Synlett R. A. Ábrahámi et al. Letter

A *De Novo* Synthetic Route to 1,2,3,4-Tetrahydroisoquinoline Derivatives

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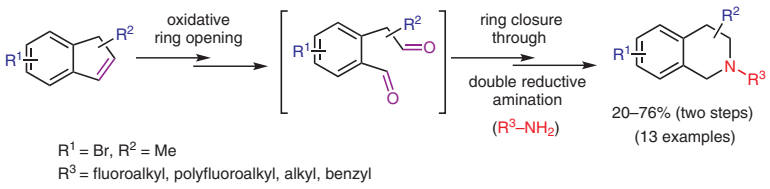


Received: 09.02.2018
Accepted after revision: 07.03.2018
Published online: 22.03.2018
DOI: 10.1055/s-0037-1609494; Art ID: st-2018-v0088-l

Abstract A novel synthetic approach was developed for the construction of the 1,2,3,4-tetrahydroisoquinoline framework possessing varied functions. The synthetic strategy was based on oxidative ring opening of some indene derivatives through their C=C bond, followed by double reductive amination of the dicarbonyl intermediates with various primary alkyl- or fluoroalkylamines.

Key words tetrahydroisoquinolines, ring opening, ring closure, reduction, amination, fluorination

The 1,2,3,4-tetrahydroisoquinoline framework is a commonplace and important structural element found in a number of structural units of numerous natural products. Many of these natural products, for example, some alkaloids, exhibit various valuable biological properties. Moreover, several drugs, such as some antidiuretics, antidepressants, hallucinogens, and antihypertensive agents, also contain a tetrahydroisoquinoline core.[1] Because of the importance of products possessing the 1,2,3,4-tetrahydroisoquinoline skeleton, many synthetic approaches to the creation of an isoquinoline or 1,2,3,4-tetrahydroisoquinoline core have been described.[2]

As a consequence of their high biological potential, fluorinated organic compounds have generated increasing attention in organic and medicinal chemistry over the past decade. The replacement of one or more hydrogen atoms by fluorine in various biomolecules can generate remarkable changes in their physical, chemical, and biological properties.[3] Fluorine-containing tetrahydroisoquinoline or isoquinoline derivatives constitute an important segment in the family of fluorinated molecules, either as pharmaceuticals or agrochemicals (Figure 1). However, tetrahydroisoquinoline derivatives incorporating fluorine in their structure are not very abundant.[4] The synthesis of fluorinated, fluoroalkylated, or fluoroarylated isoquinoline derivatives with valuable biological properties continues to be a field of considerable interest in medicinal and organic chemistry. Several methods for the creation of monofluorinated, trifluoromethylated, or fluoroarylated isoquinolines have been developed in recent years.[4]

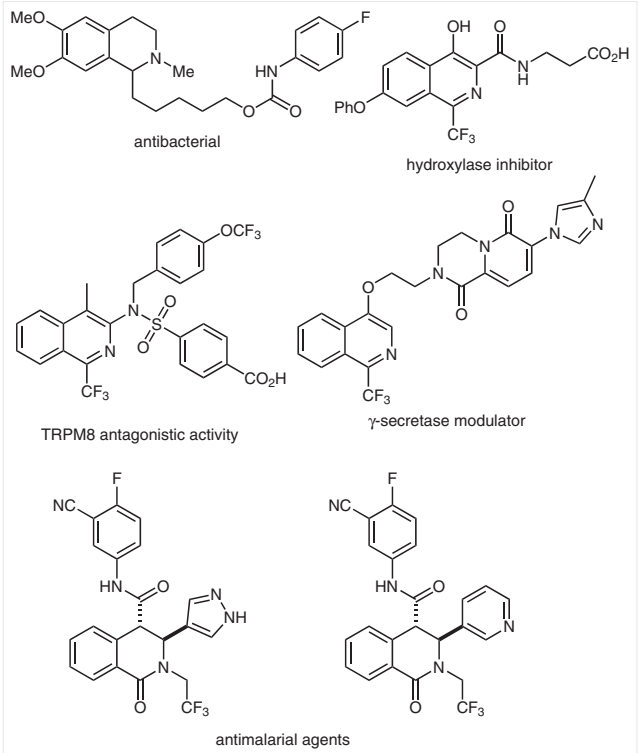
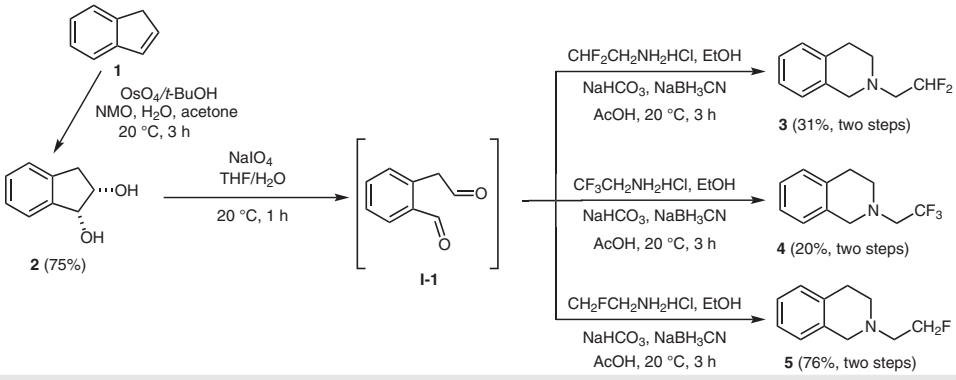


