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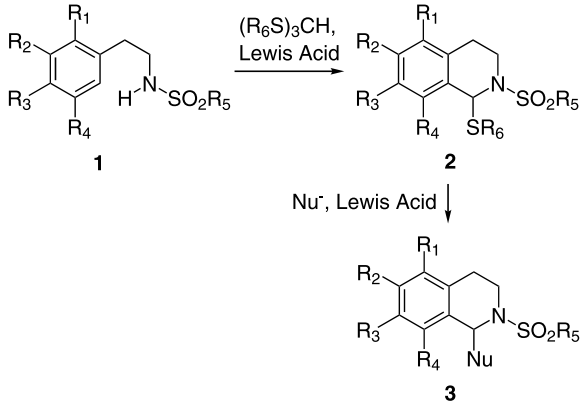
Abstract—The elaboration of 1-alkylthio- and 1-arylthio-tetrahydroisoquinolines by means of the activated Pictet–Spengler reaction of *N*-sulfonyl-β-phenethylamines with thioorthoesters as electrophiles, and their use as sulfonyl iminium ion precursors for carbon–carbon bond formation, leading to 1-substituted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

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.[2] In spite of the fact that alternative mechanisms may account for its outcome,[3a] 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 acetals and enol ethers,[4] chloro(methylthio)acetate[3] and various α-chloro-α-phenylchalcogeno carbonyls,[5] 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.[6] On the contrary, the use of thioorthoesters as precursors of electrophilic species has only few and scattered precedents.[7]



Scheme 1. Activated Pictet–Spengler with thioorthoesters.

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

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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;[8] 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.[9] 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.

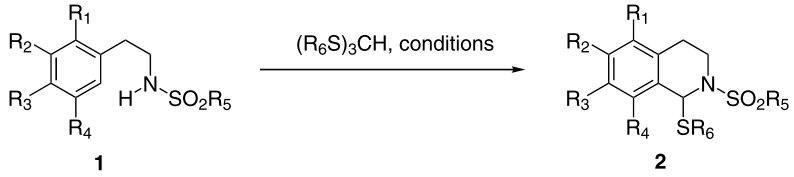
Interestingly, comparison between analogous dimethoxy and methylenedioxy substituted substrates (entries 6 and 10) evidenced the poor performance of the latter, while examination of the results obtained using $HC(SPh)_3$ and $HC(SEt)_3$ indicated that the former was more efficient, requiring milder conditions 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



1 **2**

Entry no	R_1	R_2	R_3	R_4	R_5	R_6[a]	Solvent	Temperature	Time (h)	Yield (%)
1	H	H	H	H	Ts	Ph	$ClCH_2CH_2Cl$	Reflux	8	–
2	H	H	Cl	H	Ts	Ph	$ClCH_2CH_2Cl$	Reflux	8	–
3	H	H	Me	H	Ts	Ph	$ClCH_2CH_2Cl$	Reflux	8	–
4	H	OMe	H	H	Ts	Ph	CH_2Cl_2	−78°C→rt	6	54
5	OMe	OMe	H	H	Ts	Ph	CH_2Cl_2	−78°C→rt	6	44
6	H	OMe	OMe	H	Ts	Ph	CH_2Cl_2	−78°C→rt	5	82
7	H	OMe	OMe	H	Ts	Et	$ClCH_2CH_2Cl$	Reflux	20	47
8	H	OMe	OMe	H	Cs	Ph	CH_2Cl_2	−78°C→rt	5	93[b]
9	H	OMe	OMe	H	Cs	Et	$ClCH_2CH_2Cl$	Reflux	20	53[c]
10	H	-OCH$_2$O-		H	Ts	Ph	CH_2Cl_2	−78°C→rt	6	29
11	H	OMe	OMe	OMe	Ts	Ph	CH_2Cl_2	−78°C→rt	6	65
12	H	OMe	OMe[d]	OMe	Ts	Et	$ClCH_2CH_2Cl$	Reflux	48	25
13	H	OMe	OMe	H	Ts	Ph	CH_2Cl_2	−78°C→rt	6	–[e]

[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 (R_3 = OH) was obtained.
[e] Tris(phenylseleno)methane was employed, resulting in a complex mixture of inseparable products.

