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1-Substituted β-Carbolines by a Pictet–Spengler Cyclization with Thioortho Esters and Carbon–Carbon Bond Formation via *N*-Sulfonyl Iminium Ions Generated from *N,S*-Sulfonyl Acetals

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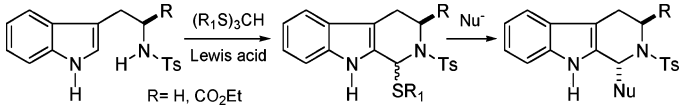
ABSTRACT



The reaction of *N*-tosyltryptamines with thioortho esters, leading to 1-thiosubstituted tetrahydro-β-carbolines under modified Pictet–Spengler conditions, is described. The 1-heterosubstituted β-carbolines furnished 1-substituted β-carbolines upon reaction with Grignard reagents and silyl derivatives under Lewis acid promotion.

Numerous naturally occurring alkaloids, many of which display useful and interesting biological activities, include tetrahydro-β-carboline or tetrahydroisoquinoline cores. One of the most widely used methods to build these kinds of compounds is the classical Pictet−Spengler cyclization, which involves the acid-catalyzed cyclocondensation of a β-arylethylamine with an aldehyde or ketone.[1]

The original strategy has been modified, allowing the use of *N*-acyl-, *N*-sulfinyl-, and *N*-sulfonyl-β-arylethylamines as substrates.[2] On the other hand, masked ketones, aldehydes, and aldehyde equivalents such as ketals, acetals and enol ethers,[3] chloro(methylthio)acetate, and various other α-chloro-α-alkyl/aryl-chalcogeno carbonyls[4] have been employed as electrophilic components. Acetylene sulfoxides, enamines, azalactones, and perhydro-1,3-heterocycles have also been used.[5]

Being valuable synthetic tools for the introduction of masked carbonyl functions, the use of thioortho esters as nucleophiles is widely reported in the current chemical literature;[6] on the contrary, the use of thioortho esters as

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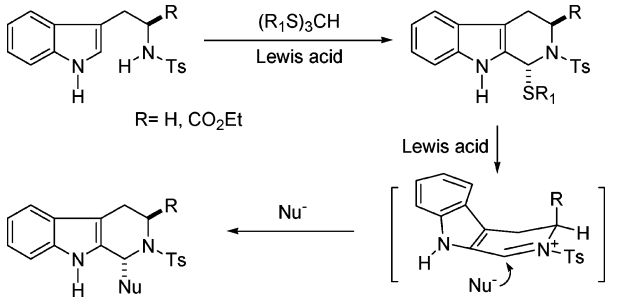
precursors of electrophilic species has only scarce and scattered precedents.[7]

Recently, we disclosed the use of thioortho esters as electrophilic partners in the Pictet−Spengler reaction of *N*-sulfonyl-β-phenethylamines affording 1-heterosubstituted tetrahydroisoquinolines.[8] This strategy improved the scope of the Pictet−Spengler cyclization, giving access to a new family of compounds, some of them otherwise difficult to obtain.

Here, we wish to report the synthesis of 1-arylthio- and 1-alkylthio-β-carboline derivatives by reaction of *N*-tosyltryptamines with thioortho esters as electrophiles under Lewis acid conditions. We also disclose the use of the resulting 1-heterosubstituted β-carboline intermediates as *N*-sulfonyliminium ion precursors for the elaboration of 1-substituted β-carbolines upon their reaction with suitable carbon nucleophiles (Scheme 1) under Lewis acid promotion. This

Scheme 1. Pictet−Spengler Condensation of *N*-Tosyltryptamine Derivatives with Thioortho Esters



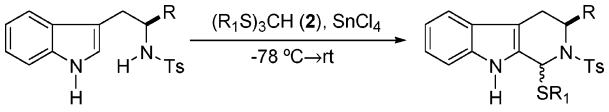
strategy allows product diversification at C_1 without the need of costly aldehyde components and avoids low yields due to their competitive self-condensation. Thus, some of the primary limitations of the conventional Pictet−Spengler reaction are overcome.

