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Synthesis of tetrahydroquinolines and quinoline derivatives through the Lewis acid catalysed Povarov reaction: A comparative study between multi step and multi-component methods

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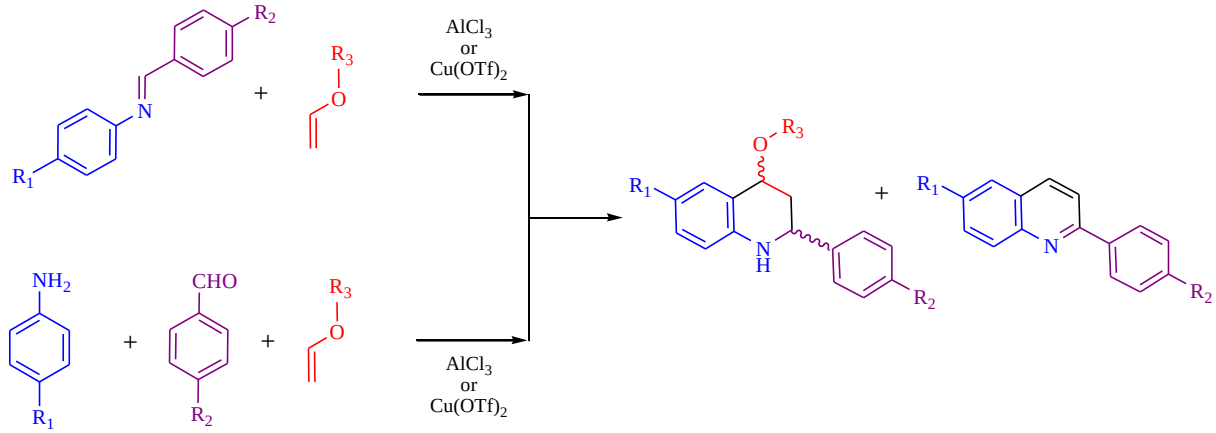

Abstract: In this work, we have synthesised a new disubstituted tetrahydroquinolines by the Povarov [4+2] cycloaddition reaction between imines derivatives and an electron-rich olefin such as vinyl ethers. These reactions were carried out in the presence of different acid catalysts in its two versions, multi-step reaction starting with imine synthesis and multi-component reaction in which the imine is formed in situ. The reactivity of the cycloaddition reaction is directly attributed to the nature of the reagents, the used synthetic strategy, in which the obtained yield is found in the case of multi-step

reactions lower than that in the multi-component reaction one. Additionally, the multi-step reactions are faster kinetically in comparison with that of the multi-component one. The nature of the catalyst directly increases the rate and enhances the yield of the reactions.

Keywords: Quinoline, Lewis acid catalyst , Povarov, Cycloaddition, imine, vinyl ethers.

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Introduction

The tetrahydroquinoline [1] and quinolones [2] skeleton are one of an important heterocyclic scaffolds found in wide number of natural and unnatural bioactive products and plays a pivotal role in the realm of pharmaceuticals and is also encountered in several alkaloids exhibiting therapeutic properties. Medicinal chemists consider this category of compound to be compelling tool for the purpose of devising and advancing novel pharmaceutical agents. Some quinolines derivatives are given by Ouldouz Ghashghaei and his collaborators [3]; the Oxamniquine that is an oral anthelmintic drug, the Virantmycin which is an antiviral antibiotic with antifungal activity and Mefloquine that is an antimalarial drug in clinical use (Figure 1).

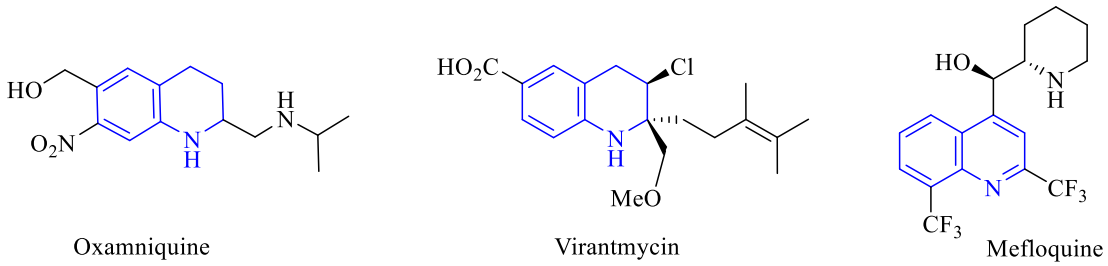


Fig 1. Structures of some bioactive tetrahydroquinolines and Quinolines.

