Pergamon

Tetrahedron Letters 40 (1999) 4969–4972

TETRAHEDRON LETTERS

Pictet-Spengler Condensation of *N*-Sulfonyl-β-Phenethylamines with α-Chloro-α-Phenylselenoesters. New Synthesis of 1,2,3,4-Tetrahydroisoquinoline-1-Carboxylates[§]

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Received 27 January 1999; accepted 14 May 1999

Abstract: *The reaction of N-sulfonyl-β-phenethylamines with α-chloro-α-phenylseleno acetate/propionate esters under Lewis acid promotion gives moderate to good yields of the corresponding 1,2,3,4-tetrahydroisoquinoline-1-carboxylates. Varying degrees of diastereoselection were obtained using chiral sulfonamides and/or esters. Employing this strategy, the achievement of a new total synthesis of Calycotomine is reported.*

The Pictet-Spengler condensation, in which β-arylethylamines are activated towards electrophilic attack under acidic conditions by reaction with aldehydes to form iminium ions, is a well known synthetic method for the elaboration of 1,2,3,4-tetrahydroisoquinolines and other heterocycles.[1] However, this transformation shows some disadvantages in terms of product yields when the starting β-phenethylamines lack activating hydroxyl or alkoxyl groups at the position *para* to the ring closure, because drastic conditions are usually required to effect the cyclization. Modifications of the original strategy to increase the electrophilicity of the iminium intermediate, which employ electron withdrawing groups on the nitrogen such as acyl[2] or sulfonyl[3] moieties are known.

During the course of our studies concerning the structure and synthetic applications of carbocations directly linked to an organoselenium group,[4] we have developed new carbon-carbon bond forming reactions of α-halo-α-phenylselenoesters with arenes,[5] alkenes[6] and silyl enolethers,[7] which exploit the ability of the organoselenium group to stabilize a carbenium ion adjacent to an ester group.

The recent report of Kohno and co-workers[8] on the use of ethyl chloro(methylthio)acetate for the synthesis of polysubstituted tetrahydroisoquinoline derivatives prompted us to describe our results on the reactivity of the α-chloro-α-phenylseleno acetate and propionate esters as aldehyde surrogates in the modified Pictet-Spengler cyclization of *N*-sulfonyl-β-phenethylamines, including the use of chiral sulfonamides and seleno esters, and a new total synthesis of Calycotomine, a 1-hydroxymethyl-tetrahydroisoquinoline isolated from *Calycotomine spinosa* and other Leguminosae.

As shown in Table 1, the reaction of ethyl α-chloro-α-phenylseleno acetate (**1**) with *N*-sulfonyl-β-arylethylamines[9] **3** and **4**, carrying activating substituents *para* to the ring closure position (entries 1 and 2) provided good yields of the expected products;[10] surprisingly, however, their activated congeners **5** and **9** did not react at all (entries 3 and 13); the former requiring the use of a different promoter such as $ZnBr_2$, which caused concomitant debenzylation of the product (entry 4).

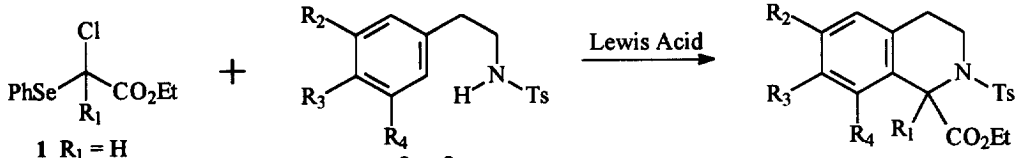
[§]*Dedicated to Professor N. Petragnani on the occasion of his seventieth birthday.*

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00958-2

Interestingly, *N*-sulfonyl-β-phenethylamines such as **6**, **7** and **8** containing less activated aromatic rings also furnished the corresponding cyclized products in reasonable yields, albeit longer reaction times or more rigorous conditions were required.

Unlike the case of the sulfur-based reagent employed by Kohno,[8] no Friedel-Crafts products were detected[5] when activated phenethylamines were cyclized. In spite that the ease of cyclization showed some dependence on the electron density of the aromatic ring, proper selection of reaction conditions provided similar yields of tetrahydroisoquinolines regardless of the nature of the substituents on the aromatic moiety.

TABLE 1: Synthesis of 1,2,3,4-tetrahydroisoquinoline-1-carboxylate derivatives by Lewis acid promoted reaction of *N*-sulfonyl-β-phenethylamines with α-halo-α-phenylselenoesters **1** and **2**.



