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Tetrahedron
Tetrahedron 63 (2007) 673–681

CAN-catalyzed three-component reaction between anilines and alkyl vinyl ethers: stereoselective synthesis of 2-methyl-1,2,3,4-tetrahydroquinolines and studies on their aromatization

Vellaisamy Sridharan, Carmen Avendaño and J. Carlos Menéndez*

Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain

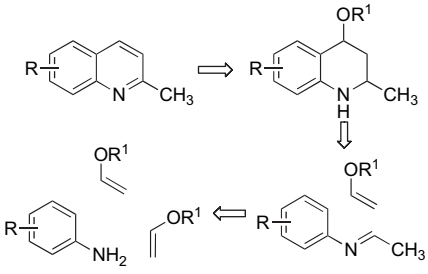
Received 9 October 2006; revised 30 October 2006; accepted 1 November 2006
Available online 28 November 2006

Abstract—The CAN-catalyzed reaction between anilines and vinyl ethers at room temperature provides a convenient and efficient access to 4-alkoxy-2-methyl-1,2,3,4-tetrahydroquinolines. This reaction is stereoselective, favouring a *cis* arrangement for the alkoxy and methyl groups, and involves a three-component process that leaves a molecule of alcohol as the only side product. 2-Methylquinoline derivatives were efficiently prepared from 4-alkoxy-2-methyl-1,2,3,4-tetrahydroquinolines by Pd–C-promoted dehydrogenation.

1. Introduction

2-Methylquinolines are important synthetic intermediates, and have been employed as starting materials for the preparation of many types of biologically active heterocyclic compounds. Some relevant examples include the use of 8-hydroxy-2-methylquinoline as an intermediate in a synthesis of lavendamycin methyl ester,[1] a member of the streptonigrin family of antitumour alkaloids,[2] and the preparation of styrylquinolines, some of which are HIV integrase inhibitors,[3,4] by condensation of 2-methylquinolines with aromatic aldehydes. Additionally, 2-methylquinolines also have interesting biological properties, including chemotherapeutic[5] (antibacterial, antimalarial and antitumour) and antiplatelet[6] activities. The synthesis of 2-methylquinoline derivatives[7,8] has usually relied on the traditional Doebner–von Miller,[7–9] Combes,[7,8] Conrad–Limpach–Knorr,[7,8] Friedländer,[10] Niementowski[7,8] and Pfitzinger[7,8] syntheses. Although they have the advantage of their simplicity, these methods also have considerable drawbacks such as low yields and the use of harsh reaction conditions and highly acidic reaction media, although in some cases improvements of the classical reactions have been reported.[9,10] More recent methods for quinoline synthesis that can be applied to the preparation of 2-methyl derivatives include treatment of *N*-arylimines with a benzotriazole-derived Vilsmeier-type reagent,[11] heterocyclization of 2-aminobenzonitriles with ketenes[12] and dimethyltitanocene methylenation of *N*-(alkoxycarbonyl)amides derived from 2-allylanilines followed by ring-closing metathesis of the resulting enamides.[13] In spite of this progress, the development of new methods for quinoline synthesis continues to be a very active research area.

Within this context, we envisioned that a three-component reaction starting from anilines and non-cyclic vinyl ethers, which can be considered as acetaldehyde enol ethers, would allow access to 2-methyl-1,2,3,4-tetrahydro-quinolines, which would in turn be precursors to 2-methylquinolines (Scheme 1). Such an approach has the advantage of proceeding in only two steps, while simultaneously allowing the study of the intermediate tetrahydroquinolines, which are important in themselves due to the broad range of biological properties of this class of compounds in the agrochemical and pharmaceutical fields.[14] To name just one example, 2-methyl-5-hydroxy-1,2,3,4-tetrahydroquinoline is a potent analgesic.[15]



Scheme 1.

The three-component reaction between anilines[16] and cyclic vinyl ethers, like tetrahydropyran and dihydrofuran, has been previously reported using a variety of catalysts that

* Corresponding author. Tel.: +34 91 3941840; fax: +34 91 3941822; e-mail: josecm@farm.ucm.es

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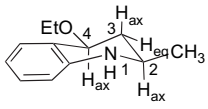
doi:10.1016/j.tet.2006.11.002

include $Dy(OTf)_3$,[17] indium trichloride,[18] iodine,[19] a cation exchange resin,[20] Montmorillonite clay[21] and $Sc(OTf)_3$ in ionic liquids.[22] On the other hand, the related reaction with non-cyclic ethers is almost unknown, and to our knowledge it has been reported only once, in a procedure that involves the use of the very expensive hexafluoropropanol as the reaction medium.[23] Indeed, with this exception, C-2 aliphatic substituted tetrahydroquinolines were previously inaccessible using the Povarov reaction, because of the instability of the intermediate aliphatic *N*-arylaldimine. We report here that catalysis by cerium ammonium nitrate (CAN) allows to carry out the proposed synthesis of 2-methyltetrahydroquinolines under very mild conditions.[24] The reaction uses a non-toxic catalyst, proceeds with maximum atom economy and its only side product is one molecule of R^3OH. It is relevant to note that, although cerium is the most common lanthanide, the use of its salts as Lewis acids has received relatively little attention, and most of this work has focused on Ce(III) species.[25] However, Ce(IV) compounds have good qualities such as their low toxicities and their stability in water. Although Ce(IV) derivatives are normally employed as one-electron oxidants, the use of the commercially available, inexpensive and easily handled CAN in C–C bond forming reactions has recently attracted much attention,[26] although these studies are still in their early stages. One of the main goals to be achieved in this area is the development of reactions that allow the use of catalytic amounts of CAN.[26c] We also report here our studies on the aromatization of 2-methyl-1,2,3,4-tetrahydroquinoline derivatives.

