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Synthesis of Tetrahydroquinoline Derivatives from α-CF_3-N-Arylaldimine and Vinyl Ethers

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Abstract :

$BF_3.Et_2O$ or $Yb(OTf)_3$ catalyzed [4+2] cycloaddition reaction of α-CF_3-N-arylaldimines with nucleophilic olefins afforded CF_3-substituted tetrahydroquinoline derivatives.

Keywords : *aza-Diels-Alder; α–CF_3-N-Arylaldimine; Lewis acids, vinyl ethers.*

Tetrahydroquinoline derivatives are an important class of natural products and exhibit biological activities in various fields [1]. Lewis acid promoted aza-Diels-Alder reactions between N-arylimines and different dienophiles is one of the most powerful synthetic tools for constructing N-containing six-membered heterocyclic compounds such as tetrahydroquinolines [2-12]. Since the pioneering work of Povarov [13], this reaction has been extensively studied with the use of different Lewis acids such as lanthanide salts [14-16] and search for new reaction conditions [14,15,17]. Considering the extraordinary potential of fluoroalkyl containing biologically relevant molecules due to the unique feature of fluorine atom [18], we envisaged to study the aza-Diels-Alder reaction with α–CF_3-N-arylaldimines. Although this cycloaddition is known to be less efficient with alkyl aldimines, a CF_3 substituent lowers the LUMO level [19] and could favor cycloaddition reactions [20]. However concomitantly a trifluoromethyl group also significantly reduces the basicity of carbonyl and imine groups and hence the strength of complexation with a Lewis acid [19]. Effectively the only example of aza-Diels-Alder reaction reported in fluorinated series, is a cationic dipolar reaction starting from a preformed aryliminium salt [21].

In this paper we describe the synthesis of tetrahydroquinoline derivatives bearing a CF_3 group at C-2 position, by an intermolecular [4+2] cycloaddition of the α-CF_3-N-arylaldimine **1** derived from trifluoroacetaldehyde and *p*-anisidine [22], with electron-rich alkenes under Lewis acid catalysis.

The reaction has been explored with two different catalysts, $BF_3.Et_2O$ and $Yb(OTf)_3$. With $BF_3.Et_2O$, the reaction between aldimine **1** and enol ether **2a** was first performed at room temperature and led to a complex mixture. However when the reaction was carried out at -78°C in toluene (it was the best solvent among all other tested such as dichloromethane, ether, THF) in presence of 10% of Lewis acid, the tetrahydroquinoline **3a** was obtained in a 56% yield. Reactions with other enol ethers **2b-d** afforded tetrahydroquinoline derivatives in moderate to good yields and with a high level of selectivity (Table 1). Tetrahydroquinolines **3a** and **3b**

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were obtained as only one regio- and stereoisomer. No other isomer could be detected. Relative configuration of the newly created stereocenters is *cis*, indicating on endo approach of the enol ether. The reaction with the 2,3-dihydrofuran **2c** afforded the tetrahydroquinoline **3c** as a 90/10 mixture of *cis* and *trans* diastereoisomer which were separated by column chromatography. With the 3,4-dihydro-2*H*-pyran **2d**, one equivalent of $BF_3.Et_2O$ was required to obtain the tetrahydroquinoline **3d** in a 64/36 ratio. All structures were determined by ^1H, ^{19}F and ^{13}C NMR spectra. Stereochemistry was assigned by coupling constants and by $\{^{19}F\}$-^1H Nuclear Overhauser Effect measurements.

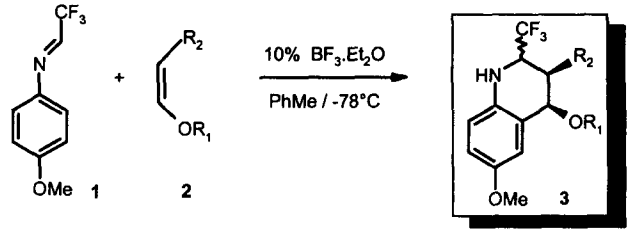
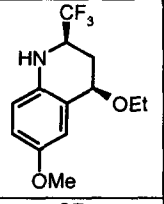
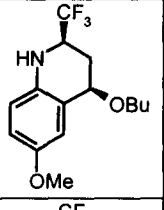
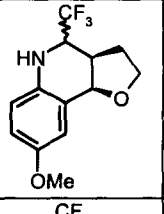
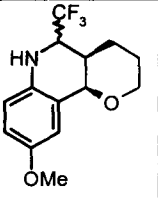


Table 1 : Syntheses of tetrahydroquinoline derivatives ($BF_3.Et_2O$)

