Pergamon

Tetrahedron Letters 42 (2001) 8947–8950

TETRAHEDRON LETTERS

Elaboration of 1-benzoyltetrahydroisoquinoline derivatives employing a Pictet–Spengler cyclization with α-chloro-α-phenylthioketones. Synthesis of *O*-methylvelucryptine

Claudio C. Silveira,[a,*] Carmem R. Bernardi,[a] Antonio L. Braga[a] and Teodoro S. Kaufman[b]

[a]*Departamento de Química, Universidade Federal de Santa Maria, 97105.900, Santa Maria, RS, Brazil*
[b]*Instituto de Química Orgánica de Síntesis (CONICET-UNR), Suipacha 570, S2002LRK Rosario, Argentina*

Received 25 September 2001; revised 17 October 2001; accepted 24 October 2001

Abstract—The reaction of *N*-tosyl-β-phenethylamines with α-chloro-α-phenylthioketones, leading to 1-benzoyl- and 1-pivaloyl-tetrahydroisoquinolines under modified Pictet–Spengler conditions, is described. The synthesis of *O*-methylvelucryptine employing this transformation as a key step is reported. © 2001 Elsevier Science Ltd. All rights reserved.

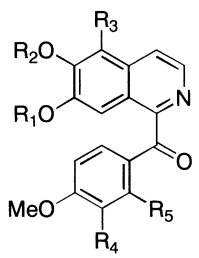
Being a very numerous class of natural products and covering a wide range of structural types, 1-benzylisoquinoline alkaloids and their derivatives are attractive targets for synthesis and drivers of the development of new synthetic methodologies.[1]

1-Benzoylisoquinolines constitute a small group within the 1-benzylisoquinolines, with most of its members having been isolated during the past two decades. They are represented by natural products such as xanthaline (**1**) also known as papaveraldine, a degradation product and contaminant of the pharmaceutically useful papaverine,[2] rugosinone (**2**),[3] thalmicrinone (**3**)[4] and the unnamed base **4**.[5]

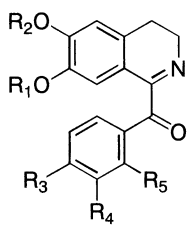
It has been proposed[1] that fully aromatic members result from biochemical dehydrogenation of their corresponding tetrahydroisoquinoline precursors, being the 3,4-dihydroisoquinolines like velucryptine (**5**),[6] dihydrorugosinone (**6**), canelillinoxine (**7**),[7] longifolonine[8] (**8**) and oxo-3,4-dihydrodoryafranine (**9**),[5] produced as intermediates during this process.

Interestingly, the in vitro air oxidation of certain tetrahydroisoquinolines to produce 1-benzoyl-3,4-dihydroisoquinolines has been observed.[9] In addition, 1-benzoylisoquinolines are also structurally related to other oxidized alkaloids, such as oxocularines[10,11] and oxoaporphines.

Few and scattered syntheses of these compounds are known. 1-Benzoylisoquinolines have been elaborated by oxidation of 1-benzyl-3,4-dihydroisoquinolines obtained by the Bischler–Napieralski cyclization,[6,12]



1 R_1=R_2= Me, R_3=R_5= H, R_4= OMe
2 R_1R_2= CH_2, R_3= OH, R_4=R_5= H
3 R_1=R_2= Me, R_3= OMe, R_4=R_5= H
4 R_1R_2= CH_2, R_3=R_4=R_5= H



5 R_1= H, R_2= Me, R_3= OMe, R_4= R_5= H
6 R_1=R_2= CH_2, R_3=R_4= OMe, R_5= OH
7 R_1= H, R_2= Me, R_3= OMe, R_4=R_5= H
8 R_1= H, R_2= Me, R_3= OH, R_4= R_5= H
9 R_1R_2= CH_2, R_3= OH, R_4=R_5= H

Keywords: 1-benzoyltetrahydroisoquinolines; Pictet–Spengler; α-chloro-α-phenylthioketones; *O*-methylvelucryptine.
* Corresponding author. Tel./fax:+ 55 55 220 8754; e-mail: silveira@quimica.ufsm.br

