

# Antimony chloride HAP catalyzed synthesis of *trans*-furo[3,2-*c*]quinolines *via* inverse electron demand Diels-Alder reaction

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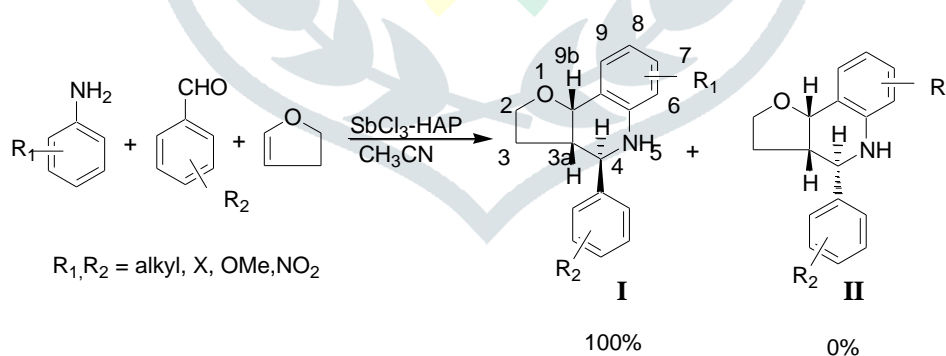
## Abstract

Antimony chloride HAP is used to catalyze the reaction between anilines, benzaldehydes and dihydrofuran in one pot to construct stereoselective *trans* hexahydrofuro[3,2-*c*]quinolones in excellent yields. The catalyst is recyclable.

**Index Terms:** Aza Diels –Alder reaction, SbCl<sub>3</sub>-HAP, stereoselective, quinolines

## I. Introduction

Furoquinolines possess various biological activities such as psychotropic,<sup>1</sup> antiallergenic,<sup>2</sup> antiinflammatory<sup>3</sup> and anti-arrhythmic<sup>4</sup> properties. An easy way to construct nitrogen containing six member heterocyclic ring is the inverse electron demand Diels-Alder reaction<sup>5</sup> also known as Aza Diels-Alder reaction occurring between N-aryl imines and nucleophilic olefins. Various Lewis acid catalysts have been used for this purpose. Antimony (III) chloride has been used catalytically in various organic reactions as an efficient Lewis acid. In our ongoing pursuits to explore the uses of SbCl<sub>3</sub> as a Lewis acid catalyst in organic synthesis, we wished to employ SbCl<sub>3</sub> over HAP<sup>6</sup> to effect the reaction between anilines, benzaldehydes and dihydrofuran in one pot to construct *trans* hexahydrofuro[3,2-*c*]quinoline skeleton, in extension to our work.<sup>7</sup>



Scheme 1

## II. Results and Discussion

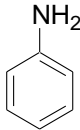
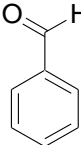
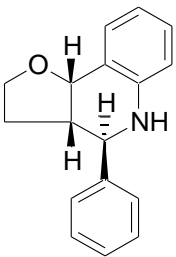
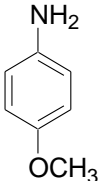
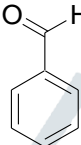
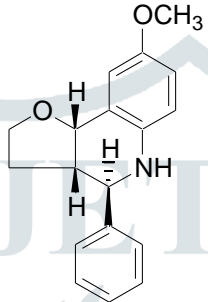
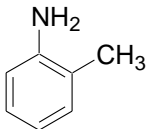
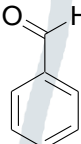
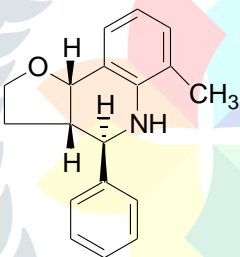
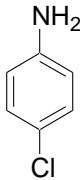
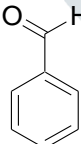
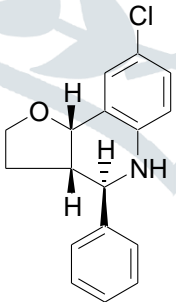
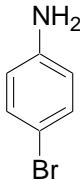
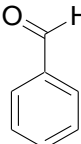
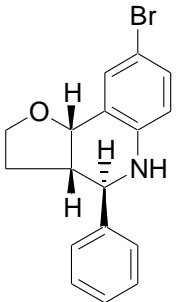
A mixture of benzaldehyde (1 mmol) and aniline (1 mmol) was stirred and refluxed in acetonitrile in presence of SbCl<sub>3</sub> – HAP ( 1.6 mol% )<sup>8</sup> with stirring under N<sub>2</sub> atmosphere till the formation of benzyldeneaniline; as revealed by TLC and at this point was added dihydrofuran (1.1 mmol) to the same reaction flask and the reaction was continued to reflux (Scheme 1). The formation of a newer product was noticed in approx. 1.3 hour which was isolated in 90% yield by column chromatography over silica gel. This compound was found to be *trans*-4-Phenyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline as revealed by the comparison of its spectral and physical data with that of the authentic sample.<sup>9</sup> <sup>1</sup>H NMR spectrum showed