Entry	2	t	3	*cis/trans*	Rdt (%)[a]
1	 **2a**	20 min		100/0	56
2	 **2b**	30 min		100/0	60
3	 **2c**	70 min		90/10	84
4	 **2d**	2 h		64/36	86[b]

a) Isolated yield
b) 1 eq of Lewis Acid was required

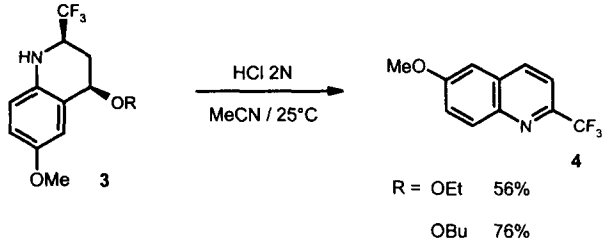
For comparison we also explored this reaction under $Yb(OTf)_3$ catalysis. Results were similar to those obtained with $BF_3.Et_2O$ (Table 2). However some slight differences were observed. With **2c** and **2d**, tetrahydroquinolines **3c**, **3d** were obtained as a 70/30 mixture of *cis* and *trans* isomers. In the case of vinyl ether **2d**, only 5% of lanthanide was required. Morever the great advantage is that this reaction occurred cleanly at room temperature.

Table 2 : Syntheses of tetrahydroquinoline derivatives ($Yb(OTf)_3$, MeCN, r.t.)

Entry	2	t	3	*cis/trans*	Rdt (%)[a]
1	**2a**	15 min	**3a**	100/0	56
2	**2b**	40 min	**3b**	100/0	67
3	**2c**	30 min	**3c**	70/30	74
4	**2d**	6 h	**3d**	70/30	87

a) Isolated yield

The tetrahydroquinolines **3a** and **3b** could be easily converted into quinoline **4** under acidic condition (HCl 2N) [14] in MeCN over 16 hours at room temperature.



In conclusion, the electronwithdrawing character of a CF_3 group has been proved to be very effective in [4+2] aza-Diels-Alder reactions. The α-CF_3-N-arylimine **1** could react with various vinyl ethers to afford tetrahydroquinoline derivatives bearing a CF_3 substituent at C-2 position, in moderate to good yields.

Typical Procedure for the Reaction between the imine 1 and dihydrofuran 2c :

With $BF_3.Et_2O$ (Table 1)

To a solution of **1** (1.5 mmol, 306 mg) in dry toluene (5 mL) was added, at -78°C, $BF_3.Et_2O$ (0.15 mmol, 0.02 mL). After stirring for 10 minutes, 2,3-dihydrofuran **2c** (2.26 mmol, 0.17 mL) in dry toluene (1 mL) was added. The reaction mixture was stirred for 70 minutes, then saturated aqueous $NaHCO_3$ (10 mL) was added and the product was extracted with ether (10 mL x 3). After usual workup, a chromatography on silica gel (petroleum ether/ethylacetate : 80/20) afforded 345 mg (84%) of **3c** (*cis/trans* : 90/10).

Isomer *cis*:

^1H NMR ($CDCl_3$, 400 MHz) : δ 6.89 (d, 1H, J=3 Hz); 6.72 (dd, 1H, J=9, 2.9 Hz); 6.58 (d, 1H, J=9 Hz); 5.2 (d, 1H, J=7.5 Hz); 4.01 (qddd, 1H, J=7, 2.4, 1.5, 0.7 Hz); 3.87 (td, 1H, J=8, 7.4 Hz);3.81 (td, 1H, J=9, 4 Hz); 3.75 (s, 3H, OMe); 3.67 (s, 1H, NH); 2.84 (m, 1H); 2.22 (m, 1H); 1.99 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) : δ 153.9, 135.8, 125.3, 123.1, 116.7, 116.1, 113.1, 75.3, 66.8, 54.7, 37.2, 24.1. ^{19}F NMR ($CDCl_3$, $CFCl_3$) : -76.1 (d, J=7 Hz).

isomer *trans*

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 6.9 (d, 1H, J=3 Hz); 6.74 (dd, 1H, J=9, 3 Hz); 6.58 (d, 1H, J=9 Hz); 4.77 (d, 1H, J=6.5 Hz); 3.93 (td, 1H, J=8.5, 5 Hz); 3.85 (td, 1H, J=8, 7.2 Hz); 3.75 (s, 3H, OMe); 3.56 (qdd, 1H, J=7, 6.6, 2 Hz); 2.27 (dtd, 1H, J=13, 8, 5 Hz); 2.12 (dq, 1H, J=13, 7 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) : δ 153.0, 135.0, 125.5, 121.0, 115.8, 116.4, 113.5, 73.9, 65.6, 55.7, 54.8, 35.9, 29.2. ^{19}F NMR ($CDCl_3$, $CFCl_3$) : -75.95 (d, J=7Hz).

With Yb(OTf)$_3$ (Table 2)

To a solution of $Yb(OTf)_3$ (0.05 mmol, 21 mg) in MeCN (1 mL) was added imine **1** (1 mmol, 203 mg) and **2c** (1.5 mmol, 0.13 mg) in MeCN (1.5 mL) at r.t.. The reaction mixture was stirred for 30 minutes, then a saturated aqueous $NaHCO_3$ solution (10 mL) was added and the product was extracted with ether (10 mL x 3). After usual workup, a chromatography on silica gel afforded 202 mg (74%) of **3c** (*cis/trans* : 70/30).

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