Given the importance of this kind of heterocyclic sytems, numerous methods have been revealed for the synthesis of such compounds. The Povarov reaction stands out as a highly utilized and effective synthetic strategy, achievable from simple and readily available starting materialsusing straight forward reaction conditions [4]. This reaction [5] is an inverse electron-demand aza-Diels-Alder between an N-arylimine and electron-rich olefins, which mainly catalyzed by Lewis or Brønsted acid. Two known ways to perform this reaction; a multi-steps strategy that is the classical Povarov reaction [6,7] between an aldimine, previously prepared by a simple condensation of an aromatic primary amine with an aldehyde, and the electron rich olefins, which allows a rapid formation of tetrahydroquinolines compounds. The

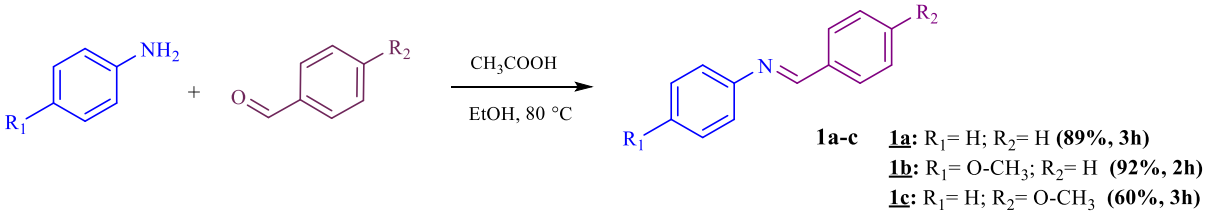
second method is the multi-component strategy starting from an aldehyde, aromatic amine and electron-rich olefins by introducing acid catalyst as that in the multi-steps method [8–10].

The asymmetric catalysis of Povarov reaction caught the attention of organic chemists, but only a handful of examples have been reported[11–13] and met with limited success[12].

In continuation of our research program in the field of enantioselective synthesis of the heterocyclic compounds by cycloaddition reactions[14,15], herein, we have interested for the synthesis of some tetrahydroquinolines and or the corresponding quinolines using the Povarov reaction ([4+2] cycloaddition reaction).

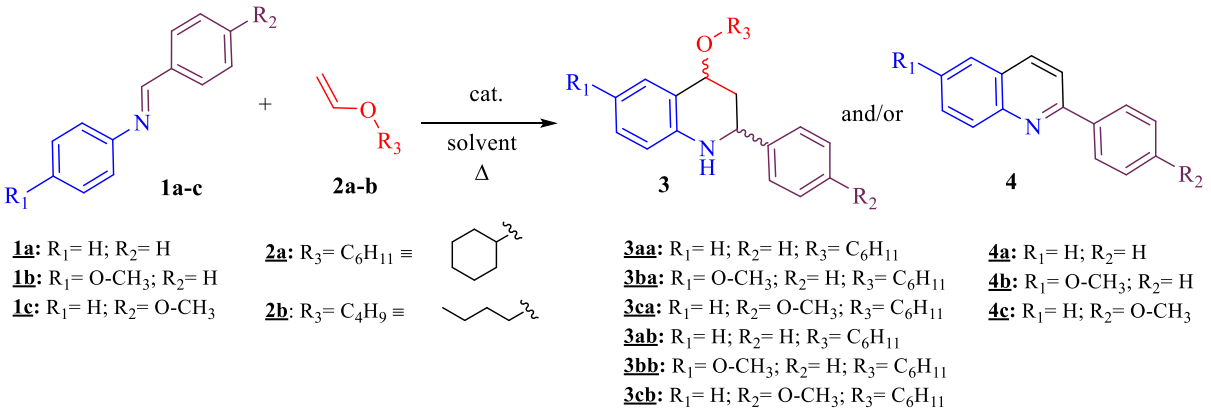
Results and discussion

In the first time, we have begun by the synthesis of aromatic aldimines compounds (Scheme 1). These lasts are obtained by a simple condensation of primary aromatic amines with a substituted benzaldehyde [16, 17]. The obtained aldimines will then be used in [4+2] cycloaddition with an electron-rich olefin such as vinyl ethers, which interact under an acid catalysis to afford the corresponding final products (Scheme 2).



Scheme 1. Synthesis of aldimines by the condensation reaction between substituted benzaldehyde and primary aromatic amines

After surveying the reaction conditions of [4+2] cycloaddition by varying solvent, temperature and stoichiometry, we have found basing on the yield, reaction time and selectivity that the best conditions reaction in the case of multi-step fashion are EtOH as solvent at 40 °C in the presence of 10 mol % of catalyst such as Cu(OTf)2 or in Et2O solvent at 30 °C in the presence of 1 equivalent of AlCl3 catalyst. Moreover, within the context of a multi-component reaction, optimization of the reaction is also achieved. The most optimal outcomes were observed when using toluene as solvent at 45°C, accompanied by a catalytic amount of 10 mol %, regardless of whether utilizing Cu(OTf)2 or AlCl3.