Figure 1 Some biologically important fluorine-containing isoquinoline derivatives.

Because of the high biological importance of 1,2,3,4-tetrahydroisoquinoline alkaloids and the increasing relevance of various organofluorine scaffolds, our goal was to develop an efficient procedure for accessing various fluorinated 1,2,3,4-tetrahydroisoquinoline derivatives. The novel synthetic route that we developed is based on oxidative ring opening/ring closing with reductive amination protocol.[5] Briefly, it starts from indene or a substituted indene derivative, and it includes the key steps of olefin-bond cleavage through dihydroxylation/$NaIO_4$-mediated oxidation and subsequent cyclization with primary amines through reductive amination.

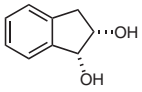
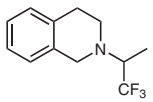
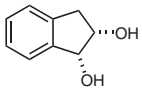
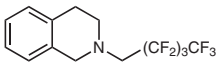
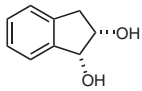
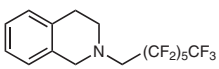
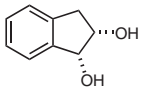
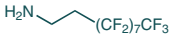
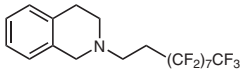
First, we started with the transformation of unsubstituted 1*H*-indene (**1**). Thus, diol **2**,[6] derived by OsO_4-catalyzed dihydroxylation of 1*H*-indene (**1**), was subjected to ring cleavage with $NaIO_4$ (Scheme 1). The resulting unstable diformyl intermediate compound **I-1** was further transformed, without isolation, with various commercially available fluorine-containing primary amines to give the target compounds in two steps. Reductive amination of **I-1** with (2,2-difluoroethyl)amine, (2,2,2-trifluoroethyl)amine, or (2-fluoroethyl)amine in the presence of $NaBH_3CN$ provided, through cyclization, modest yields of the corresponding tetrahydroisoquinoline derivatives **3**, **4**,[7] and **5**, containing a mono-, di-, or trifluoromethyl group, respectively (Scheme 1).[8] It is clear from the above results that the yield of the isoquinoline product decreased on increasing the number of fluorine atoms in the amine. It should be mentioned that attempt to carry out the transformation of **2** into the tetrahydroisoquinoline derivatives in one-pot manner failed.

The method was further extended to synthesize other novel fluorine-containing tetrahydroisoquinoline derivatives by starting from diol **2**. Oxidative ring opening followed by treatment of the resulting dialdehyde **I-1** with various commercially available trifluoromethylated or polyfluorinated amines gave the corresponding N-heterocycles **6**–**9** (Table 1).



Scheme 1

Table 1 Synthesis of N-Heterocycles **6–9**

Starting Compound	Fluorinated Amine	Product	Yield (%)[a]
		 **6**	34
		 **7**	24
		 **8**	53
		 **9**	28

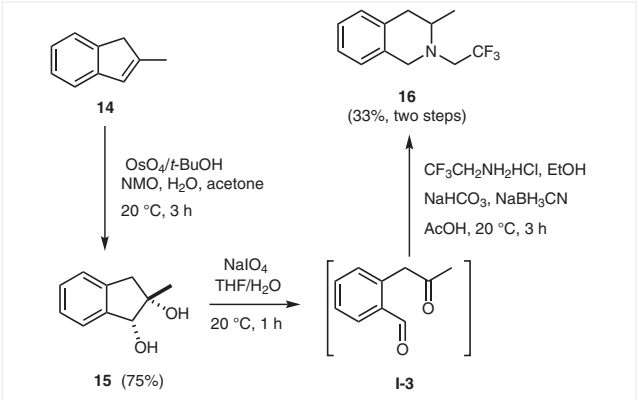
[a] Yield over two steps.