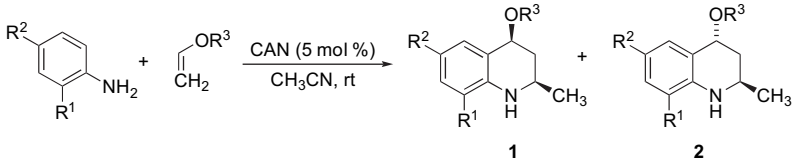
2. Results and discussion

As shown in Scheme 2 and Table 1, treatment of aniline derivatives with vinyl ethers in the presence of 5 mol % CAN in acetonitrile at room temperature led to the corresponding 2-methyl-1,2,3,4-tetrahydroquinolines **1** (*cis*) and **2** (*trans*), in good to excellent yields, and typically with about 9/1 *cis*/*trans* diastereoselectivity. An increase in the amount of CAN to 15 mol % led to decreased reaction times (e.g., 1 h for **1**, **2h** and 2 h for **1**, **2i**) without significantly affecting the yields or the *cis*/*trans* ratios (entries 9 and 11). The stereochemistry of compounds **1** and **2** was determined by study of their ^1H NMR spectra. The major isomer obtained in the reaction between aniline and ethyl vinyl ether (compound **1a**) shows large coupling constants between H-4 and H-3_{ax} (10.5 Hz) and H-2 and H-3_{ax} (12.2 Hz), which are consistent with a *trans*-diaxial relationship between these protons and hence with a *cis* relationship between the ethoxy and methyl groups. In agreement with this assignment, the H-4_{eq} proton of the minor product **2a** appears as a triplet with J=2.9 Hz.



1a **2a**

Regarding the mechanism of the reaction, radical intermediates could be in principle expected due to the strong oxidant properties of CAN. However, an experiment involving the addition of large amounts of 1,1-diphenylethylene, a well-known radical trap, proved that this assumption was wrong, since the reaction was not altered, and therefore CAN must be assumed to act as a Lewis acid. Literature contains at least one previous case where CAN was shown to remain in the Ce(IV) oxidation state by cyclic voltammetry measurements, and hence to behave as a Lewis acid.[27] We propose for our CAN-catalyzed transformation the domino mechanism[28] summarized in Scheme 3, that comprises five individual steps. Thus, the CAN-catalyzed condensation between the starting aniline and one molecule of the alkyl vinyl ether, which can be regarded as an enol ether derived from acetaldehyde, affords imine **3**, which then undergoes



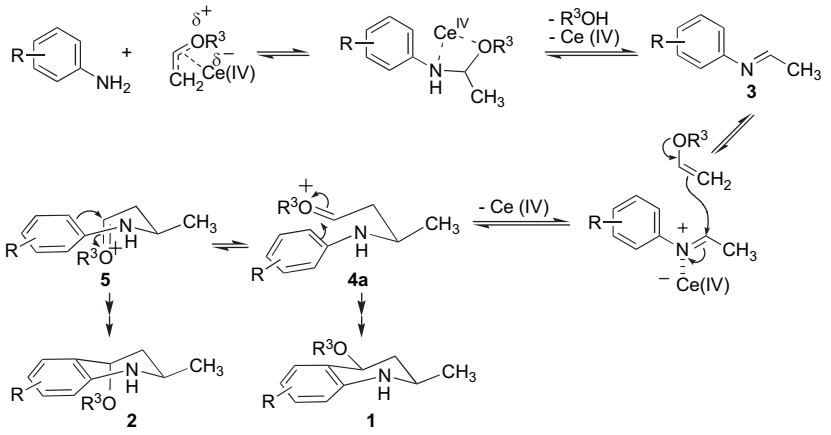
1 **2**

Scheme 2.

Table 1. CAN-catalyzed synthesis of 2-methyl-1,2,3,4-tetrahydroquinolines

Entry	Compound	R^1	R^2	R^3	Reaction time	CAN, mol %	Yield, %	**1/2** ratio[a]
1	**a**	H	H	CH_2CH_3	1 h	5	75	89/11[b]
2	**b**	H	H	^{n}Pr	1 h	5	73	91/9
3	**c**	H	H	^{n}Bu	1 h	5	76	91/9
4	**d**	OCH_3	H	CH_2CH_3	45 min	5	80	90/10[b]
5	**e**	OCH_3	H	^{n}Pr	45 min	5	88	91/9
6	**f**	OCH_3	H	^{n}Bu	45 min	5	90	93/7
7	**g**	CH_3	H	CH_2CH_3	1 h	5	64	93/7
8	**h**	H	CH_3	CH_2CH_3	3 h	5	70	87/13
9	**h**	H	CH_3	CH_2CH_3	1 h	15	72	87/13
10	**i**	H	OCH_3	CH_2CH_3	4 h	5	71	85/15[b]
11	**i**	H	OCH_3	CH_2CH_3	2 h	15	75	85/15
12	**j**	H	Cl	CH_2CH_3	45 min	5	74	80/20[b]

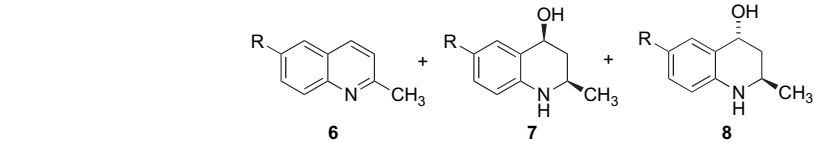
[a] The *cis*/*trans* ratios were calculated from the ^1H NMR spectra of the crude reaction products.
[b] The minor *trans* product was isolated and characterized in these cases.



