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Facile one pot synthesis of furo/pyrano [3,2-*c*]-1, 2, 3, 4-tetrahydroquinolines from nitro benzenes and 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran in methanol catalyzed by $SnCl_2.2H_2O$

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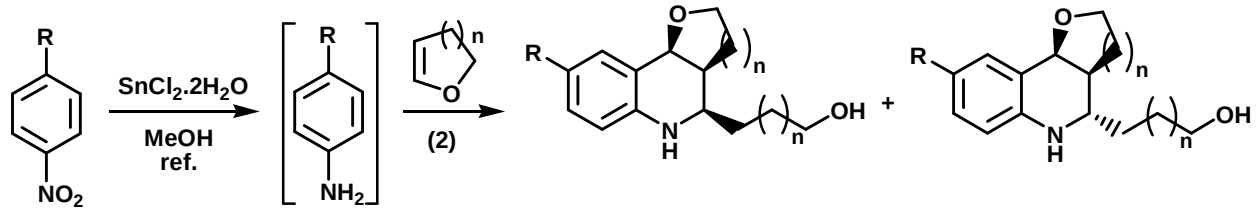
ABSTRACT

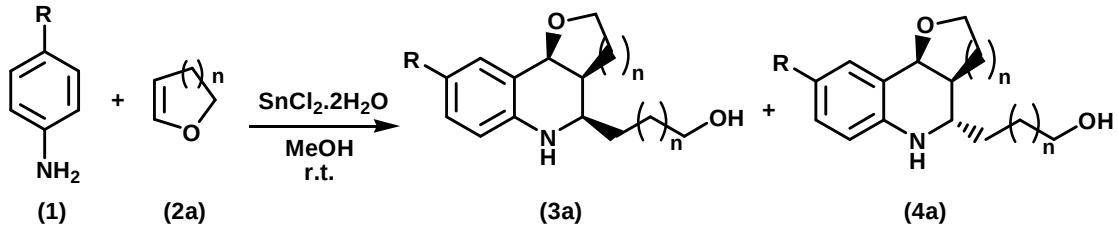
Various nitro benzenes react immediately with 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran in one pot to produce 1,2,3,4-tetrahydrofuro/pyrano quinolines in presence of $SnCl_2.2H_2O$ as reducing agent and catalyst at reflux temperature in methanol.$SnCl_2.2H_2O$ was found to reduce $-NO_2$ to $-NH_2$ efficiently, also facilitate imino Diels-Alder reaction of imine formed by the reaction between aryl amines, which was generated during reduction of aryl nitro compounds and with 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran.