Entry	Comp.[c]	R_1	R_2	R_3	R_4	Reaction Conditions	Yield[a] %
1	**3**	H	OMe	OMe	H	CH_2Cl_2, $SnCl_4$, -78°C→RT	61(72)[d]
2	**4**	H	OMe	OMe	OMe	CH_2Cl_2, $SnCl_4$, -78°C→RT	51(64)[d]
3	**5**	H	OMe	OBn	H	CH_2Cl_2, $SnCl_4$, -78°C→RT	0
4	**5**	H	OMe	OBn	H	CH_2Cl_2, $ZnBr_2$, -15°C→RT	41[b]
5	**6**	H	Me	H	H	$ClCH_2CH_2Cl$, $SnCl_4$, reflux, 3 h	53
6	**6**	H	Me	H	H	CH_2Cl_2, $ZnBr_2$, RT, 8 h	50
7	**7**	H	H	H	H	CH_2Cl_2, $TiCl_4$, -78°C→RT	0
8	**7**	H	H	H	H	$ClCH_2CH_2Cl$, $ZnBr_2$, reflux, 30 h	56
9	**7**	H	H	H	H	$ClCH_2CH_2Cl$, $SnCl_4$, reflux, 3 h	12
10	**8**	H	H	Cl	H	CH_2Cl_2, $SnCl_4$, reflux, 3 h	38
11	**8**	H	H	Cl	H	$ClCH_2CH_2Cl$, $SnCl_4$, reflux, 3 h	45(68)[d]
12	**3**	Me	OMe	OMe	H	CH_2Cl_2, $SnCl_4$, -78°C→RT	57
13	**9**	H	OMe	H	H	$ClCH_2CH_2Cl$, $ZnBr_2$, reflux, 30 h	0[e]
14	**9**	Me	OMe	H	H	CH_2Cl_2, $SnCl_4$, -78°C→RT	31(43)[d]

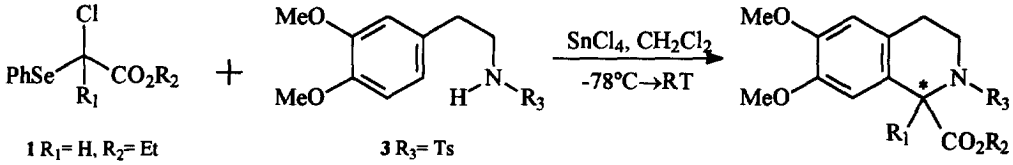
[a] Isolated yield after flash chromatography; [b] Yield of debenzylated product; [c] Starting *N*-sulfonyl-β-arylethylamine; [d] Corrected yield based on recovered starting material; [e] Starting material was recovered almost quantitatively.

When ethyl α-chloro-α-phenylseleno propionate (**2**) was employed, however, reactivity differences were clearly observed. While compounds **3** and **9** smoothly furnished the corresponding products (entries 12 and 14), the highly activated trimethoxy derivative **4** was unable to react, being almost quantitatively recovered, presumably due to strong steric interactions at the ring closure position; on the other hand, less activated β-phenethylamines **6**, **7**, and **8** did not cyclize, probably due to the inability of the selenium reagent to withstand the more drastic reaction conditions required.

By use of the optically active sulfonamide **10**, derived from 1*S*-(+)-10-camphorsulfonic acid, we next examined the ability of the chiral moiety to induce asymmetry on the newly formed chiral center. As depicted in Table 2, while the recorded chemical yields were comparable to those obtained using *p*-tosylamide **3** (entries 1 and 2), a 1:1 mixture of diastereomers was observed when **1** was employed.[14]

The proposal that equilibration of the adjacent tertiary and benzylic center caused by carbonyl enolization, was responsible for the observed results was discarded after a 1.5:1 diastereomeric ratio was measured using the more sterically demanding ester **2**, which generates a quaternary center (entry 4). These results confirmed the poor asymmetry inducing ability of the camphorsulfonyl moiety, probably due to its remoteness from the reaction site and the flexibility of the cyclizing intermediate; therefore, reaction with ester **11**, derived from natural (-)-menthol,[11] was explored.

TABLE 2: Diastereoselective synthesis of 1,2,3,4-tetrahydroisoquinoline-1-carboxylate derivatives by Lewis acid promoted reaction of *N*-sulfonyl-β-phenethylamines with α-halo-α-phenylselenoesters **1**, **2** and **11**.