The required thioortho esters were conveniently prepared in high yields by the $BF_3{\cdot}Et_2O$-catalyzed reaction of $(EtO)_3CH$ or $(MeO)_3CH$ with the corresponding mercaptans.[8,9]

Initial attention was focused on the use of tris(phenylthio)-methane as an electrophile, employing its cyclocondensation with *N*-tosyltryptamine as a model reaction, leading to compound **3a**. The transformation was next explored using $ZnBr_2$, $TiCl_4$, and $SnCl_4$ as Lewis acids and different solvent systems (CH_2Cl_2, CH_3CN, CH_3CN/CH_2Cl_2, $ClCH_2CH_2Cl$). Among these conditions, addition of $SnCl_4$ to the mixture of the sulfonamide and the thioortho ester in CH_2Cl_2 at −78 °C, followed by slow warming to room temperature 1 h after the addition of the Lewis acid, provided the best results. In every case, the product was easily purified by silica gel flash chromatography.

These optimized conditions were subsequently applied to reactions of *N*-tosyltryptamines **1** with different thioortho esters (**2**), generally furnishing very good yields of compounds **3**, as shown in Table 1.[10] The high yields obtained could be a result of the enhanced stability of the cyclizing species due to the presence of an additional heteroatom in the intermediate carbenium ion, which may facilitate its formation.

Table 1. Pictet−Spengler Reaction of Thioortho Esters with *N*-Tosyltryptamines



1 **3**

entry	R	R_1	time (h)	product	yield (%)
1	H	C_6H_5	6	**3a**	96
2	H	4-Cl-C_6H_4	8	**3b**	92
3	H	4-MeO-C_6H_4	8	**3c**	93
4	H	Et	10	**3d**	78
5	H	$Me(CH_2)_{11}$	12	**3e**	70
6	H	$EtO_2C(CH_2)_2$	6	**3f**	88
7	H	$MeCH_2(Me)CH$	8	**3g**	68
8	H	Me_3C	24	**3h**	
9	CO_2Et	C_6H_5	8	**3i**	80

On the other hand, comparison of the results recorded using arylthioortho esters and their alkyl counterparts indicated that the former were more efficient in product generation, providing the desired products in higher yields. This reaction outcome can be ascribed to the better charge

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(10) All new compounds gave single spots on TLC plates run in different solvents. Compounds were fully characterized by IR and ^1H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry or elemental analysis; data completely agreed with their assigned structures.

stabilization ability of the phenylthio moieties in relation to their alkylthio congeners. Interestingly enough, the Hevesi group has previously noted a similar behavior between these organochalcogen derivatives while working with methyl- and phenyl-selenoesters,[7a] and in a recent study we reported a similar but more evident trend when alkyl- and arylthioortho esters were reacted with β-phenethylamines to produce 1-thiosubstituted tetrahydroisoquinolines.[8] Interestingly, however, it was not possible to obtain any cyclized product when a highly hindered thioorthoformate such as tris(*tert*-butylthio)methane was employed as the masked carbonyl component (entry 8).

By use of the optically active *N*-tosyltryptophan (entry 9), we examined the possibility of 1,3-chirality transfer within this system. When the cyclization of this chiral substrate was carried out with tris(phenylthio)methane, a 3:1 diastereomeric mixture of tetrahydro-β-carboline derivatives **3i** was isolated in a combined 80% yield.

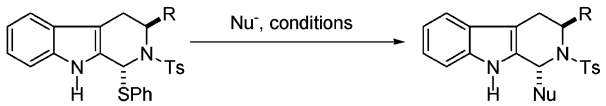
Although spiroindolenines have been invoked as intermediates in the Pictet−Spengler synthesis of tetrahydro-β-carbolines, the preferential formation of the 1,3-trans diastereomer of **3i** is probably a consequence of the pseudoaxial disposition of the ester moiety, to minimize interactions with the bulky tosyl group, which thus hinders the ring closure path leading to the 1,3-cis diastereomer.[11] In addition, it has been found that under acidic conditions, the less stable 1,3-cis compounds readily epimerize to their corresponding 1,3-trans diastereomers by scission of the C_1−N bond, in a retro-Pictet−Spengler type process.[12]

The arylthio or alkylthio groups linked to C_1 of the β-carbolines form *N*,*S*-acetals, which can be useful carbon−carbon bond-forming precursors. Indeed, it has been shown that 3-heterosubstituted tetrahydroisoquinolines bearing *N*,*O*- and *N*,*S*-sulfonylacetal moieties are capable of generating *N*-tosyliminium ions under Lewis acid promotion,[13a] which in turn can react with a variety of carbon nucleophiles.