INTRODUCTION

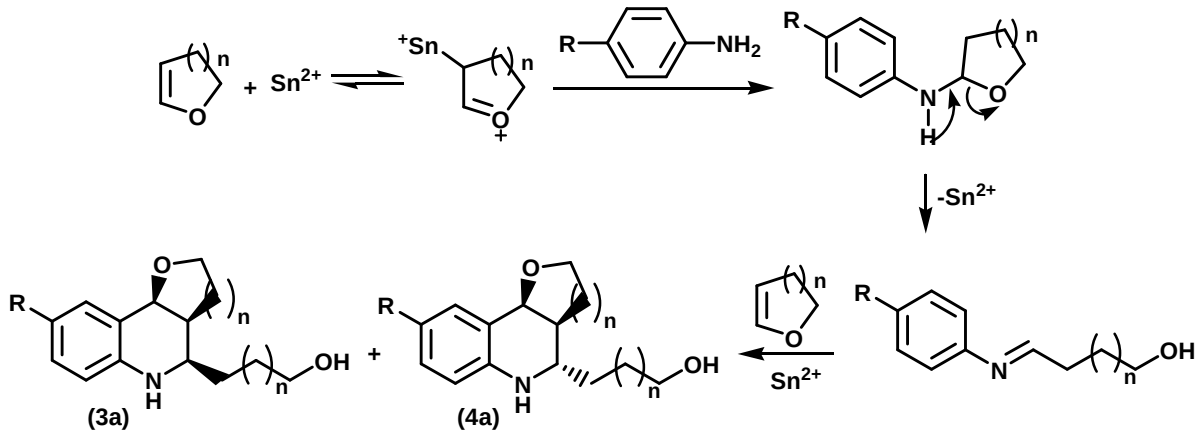
Domino reaction in the synthesis of tetrahydrofuro/pyrano quinolines is a classical method that involves the reaction of aromatic amines and cyclic enol ethers, which are extremely reactive, undergoing [4+2] imino Diels alder reaction in the presence of lewis acids, $GdCl_3$[1], VCl_3[2], ZrOCl[3], $BiCl_3$[4], cation-exchange resin in water[5], $InCl_3$[6]. Therefore, various methods have been engineered to generate these species in the presence of various *Lewis* acids necessary for the reaction allowing for the generation and *in situ* formation of imines formed by the condensation of aromatic amine and cyclic enol ethers and immediate consumption of another molecule of cyclic enol ethers such as 2, 3-dihydrofuran or 3, 4-dihydro-2*H*-pyran to undergo [4+2] imino Diels-Alder reaction[7,8]. But recently Chao-Jun Li et al.[9], has reported the application of aryl nitro compounds in spite of aryl amines for domino reaction. Although many efficient nitro reducing reagents are available in literature, still many remain unexplored in this domino reaction. Due to more susceptibility in self oxidation of anilines, prompted us to investigate corresponding nitro compounds directly to Domino reaction in the synthesis of 1, 2, 3, 4-tetrahydrofuro/pyrano quinolines with cyclic enol ethers in presence of mole equivalent of $SnCl_2.2H_2O$ as reducing agent as well as catalyst in the subsequent [4+2] imino Diels-Alder reaction. This is in continuation of work on searching of newer methodologies and modification of existing experimental methods in terms of simple environmentally benign, high yield, and easy isolation protocols in various organic syntheses[10-18].



Scheme 1



Scheme 2



Scheme 3

RESULT AND DISCUSSION

As a part of our continued programme on the development of newer processes for tetrahydroquinolines synthesis in our laboratory[19,20], here our attention was drawn into two protocols, in one of which, the aryl amines was generated *in situ* from corresponding nitro compounds which react immediately with 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran in one pot to produce a 1,2,3,4-tetrahydrofuro/pyrano quinolines in presence of reducing agent such as $SnCl_2.2H_2O$ and the direct involvement of aryl amine with cyclic enol ethers in presence of catalytic amount of $SnCl_2.2H_2O$. In order to ascertain the catalytic activity of $SnCl_2.2H_2O$ in *imino* Diels alder reaction between anilines and 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran in addition to act as reducing agent these two separate reactions were carried out and confirmed the catalytic activity of $SnCl_2$ $2H_2O$ in the reaction between anilines and cyclic enol ethers.

Hence we report the results of $SnCl_2.2H_2O$ catalyzed domino reaction of aromatic nitro compounds with 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran. Initially this reaction was carried out using $SnCl_2.2H_2O$ as the reductant ($-NO_2$ to $-NH_2$) and also the self facilitator of imine formed by the reaction between aryl amines, which was generated during reduction of aryl nitro compounds and with 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran. These imines immediately undergo imino Diels-Alder reaction with another molecule of 2,3-dihydrofuran or

