines,5 in principle, this could improve the scope of the cyclization and lead to new classes of products. In addition, the enhanced stability of the cyclizing intermediate due to the presence of a second heteroatom in the carbenium ion may facilitate its formation, leading to cyclized products in better yield.

To begin the study, tris(ethylthio)- and tris(phenylthio)methane were synthesized by the known boron trifluoride etherate catalyzed reaction of ethyl orthoformate with ethyl mercaptan and thiophenol, respectively. Then, they were reacted with various N-sulfonyl-β-phenethylamines, bearing different substituents and substitution patterns under tin(IV) chloride catalysis, smoothly affording cyclized products after 5–48 h.10 The results, consigned in Table 1, revealed that unactivated tetrahydroisoquinoline precursors (entries 1–3) were unreactive even when submitted to reaction in refluxing 1,2-dichloroethane, while aromatics carrying the oxygenated substitution patterns most commonly found in natural products, furnished the expected products in moderate to good yields.

Interestingly, comparison between analogous dimethoxy and methylenedioxy substituted substrates (entries 6 and 10) evidenced the poor performance of the latter, while examination of the results obtained using HC(SPh)3 and HC(SEt)3 indicated that the former was more efficient, requiring milder conditions and shorter reaction times.

These results could be ascribed to the better charge stabilization ability of the phenylthio moiety, vis-à-vis its ethylthio congener. The group of Hevesi, while studying methyl and phenyl selenoorthoesters, previously noted a similar but less evident trend.7a

Noteworthy, the more rigorous conditions required for cyclization with tris(ethylthio)-methane brought about the selective demethylation of the ortho-disubstituted methyl ether function of the starting material in the experiment of entry 12, probably as a consequence of the formation of a type of Lewis acid-thiol ether cleaving reagent.11

The synthesis of optically active intermediates was also pursued with both tested thioorthoesters, employing a chiral β-phenethyl sulfonamide derivative (mp 109.5–

Table 1. Activated Pictet–Spengler synthesis of 1-thiosubstituted tetrahydroisoquinolines (2) employing thioorthoesters as electrophiles

<table>
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<tr>
<th>Entry no</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>R₅</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time (h)</th>
<th>Yield (%)</th>
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<td>Cl</td>
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<td>H</td>
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*a: Ts: toluene-p-sulfonyl; Cs: (1S)-10-camphorsulfonyl (see text).
*b: Diastereoisomeric ratio = 2:1.
*c: Diastereoisomeric ratio = 1:1.
*d: The mono demethylated product (R₅ = OH) was obtained.
*e: Tris(phenylseleno)methane was employed, resulting in a complex mixture of inseparable products.
allyl derivative. These reactions furnished 90% of the expected trimethylsilane (Scheme 2). Under Lewis acids assistance from pinacolone and acetophenone, as well as with allyl (Table 1), was reacted with the silyl enol ethers derived from ritchii 3c quinoline.

This outcome is probably a result of both, the ability of tris(phenylthio)-methane to produce cyclized products at lower temperature and the bulk of the phenylthio moiety.

Interestingly, the 1-phenylthio-tetrahydroisoquinolines obtained by the reported activated Pictet-Spengler cyclization with tris(phenylthio)-methane can be regarded as sulfur analogs of 1-benzyl-tetrahydroisoquinolines. The latter have been intensive targets for organic synthesis because they constitute an important and widespread family of natural products, with many of its members displaying interesting physiological and pharmacological actions.12

Although very few cases are documented in the literature, N,S-acetalts can be useful carbon–carbon bond forming precursors. We have recently shown that 3-heterosubstituted tetrahydroisoquinolines bearing N,O- and N,S-sulfonylacetal moieties are capable of generating N-tosyliminium ions under Lewis acid promotion 13 which, in turn, can react with a variety of carbon nucleophiles, offering convenient entries to polyfunctionalyzed simple tetrahydroisoquinolines. In addition, the participation of phenylsulfanylactams in carbon–carbon bond formation via radical chemistry has been reported a few years ago.14

Therefore, in order to examine the synthetic utility of the new N,S-sulfonylacetals as sulfonyliminium ion precursors for the preparation of 1-substituted tetrahydroisoquinolines, the 1-phenylthio tetrahydroisoquinoline 2a, obtained as shown in entry 6 of Table 1, was reacted with the silyl enol ethers derived from pinacolone and acetophenone, as well as with allyl trimethylsilylane (Scheme 2). Under Lewis acids assistance, these reactions furnised 90% of the expected allyl derivative 3a,15 as well as ketones 3b and 3c in yields of 58 and 67%, respectively.16 Phenethyl isoquinoline 3c is reminiscent of several natural products, some of them isolated from Colchicum szovitsii and C. ritchii.17