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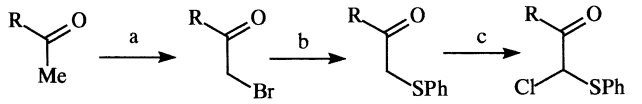
PII: S0040-4039(01)01998-0



Scheme 1. *Reagents and conditions*: (a) Br_2, Et_2O, rt (72–87%); (b) NaH, PhSH, THF, rt (83–84%); (c) NCS, Cl_4C, BPO (65–73%).

and in a one-pot reaction of phenethylamines with vicinal diketoesters under modified Pictet–Spengler conditions, involving hydrolysis and decarboxylation of a 1,1-disubstituted tetrahydroisoquinoline carboxylate intermediate.[9] Non-natural 1-benzoylisoquinolines have also been obtained by photolysis of berberinium salts[13] and as intermediates during the synthesis of phthalideisoquinolines from modified berberines.[14]

Recently, α-chloro-α-methylthiocarbonyl derivatives have been employed as masked aldehydes in isoquinoline syntheses,[15] including the cyclization of unactivated aromatic rings[16] and we have informed on the use of α-chloro-α-phenylselenocarboxylates as aldehyde surrogates in the elaboration of 1,2,3,4-tetrahydroisoquinoline-1-carboxylates by means of a modified Pictet–Spengler type cyclization.[17] Here, we wish to report the synthesis of 1-benzoyl- and 1-pivaloyl-tetrahydroisoquinoline derivatives by Pictet–Spengler condensation of substituted β-phenethylamines with the α-chloro-α-phenylthioketones **10** and **11** and the of this strategy as the key step for the elaboration of the natural product **4** and *O*-methylvelucryptine (**12**).

The synthesis of the organosulfur reagents was conveniently carried out in three high-yielding steps from acetophenone and pinacolone, as shown in Scheme 1. The starting methylketones were cleanly α-brominated with bromine in diethyl ether (72–87%), the resulting bromides were nucleophilically displaced with thiophenolate (83–84%) and the product subsequently chlorinated with *N*-chlorosuccinimide under benzoyl peroxide promotion (65–73%).[18]

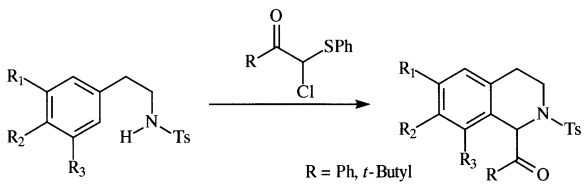
As shown in Table 1, upon reaction of the organochalcogen ketones with *N*-tosyl-β-phenethylamines under Lewis-acid catalysis, smooth production of the expected 1-substituted tetrahydroisoquinoline derivatives was observed.

Yields were fair to good. Oxygenated aromatic rings, including the improperly activated system of entries 5 and 6 were cleanly transformed with $SnCl_4$, while deactivated (entries 11 and 12) or unactivated (entries 9, 10, 13 and 14) ring systems, required more drastic conditions ($ZnCl_2$ in refluxing 1,2-dichloroethane).

In a pairwise comparison, it was observed that methoxy substituted phenethylamines performed better with **11** than with its congener **10** (entries 1–6), while no significant differences were observed in the yields of products when the starting phenethylamine carried other substituents.

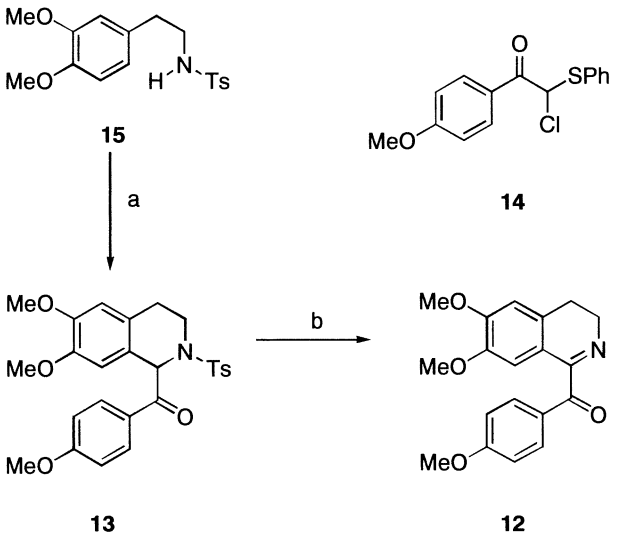
The elaboration of 1-benzoyl-2-tosyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (entry 2) is representative