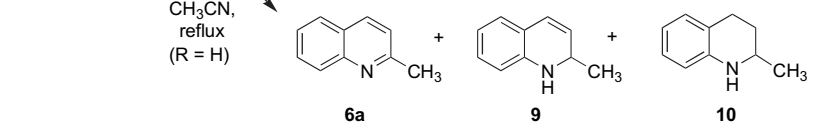
Scheme 3.

a CAN-catalyzed imino Diels–Alder reaction with a second molecule of alkyl vinyl ether, now acting as an electron-rich dienophile, to give the observed tetrahydroquinolines. The imino Diels–Alder reaction (also known as the Povarov reaction) is known to proceed in a stepwise manner, as proved by the trapping of the intermediate oxonium species when the reaction is carried out in the presence of nucleophiles,[29] and therefore generation of intermediates **4** and **5** is expected. The final cyclization step should take place through a chair-like transition state, explaining the preference for an equatorial arrangement of the alkoxy substituent, and hence the *cis* stereochemistry observed for the major products, and would be followed by deprotonation to give compounds **1** and **2**. Previous explanations for the stereoselectivity of Povarov-like reactions that have assumed a concerted mechanism[23] can now be discarded.

With an efficient synthesis of 1-methyl-1,2,3,4-tetrahydroquinolines in hand, we next examined their transformation into 2-methylquinolines. We first studied their behaviour under acidic conditions, since 2-phenyl-[30] and 2-trifluoromethyl-1,2,3,4-tetrahydroquinolines[31,32] are known to aromatize efficiently by treatment with aqueous HCl. However, in our case the typical literature conditions (2 M HCl–CH_3CN, rt) led to mixtures of the desired aromatic compounds **6** and alcohols **7** and **8** (Scheme 4). The formation of the latter compound is probably due to its stabilization by intramolecular hydrogen bonding between the NH and the axial OH group, arising from the addition of water to a benzylic cation generated by elimination of ethanol from **1** in the acidic reaction medium. Reflux conditions, rather surprisingly, allowed the isolation of dihydroquinoline **9**, which can be considered to be an intermediate of the process since it can generate equimolecular mixtures of the quinoline **6a** and the tetrahydroquinoline derivative **10** through dismutation involving a Brønsted acid-catalyzed hydrogen transfer process (Scheme 5). The last transformation can be considered as closely related to the recently described reduction of quinolines by Hantzsch dihydropyridines in the presence of Brønsted acids.[33]

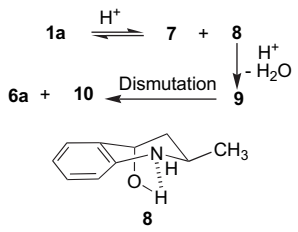


Starting compound	R	Time (h)	Overall yield (%)	**6 : 7 : 8**
1a	H	8	95	15 : 30 : 55
1a	H	14	96	29 : 27 : 44
1i	OCH_3	16	86	7 : 32 : 61



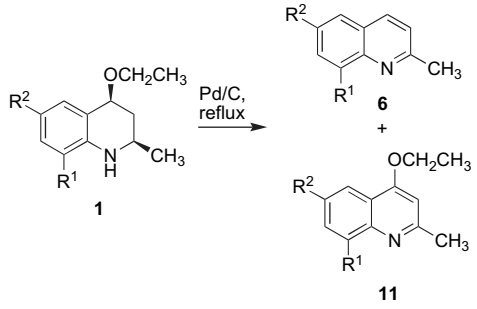
Starting compound	Time (h)	Overall yield (%)	**6a : 9 : 10**
1a	0.5	96	20 : 60 : 20
1a	2	95	40 : 20 : 40

Scheme 4.



Scheme 5.

In view of these results, alternative methods for the aromatization of compounds **1** were investigated. The most reliable one was dehydrogenation in the presence of palladium, which, to our knowledge, had not been previously applied to the transformation of 4-alkoxy-1,2,3,4-tetrahydroquinolines into 4-unsubstituted quinoline derivatives. As shown in Scheme 6 and Table 2, refluxing compounds **1** in the presence of Pd–C resulted in their efficient transformation into the 4-unsubstituted 2-methylquinoline derivatives **6** where ethanol elimination has taken place concomitantly with dehydrogenation. These compounds were accompanied in some instances by small amounts of the 4-ethoxy-2-methylquinolines **11**. Aromatization of the chloro derivative **1j** led to a mixture of **6j** and **6a**, the latter compound being generated from hydrogenolysis of the C–Cl bond in **6j** by the hydrogen liberated in the aromatization process.



Scheme 6.

In conclusion, we have shown that addition of CAN allows the efficient and stereoselective preparation of 2-methyl-1,2,3,4-tetrahydroquinolines in a three-component protocol starting from anilines and vinyl ethers. This user-friendly new method proceeds under very mild conditions, using a non-toxic and inexpensive catalyst, with an alcohol molecule as the only side product. The efficient aromatization of the 4-alkoxy-2-methyltetrahydroquinoline derivatives thus obtained to 2-methylquinolines in the presence of Pd–C was also demonstrated.

Table 2. Aromatization of 1-alkoxy-1,2,3,4-tetrahydroquinolines **1** in the presence of Pd–C

Starting compd	R^1	R^2	Solvent	Time (h)	Overall yield (%)	**6/11** ratio[a]
1a	H	H	Toluene	5	93	81/19
1d	OCH_3	H	Toluene	5	85	100/0
1g	CH_3	H	Toluene	4	82	100/0
1h	H	CH_3	Toluene	5	92	88/12
1i	H	OCH_3	Toluene	5	96	74/26
1i	H	OCH_3	Methanol	18	85	62/23[b]
1j	H	Cl	Toluene	4	95	—[c]

[a] This ratio was calculated from the ^{1}H NMR spectra of the crude reaction products.
[b] These products were accompanied by 15% of *trans*-1-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline (compound **12**).
[c] An inseparable mixture of **6j** and **6a** was isolated in 60/40 ratio.