111.0°C, $[\alpha]_D = +25.3$, $c = 0.93$, $CHCl_3$) derived from (1*S*)-10-camphorsulfonyl chloride (entries 8 and 9). Not unexpectedly, however, poor diastereoisomeric product ratios were obtained,[5] being 2:1 that recorded when tris(phenylthio)-methane was employed, while formation of an equimolecular amount of diastereoisomers was observed when tris(ethylthio)-methane was used. 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.

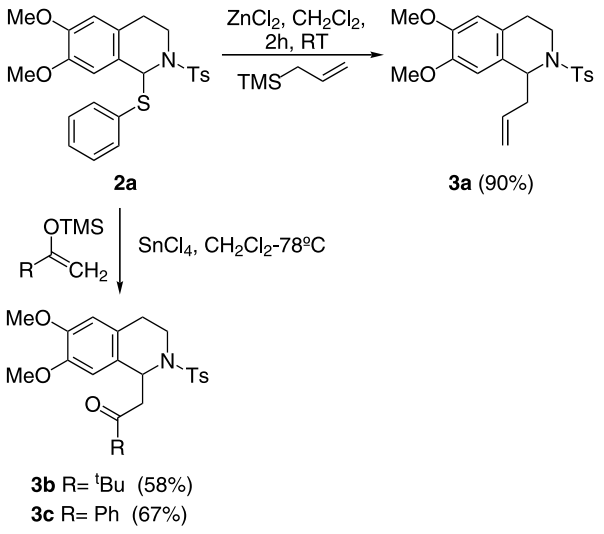
Unfortunately, attempts to prepare related 1-phenylselenyl tetrahydroisoquinoline derivatives employing tris(phenylseleno)-methane (prepared from phenylselenol, ethyl orthoformate and boron trifluoride etherate)[9] under similar conditions met with failure, resulting in a complex mixture of inseparable products (entry 13).

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*-acetals 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 polyfunctionalized simple tetrahydroisoquinolines. In addition, the participation of phenylsulfanyllactams 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-subtituted 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 trimethylsilane (Scheme 2). Under Lewis acids assistance, these reactions furnished 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



Scheme 2. Synthesis of 1-substituted tetrahydroisoquinolines.

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.

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16. The elaboration of 3,3-dimethyl-1-[6,7-dimethoxy-2-(tosyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]-butan-2-one (**3b**) is representative of a typical experimental procedure. A solution of 3,4-dimethoxy-*N*-tosyl-β-phenethylamine (335 mg, 1 mmol) and $HC(SPh)_3$ (442 mg; 1.3 mmol) in anhydrous CH_2Cl_2 (5 mL) was cooled to −78°C and treated dropwise with $SnCl_4$ (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 CH_2Cl_2 (3×20 mL), washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was flash chromatographed, resulting in the *N*,*S*-sulfonylacetal **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}; ^{1}H NMR (200 MHz, $CDCl_3$, *δ*): 2.33 (s, 3H), 2.39–2.63 (m, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 3.75–3.79 (m, 2H), 6.40 (s, 1H), 6.58 (s, 1H), 6.72 (s, 1H), 7.06–7.10 (m, 2H), 7.29–7.32 (m, 3H) and 7.54–7.52 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$, *δ*): 21.39, 26.04, 38.06, 55.80, 55.90, 65.79, 110.17, 111.06, 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 $C_{24}H_{25}NO_4S_2Na$ 478.1123. Under a nitrogen atmosphere, an aliquot of the *N*,*S*-sulfonyl acetal **2a** (228 mg, 0.5 mmol) was dissolved in dry CH_2Cl_2 (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 $SnCl_4$ (0.25 mL). After stirring for 2 h, the reaction was quenched with water, warmed, and the reaction products were extracted with CH_2Cl_2 (3×15 mL). Drying ($MgSO_4$), 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, 991 and 659 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, *δ*): 1.01 (s, 9H), 2.35 (s, 3H), 2.61–2.70 (m, 2H), 2.89 (dd, *J*=7 and 17 Hz, 1H), 3.10 (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); ^{13}C NMR (50 MHz, $CDCl_3$, *δ*): 21.39, 25.88 (3 C), 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 212.38. HRFABMS $[M+Na]^+$ *m*/*z* 468.1815; calcd for $C_{24}H_{31}NO_5SNa$ 468.1821.
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