peaks at  $\delta$  7.4 - 6.6 for nine aromatic protons, one proton at position 4 as doublet at  $\delta$  5.1 with  $J = 8.1$  Hz, one CH at  $\delta$  4.7 showing doublet, broad singlet at  $\delta$  4.0 corresponding to N-H, CH<sub>2</sub> at  $\delta$  3.8 – 3.7 as multiplet, one proton at  $\delta$  2.8 – 2.7 as multiplet and two protons (CH<sub>2</sub>) showing multiplet peaks at  $\delta$  1.5 – 1.4. <sup>13</sup>C NMR spectrum showing peaks at  $\delta$  145, 141, 131, 128, 120, 118, 114, 76, 65, 57, 43 and 28. The IR and mass spectra were also in consonance with the structure envisaged. There is strong NH stretching band at 3340 cm<sup>-1</sup> in the IR spectrum. The product displayed the most diagnostic feature for structural assignment in <sup>1</sup>H NMR and that is the scalar coupling constant  $J(3a,4) = 10.8$  Hz, indicative of *trans* disposition of protons H-3a and H-4. The most significant and notable feature of the present reaction is the formation of single *trans* isomer in contrast to the earlier observations<sup>100</sup> where the formation of *cis* product has also been noticed. The <sup>1</sup>H-<sup>1</sup>H- COSY analysis confirms this structural assignment; a strong reciprocal interaction is found between H-3a and H-9b, a weak one between protons H3 and H-4, but none between protons H-9b and H-4, all in accord with a *trans* configuration.

Two step reactions would be required for the formation of condensed quinolines. First, the synthesis of imines from anilines and benzaldehydes and second, the inverse electron demand Diels-Alder reaction. Since most of the imines are hygroscopic in nature, decompose at high temperature and difficult to purify by distillation or column chromatography, we contemplated to perform both the reactions in one pot i.e. *in situ* formation of imines from benzaldehydes and anilines followed by the Diels-Alder reaction with DHF in the presence of SbCl<sub>3</sub>-HAP. Benzaldehyde (1 mmol), aniline (1 mmol) and SbCl<sub>3</sub>-HAP were refluxed in dry acetonitrile with stirring under N<sub>2</sub> atmosphere, the complete formation of benzylideneaniline was observed in fifteen minutes and at this point was added DHF (1.1 mmole) to the same reaction flask and the reaction was continued to reflux. To our delight, imino Diels-Alder reaction was completed in 1.5 hour resulting in the formation of *trans* product. A notable feature of SbCl<sub>3</sub>-HAP catalyst is its reusability. The catalyst was used ten times with no considerable decrease in its efficiency. The qualitative test for the presence of antimony (III) ions in the water as solvent was done and was found to be negative. The mechanism of the reaction seems to be SbCl<sub>3</sub> – HAP catalyzed formation of imines followed by Diels-Alder reaction of N-benzylideneanilines as diene and DHF as dienophile.

Substituted anilines and benzaldehydes were used and the results are shown in Table 1. Anilines with electron releasing groups react comparatively faster as compared with anilines with electron withdrawing groups. However, benzaldehydes with deactivating groups react comparatively faster.