3. Experimental

3.1. General

All reagents were of commercial quality (Aldrich, Fluka, SDS, Probus) and were used as received. Solvents (from SDS) were dried and purified using standard techniques. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 40–63 μm particle size). Melting points were measured with a Reichert 723 hot stage microscope, and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrophotometer, with all compounds examined as films on a NaCl disk. NMR spectra were obtained on a Bruker Avance instrument (250 MHz for ^{1}H, 62.9 MHz for ^{13}C), maintained by the Servicio de RMN, Universidad Complutense, with $CDCl_3$ as solvent. Combustion elemental analyses were determined by the Servicio de Microanálisis Elemental, Universidad Complutense, using a Leco 932 CHNS microanalyzer.

3.2. General procedure for the synthesis of tetrahydroisoquinolines

To a stirred solution of the starting aniline (3 mmol) and alkyl vinyl ether (7.5 mmol) in acetonitrile (15 mL) was added CAN (5 mol %). Stirring was continued for the time period specified in Table 1. After completion of the reaction, as indicated by TLC, the mixture was extracted with dichloromethane (2×20 mL), dried (anhydrous Na_2SO_4) and evaporated. The ratio of *cis*/*trans* isomers was calculated from the crude ^{1}H NMR spectra and the mixture was separated by silica gel column chromatography eluting with a petroleum ether–ethyl acetate (96/4, v/v) mixture. Characterization data are given below.

3.2.1. (±)-*cis*-4-Ethoxy-2-methyl-1,2,3,4-tetrahydroquinoline (1a).[23] Viscous oil. IR (neat) 3374.1, 2970.3, 2925.8, 1609.0, 1487.6, 1310.7, 1095.2 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.26–1.35 (m, 6H), 1.70 (q, J=12.2 Hz, 1H), 2.27 (ddd, J=12.2, 5.7, 2.6 Hz, 1H), 3.52–3.78 (m, 4H), 4.70 (dd, J=10.5, 5.7 Hz, 1H), 6.50 (dd, J=8.0, 1.0 Hz, 1H), 6.72 (td, J=7.5, 1.1 Hz, 1H), 7.05 (td, J=7.5, 1.0 Hz, 1H), 7.38 (d, J=7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 16.1, 23.0, 36.5, 46.8, 63.8, 74.1, 114.3, 117.9, 123.0, 127.7, 128.5, 145.0. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.46; H, 8.87; N, 7.68.

3.2.2. (±)-*trans*-4-Ethoxy-2-methyl-1,2,3,4-tetrahydroquinoline (2a). Viscous oil. IR (neat) 3382.1, 2968.3, 2918.4, 1610.9, 1493.2, 1316.7, 1158.0, 1077.6 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.22–1.29 (m, 6H), 1.51 (ddd, J=13.5, 12.1, 3.1 Hz, 1H), 2.13 (dt, J=13.5,

2.7 Hz, 1H), 3.57–3.68 (m, 3H), 3.93 (br s, 1H), 4.33 (t, J=2.9 Hz, 1H), 6.56 (dd, J=8.0, 0.7 Hz, 1H), 6.67 (td, J=7.4, 1.0 Hz, 1H), 7.06–7.16 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 16.1, 22.7, 35.9, 42.6, 63.5, 73.3, 114.9, 116.8, 120.2, 129.5, 131.5, 145.4. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 76.05; H, 8.60; N, 7.97.

3.2.3. (±)-*cis*-4-Propoxy-2-methyl-1,2,3,4-tetrahydroquinoline (1b). Viscous oil. IR (neat) 3384.5, 2960.6, 2922.7, 2871.9, 1609.0, 1487.5, 1310.5, 1090.8 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.05 (t, J=7.5 Hz, 3H), 1.30 (d, J=6.3 Hz, 3H), 1.64–1.78 (m, 3H), 2.29 (ddd, J=12.2, 5.7, 2.6 Hz, 1H), 3.46–3.73 (m, 4H), 4.70 (dd, J=10.5, 5.7 Hz, 1H), 6.51 (dd, J=8.0, 1.1 Hz, 1H), 6.73 (td, J=8.0, 1.0 Hz, 1H), 7.06 (td, J=8.0, 1.0 Hz, 1H), 7.41 (dd, J=8.0, 1.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 11.3, 23.0, 23.9, 36.4, 46.8, 70.3, 74.3, 114.3, 117.9, 123.1, 127.8, 128.5, 145.0. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.48; H, 8.93; N, 7.61.

3.2.4. (±)-*cis*-4-Butoxy-2-methyl-1,2,3,4-tetrahydroquinoline (1c). Viscous oil. IR (neat) 3375.9, 2957.7, 2929.2, 2868.5, 1609.5, 1487.4, 1310.2, 1093.2 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.99 (t, J=7.2 Hz, 3H), 1.28 (d, J=6.3 Hz, 3H), 1.44–1.57 (m, 2H), 1.62–1.76 (m, 3H), 2.28 (ddd, J=12.2, 5.8, 2.6 Hz, 1H), 3.49–3.60 (m, 2H), 3.66–3.75 (m, 2H), 4.68 (dd, J=10.4, 5.8 Hz, 1H), 6.50 (dd, J=8.0, 1.0 Hz, 1H), 6.73 (td, J=8.0, 1.0 Hz, 1H), 7.05 (td, J=8.0, 1.0 Hz, 1H), 7.39 (dd, J=8.0, 1.0 Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.4, 19.9, 23.0, 32.8, 36.4, 46.7, 68.3, 74.3, 114.3, 117.9, 123.1, 127.7, 128.5, 145.0. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.78; H, 9.33; N, 6.73.

3.2.5. (±)-*cis*-4-Ethoxy-8-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (1d).[23] Viscous oil. IR (neat) 3411.0, 2969.2, 2926.6, 2837.9, 1588.0, 1494.5, 1457.1, 1330.3, 1248.0, 1167.8, 1089.5 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.28–1.34 (m, 6H), 1.74 (q, J=12.2 Hz, 1H), 2.27 (ddd, J=12.2, 5.7, 2.4 Hz, 1H), 3.31–3.80 (m, 3H), 3.87 (s, 3H), 4.15 (br s, 1H), 4.75 (dd, J=10.4, 5.7 Hz, 1H), 6.67–6.70 (m, 2H), 7.03–7.06 (m, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 16.2, 23.0, 36.4, 46.5, 55.8, 63.6, 74.2, 108.8, 116.8, 119.7, 123.0, 135.0, 146.2. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.98; H, 8.70; N, 6.74.