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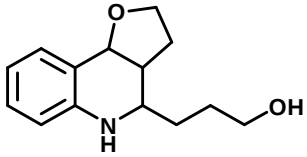
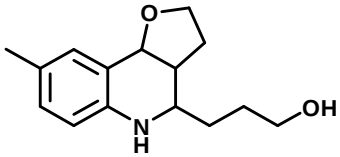
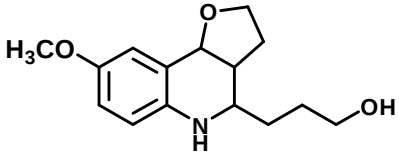
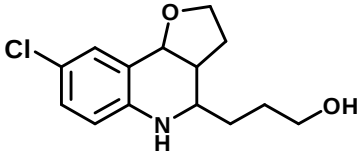
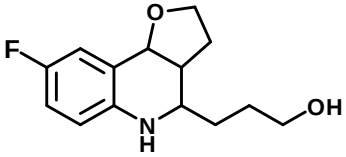
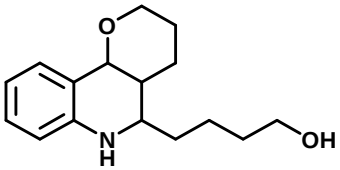
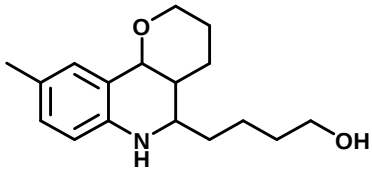
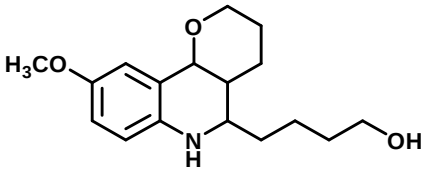
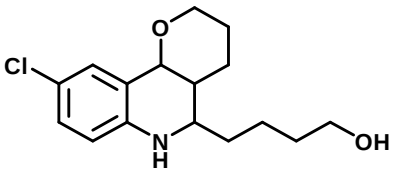
TABLE 1 : Reaction of Aniline's or Aryl amines aniline compounds with 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran in methanol

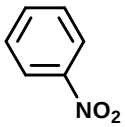
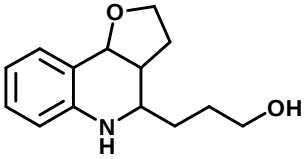
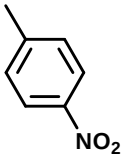
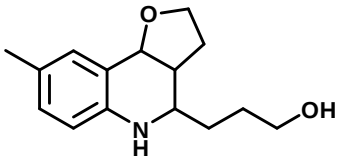
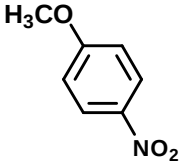
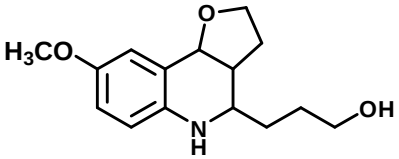
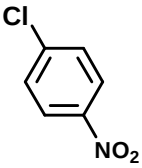
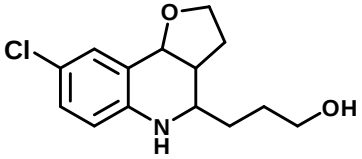
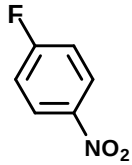
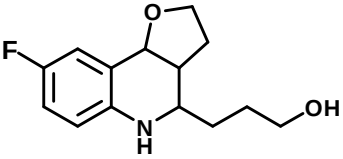
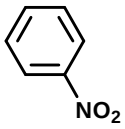
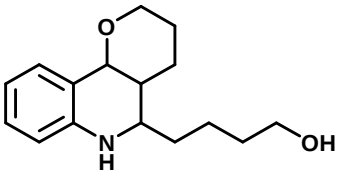
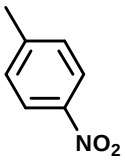
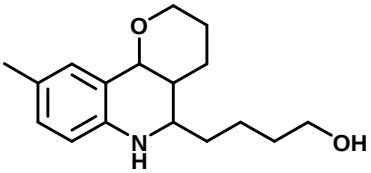
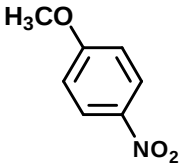
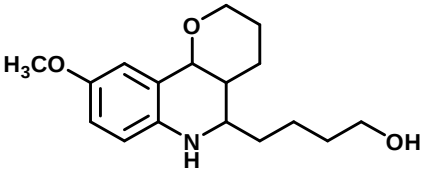
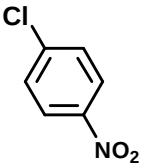
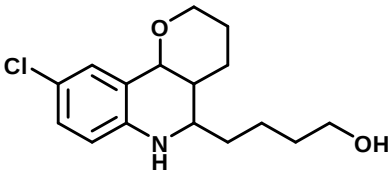
Entry	R	*Cis* / *Trans*	Product	Time / hr	Yield (%)[a]
a	H	78:22		4	84
b	CH_3	81:19		3	83
c	OCH_3	87:13		2.5	81
d	Cl	74:26		4	65
e	F	87:13		4	40
f	H	68:32		3	85
g	CH_3	67:43		2	88
h	OCH_3	66:34		2	78
i	Cl	57:43		3	68