Table 1: SbCl<sub>3</sub>-HAP catalysed synthesis of *trans*-furo-[3,2-*c*]quinolines

Entry	Aniline	Aldehyde	Product	Time (hour)	Yield <sup>a</sup> (%)	Melting point (°C) <sup>b</sup> Obs. (lit.) <sup>10</sup>
1			 <b>1a</b>	1.5	90	118–120 (117-118)
2			 <b>1b</b>	2.0	85	130 – 132 (132-133)
3			 <b>1c</b>	2.0	85	101 – 102 (101-103)
4			 <b>1d</b>	2.5	82	152-154 (153–155)
5			 <b>1e</b>	3.0	82	133-134 (134 –136)

<sup>a</sup> Isolated yields. <sup>b</sup> Melting points are uncorrected.

### III. Experimental Section

All experiments were performed in an oven dried glass apparatus. Melting points were measured in open capillaries on Perfit melting point apparatus and are uncorrected. The progress of the reaction was monitored by TLC (0.5-mm-thick plates) using SISCO silica gel G as adsorbent. The visualization of spots was effected by exposure to iodine vapors and 2,4-dinitrophenylhydrazine in ethanol containing few drops of conc. H<sub>2</sub>SO<sub>4</sub> and 5% anisaldehyde solution in acidic ethanol and on heating. The plates were developed with ceric ammonium sulfate in H<sub>2</sub>SO<sub>4</sub>. Column chromatography was performed on silica gel (60-120 mesh) and compounds were eluted with graded solvent systems of petroleum ether (60-80) and ethyl acetate. Elemental analysis was performed on Leco CHNS-932. IR spectra on KBr were recorded on Perkin-Elmer FTIR spectrophotometer. NMR (<sup>1</sup>H broadband decoupled and <sup>13</sup>CNMR) spectra were recorded on Bruker Ac-200 (400 MHz and 100 MHz respectively) spectrometer. ESI-MS spectra were recorded on Micro-Mass VG-7070 H mass spectrometer. All organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and solvents were removed on rotavapour under reduced pressure. Commercial grade solvents were dried as per established procedure before use.

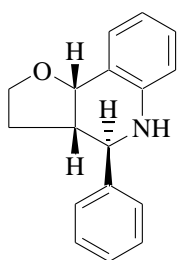
### IV. General Procedure

A mixture of benzaldehyde (1 mmol), aniline (1 mmol) and SbCl<sub>3</sub>-HAP (0.5g) was refluxed in acetonitrile (1 mL) in the presence of 4 Å molecular sieves with stirring under N<sub>2</sub> atmosphere for about 20 minutes till the formation of imine is complete (TLC). To the reaction mixture, DHF (1.1 ml) was added and refluxed for another 1.5 - 3.5 hour till the completion of the reaction (TLC). Acetonitrile was distilled off under reduced pressure; the reaction mixture was diluted with ethyl acetate (30 mL) and filtered. The filtrate was washed with brine (2 × 15 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and the resultant was directly charged over small silica gel (60-120 mesh) column to afford pure *trans*-furo[3,2-*c*]quinolines (82 - 90%). The spectral data of all the known compounds was found to be identical with that of the authentic samples.<sup>10</sup>

### V. Physical and Spectral data of *trans*-products

#### 1a. 4-Phenyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline

M.pt. 118 -120 °C.



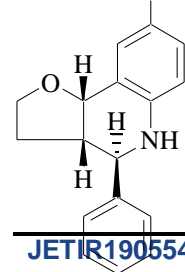
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.4 – 6.6 (9H, m), 5.1 (1H, d, *J* = 8.1 Hz), 4.7 (1H, d, *J* = 3.0 Hz), 4.1 (1H, br s), 3.8 – 3.7 (2H, m), 2.8 – 2.7 (1H, m), 1.5 – 1.4 (2H, m).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ: 145, 141, 131, 128, 120, 118, 114, 76, 65, 57, 43, 28.

IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3340, 3325, 2985.

ESI-MS *m/z* = 252 (M+H)<sup>+</sup>.