Scheme 2. Synthesis of tetrahydroquinolines and or the corresponding quinolines using Povarov cycloaddition reactions of generated aromatic aldimines and electron-rich alkenes

The results of the Lewis acid catalyst effect and the on the synthesis of the different tetrahydroquinolines are shown in Table 1.

The effect result of Lewis acid catalyst and the electron-neutral and rich aromatic aldehyde and amine all served as appropriate substrates, providing diverse tetrahydroquinolines, as shown in Table 1.

Table 1. Experimental results of the Synthesis of tetrahydroquinolines and or the corresponding quinolines using Povarov cycloaddition reactions of the generated aromatic aldimines with electron-rich alkenes

Entry	Imine	Vinyl ether	Conditions	Products	Yield of 3 (%) Isomer ratio[a, b]	Yield of 4[a, b] (%)
1	1a	2a	$AlCl_3$ (1eq), Et_2O, 30°C, 50min	3aa/4a	46 (90:10)	46
2	1b	2a	$AlCl_3$ (1eq), Et_2O, 30°C, 60 min.	3ba/4b	37 (>98:2)	39,5
3	1c	2a	$AlCl_3$ (1eq), Et_2O,30°C, 75min.	3ca/4c	31 (70:30)	22.8
4	1a	2a	$Cu(OTf)_2$ (10mol%), EtOH, 40°C, 40 min.	3aa/4a	28 (100:0)	21.36
5	1b	2a	$Cu(OTf)_2$ (10mol%), EtOH, 40°C, 60 min.	3ba/4b	10 (>98:2)	32
6	1c	2a	$Cu(OTf)_2$ (10mol%), EtOH, 40°C, 60 min.	3ca/4c	-	24.19
7	1a	2b	$AlCl_3$ (1eq), Et_2O, 30°C, 30min	3ab/4a	53 (80:20)	18
8	1b	2b	$AlCl_3$ (1eq), Et_2O, 30°C, 45min.	3bb/4b	41 (80:10)	42
9	1c	2b	$AlCl_3$ (1eq), ET_2O, 30°C, 60min	3cb/4c	33 (95:5)	27.4
10	1a	2b	$Cu(OTf)_2$ (10mol%), EtOH, 40°C, 20min.	3ab/4a	30 (95:5)	22
11	1b	2b	$Cu(OTf)_2$ (10mol%), EtOH, 40°C, 20min.	3bb/4b	Trace	35.60
12	1c	2b	$Cu(OTf)_2$ (10mol%), EtOH, 40°C, 45min.	3cb/4c	19 (100:0)	27

[a] The product ratios were determined by GC/MS.

[b] Determined by 1H NMR analysis of the crude reaction mixture.

The Povarov reactions of N-aryl aldimine **1a-c** with vinyl ether **2a-b** under Lewis acid catalysis ($AlCl_3$ or $Cu(OTf)_2$) gave mixtures of cycloadduct **3** together with the corresponding quinoline **4** (Table 1), in which the 2,4-substituted tetrahydroquinolines **3** were converted into the corresponding quinoline **4**.

Depending on the reaction conditions, the tetrahydroquinolines or quinolines are formed with different proportions, which were determined by the spectroscopic analysis of the mixture of the crude product (see Table 1).

In all the studied reactions, the achieved yield is generally limited. This can be elucidated by the inherent instability of the imine compound under the influence of Lewis acids. The appearance of several products resulting from imine confirms this low stability, this could potentially be attributed to the competitive isomerization of the aldimine **2** to the corresponding enamines[18–20].

When the reaction was performed using $AlCl_3$ as catalyst, at 30 °C in Et_2O with an equimolecular quantity of aldimines **1a-c** and vinyl ethers **2a-b**, the tetrahydroquinoline **3** was obtained in moderate yield from 31 to 53% (see Table 1, entry 1,2,3,7,8 and 9). However, the use of $Cu(OTf)_2$ as catalyst (10mol %) in EtOH as solvent at 40°C reduce the yield of cycloadduct **3** to 0-30% (Table 1, entries 4,5,6,10,11 and 12).

The reactivity of Povarov reaction is directly related to the used reagents, in which the yield of cycloadduct **3** is increased when R_1= H and R_2= H (entries 1, 4 , 7 and 10). However, in the presence of a methoxy group at *para* position (*p*-O-CH_3) of the amine or the used aldehyde for the synthesis of aldimine, the yield of tetrahydroquinoline **3** is clearly becomes low, especially, in the case where R_1= H and R_2= O-CH_3.