[a]**Isolated Yield**

3,4-dihydro-2*H*-pyran to give various 1, 2, 3, 4-tetrahydrofuro/pyrano quinolines and the results are summarized in TABLE 1.

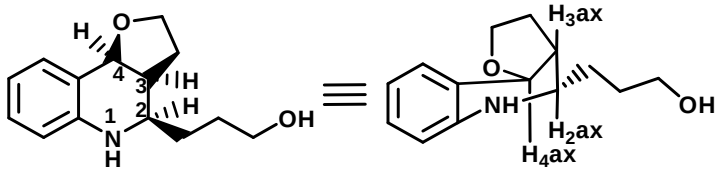
In order to demonstrate the feasibility of the hypothesis, we carried out model study, and in this chapter we report the results obtained from this effort. Our

TABLE 2 : Reaction of Aryl nitro compounds with 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran in methanol

Entry	Nitro compounds	*Cis* / *Trans*	Product	Yield (%)[a]
a		48:52		87
b		81:19		83
c		47:53		81
d		55:45		77
e		52:48		65
f		68:32		85
g		67:43		88
h		66:34		78
i		57:43		68

[a]**Isolated Yield**

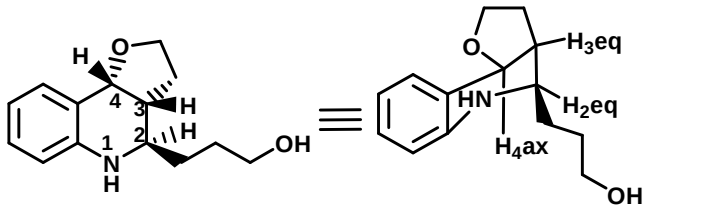
first concern was whether the aryl nitro compound cyclises to the tetrahydroquinoline ring system in presence of $SnCl_2.2H_2O$ as reducing agent as well as catalyst in one pot with 2,3-dihydrofuran or 3,4-dihydro-



C_4H and C_2H are cis configuration

C_4H and C_2H are axial to each other hence large coupling constant

Structure A



C_2H and C_4H are trans configuration

C_2H is in equatorial position where C_4H present at axial position

Structure B

2*H*-pyran. So, we evaluated the domino reaction by coupling of nitrobenzene **(1)** with, 2,3-dihydrofuran **(2a)** using appropriate mole equivalent of $SnCl_2.2H_2O$ as a catalyst (Scheme 1). Gratifyingly, this reaction indeed proceeded to give compound **(3)** and **(4)**, in relatively good yield.