This synthetic route was further extended by using indene derivatives with substituents on the benzene ring. For this purpose, we selected 7-bromo-1*H*-indene (**10**) as a model compound, which was transformed into the corresponding diol **11** through *cis*-dihydroxylation. Oxidative cleavage of the vicinal diol **11** with $NaIO_4$ in THF–H_2O at room temperature, as in the case of the unsubstituted derivative, gave the corresponding unstable diformyl-substituted intermediate **I-2**. Without isolation or characterization, this reacted further with (2,2,2-trifluoroethyl)amine or (2,2-difluoroethyl)amine under reductive conditions in the presence of $NaBH_3CN$ in EtOH at room temperature for three hours to give the corresponding trifluorinated and difluorinated tetrahydroisoquinoline derivatives **12** and **13**, respectively, through double reductive amination (Scheme 2).

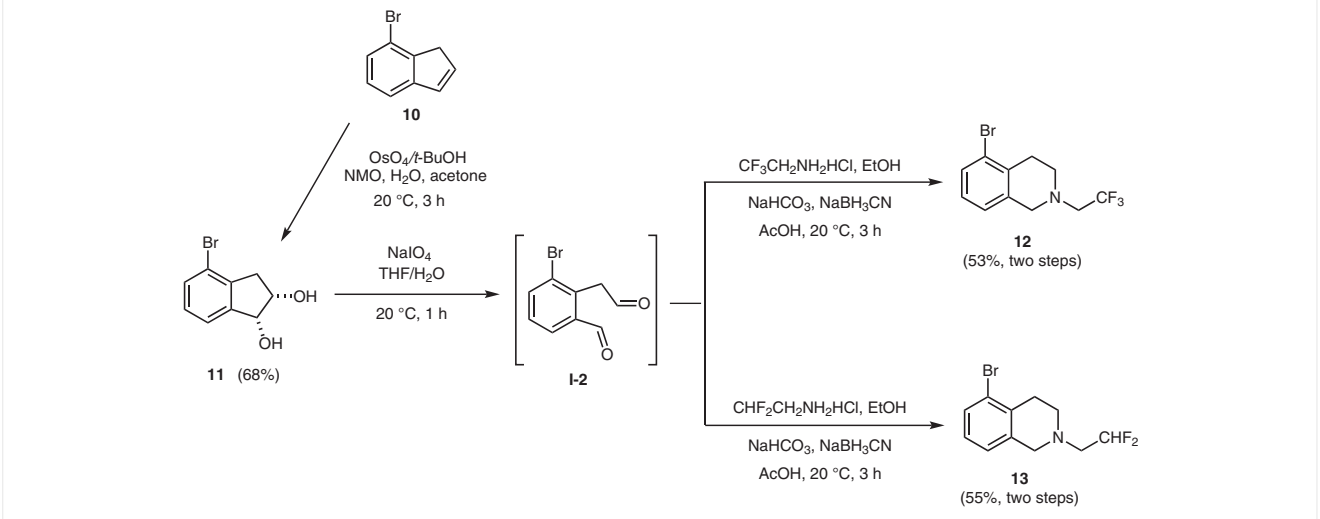
A further extension of this method was attempted with another substituted indene derivative bearing a substituent on the five-membered ring moiety. Thus, 2-methyl-1*H*-indene (**14**) was selected as a model substrate for the isoquinoline ring construction. Dihydroxylation of **14** smoothly gave diol **15**,[9] which underwent ring cleavage with $NaIO_4$ to give the dicarbonyl derivative **I-3** (Scheme 3). After workup, this immediately reacted with (2,2,2-trifluoroethyl)amine to give the isoquinoline derivative **16**, with a newly generated chiral center, in moderate yield (33%, two steps from **15**).

Finally, we attempted to apply the tetrahydroisoquinoline ring-creation method described above to various nonfluorinated reactants. The generality of the developed method was demonstrated by using three different primary amines: ethylamine (as the nonfluorinated counterpart of the previously used mono-, di-, or trifluoroethylamines), butylamine, and benzylamine. Cyclization of the diformyl intermediate **I-1** (derived from diol **2**) by reaction with these amines gave modest yields of the corresponding N-substituted tetrahydroisoquinoline derivatives **17**,[10] **18**,[11] and **19**,[12] respectively (Scheme 4). The highest yield was obtained from benzylamine (69%, two steps).