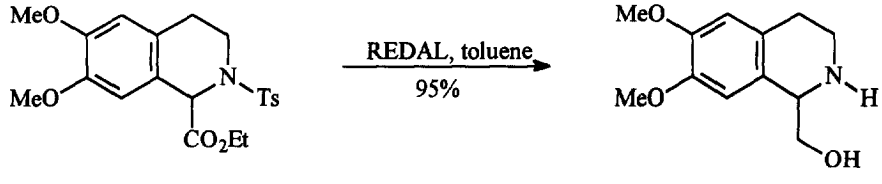
1 R_1= H, R_2= Et
2 R_1= Me, R_2= Et
11 R_1= Me, R_2= Men[a]

3 R_3= Ts
10 R_3= Cam[b]

Entry	α-halo-α-phenylselenoester	*N*-sulfonyl-β-phenethylamine	Yield (%)	Diast. ratio
1	**1**	**3**	61(72)[c]	-
2	**2**	**3**	57	-
3	**1**	**10**	60	1:1
4	**2**	**10**	66	1.5:1
5	**11**	**3**	60(92)[c]	4:1(8.4:1)[d]
6	**11**	**10**	62(72)[c]	>25:1

[a] (1*R*,2*S*,5*R*)-menthyl; [b] (1*S*)-10-camphorsulfonyl; [c] Corrected yield for recovered starting material in parentheses; [d] Diastereomeric ratio after crystallization in parentheses.

A preliminary experiment carried out by reacting sulfonamide **3** with chiral ester **11** led to an increased diastereoselectivity of 4:1, which was improved to a diastereomeric ratio of 8.4:1 after a single crystallization of the crude product. Thus, cyclization of **10** with ester **11** as a superior inducing agent was carried out, providing only one diastereoisomeric tetrahydroisoquinoline derivative (entry 6).[13]



13 **Calycotomine, 12**

SCHEME

An interesting application of this cyclization strategy was as a key step for the total synthesis of Calycotomine (**12**), a widespread simple tetrahydroisoquinoline which displays the highly uncommon 1-hydroxymethyl substitution pattern. To this end, tetrahydroisoquinoline **13**, resulting from the condensation of **3** with ester **1** was subjected to simultaneous reductive detosylation and ester reduction with REDAL in toluene,[3a] furnishing the natural product in 95% yield,[12] as shown in the Scheme.

In conclusion, we have shown that the modified Pictet-Spengler cyclization of *N*-sulfonyl-β-phenethylamines with α-halo-α-phenylselenyl esters provides moderate to good yields of tetrahydroisoquinoline derivatives, even when poorly activated starting sulfonamides are employed. This transformation showed some degree of diastereoselection when chiral sulfonamides and/or optically active esters were employed as inductors. In addition, this strategy can be used as a key step for the elaboration of interesting compounds, as demonstrated through the development of a new total synthesis of the naturally occuring Calycotomine.

Acknowledgements: The authors thank CNPq, FAPERGS and CONICET for financial support. CRB thanks CAPES for a master fellowship.

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9. Starting *N*-sulfonyl-β-arylethylamines were conveniently synthesized in three steps from the corresponding aldehydes by a Henry reaction (CH_3NO_2, NH_4OAc-AcOH), followed by $LiAlH_4$ reduction of the resulting β-nitrostyrenes and conventional sulfonamidation (R-SO_2Cl, NaOH, CH_2Cl_2). All new products gave correct analytical and spectroscopic data.
10. In a typical procedure, $SnCl_4$ (0.098 mL, 0.897 mmol) was added dropwise to a stirred solution of *N*-*p*-tosyl-3,4-dimethoxyphenethylamine (100 mg, 0.299 mmol) and ethyl α-chloro-α-phenylselenoacetate (114 mg, 0.41 mmol) in anhydrous CH_2Cl_2 (3 mL) at –78°C under an argon atmosphere. After 1 h, the reaction was slowly warmed to room temperature and stirred for a further period of 4 h. Then, the mixture was quenched with water and extracted with EtOAc (3 x 30 mL). The organic extract was washed with brine, dried ($MgSO_4$), concentrated and the remaining oil was flash-chromatographed [silica gel, hexane-EtOAc (65:35)] furnishing 1-carbethoxy-2-*p*-tosyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (76 mg, 0.182 mmol, 61%).
11. Menthyl ester **11** was obtained in 66% overall yield by esterification of 2-chloropropionic acid with (1*R*,2*S*,5*R*)-(-)-menthol in benzene under tosic acid catalysis, followed by LDA-mediated deprotonation of the resulting ester in THF at –78°C and reaction of the anionic species with PhSeBr. Analogously, **2** was prepared from commercially available ethyl 2-chloro propionate; see Ganem, B.; Ikota, N. *J. Org. Chem.* **1978**, *43*, 1607.
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14. The Pictet-Spengler condensation of sulfonamide **10** with piperonal, giving a 3:4 diastereomeric mixture of products has been recently reported; see Nagarajan, K.; Chandrasekharan, J.; Rodrigues, P. J. *J. Ind. Inst. Sci.* **1994**, *74*, 247.