Table 1. Synthesis of 1-benzoyl- and 1-pivaloyl-tetrahydroisoquinoline derivatives by reaction of α-chloro-α-phenylthioketones with *N*-tosyl-β-phenethylamines under Lewis-acid promotion



Entry	R	R_1	R_2	R_3	Reaction conditions[a]	Yield (%)[b]
1	*t*-Butyl	OMe	OMe	H	$SnCl_4$, CH_2Cl_2, −78°C→rt 5 h	64
2	Ph	OMe	OMe	H	$SnCl_4$, CH_2Cl_2, −78°C→rt 5 h	73
3	*t*-Butyl	OMe	OMe	OMe	$SnCl_4$, CH_2Cl_2, −78°C→rt 5 h	46
4	Ph	OMe	OMe	OMe	$SnCl_4$, CH_2Cl_2, −78°C→rt 5 h	62
5	*t*-Butyl	H	OMe	H	$SnCl_4$, CH_2Cl_2, −78°C→rt 5 h	32
6	Ph	H	OMe	H	$SnCl_4$, CH_2Cl_2, −78°C→rt 5 h	56
7	*t*-Butyl	OCH_2O	OCH_2O	H	$SnCl_4$, CH_2Cl_2, −78°C→rt 5 h	58
8	Ph	OCH_2O	OCH_2O	H	$SnCl_4$, CH_2Cl_2, −78°C→rt 5 h	57
9	*t*-Butyl	H	H	H	$ZnBr_2$, $ClCH_2CH_2Cl$, reflux 8 h	77
10	Ph	H	H	H	$ZnBr_2$, $ClCH_2CH_2Cl$, reflux 8 h	82
11	*t*-Butyl	Cl	H	H	$ZnBr_2$, $ClCH_2CH_2Cl$, reflux 8 h	61
12	Ph	Cl	H	H	$ZnBr_2$, $ClCH_2CH_2Cl$, reflux 8 h	54
13	*t*-Butyl	H	Me	H	$ZnBr_2$, $ClCH_2CH_2Cl$, reflux 8 h	60
14	Ph	H	Me	H	$ZnBr_2$, $ClCH_2CH_2Cl$, reflux 8 h	60
15[c]	*t*-Butyl	OMe	OMe	H	$SnCl_4$, CH_2Cl_2, −78°C→rt 5 h	51

[a] A 5.0:1.0:1.3 relationship between Lewis acid, β-phenethylamine and haloketone, respectively, was used.
[b] Isolated yield after column chromatography purification.
[c] Reaction of **10** with the *N*-carbamoyl-β-phenethylamine.



Scheme 2. *Reagents and conditions*: (a) **14**, $SnCl_4$, CH_2Cl_2, −78°C (66%); (b) 37% KF/Al_2O_3, microwave (490 W, 10 s, 77%).

of a typical experimental procedure. Under an argon atmosphere, a mixture of *N*-tosyl-β-phenethylamine (335 mg, 1 mmol) and α-chloro-α-phenylthiocarbonyl reagent **11** (1.3 mmol, 1.3 equiv.) were dissolved in methylene chloride (5 mL), cooled to −78°C and treated dropwise with $SnCl_4$ (0.585 mL, 5 mmol, 5 equiv.). The reaction was slowly warmed to room temperature and stirred until complete absence of starting material (by TLC) was observed. Then, the reaction mixture was poured on water, the organic products were extracted with methylene chloride (3×20 mL), dried ($MgSO_4$), concentrated and chromatographed, furnishing the corresponding 1-benzoyl 1,2,3,4-tetrahydroisoquinoline (330 mg, 73%).