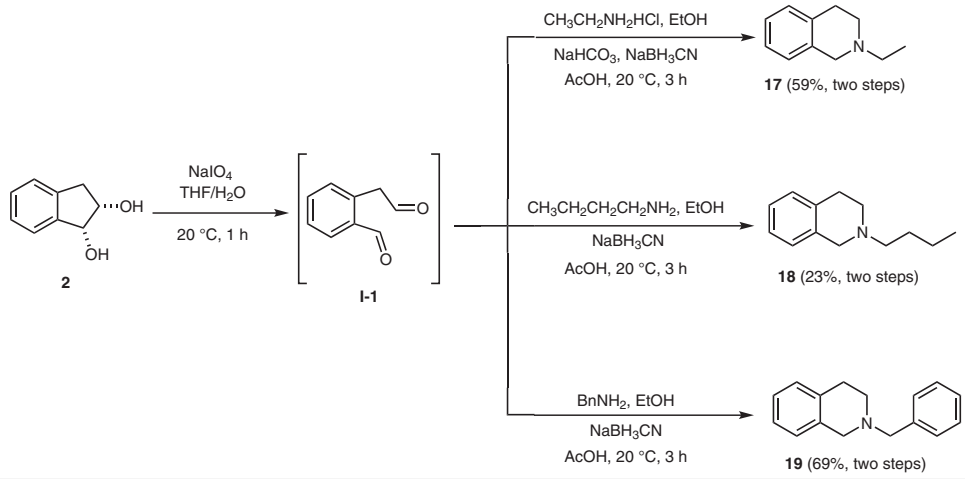
In conclusion, convenient, and efficient procedure has been developed for the construction of the 1,2,3,4-tetrahydroisoquinoline framework with various fluorine-containing or nonfluorinated substituents. The method is based on oxidative ring cleavage of the olefinic bond of 1*H*-indene or a substituted indene derivatives, followed by reductive ring closure of the diformyl intermediate with an amine. Extensions of this method to the preparation of novel substituted tetrahydroquinoline derivatives are currently being investigated in our laboratory.



Scheme 3



Scheme 2



Scheme 4

Funding Information

We are grateful to the Hungarian Research Foundation (NKFIH Nos. K 115731 and K 119282) for financial support. The financial support of the GINOP-2.3.2-15-2016-00038 project is also acknowledged. This research was supported by the EU-funded Hungarian grant EFOP-3.6.1-16-2016-00008.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609494.

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(8) **1,2,3,4-Tetrahydroquinolines 3–9, 12, and 13: General Procedure**

$NaIO_4$ (1.5 equiv) was added to a stirred solution of the dihydroxy compound **2** or **11** (4 mmol) in THF–H_2O (25 mL + 2 mL), and the mixture was stirred for 1 h at 20 °C under argon. H_2O (40 mL) was added to dissolve the precipitate, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The extracts were then combined and dried (Na_2SO_4). The crude diformyl product was immediately used in the reductive cyclization without purification. The appropriate fluorinated amine (1 equiv) and $NaHCO_3$ (2 equiv) were added to the solution of the diformyl intermediate in EtOH (20 mL), and the mixture was stirred at 20 °C for 10 min. $NaCNBH_3$ (1 equiv) and AcOH (2 drops) were added, and the mixture was stirred for a further 4 h at 20 °C. The mixture

was then diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, and the crude product was purified by column chromatography (silica gel, hexane–EtOAc).

2-(2,2-Difluoroethyl)-1,2,3,4-tetrahydroisoquinoline(3)

Brown oil; yield: 247.3 mg (31%); R_f = 0.17 (hexane–EtOAc, 20:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.77–2.84 (m, 4 H, H-3, H-4) 2.83–2.95 (td, ^1J = 15.6, ^2J = 4.3 Hz, 2 H, CH_2CHF_2), 3.71 (s, 2 H, H-1), 6.02 –6.39 (tt, ^{1}J = 55.8, ^2J = 4.3 Hz, 1 H, CHF_2), 6.98–7.18 (m, 4 H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 29.2, 51.8, 56.6, 59.5 and 59.8 and 60.02 (t, $^2J_{C,F}$= 28 Hz, $CCHF_2$), 114.5 and 116.9 and 119.3 (t, $^1J_{C,F}$= 237.5 Hz, CHF_2), 126.4, 126.9, 127.1, 129.3, 134.6, 135.3. ^{19}F NMR (376 MHz, DMSO): δ = –115.2. MS: (ESI) *m/z* = 198.2 [M + 1]; Anal. Calcd for $C_{11}H_{13}F_2N$: C, 66.99; H, 6.64; F, 19.27; N, 7.10. Found: C, 66.96; H, 6.63; F, 19.26; N, 7.10. For details of the other synthesized compounds, see the Supporting Information.

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