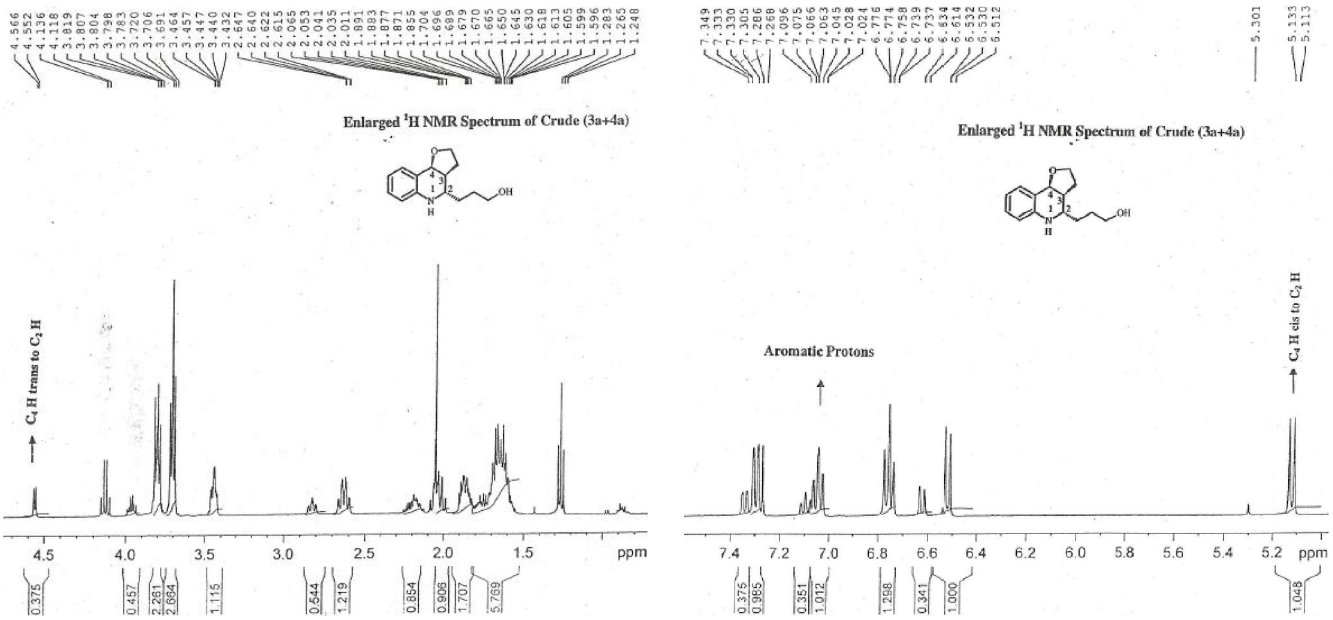
Nitrobenzene **(1)** (2 mmol) was reacted with catalytic amount of $SnCl_2.2H_2O$ (6 mmol) at reflux room temperature in methanol and subsequently with 2,3-dihydrofuran **(2)**. When the reaction mixture was stirred in methanol at room temperature for 1 day in presence of $SnCl_2.2H_2O$ (10 mol %), reaction did not occur to generate the corresponding tetrahydroquinoline derivatives. Thus the domino reaction between nitro benzene **(1)** and 2,3-dihydrofuran **(2a)**, was easily performed with mole equivalent of $SnCl_2.2H_2O$ as reducing agent for nitro group into corresponding amines in methanol at reflux temperature, which spontaneously produced the cyclized product **(3a)** and **(4a)** upon reaction with 2,3-dihydrofuran **(2a)**. This product was believed to be generated by the intramolecular [4+2] imino Diels-Alder reaction between amines and 2, 3-dihydrofuran **(2a)**. In order to confirm the structure **(3a)** and **(4a)** conclusively, we prepared the same compounds through an independent route under the same reaction condition directly from aryl amines and 2,3-dihydrofuran 2a as shown in scheme 2. The $SnCl_2$ (10 mole %) catalyzed the reaction of aniline with 2,3-dihydrofuran 2a in methanol as solvent afforded the steroisomerically same 1,2,3,4-tetrahydrofuro/pyrano quinolines and the results are summarized in TABLE 1.

Similarly, a wide range of aryl nitro compounds were screened in order to ascertain the scope of the present reaction protocol and the results are summarized in TABLE 2. It is evident from the results that aryl nitro compounds containing electron donating substituents readily cyclized and gives good yields of the products. However, lower yields were observed with electron withdrawing substituents (entries, d, e, TABLE 1).