3.2.6. (±)-*trans*-4-Ethoxy-8-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (2d).[23] Viscous oil. IR (neat) 3415.5, 2966.7, 2934.0, 2860.1, 1612.6, 1587.1, 1501.0, 1458.3, 1332.7, 1246.8, 1169.7, 1077.6 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.26 (t, J=7.0 Hz, 3H), 1.33 (d, J=6.3 Hz, 3H), 1.53 (ddd, J=13.5, 12.2, 3.2 Hz, 1H), 2.14 (dt, J=13.5, 2.3 Hz, 1H), 3.57–3.69 (m, 3H), 3.87 (s, 3H), 4.36 (t, J=2.8 Hz, 1H), 4.39 (br s, 1H), 6.64 (t, J=7.7 Hz, 1H), 6.73 (dd, J=7.9, 1.5 Hz, 1H), 6.83 (dd, J=7.5, 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 16.1, 22.7, 35.9, 42.2, 55.8, 63.6, 73.2, 109.4, 115.7, 120.2, 123.4, 135.4, 146.6. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.84; H, 8.32; N, 6.66.

3.2.7. (±)-*cis*-8-Methoxy-2-methyl-4-propoxy-1,2,3,4-tetrahydroquinoline (1e). Viscous oil. IR (neat) 3411.3, 2959.7, 2874.0, 2840.2, 1588.9, 1494.8, 1331.7, 1247.9, 1084.1 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.03 (t, J=7.5 Hz, 3H), 1.33 (d, J=6.3 Hz, 3H), 1.67–1.81 (m, 3H), 2.28 (ddd, J=12.2, 5.7, 2.6 Hz, 1H), 3.44–3.70 (m, 3H), 3.86 (s, 3H), 4.17 (br s, 1H), 4.74 (dd, J=10.5, 5.7 Hz, 1H), 6.68–6.73 (m, 2H), 7.03–7.06 (m, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 11.3, 22.9, 23.9, 36.3, 46.5, 55.8, 70.2, 74.3, 108.8, 116.8, 119.8, 123.2, 134.9, 146.2. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.65; H, 8.70; N, 6.28.

3.2.8. (±)-*cis*-4-Butoxy-8-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (1f). Viscous oil. IR (neat) 3410.5, 2957.4, 2929.2, 2868.0, 1588.8, 1494.6, 1331.6, 1248.1, 1086.3 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.98 (t, J=7.2 Hz, 3H), 1.32 (d, J=6.3 Hz, 3H), 1.41–1.56 (m, 2H), 1.62–1.80 (m, 3H), 2.27 (ddd, J=12.2, 5.7, 2.6 Hz, 1H), 3.48–3.59 (m, 2H), 3.64–3.73 (m, 1H), 3.86 (s, 3H), 4.16 (br s, 1H), 4.73 (dd, J=10.5, 5.7 Hz, 1H), 6.68–6.70 (m, 2H), 7.03–7.07 (m, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.4, 19.9, 22.9, 32.8, 36.3, 46.5, 55.8, 68.2, 74.3, 108.8, 116.8, 119.8, 123.2, 134.9, 146.2. Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.50; H, 9.28; N, 5.82.

3.2.9. (±)-*cis*-4-Ethoxy-2,8-dimethyl-1,2,3,4-tetrahydroquinoline (1g).[34] Viscous oil. IR (neat) 3408.7, 2969.2, 2925.0, 2856.9, 1601.1, 1493.8, 1474.2, 1335.0, 1119.4 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.30–1.36 (m, 6H), 1.66–1.79 (m, 1H), 2.13 (s, 3H), 2.28 (ddd, J=12.2, 5.7, 2.6 Hz, 1H), 3.50 (br s, 1H), 3.55–3.78 (m, 3H), 4.75 (dd, J=10.5, 5.7 Hz, 1H), 6.69 (t, J=7.9 Hz, 1H), 6.98 (dd, J=7.9, 1.5 Hz, 1H), 7.31 (dd, J=7.9, 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 16.1, 17.8, 23.2, 36.2, 46.7, 63.6, 74.3, 117.2, 121.1, 122.5, 125.5, 129.5, 143.0. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.76; H, 9.21; N, 6.87.

3.2.10. (±)-*cis*-4-Ethoxy-2,6-dimethyl-1,2,3,4-tetrahydroquinoline (1h). Viscous oil. IR (neat) 3371.3, 2969.4, 2918.2, 2856.4, 1617.9, 1506.0, 1338.8, 1300.5, 1172.1, 1097.0 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.28 (d, J=6.3 Hz, 3H), 1.34 (d, J=7.0 Hz, 3H), 1.61–1.75 (m, 1H), 2.24–2.31 (m, 4H), 3.47–3.79 (m, 4H), 4.68 (dd, J=10.4, 5.9 Hz, 1H), 6.44 (d, J=8.1 Hz, 1H), 6.86 (dd, J=8.1, 1.5 Hz, 1H), 7.20 (d, J=1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 16.2, 21.0, 23.0, 36.7, 46.9, 63.8, 74.2, 114.6, 123.1, 127.3, 128.1, 129.2, 142.7. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.36; H, 9.15; N, 7.32.