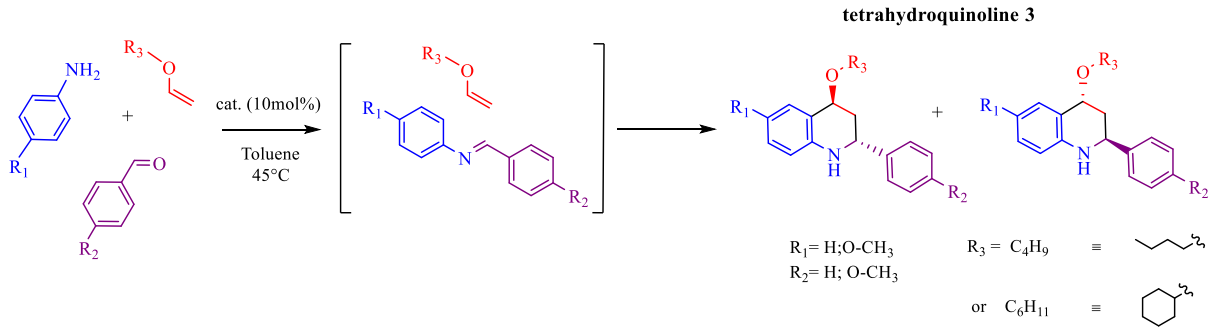
For the analysis of the necessary time to performing these reactions, we can deduce that the Povarov reaction in its multi-steps version is very fast kinetically, in which the desired product can be formed after 20 minutes (see Table 1), especially, when the reaction is catalyzed by $Cu(OTf)_2$ despite the obtained low yield. Thereby, we can say that the use of $Cu(OTf)_2$ accelerates the reaction and decreases the yield of the formed tetrahydroquinoline product.

Through a comparison of the reaction times conducted under identical conditions, we notice that the rate of the cycloaddition reaction is also influenced by the nature of alkyl groups R_1, R_2 and R_3. Thus, the aldimine **1a** reacts better than **1b** as well as **1c** and the vinyl ether **2b** is slightly more reactive than **2a** one. With alkene **2b**, the reaction gave 46% of **3** in 60min and with alkene **2a** gave 53% of **3** in 30min (entries 1 and 7 of Table 1).

The spectroscopic analysis of 1H NMR and GC/MS of the crude reaction mixture shows that the Povarov reaction generally leads to the formation of one diastereoisomer, especially, when $Cu(OTf)_2$ was used as catalyst. In addition, in some cases gave a mixture of two diastereoisomers with high stereoselectivity. This is clearly observable in the 1H NMR of the crude product, where a splitting of the characteristics peaks of the resulting cycloadducts is noted, exhibiting varying proportions. In the case of anilines carriyng a methoxy group on the *para* position of the aroamtic ring of aldimine, also demonstrated that the steric effect has also an influence on the reaction. While, in the case of aromatic aldimine with *p*-methoxy group on the aromatic ring of the aldehyde reduces the selectivity as well as the yield (Table 1, entry 3).

While, when $Cu(OTf)_2$ was used in this reaction, the 2,4-substituted tetrahydroquinolines **3aa-ac** and **3ba-bac** were obtained in low yield, but in good regio and stereoselectivities (100%). However, it was found also that $AlCl_3$ promotes better the Povarov reaction of N-aryl aldimine **1a-c** and vinyl ether **2a-b** to afford the corresponding tetrahydroquinoline **3** in moderate yield and in highly stereoselectivity manner.

Due to these limited results, we have planned to achieve an alternative method in order to improve the reactivity of the reaction and increase the yield of tetrahydroquinoline **3**. Thus, for doing this, the Povarov reaction can be performed in a multi-component fashion by the coupling of alkenes, aldehydes, and amines. The reaction began by forming the aldimines from the reaction between benzaldehyde derevatives and aniline, then this last react *in situ* with the electron rich alkenes to form the corresponding tetrahydroquinoline compounds (Scheme 3). The obtained results are gathered in Table 2.



Scheme 3.Three-component Povarov reaction for the synthesis of tetrahydroquinolines

Table 2. Experimental results of the Synthesis of tetrahydroquinolines using multicomponent method of Povarov cycloaddition reactions between an in situ formed aldimines and vinyl ether.

Entry	R1	R2	R3	cat.	time	Products	Yield (%) Isomer ratio[a,b]

13	H	H	C_6H_{11}	$AlCl_3$	4h	3aa	77 (60:40)
14	O-CH_3	H	C_6H_{11}	$AlCl_3$	6h	3ba	70 (70:30)
15	H	O-CH_3	C_6H_{11}	$AlCl_3$	6h	3ca	70 (80:20)
16	H	H	C_6H_{11}	$Cu(OTf)_2$	8h	3aa	58 (80:20)
17	O-CH_3	H	C_6H_{11}	$Cu(OTf)_2$	8h	3ba	50 (85:15)
18	H	O-CH_3	C_6H_{11}	$Cu(OTf)_2$	10h	3ca	47 (85:15)
19	H	H	C_4H_9	$AlCl_3$	3h	3ab	87 (55:45)
20	O-CH_3	H	C_4H_9	$AlCl_3$	4h	3bb	78 (65:35)
21	H	O-CH_3	C_4H_9	$AlCl_3$	4h	3cb	74 (100:0)
22	H	H	C_4H_9	$Cu(OTf)_2$	7h	3ab	61 (95:5)
23	O-CH_3	H	C_4H_9	$Cu(OTf)_2$	7h	3bb	60 (>98:2)
24	H	O-CH_3	C_4H_9	$Cu(OTf)_2$	4h	3cb	58 (100:0)

[a] The product ratios were determined by GC/MS.