The compounds 3 and 4 obtained from two independent routes were well characterized by ^1H NMR and LCMS studies. ^1H NMR and ^{13}C NMR were consistent with the structure assigned to all the newly synthesized compounds which are in comparison with the reported spectral evidences in the literature[21].

The structure of two isomers was established on the basis of spectroscopic evidence and analytical data. From the ^1H NMR spectra, the ratio of two isomers was determined conveniently by comparing the integrations of proton in the crude ^1H NMR of compound **(3)**. It was found that the *cis* isomer is slightly more favoured product in most of the cases when the anilines were reacted with 2,3-dihydrofuran/pyran.

The enhanced *cis* diastereoselectivity (to form **(3a)** and **(4a)**) was observed in each case of the investigation similar to as it was reported in literature[21].



^{1}H NMR spectrum of crude (3a+4a)

In structure "A" the C_2H and C_4H carbons are *cis* and hence they are *trans* 1-3 diaxial to each other. Therefore they show large coupling constant between H_2 and H_4 at C_2 and C_4 carbon atoms. The C_2H exhibited coupling constant J = 7.2 Hz and C_4H exhibited coupling constant J=8.0 Hz which are in consistent with *trans* diaxial relationships between C_2H and C_4H protons. Hence they are *cis* to each other in structure-A. Similarly structure-B was also established.

Further all other derivatives were authenticated by comparing with the reported spectroscopic data[21]. Similarly several amines were examined and in all cases, the three-component one pot reaction proceeded smoothly to give the corresponding 1, 2, 3, 4-tetrahydrofuro/pyrano quinolines **(3a-h)** and **(4a-h)** respectively. All these compounds could be separated by column chromatography in most cases. The structure of compounds was characterized by IR, ^{1}H NMR, ^{13}C NMR, LC-MS and elemental analysis.

A tentative mechanism to rationalize the product formation is shown in scheme 3. The reduction of nitro benzene with $SnCl_2.2H_2O$ will generate aniline intermediate, which undergo condensation with 2,3-dihydrofuran **(3)** to produce corresponding imine under the same reaction condition. Finally, an aza Diels-Alder reaction of the imine with another molecule of 2,3-dihydrofuran 3 produced tetrahydroquinoline derivatives **(3a)** and **(4a)**.

In conclusion, first time we developed the highly efficient domino reaction of aromatic nitro compounds with cyclic enol ether in presence of $SnCl_2.2H_2O$. $SnCl_2.2H_2O$ as the self facilitator of imine formation formed by the reaction between aryl amines, which is generated during reduction of aryl nitro compounds and subsequently react with 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran to provide 1, 2, 3, 4-tetrahydrofuro/pyrano quinoline derivatives. The scope, mechanism and synthetic applications of this reaction with various other catalysts are currently under investigation in our laboratory.

EXPERIMENTAL

Synthesis of 1, 2, 3, 4-tetrahydrofuro/pyrano quinolines: A general procedure

Typically, $SnCl_2.2H_2O$ (7.17 g, 28.45 mmol) was added to a stirred solution of nitrobenzene (1.0 g, 8.13 mmol) in methanol (50 ml). The resulting mixture was refluxed on water bath for 1 hr. The 2,3-dihydrofuran (1.13 g, 16.26 mmol) was added to the reaction mixture slowly with continues stirring. Progress of the reaction was monitored by TLC. Following evaporation of the MeOH, the mixture was extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, filtered and concentrated in vacuum. After evaporation of the solvent, the residue was subjected