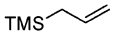
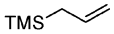
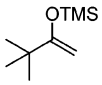
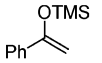
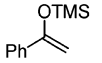
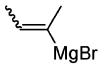
In addition, the preparation of 1-substituted tetrahydroisoquinolines from 1-phenylthio-tetrahydroisoquinolines in a Lewis acid-catalyzed transformation was recently reported.[8] Therefore, with the *N*,*S*-sulfonylacetals at our disposal and in order to examine their synthetic utility as sulfonyliminium ion precursors[13b] for the preparation of 1-substituted β-carbolines, the 1-phenylthio-β-carbolines **3a** and **3i** were submitted to reaction with various model nucleophiles such as silyl enol ethers, allyltrimethylsilane, TMSCN, diethyl zinc, and Grignard reagents.

As shown in Table 2, upon the reaction of the 1-phenylthio-β-carbolines with the different nucleophiles under

Table 2. Synthesis of 1-Substituted Tetrahydro-β-carbolines



3a R= H, **3i** R= CO_2Et **4**

entry Nº	nucleophile	R	cond.[a]	time (h)	product Nº	yield (%)
1		H	A	2	**4a**	93
2		CO_2Et	B	3	**4b**	78
3		H	B	2	**4c**	85
4		H	B	2	**4d**	96
5		CO_2Et	B	2	**4e**	80
6	TMSCN	H	B	10	**4f**	65
7	TMSCN	CO_2Et	B	10	**4g**	75
8	PhMgBr	H	C	0.2	**4h**	98
9	EtMgBr	H	C	0.2	**4i**	98
10		H	C	0.5	**4j**	70
11	Et_2Zn	H	D	24	**4i**	-

[a] Reaction conditions: (A) $SnCl_4$, CH_2Cl_2, −78 °C→rt. (B) $ZnBr_2$, CH_2Cl_2, rt. (C) THF, rt. (D) $SnCl_4$, CH_2Cl_2, reflux.

Lewis acid catalysis, smooth production of the expected 1-substituted tetrahydro-β-carboline derivatives **4** was observed.[10,14] Product recoveries are good in most of the cases. In general, the 3-substituted β-carbolines furnished lower yields of products in relation to their nonsubstituted analogues (entries 1, 3, and 4 vs entries 2 and 5), except when TMSCN was used as the nucleophile (entries 6 and 7).

The addition of stronger nucleophiles such as Grignard reagents was also tried (entries 8−10), and higher yields were obtained in comparatively shorter reaction times. Interestingly, the use of an additional Lewis acid in these cases was not necessary, suggesting that the magnesium ion may be acting as a Lewis acid facilitating the formation of the *N*-tosyliminium ion intermediate.

Unfortunately, attempts to prepare 1-ethyl-tetrahydro-β-carboline **4i** employing diethylzinc (entry 11) failed. Even with $SnCl_4$ and prolonged reflux conditions, the starting 1-phenylthio-tetrahydro-β-carboline **3a** was recovered unchanged after 24 h. This is in contrast to the facile addition of this organometallic reagent to α-acetoxyethers.[15]

By analogy with related systems, the diastereoselective formation of **4b**, **4e**, and **4g** might be the result of the

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influence of stereoelectronic effects. Thus, to avoid the development of strain A[1,3] between the *N*-tosyl moiety and the carboxyethyl group, the latter may adopt a conformation in which the ester is pseudoaxially oriented in the intermediate iminium ion. Attack of the incoming nucleophile would take place from the less hindered face of this intermediate (Scheme 1), with the nitrogen lone-pair developing pseudoaxial and trans-periplanar to it.[16]

In summary, this work has demonstrated the usefulness of thioortho esters as electrophiles in a variation of the Pictet−Spengler synthesis of tetrahydro-β-carbolines. Alkyl- and arylthioortho esters were employed for the preparation of 1-heterosubstituted β-carbolines, with the latter being more effective. The resulting *N*,*S*-acetals were used as convenient substrates for the elaboration of 1-substituted β-carboline derivatives by carbon−carbon bond formation via tosyliminium ions.