[b] Determined by ^1H NMR analysis of the crude reaction mixture.

The 2,4-substituted tetrahydroquinolines **3** have been synthesized by three-component reaction from appropriately substituted benzaldehydes, anilines, and vinyl ethers, catalyzed by the previous Lewis acids used in the multi steps system, $AlCl_3$ and $Cu(OTf)_2$. The main remaquable efficiency of this method is the obtained good yield of tetrahydroquinoline **3** in comparison with that obtained in the previous reaction (Table 1). On the other hand, the stereochemical aspects and reaction time does not change (Table 2). Also, we found that the quinolines **4** are formed from the transformation of the corresponding tetrahydroquinoline **3** in low quantities, the reasons in which we have not taken it in consideration in this study.

From the obtained results, we can notice that the values of the obtained yield, the reaction time and the selectivity are related to the catalyst's type and the nature of alkyl groups R_1, R_2 and R_3 of the used reagents. The good yield of 87% was obtained when R_1=H, R_2=H and R_3=C_4H_9 with the used of $AlCl_3$ (entry 19, Table 2). While the low selectivity was obtained in this case (55:45). When the reaction was performed using $Cu(OTf)_2$ as catalyst with the same reagent of entry 19, the reaction become more stereoselective (100:0) and the yield has decreased at 58% (entry 24, Table 2). The benzalhehydes carriyng of methoxy group on the *para* position of the benzene ring also demonstrated the importance of the steric effect on this reaction (entry 15, 18, 21 and 24; Table 2).

Material and methods

General

All reactions were carried out in dried reaction glassware under argon, using a parallel reactor that will allow us to run multiple reactions simultaneously and under the same conditions; stirring speed and temperature.The temperatures of the reaction are reported as the temperature of the used hot plate. All solvents used in these reactions were freshly distilled and dried over molecular sieves of 3 Å before use.The commercial products were obtained from Sigma Aldrich, Alfa Aesar, Acros, Fluka and Janssen and was typically used without further purication except the benzaldehyde reagent which is used freshly distilled. The 1H NMR spectra of the products were recorded on a Bruker Ultra shield 400 MHz. Chemical shifts (δ) are expressed on parts per million (ppm) relative to external reference TMS. The NMR spectra were performed in CDCl3 and referenced to the residual peak of CHCl3 at δH= 7.26 ppmδC= 77.00 ppm for 1H and 13C, respectively. Infrared spectra (IR) were recorded with a Spectrometer Perkin-Elem Spectrum version 10.03.05 using a diamond crystal detection cell. the GC/MS spectra were recorded on a SHIMADZU, QP2010SE model with Phenomenex Zebron colomnn ZB-5m (Tagged 5% phenyl / 95% Dimethylpolysiloxane) with 20m in lengths, the diameter less than 0.18mm and 0,18µm thickness of the stationary phase. The injection is performed in splitless mode. Injection volume: 1mL of crude mixture reaction in solution. The oven temperature has been programmed from 50°C to 280°C with 2 min frame. Carrier gas: helium (0.7ml/min), regulator 970 kPa, scan speed 50 scans/s, acquisition speed 10000 uma/s. All reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 F254 TLC plates; the revelation was attended up with UV light, and a colored solution of Potassium permanganate, Vanillin and Ninhydrin followed by simple heating.Ethyl acetate (EtOAc) and petroleum ether (PE) were used as eluent. All manipulation and spectroscopic analyses were carried out at the laboratory of molecular architecture and nanostructured materials AM2N at the higher normal school of chimestry of montpellier-France ENSCM.

General procedure for synthesis of imine **1a-c**

The aldehyde (1eq, 0.02mol), primary aromatic amine (1eq, 0.02mol) and acetic acid (2-3 drop) in ethanol (60ml) was stirred at reflux. After completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure. The desired product was purified by re-crystallization in EtOAc.

General procedure for the synthesis of tetrahydroquinoline derivative **3** and/ or quinoline **4** with multi-step method:

With $AlCl_3$ catalyst

An equimolecular amount (1.25 mmol) of the aromatic imine and the $AlCl_3$Lewis acid introduced on tube of a parallel reactor and dissolved in anhydrous diethyl ether freshly distilled (3 ml) under argon atmosphere and stirred at 30°C. The olefins (1.12 eq, 1.41 mmol) was added after 5 minutes. The reaction evolution was monitored by TLC. After completion of the reaction, the reaction mixture was then cooled to room temperature. A basic solution of NaOH (10%, 1.25mmol) has been added and the mixture was extracted with EtOAc. The combined organic layer was dried with $MgSO_4$.The solvent was removed under reduced pressure, and the crude reaction mixture was analysed by ^{1}H NMR and GC/MS.