3.2.11. (±)-*cis*-4-Ethoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (1i).[34] Viscous oil. IR (neat) 3364.2, 2969.3, 2869.3, 1500.8, 1339.4, 1267.5, 1231.9, 1154.5, 1095.0 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.26 (d, J=6.3 Hz, 3H), 1.32 (t, J=7.0 Hz, 3H), 1.60–1.74 (m, 1H), 7.26 (ddd, J=12.2, 5.9, 2.3 Hz, 1H), 3.44–3.77 (m, 4H), 3.79 (s, 3H), 4.70 (dd, J=10.6, 5.9 Hz, 1H), 6.48 (d, J=8.7 Hz, 1H), 6.67 (dd, J=8.7, 2.9 Hz, 1H), 6.99 (d, J=2.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 16.2, 23.0, 36.6, 47.1, 56.2, 63.6, 74.3, 112.6, 115.2, 115.8, 124.3, 139.2, 152.7. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.18; H, 8.37; N, 6.54.

3.2.12. (±)-*trans*-4-Ethoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (2i).[34] IR (neat) 3375.6, 2967.6, 2927.1, 2862.1, 1503.6, 1346.9, 1254.0, 1156.2, 1077.5, 1040.1 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 1.24–1.29 (m, 6H), 1.49 (ddd, J=13.6, 12.0, 3.3 Hz, 1H), 2.12 (dt, J=13.6, 2.5 Hz, 1H), 3.52–3.71 (m, 3H), 3.77 (s, 3H), 4.29 (t, J=2.8 Hz, 1H), 6.53 (d, J=9.4 Hz, 1H), 6.72–6.76 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 16.1, 22.7, 35.9, 42.9, 56.3, 63.8, 73.5, 116.1, 116.2, 116.3, 121.4, 139.7, 151.8. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.85; H, 8.30; N, 6.72.

3.2.13. (±)-*cis*-6-Chloro-4-ethoxy-2-methyl-1,2,3,4-tetrahydroquinoline (1j).[34] IR (neat) 3397.2, 2971.5, 2927.1, 2869.1, 1604.0, 1488.8, 1339.3, 1229.4, 1251.8, 1101.9 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 1.26 (d, J=6.3 Hz, 3H), 1.32 (t, J=7.0 Hz, 3H), 1.56–1.69 (m, 1H), 2.27 (ddd, J=12.2, 5.7, 2.6 Hz, 1H), 3.50–3.82 (m, 4H), 4.60 (dd, J=10.6, 5.7 Hz, 1H), 6.40 (d, J=8.5 Hz, 1H), 6.97 (dd, J=8.5, 2.5 Hz, 1H), 7.33 (d, J=2.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 16.1, 22.8, 36.1, 46.7, 64.2, 73.8, 115.3, 122.4, 124.5, 127.4, 128.4, 143.4. Anal. Calcd for $C_{12}H_{16}ClNO$: C, 63.85; H, 7.14; N, 6.21. Found: C, 63.06; H, 6.92; N, 6.41.

3.2.14. (±)-*trans*-6-Chloro-4-ethoxy-2-methyl-1,2,3,4-tetrahydroquinoline (2j).[34] IR (neat) 3403.9, 2970.0, 2919.9, 2867.4, 1608.0, 1492.1, 1348.0, 1309.6, 1268.3, 1160.0, 1077.6 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 1.23–1.29 (m, 6H), 1.46 (ddd, J=13.6, 12.0, 3.2 Hz, 1H), 2.11 (dt, J=13.6, 2.6 Hz, 1H), 3.56–3.67 (m, 3H), 3.95 (br s, 1H), 4.27 (t, J=2.9 Hz, 1H), 6.47 (d, J=8.6 Hz, 1H), 7.03 (dd, J=8.6, 2.4 Hz, 1H), 7.11 (d, J=2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 16.0, 22.5, 35.5, 42.6, 63.8, 73.0, 116.0, 121.1, 121.6, 129.3, 130.8, 144.0. Anal. Calcd for $C_{12}H_{16}ClNO$: C, 63.85; H, 7.14; N, 6.21. Found: C, 64.08; H, 7.01; N, 6.38.

3.3. Reaction of tetrahydroquinolines 1 with 2 M HCl

To a solution of tetrahydroquinoline **1** (400 mg) in acetonitrile (20 mL) was added 2 M hydrochloric acid (6 mL). The mixture was stirred at room temperature or heated under reflux. After the time period specified in Scheme 4, the reaction was quenched by saturated $NaHCO_3$ solution, extracted with CH_2Cl_2, dried (anhydrous Na_2SO_4) and evaporated. Pure products were separated through silica gel column chromatography using a petroleum ether–ethyl acetate mixture (97/3, v/v) as the eluant. Compounds **7** and **8** were obtained as inseparable mixtures. Characterization data are given below.

3.3.1. (±)-2-Methyl-1,2,3,4-tetrahydroquinolin-4-ol *cis–trans* mixture (7a and 8a). ^1H NMR ($CDCl_3$, 250 MHz) δ 1.25 (d, J=6.5 Hz, 3H, **7a**), 1.28 (d, J=7.1 Hz, 3H, **8a**), 1.55–1.68 (m, 2H, **7a** and **8a**), 2.03 (dt, J=13.6, 2.6 Hz, 1H, **8a**), 2.25 (ddd, J=12.1, 5.9, 2.3 Hz, 1H, **7a**), 3.52–3.61 (m, 2H, **7a** and **8a**), 3.90 (br s, 2H, **7a** and **8a**), 4.74 (t, J=2.9 Hz, 1H, **8a**), 4.92 (dd, J=10.6, 5.9 Hz, 1H, **7a**), 6.51 (dd, J=7.8, 0.9 Hz, 1H, **7a**), 6.56 (dd, J=7.8, 0.5 Hz, 1H, **8a**), 6.67–6.77 (m, 2H, **7a** and **8a**), 7.03–7.14 (m, 2H, **7a** and **8a**), 7.22 (d, J=7.8, 0.5 Hz, 1H, **8a**), 7.41 (d, J=7.8 Hz, 1H, **7a**). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 20.6, 20.9, 36.6, 39.3, 40.3, 45.0, 64.4, 65.6, 112.6, 113.2, 115.9, 116.3, 120.9, 123.2, 125.5, 127.0, 127.9, 128.9, 142.9, 143.4.