This tactical combination leading to the successful two-step preparation of C_1-functionalized β-carbolines **4** is flexible and allows many variations at C_1; it is also of importance because despite the fact that iminium-ion-mediated carbon−carbon bond formation has become part of the current arsenal of efficient synthetic transformations, examples of the preparation and use of *N*,*S*-sulfonylacetals as iminium ion precursors are still relatively rare.[17]

Acknowledgment. The authors are indebted to Fundação Vitae (Grant B-11487/9B004), FAPERGS, CNPq, and CAPES for financial support of this research and are grateful to Prof. Gary A. Molander (University of Pennsylvania) for help with the HRMS determinations. T.S.K. also thanks CONICET and ANPCyT (Grant 12532).

Supporting Information Available: Experimental procedures for the preparation of intermediates **3a**−**g** and **3i** and final compounds **4a**−**j** and spectra and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Synthesis of **4a** is representative of a typical experimental procedure. A solution of *N*-tosyltryptamine (314 mg, 1 mmol) and $HC(SPh)_3$ (442 mg, 1.3 mmol) in anhydrous CH_2Cl_2 (8 mL) was cooled to −78 °C and treated dropwise with $SnCl_4$ (0.29 mL, 2.5 mmol). The reaction system was allowed to attain room temperature; after stirring 5 h at rt, an aqueous solution of $NaHCO_3$ (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, affording the *N*,*S*-sulfonylacetal **3a** (416 mg, 0.96 mmol) as an oil: IR (neat, υ) 3018, 2971, 1300 and 1140 cm^{-1}; HRMS (CI) *m*/*z* calcd for $C_{24}H_{22}N_2O_2S_2$ 434.3001, found 457.1023 $(M + Na)^+$; ^1H NMR (500 MHz, $CDCl_3$, δ) 8.02 (s, 1H), 7.86 (dd, J = 5.0 and 14.0 Hz, 1H), 7.53 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.33−7.10 (m, 7H), 7.28 (d, J = 8.3 Hz, 2H), 6.73 (s, 1H), 3.91 (ddd, 1H, J = 1.0, 4.0 and 13.0 Hz), 3.46−3.42 (m, 1H), 2.56−2.45 (m, 2H) and 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ) 143.6, 138.0, 136.2, 134.9 (2C), 131.9 (2C), 129.6 (2C), 129.5, 129.2 (2C), 128.9, 127.3 (2C), 126.4, 123.1, 119.8, 118.7, 111.3, 110.9, 62.3, 39.5, 21.6 and 20.33. Under a nitrogen atmosphere, an aliquot of the *N*,*S*-sulfonyl acetal **3a** (217 mg, 0.5 mmol) was dissolved in dry CH_2Cl_2 (5 mL); $SnCl_4$ (0.5 mmol, 0.06 mL) was added, and the system was cooled to −78 °C when it was treated with allyl trimethylsilane (0.1 mL, 0.7 mmol). After stirring for 2 h, the reaction was quenched with water and extracted with CH_2Cl_2 (3 × 10 mL). Drying ($MgSO_4$), concentration, and flash chromatography of the combined organic extracts furnished the tetrahydro-β-carboline **4a** (172 mg, 0.46 mmol) as an oil: IR (neat, υ) 3059, 2924, 1731, 1328 and 866 cm^{-1}; HRMS (CI) *m*/*z* calcd for $C_{21}H_{22}N_2O_2S$ 366.2341, found 389.1315 (M + Na); ^1H NMR (500 MHz, $CDCl_3$, δ) 7.89 (s, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.16−7.12 (m, 3H), 7.06 (t, J = 7.8 Hz, 1H), 6.01−5.92 (m, 1H), 5.21−5.16 (m, 3H), 4.15 (dd, J = 5.5 and 14.0 Hz, 1H), 3.45−3.39 (m, 1H), 2.73−2.66 (m, 2H), 2.57−2.53 (m, 1H), 2.49−2.43 (m, 1H) and 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ) 143.2, 138.0, 135.7, 133.9, 132.4, 139.5 (2C), 126.7 (2C), 126.4, 122.0, 119.4, 119.0, 118.1, 110.9, 108.0, 52.6, 40.4, 40.0, 31.3 and 20.0.

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