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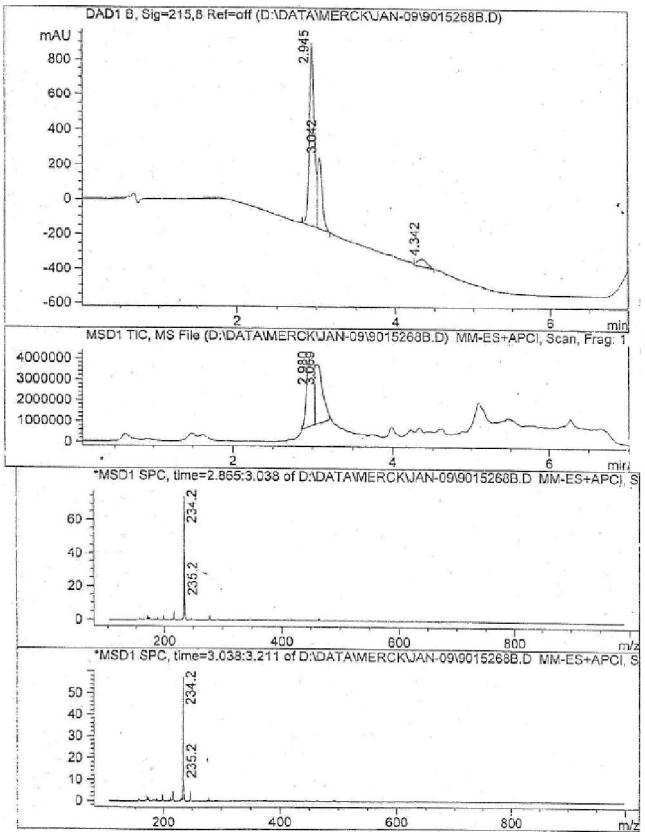

Mass spectrum of 3a

to column chromatography to obtain analytically pure compounds.

Synthesis of 1, 2, 3, 4-tetrahydrofuro/pyrano quinolines from anilines: A general procedure

A mixture of aromatic amine (2 mmol), cyclic enol ether or 2-hydroxycyclic ether (4-6 mmol), and $SnCl_2.2H_2O$ (0.2-0.4 mmol) in 20 ml of methanol was stirred at room temperature and the progress reaction was monitored by TLC. When the reaction was completed, the reaction mixture was extracted with ethyl acetate. The combined organic phases was dried with anhydrous sodium sulfate, filtered and concentrated in vacuum. The crude material was separated by column chromatography (pet ether: ethyl acetate, 9:1) to give the analytically pure isomeric mixture of tetrahydroquinoline derivatives.

2,3,3a,4,5,9b-Hexahydro-4-(3-hydroxypropyl)-furano[3,2-c]quinoline **(3a, 4a)**.

Cis-isomer

^{1}H NMR ($CDCl_3$) δ =7.26-7.34 (m, 1H), 7.02-7.10 (m,1H), 6.73-6.77 (m, 1H), 6.51-6.53 (m, 1H), 5.12 *(C_4H cis to C_2H d, J = 8.0 Hz, 1H)*, 4.11-4.13(*C_2H cis to C_4H dd, J =7.2 Hz, 1H*), 3.69-3.81(m, 4H), 3.43-3.46 (m, 1H), 2.62 (d, *J* = 2.8 Hz, 1H) 2.01-2.06 (m, 2H), 1.85-1.90 (m, 1H), 1.59-1.70 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$): 145.24, 130.25, 128.55, 122.84, 118.94, 114.86, 76.02, 66.81, 62.52, 52.68, 42.69, 30.93, 29.21, 24.22 ppm.

Trans-isomer

^{1}H NMR ($CDCl_3$) δ = 7.34 (d, J = 6.4 Hz, 1H), 7.09 (m, 1H), 6.76 (m, 1H), 6.64 (d, J = 8.0 Hz, 1H), *4.56 (C_4H trans to C_2H d, J = 5.6 Hz, 1H)*, 4.11 (d, *J=7.2 Hz*, 1H), 3.95 (*C_2H trans to C_4H dd, J =4.0 Hz, 1H*), 3.70 (m, 2H), 2.82 (m, 1H), 2.64 (s, 1H), 2.06 (m, 1H), 1.55-1.90 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$): 145.16, 131.20, 129.10, 120.48, 118.42, 115.08, 76.10, 65.76, 62.64, 52.16, 41.39, 30.09, 29.37, 28.79 ppm. MS: *m/ z* =234.2 (M+1).

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