3.3.2. (±)-6-Methoxy-2-methyl-1,2,3,4-tetrahydroquinolin-4-ol *cis–trans* mixture (7i and 8i). ^1H NMR ($CDCl_3$, 250 MHz) δ 1.22 (d, J=6.4 Hz, 3H, **7i**), 1.25 (d, J=6.3 Hz, 3H, **8i**), 1.49–1.62 (m, 2H, **7i** and **8i**), 1.99 (dt, J=13.6, 2.6 Hz, 1H, **8i**), 2.22 (ddd, J=12.1, 5.9, 2.3 Hz, 1H, **7i**), 3.43–3.52 (m, 2H, **7i** and **8i**), 3.75 (s, 6H, **7i** and **8i**), 4.68 (t, J=2.9 Hz, **8i**), 4.88 (dd, J=10.6, 5.9 Hz, 1H, **7i**), 6.46 (d, J=8.6 Hz, 1H, **7i**), 6.53 (d, J=8.7 Hz, 1H, **8i**), 6.68 (dd, J=8.6, 2.9 Hz, 1H, **7i**), 6.74 (dd, J=8.7, 2.9 Hz, 1H, **8i**), 6.80 (d, J=2.9 Hz, 1H, **8i**), 7.01 (d, J=2.9 Hz, 1H, **7i**). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 22.4, 22.8, 38.9, 41.4, 42.5, 47.2, 56.2, 56.3, 66.4, 67.6, 112.2, 115.1, 115.6, 115.9, 116.4, 116.7, 123.7, 126.4, 138.8, 139.4, 152.3, 152.8. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.65; H, 7.53; N, 7.38.

3.3.3. 2-Methyl-1,2-dihydroquinoline (9). Viscous liquid. IR (neat) 3386.6, 3052.3, 2923.0, 2844.2, 1603.5, 1498.2, 1310.6, 1153.3, 1122.1, 1039.0 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 1.34 (d, J=6.5 Hz, 3H), 3.73 (br s, 1H), 4.43–4.47 (m, 1H), 5.58 (dd, J=9.8, 3.6 Hz, 1H), 6.33 (dd, J=9.8, 1.5 Hz, 1H), 6.43 (d, J=7.9 Hz, 1H), 6.63 (td, J=7.4, 1.1 Hz, 1H), 6.89 (dd, J=7.4, 1.4 Hz, 1H), 7.00 (td, J=7.7, 1.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 24.7, 48.7, 113.0, 117.9, 120.8, 125.6, 127.1, 127.5, 129.1, 144.3. Anal. Calcd for $C_{10}H_{11}N$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.60; H, 7.59; N, 9.63.

3.3.4. 2-Methyl-1,2,3,4-tetrahydroquinoline (10). Viscous liquid. IR (neat) 3394.6, 3050.5, 2961.5, 2844.2, 1608.1, 1489.4, 1309.6, 1257.5, 1153.5, 1124.5, 1039.8 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 1.26 (d, J=6.3 Hz, 3H), 1.56–1.72 (m, 1H), 1.93–2.03 (m, 1H), 2.72–2.96 (m, 2H), 3.38–3.51 (m, 1H), 3.74 (br s, 1H), 6.51 (dd, J=8.5, 1.2 Hz, 1H), 6.66 (td, J=7.4, 1.2 Hz, 1H), 6.99–7.05 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 23.0, 27.0, 30.5, 47.6, 114.6, 117.6, 121.7, 127.1, 129.7, 145.0. Anal. Calcd for $C_{10}H_{13}N$: C, 81.59; H, 8.90; N, 9.51. Found: C, 81.14; H, 8.60; N, 9.24.

3.4. General procedure for the synthesis of 2-methylquinolines by aromatization of compounds 1

A mixture of 200 mg of the suitable tetrahydroquinoline **1** and 200 mg of 10% Pd on activated carbon (Pd–C) in 10 mL of toluene (or methanol) was refluxed for the time period specified in Table 2. The progress of the reaction was monitored by TLC. After completion, the mixture was filtered through Celite and the solvent was evaporated under reduced pressure. 2-Methylquinoline derivatives **6** and **11** were separated through silica column using a mixture of petroleum ether and ethyl acetate as eluent (80/20, v/v). Characterization data for these compounds are given below.

3.4.1. 2-Methylquinoline (6a).[9c] Viscous liquid. IR (neat) 3051.6, 2958.5, 2917.8, 1601.7, 1559.9, 1507.0, 1423.4, 1373.6, 1312.0 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 2.75 (s, 3H), 7.26 (d, J=8.5 Hz, 1H), 7.47 (td, J=8.0, 1.0 Hz, 1H), 7.68 (td, J=8.0, 1.0 Hz, 1H), 7.76 (d, J=8.0 Hz, 1H),

8.00–8.06 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 25.8, 122.4, 126.1, 126.9, 127.9, 129.0, 129.8, 136.6, 148.2, 159.4. Anal. Calcd for $C_{10}H_9N$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.24; H, 6.54; N, 9.71.

3.4.2. 4-Ethoxy-2-methylquinoline (11a).[35] Viscous liquid. IR (neat) 3063.4, 2980.9, 2929.5, 1594.3, 1566.5, 1509.0, 1423.5, 1381.0, 1345.7, 1233.6 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.57 (t, J=7.0 Hz, 3H), 2.70 (s, 3H), 4.23 (q, J=7.0 Hz, 2H), 6.60 (s, 1H), 7.44 (td, J=8.4, 1.5 Hz, 1H), 7.66 (td, J=8.4, 1.5 Hz, 1H), 7.96 (d, J=8.4 Hz, 1H), 8.18 (dd, J=8.4, 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.9, 26.4, 64.4, 101.5, 120.3, 122.1, 125.1, 128.4, 130.1, 149.2, 160.5, 162.0. Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.62; H, 7.03; N, 7.51.