The iminium ion-based elaboration of C-1 substituted tetrahydroisoquinolines has been previously accomplished by Grignard addition to iminium, acyliminium and tosyliminium intermediates;18 however, the use of silyl derivatives for the same purpose has only a few precedents.15 This successful C-1 functionalization of the tetrahydroisoquinoline nucleus is also of importance because in spite that iminium-ion mediated carbon–carbon bond formation has become part of the current arsenal of efficient synthetic organic transformations, examples of the preparation and use of N,S-sulfonylacetals as iminium ion precursors are still rare.19

In conclusion, we have developed a new variation of the activated Pictet-Spengler tetrahydroisoquinoline synthesis, in which alkyl and aryl thioorthoesters were employed as electrophiles for the preparation of 1-heterosubstituted tetrahydroisoquinolines. In turn, these were used as convenient substrates for the elaboration of 1-substituted tetrahydroisoquinoline derivatives by carbon–carbon bond formation via sulfonyliminium ions. Application of this strategy to the synthesis of natural products is under study and will be reported in due time.

Acknowledgements

The authors acknowledge the financial support provided by Fundação VITAE (Grant No B-11487/9B004), FAPERGS, CNPq and CAPES. T.S.K. also thanks CONICET.

References

16. The elaboration of 3,3-dimethyl-1-[6,7-dimethoxy-2-(tosyl)-1,2,3,4-tetrahydroisoquinolin-1-y]-butan-2-one (3b) is representative of a typical experimental procedure. A solution of 3,4-dimethoxy-N-tosyl-b-phenethylamine (335 mg, 1 mmol) and HCl(SPh) (442 mg; 1.3 mmol) in anhydrous CH2Cl2 (5 mL) was cooled to −78°C and treated dropwise with SnCl4 (0.47 mL, 4 mmol). The reaction system was left to attain room temperature; after stirring 5 h, water (10 mL) was added, the organic layer was separated, and the aqueous phase was extracted with CH2Cl2 (3×20 mL), washed with brine and dried (MgSO4). The solvent was removed under reduced pressure and the residue was flash chromatographed, resulting in the N,S-sulfonylacta 2a (374 mg, 82%), as a white solid, mp 143.0–145.0°C. IR (KBr, ν): 2936, 1610, 1595, 1581, 1519, 1463, 1159, 1113, 872, 735 and 567 cm−1; 1H NMR (200 MHz, CDCl3, δ): 2.33 (3, 3H), 2.39–2.63 (2H), 3.79 (3, 3H), 3.82 (3, 3H), 3.75–3.79 (2, 2H), 6.40 (1, 1H), 6.58 (1, 1H), 6.72 (1, 2H), 7.06–7.10 (7, 3H) and 7.54–7.52 (7, 3H); 13C NMR (50 MHz, CDCl3, δ): 21.39, 26.04, 38.06, 55.80, 55.90, 65.79, 110, 117, 116, 125.04, 125.73, 127.18 (2, C), 128.37, 128.90 (2, C), 129.32 (2, C), 133.15, 134.47 (2, C), 137.33, 143.19, 147.35 and 148.79. HRFABMS: [M+Na]+ m/z 478.1105; calcd for C25H23NO5SNa m/z 478.1123. Under a nitrogen atmosphere, an aliquot of the N,S-sulfonylacta 2a (228 mg, 0.5 mmol) was dissolved in dry CH2Cl2 (3 mL), pinacolone TMS enol ether (234 mg, 1.5 mmol) was added and the system was cooled to −78°C, when it was treated with SnCl4 (0.25 mL). After stirring for 2 h, the reaction was quenched with water, warmed, and the reaction products were extracted with CH2Cl2 (3×15 mL). Drying (MgSO4), concentration and flash chromatography of the extracts furnished 3b (129 mg, 0.29 mmol, 58%), as a solid, mp 163.0–165.0°C. IR (KBr, ν): 2957, 2929, 1736 (w), 1674, 1518, 1337, 1227, 1161, 680 cm−1; 1H NMR (200 MHz, CDCl3, δ): 1.01 (s, 9H), 2.35 (3, 3H), 2.61–2.70 (2H), 2.89 (dd, J = 7 and 17 Hz, 1H), 3.43–3.57 (m, 1H), 3.50–3.80 (m, 1H), 3.77 (s, 3H), 3.78 (s, 3H), 5.50 (dd, J = 4.7 and 8 Hz, 1H), 6.43 (s, 1H), 6.57 (s, 1H), 7.18 (d, J = 8 Hz, 2H) and 7.66 (d, J = 8 Hz, 2H); 13C NMR (50 MHz, CDCl3, δ): 21.39, 25.88 (3C), 27.11, 40.53, 44.09, 46.29, 51.61, 55.78, 55.86, 109.59, 111.18, 124.83, 127.15 (2, C), 128.75, 129.42 (2, C), 136.97, 143.10, 147.49, 147.83 and 148.79. HRFABMS: [M+Na]+ m/z 468.1815; calcd for C25H23NO5SNa m/z 468.1821.