With $Cu(OTf)_2$ catalyst

On the tube of a parallel reactor, we introduce 1.25 mmol of aromatic imine, 10mol% of $Cu(OTf)_2$ and 4 ml of ethanol freshly distilled under argon atmosphere. The mixture was stirred at 40°C. The olefins (1.12 eq, 1.41 mmol) was added after 5 minutes and the reaction evolution was monitored by TLC. After completion of the reaction, the reaction mixture was then cooled to room temperature. The inorganic material was removed by filtration on silica gel and the solvent was removed under reduced pressure. The crude reaction mixture was analyzed by ^{1}H NMR and GC/MS.

Multi-component reaction method

The reaction was carried out in under argon condition with 150mg of molecular sieves (MS 5 Å) scale in a toluene (0.5 ml) and amine (0.1mmol), aldehyde (0.12mmol), the catalyst (0.01mmol). The reaction was stirred at room temperature for 10 min. Then, the olefins **2a-b** (0.12mmol) in toluene (0.5 mL) was added and the mixture was stirred at 45°C. After completion of the reaction (TLC monitoring), the mixture was filtered to remove molecular sieves, and washed with EtOAc. The obtained filtrate was filtrate again on silica gel. The resultant soln was concentrated under reduced pressure to give a residue, and the crude reaction mixture was analyzed by ^{1}H NMR and GC/MS.

Characterization data

N-diphenylmethanimine **1a** (M = 181.1 g/mol) yellow crystals (89% yield, 3h, R_f = 0.81: PE/AcOEt eluent 80/20)^{1}H NMR ($CDCl_3$, 400 MHz):δ 3.88 (s,3H,O-CH_3), 6.96-7.87(m,9H,H aromatic). 8.39 (s, 1H , CH=N). ^{13}CNMR ($CDCl_3$, 400 MHz):δ124.73(C_{arom}), 127.81(C_{arom}), 129.31(C_{arom}), 130.77(C_{arom}), 131.85 (C_{arom}), 138.92 (C_{arom}), 153.04 (C_{arom}), 163.10 (C=N). IR (thin film) :1625, 1380 , 1584,2887-3008 ,2359cm^{-1} .

N-(*p*-methoxyphenyl)-1-phenylmethanimine **1b** (M = 211.1 g/mol) yellow crystals (92% yield, 2h, R_f = 0.89: PE/AcOEt eluent 80/20)^{1}H NMR ($CDCl_3$, 400 MHz):δ3.840 (s,3H,O-CH_3), 6.93-7.91 (m,9H,H aromatic), 8.49 (s,1H, CH=N). ^{13}CNMR (CDCl3, 400 MHz):δ48.15(C-O),

125.13(C_{arom}), 129.37 (C_{arom}), 132.71(C_{arom}), 133.77(C_{arom}), 134.45 (C_{arom}), 159.02 (C_{arom}), 154.04 (C_{arom}), 163.00 (C=N). IR (thin film)ϑ1619,1981 ,1502 ,2900-2952, 1246, 2359cm^{-1}.

(4-methoxyphenyl)-N-phenylmethanimine **1c** (M = 211.1 g/mol) white solid (60% yield, 3h, R_f = 0.72: PE/AcOEt eluent 80/20)^{1}H NMR ($CDCl_3$, 400 MHz):δ 3.84 (s,3H,O-CH_3). δ 6.93-7.91 (m, 9H,H aromatic). 8.48 (s, 1H , CH=N). ^{13}C NMR ($CDCl_3$, 400 MHz):δ60.25 (C-O), 125.44(C_{arom}), 130.17 (C_{arom}), 132.98(C_{arom}), 134.62(C_{arom}), 135.25 (C_{arom}), 154.93 (C_{arom}), 159.52 (C_{arom}),165.09 (C=N).

IR (thin film):ϑ 2838-3074, 1625 , 1257 , 1569 , 1167, 2361cm^{-1}.

4-(cyclohexyloxy)-2-phenyl-1,2,3,4-tetrahydroquinoline **3aa** M=307g/mol

Isomer 1:R_f = 0.37 (PE/AcOEt eluent 95:5)

GC: T_r= 13.014 min. MS: 57, 82, 102, 130, 206, 307 *m/z*

^{1}H NMR (CDCl3, 400 MHz):δ1.48 (m,2H), 1.55 (m, 4H), 1,75 (q,4H), 2.98 (m, 2H), 3.451 (t, 1H, CH-O), 4.03 (m, 1H, CH_2-CH-NH), 4.841 (t, 1H, CH_2-CH-O), 6.63-7.36 ($H_{arom.}$), 8.302 (s, NH).