Yields of cyclized products with the sulfur-based reagents were more consistent and generally higher than those previously recorded for the modified Pictet–Spengler condensation of *N*-sulfonyl-β-phenethylamines with α-chloro-α-phenylselenocarboxylates;[17] therefore, attempts to evaluate the performance of the analogous selenium reagents in this transformation were made. Thus, the α-chloro-α-phenylselenoketone derived from pinacolone was uneventfully prepared by radical halogenation of the corresponding α-selenoketone.[19] Unfortunately, however, its reaction with phenethylamines furnished a complex mixture consisting mostly in unidentifiable products, and very low yield of the required tetrahydroisoquinolines.

On the other hand, when the suitability of *N*-carbamoyl-β-phenethylamines was explored, comparatively lower yields of cyclized products were observed (entry 15).

An interesting application of this cyclization strategy was found in the synthesis of *O*-methylvelucryptine (**12**);[20] this is the methylated derivative of velucryptine, isolated from *Cryptocarya velutinosa*,[6] which was also obtained by *O*-methylation of longifolonine.[21] To this end, α-halo-α-phenylthioketone **14** was prepared from the commercially available 4-methoxy acetophenone following the strategy outlined in Scheme 1 and reacted with *N*-tosyl-β-phenethylamine **15** at −78°C under $SnCl_4$ catalysis, to afford tetrahydroisoquinoline **13** in 66% yield.

In turn (Scheme 2), this was submitted to a microwave-assisted eliminative detosylation with potassium fluoride supported on alumina,[22] cleanly furnishing the final product **12** in 77% yield.

Analogously, submission of the tetrahydroisoquinoline product prepared by the reaction of the corresponding 3,4-methylenedioxy phenethylamine with **14** ($SnCl_4$, CH_2Cl_2, −78°C to rt, 5 h, 54% yield) to reaction with KF/Al_2O_3 under microwave irradiation (490 W, 60 s), provided the unnamed base **4** in 49% yield.[5,23]

This and all new products were fully characterized by spectral means, including IR, ^1H and ^{13}C NMR spectroscopy, and mass spectrometry.

In conclusion, this work demonstrated the usefulness of α-halo-α-phenylthioketones as convenient building blocks for the elaboration of 1-benzoylisoquinoline derivatives by Pictet–Spengler condensation with activated β-phenethylamines under Lewis-acid catalysis. This transformation, in conjunction with a microwave-assisted oxidative removal of the sulfonyl moiety, was employed for the synthesis of *O*-methylvelucryptine and the unnamed natural product **4**.

It is noteworthy that the latter constitutes an interesting and unprecedented use of the KF/Al_2O_3 reagent, the scope and limitations of which are currently under study. The synthetic strategy may be useful for the elaboration of other 1-benzoylisoquinolines.

Acknowledgements

The authors thank Fundação Vitae (Grant No. B-11487/9B004), FAPERGS, CNPq and CAPES for financial support. T.S.K. thanks CONICET.

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23. Compound **4**: mp 152–154°C (lit.[5] 152–153°C); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.87 (s, 3H), 6.09 (s, 2H), 6.94 (d, 2H, $J=8$ Hz), 7.14 (s, 1H), 7.84 (s, 1H), 7.60 (d, 1H, $J=5.4$ Hz), 7.93 (d, 2H, $J=8$ Hz), 8.43 (d, 1H, $J=5.4$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.52, 101.80, 102.28, 102.73, 113.73 (2C), 121.80, 123.87, 129.66, 133.18 (2C), 135.52, 140.44, 149.27, 151.10, 154.81, 164.01, 193.61.
O-Methylvelucryptine (**12**):[8] mp 91–92°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.81 (t, 2H, $J=8$ Hz), 3.77 (s, 3H), 3.87 (s, 3H), 3.92 (s, 3H), 3.87–3.95 (m, 2H), 6.74 (s, 1H), 6.92 (s, 1H), 6.94 (d, 2H, $J=8$ Hz), 8.02 (d, 2H, $J=8$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.40, 47.13, 55.49, 55.98, 56.07, 109.77, 110.52, 113.83 (2C), 119.43, 128.48, 131.10, 132.82 (2C), 147.66, 151.71, 164.24, 164.70, 192.56.