3.4.3. 2-Methyl-8-methoxyquinoline (6d).[9c] Mp 124–125 °C. IR (neat) 2999.8, 2952.3, 2836.4, 1603.4, 1565.7, 1466.3, 1427.8, 1331.0, 1261.9, 1238.3, 1110.9 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.78 (s, 3H), 4.06 (s, 3H), 7.00 (dd, J=8.4, 1.5 Hz, 1H), 7.25–7.37 (m, 3H), 7.98 (dd, J=8.4, 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 26.1, 56.4, 107.9, 119.8, 123.0, 126.1, 127.9, 136.5, 140.0, 155.1, 158.5. Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.04; H, 6.29; N, 8.26.

3.4.4. 2,8-Dimethylquinoline (6g).[36] Viscous liquid. IR (neat) 3043.8, 2921.0, 2850.6, 1602.0, 1500.2, 1425.3, 1311.3, 1266.6, 1136.2 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.83 (s, 3H), 2.89 (s, 3H), 7.31 (d, J=8.4 Hz, 1H), 7.42 (t, J=7.7 Hz, 1H), 7.59 (d, J=7.7 Hz, 1H), 7.66 (d, J=7.7 Hz, 1H), 8.04 (d, J=8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 18.5, 26.2, 122.1, 125.7, 126.0, 126.8, 129.9, 136.7, 136.9, 147.4, 158.3. Anal. Calcd for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91. Found: C, 83.78; H, 7.38; N, 8.83.

3.4.5. 2,6-Dimethylquinoline (6h).[37] Mp 72–73 °C. IR (neat) 3055.0, 2917.0, 2858.6, 1601.4, 1496.1, 1372.9, 1221.5, 1119.3, 1034.5 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.49 (s, 3H), 2.71 (s, 3H), 7.20 (d, J=8.4 Hz, 1H), 7.47–7.50 (m, 2H), 7.89–7.93 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 20.1, 23.9, 120.6, 125.0, 125.1, 126.8, 130.3, 134.0, 134.2, 145.0, 156.6. Anal. Calcd for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91. Found: C, 83.86; H, 7.06; N, 8.99.

3.4.6. 4-Ethoxy-2,6-dimethylquinoline (11h). Mp 79–80 °C. IR (neat) 3055.0, 2980.2, 2919.3, 1593.9, 1569.5, 1443.4, 1385.6, 1345.2, 1231.3, 1180.5, 1113.3 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.58 (t, J=7.0 Hz, 3H), 2.53 (s, 3H), 2.68 (s, 3H), 4.24 (q, J=7.0 Hz, 2H), 6.59 (s, 1H), 7.50 (dd, J=8.6, 2.0 Hz, 1H), 7.85 (d, J=8.6 Hz, 1H), 7.94 (d, J=2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 15.0, 22.0, 26.3, 64.3, 101.4, 120.1, 121.0, 128.2, 132.2, 134.8, 147.7, 159.5, 161.5. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.30; H, 7.35; N, 6.99.

3.4.7. 2-Methyl-6-methoxyquinoline (6i).[9c] Mp 67–68 °C. IR (neat) 3053.5, 2942.0, 2830.4, 1625.3, 1603.6, 1499.9, 1375.4, 1234.1, 1161.0, 1031.3 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.71 (s, 3H), 3.91 (s, 3H), 7.03 (d, J=2.8 Hz, 1H), 7.23 (d, J=8.4 Hz, 1H), 7.34 (dd, J=9.2, 2.8 Hz, 1H), 7.91–7.94 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 25.4, 55.9, 105.6, 122.3, 122.7, 127.7, 130.4, 135.5, 144.2, 156.7, 157.5. Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 75.99; H, 6.45; N, 8.03.

3.4.8. 4-Ethoxy-6-methoxy-2-methylquinoline (11i). Mp 61–62 °C. IR (neat) 2981.8, 2936.8, 2838.4, 1598.0, 1504.3, 1483.6, 1384.8, 1267.1, 1223.7, 1096.4, 1032.6 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.58 (t, J=7.0 Hz, 3H), 2.67 (s, 3H), 3.94 (s, 3H), 4.25 (q, J=7.0 Hz, 2H), 6.60 (s, 1H), 7.31 (dd, J=9.1, 2.9 Hz, 1H), 7.43 (d, J=2.9 Hz, 1H), 7.86 (d, J=9.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 15.0, 26.0, 55.9, 64.3, 100.3, 101.7, 120.8, 122.2, 129.9, 145.0, 157.1, 157.8, 161.1. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.74; H, 6.72; N, 6.50.

3.4.9. (±)-*trans*-4,6-Dimethoxy-2-methyl-1,2,3,4-tetrahydroquinoline (12). Viscous oil. IR (neat) 3375.2, 2961.1, 2862.3, 2822.5, 1504.4, 1447.5, 1347.4, 1254.6, 1156.6, 1077.5, 1040.3 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.25 (d, J=6.3 Hz, 3H), 1.50 (ddd, J=13.7, 12.2, 3.3 Hz, 1H), 2.14 (dt, J=13.7, 2.6 Hz, 1H), 3.48 (s, 3H), 3.50–3.57 (m, 1H), 3.78 (s, 3H), 4.18 (t, J=2.8 Hz, 1H), 6.54 (d, J=9.4 Hz, 1H), 6.73–6.79 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 22.7, 35.4, 42.8, 56.3, 56.4, 75.4, 116.1, 116.2, 116.6, 120.8, 139.6, 151.7. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.83; H, 7.98; N, 7.06.

Acknowledgements

We thank MEC (grant CTQ2006-10930) and UCM-CAM (Grupos de Investigación, grant 920234) for financial support.

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