Isomer 2: R_f = 0.34 (PE/AcOEt eluent 95:5)

GC: T_r= 13.132 min. MS: 57, 82, 102, 130, 206, 307 *m/z*

^{1}H NMR (CDCl3, 400 MHz):δ1.501 (m,2H), 1.571 (m, 4H), 1,76 (q,4H), 2,301(m, 2H), 3.459 (t, 1H, CH-O),4.13 (m, 1H, CH_2-CH-NH), 4.847 (t, 1H, , CH2-CH-O), 6.634-7.369 ($H_{arom.}$), 8.312 (s, NH).

4-(cyclohexyloxy)-6-methoxy-2-phenyl-1,2,3,4-tetrahydroquinoline **3ba** M=337,204 g/mol

Isomer 1: R_f = 0.23 (PE/AcOEt eluent 95:5)

GC:T_r= 14.034 min . MS:82, 91, 102, 121, 161, 237, 337 m/z

^{1}H NMR (CDCl3, 400 MHz):δ1.47 (m,2H), 1.551 (m, 4H), 1,76 (q, 4H), 2.87 (m, 2H), 3.56 (t, 1H, CH-O), 3.802 (s, 3H, O-CH_3), 3.92 (m, 1H, CH_2-CH-NH), 4.782 (m, 1H, CH_2-CH-O), 6.85-7.56 ($H_{arom.}$), 8.39 (s, NH).

Isomer 2: R_f = 0.25 (PE/AcOEt eluent 95:5)

GC: T_r= 13.914 min . MS: 82, 91, 102, 121, 161, 237, 337 m/z

^{1}H NMR (CDCl3, 400 MHz):δ1.48 (m,2H), 1.56 (m, 4H), 1,772 (q, 4H), 2.881 (m, 2H), 3.569 (t, 1H), 3.808 (s, 3H, O-CH_3), 3.931 (m, 1H, CH_2-CH-NH), 4.79 (m, 1H, CH_2-CH-O), 6.85-7.56 ($H_{arom.}$), 8.398 (s, NH).

4-(cyclohexyloxy)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline **3ca** M=337,204 g/mol

Isomer 1: R_f = 0.21 (PE/AcOEt eluent 95:5)

GC: T_r= 14.321min . MS: 82, 91, 130, 133, 237, 337 *m/z*

^{1}H NMR ($CDCl_3$, 400 MHz):δ1.47 (m, 2H), 1.53 (m, 4H), 1,8 (q, 4H), 2.98 (m, 2H), 3.564 (t, 1H), 3.779 (s, 3H, O-CH_3), 3.937 (m, 1H, CH_2-CH-NH), 4.806 (m, 1H, CH_2-CH-O), 6.5-7.43 ($H_{arom.}$), 8.34 (s, NH).

Isomer 2: R_f = 0.20 (PE/AcOEt eluent 95:5)

GC: T_r= 14.381min . MS: 82, 91, 130, 133, 237, 337 *m/z*

^{1}H NMR ($CDCl_3$, 400 MHz):δ1.47 (m, 2H), 1.53 (m, 4H), 1,77 (q, 4H), 2.97 (m, 2H), 3.54 (t, 1H), 3.69 (s, 3H, O-CH_3), 3.88 (m, 1H, CH_2-CH-NH), 4.811(m, 1H, CH_2-CH-O),6.5-7.43 ($H_{arom.}$), 8.34 (s, NH).

4-butoxy-2-phenyl-1,2,3,4-tetrahydroquinoline **3ab** M=281,18 g/mol

Isomer 1: R_f = 0.42 (PE/AcOEt eluent 95:5)

GC: T_r= 12.520 min . MS: 41, 56, 77, 91, 103, 118, 130, 206, 281 m/z

^{1}H NMR ($CDCl_3$, 400 MHz):δ1.114 (t, 3H), 1.56 (m, 2H), 1,68 (m,2H), 2.967 (m, 2H), 3.411 (t, 2H, CH_2-O), 3.91 (m, 1H, CH_2-CH-NH), 4.70 (t, 1H, CH_2-CH-O), 6.75-7.60 ($H_{arom.}$), 8.23 (s, NH).

Isomer 2: R_f = 0.39 (PE/AcOEt eluent 95:5)

GC: T_r= 12.617 min . MS: 41, 56, 77, 91, 103, 118, 130, 206, 281 m/z

^{1}H NMR ($CDCl_3$, 400 MHz):δ1.193 (t,3H), 1.573 (m, 2H), 1,691 (m,2H), 3.101 (m, 2H), 3.494 (t, 2H, CH_2-O), 4.092 (m, 1H, CH_2-CH-NH), 4.79 (t, 1H, CH_2-CH-O), 6.75-7.60 ($H_{arom.}$), 8.242 (s, NH).