OCH<sub>3</sub> *Anal Calcd.* for C<sub>17</sub>H<sub>17</sub>NO: C, 81.25, H, 6.80, N, 5.55. Found: C, 81.58, H, 7.12, N, 5.86.



#### 1b. 8-Methoxy-4-phenyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline

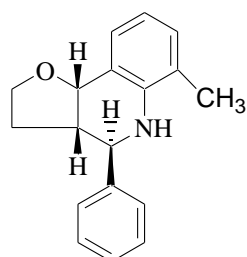
M.pt. 130 - 132 °C.

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 7.4 – 6.4 (8H, m), 5.3 (1H, d,  $J = 8.0$  Hz), 4.8 (1H, d,  $J = 3.0$  Hz), 4.0 (1H, br s), 3.8 (3H, s), 3.8 – 3.7 (2H, m), 2.7 – 2.6 (1H, m), 1.6 -1.5 (2H, m).

**IR** (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3345, 3295, 2980.

*Anal Calcd.* for  $\text{C}_{18}\text{H}_{19}\text{NO}_2$ : C 76.87, H, 6.76, N, 4.98. Found: C, 77.22, H, 6.98, N, 5.32.

### 1c. 6-Methyl-4-phenyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]quinoline



M.pt. 101 - 102 °C.

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 7.4 – 6.8 (8H, m), 5.2 (1H, d,  $J = 8.0$  Hz), 4.7 (1H, d,  $J = 3.0$  Hz), 4.0 (1H, br s), 3.7 – 3.6 (2H, m), 2.8 – 2.7 (1H, m), 2.1 (3H, s), 1.5 - 1.3 (2H, m).

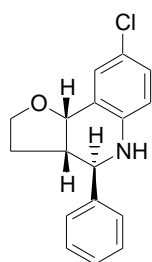
$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$ : 143, 142, 130, 129, 128, 121, 119, 117, 76, 65, 57, 43,

28, 17.

**IR** (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3400, 3310, 2980.

*Anal Calcd.* for  $\text{C}_{18}\text{H}_{19}\text{NO}$ : C, 81.48, H, 7.16, N, 5.28. Found: C, 81.82, H, 7.48, N, 5.64.

### 1d. 8-Chloro-4-phenyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]quinoline



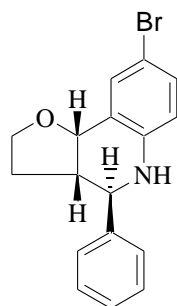
M.pt. 152 - 154 °C.

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 7.4 – 6.4 (8H, m), 5.5 (1H, d,  $J = 8.1$  Hz), 4.7 (1H, d,  $J = 3.0$  Hz), 4.0 (1H, br s), 3.6 – 3.5 (2H, m), 2.8 – 2.7 (1H, m), 1.6 - 1.5 (2H, m).

**IR** (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3345, 3310, 2985.

*Anal Calcd.* for  $\text{C}_{17}\text{H}_{16}\text{ClNO}$ : C, 71.48, H, 5.60, N, 4.90. Found: C, 71.84, H, 5.92, N, 5.23.

### 1e. 8-Bromo-4-phenyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]quinoline



M.pt. 133 - 134 °C.

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ : 7.6 – 6.6 (8H, m), 5.7 (1H, d,  $J = 8.2$  Hz), 4.7 (1H, d,  $J = 3.0$  Hz), 4.0 (1H, br s), 3.5 – 3.4 (2H, m), 2.7 – 2.6 (1H, m), 1.6 -1.4 (2H, m).

**IR** (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3360, 3310, 2985.

**ESI-MS**  $m/z = 331$  (100) ( $\text{M}+\text{H}$ ) $^+$ , 333 (93) ( $\text{M}+\text{H}$ ) $^+$ .

*Anal Calcd.* for  $\text{C}_{17}\text{H}_{16}\text{BrNO}$ : C, 61.80, H, 4.80, N, 4.20. Found: C, 61.13, H, 4.17, N, 4.56.

*Anal Calcd.* for  $\text{C}_{18}\text{H}_{19}\text{NO}$ : C, 81.35, H, 7.10, N, 5.27. Found: C, 81.66, H, 7.44, N, 5.61.

## VI. References

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