4-butoxy-6-methoxy-2-phenyl-1,2,3,4-tetrahydroquinoline **3bb** M=311,19 g/mol

Isomer 1: R_f = 0.30 (PE/AcOEt eluent 95:5)

GC: T_r= 13.507min . MS: 41, 56, 91, 117, 160, 192, 220, 235, 238, 311

^{1}H NMR ($CDCl_3$, 400 MHz):δ1.11 (t,3H), 1.54 (m, 2H), 1,67 (m,2H), 2.831 (m, 2H), 3.471 (t, 2H, CH_2-O), 3.759 (s, 3H, CH_3-O), 3.98 (m, 1H, CH_2-CH-NH), 4.652 (t, 1H, CH_2-CH-O), 6.65-7.60 ($H_{arom.}$), 8.3 (s, NH).

Isomer 2: R_f = 0.26 (PE/AcOEt eluent 95:5)

GC: T_r= 13.629min . MS: 41, 56, 91, 117, 160, 192, 220, 235, 238, 311^{1}H NMR (CDCl3, 400 MHz):δ1.12 (t,3H), 1.57(m, 2H), 1,68 (m,2H), 2.842 (m, 2H), 3.498 (t, 2H, CH_2-O), 3.77 (s, 3H, CH_3-O), 4.09 (m, 1H, CH_2-CH-NH), 4.67 (t, 1H, CH_2-CH-O), 6.85-7.56 ($H_{arom.}$), 8.37 (s, NH).

4-butoxy-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline **3cb** M = 311.189 g/mol

Isomer 1:R_f = 0.26 (PE/AcOEt eluent 95:5)

GC: T_r= 13.817 min. MS: 41, 56,77, 93, 121, 130, 167, 193, 220, 236, 238, 254, 311 *m/z*

^{1}H NMR ($CDCl_3$, 400 MHz):δ0.99 (t,3H), 1.48 (m, 2H), 1,62 (m,2H), 2.71 (m, 2H), 3.65 (t, 2H, CH_2-O), 3.83 (s, 3H, CH_3-O), 3.87 (m, 1H, CH_2-CH-NH), 4.6 (t, 1H, CH_2-CH-O), 6.75-7.24 ($H_{arom.}$), 8.21 (s, NH).

Isomer 2: R_f = 0.23 (PE/AcOEt eluent 95:5)

GC: T_r= 14.012 min . MS: 41, 56,77, 93, 121, 130, 167, 193, 220, 236, 238, 254, 311 *m/z*

^{1}H NMR ($CDCl_3$, 400 MHz):δ1.09 (t,3H), 1.49 (m, 2H), 1,79 (m, 2H), 2.78 (m, 2H), 3.79 (t, 2H, CH_2-O), 3.81 (s, 3H, CH_3-O), 3.9 (m, 1H, CH_2-CH-NH), 4.74 (t, 1H, CH_2-CH-O), 6.75-7.24 ($H_{arom.}$), 8.3 (s, NH).

2-phenylquinoline **4a** M = 205.09 g/mol R_f=0.53 (PE/AcOEt eluent 95:5)

GC: T_r= 11.120min. MS: 76, 88, 102, 117, 151, 176, 205*m/z* . ^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.22-8.81 (H_{arom})

6-methoxy-2-phenylquinoline **4b** M= 235.1 g/mol R_f=0.50 (PE/AcOEt eluent 95:5)

GC: T_r= 12.282 min. MS: 96, 118, 192, 220, 235 *m/z.*^{1}H NMR ($CDCl_3$, 400 MHz):δ 3.81 (s, 3H, CH_3-O), 7.06-8.72 (H_{arom}).

2-(4-methoxyphenyl)quinolines **4c** M= 235.1 g/mol R_f=0.47 (PE/AcOEt eluent 95:05)

GC: T_r= 12.48min and MS: 96, 118, 192, 220, 235*m/z.* ^{1}H NMR ($CDCl_3$, 400 MHz):δ 3.79 (s, 3H, CH_3-O), 7.06-8.72 (H_{arom}).

Conclusions

In this work, we have performed an experimental comparative study between two important methods for the synthesis of new tetrahydroquinoline derivatives together with the corresponding quinolines, the multi-steps and the multi-components. We have found basing on the values of the yield, the reaction time and the selectivity that the reactivity and stereoselectivity of tetrahydroquinoline derivatives synthesis *via* Povarov reaction are directly related to the reaction conditions. The synthesis strategy plays a very important role in the Povarov reaction, in which the multi-component fashion was found to be the best synthetic strategy for the synthesis of this kind of heterocyclic products. This method can be considered a very efficient protocol in organic synthesis due to the mild and simple reaction conditions, time of reaction and high yield.

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