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Aza-Diels–Alder reactions in ionic liquids: a facile synthesis of pyrano- and furanoquinolines

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Abstract—Room temperature ionic liquids are found to catalyze efficiently the three component-coupling reactions of aldehydes, amines and cyclic enol ethers such as 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran under mild and convenient conditions to afford the corresponding pyrano- and furanoquinolines in excellent yields with high *endo*-selectivity. Interestingly, 2,3-dihydrofuran afforded selectively *endo*-products under the similar reaction conditions.

1. Introduction

The hetero-Diels–Alder reaction is becoming a mainstay for heterocycle and natural product synthesis.[1] Pyranoquinoline derivatives are found to possess a wide spectrum of biological activities such as psychotropic, anti-allergenic, anti-inflammatory and estrogenic activity.[2] The imino-Diels–Alder provides easy access to the preparation of pyrano, and furanoquinolines. The imines derived from aromatic amines act as heterodienes and undergo imino-Diels–Alder reaction with various dienophiles in the presence of acid catalysts.[3–5] However, many of these reactions cannot be carried out in a one-pot operation with a carbonyl compound, amine and enol ether because the amines and water that exist during imine formation can decompose or deactivate the Lewis acids. Even when the desired reactions proceed, more than stoichiometric amounts of the Lewis acids are required because the acids are trapped by nitrogen.[1] Furthermore, most of the imines are hygroscopic, unstable at high temperatures, and difficult to purify by distillation or column chromatography. Subsequently, one-pot procedures have been developed for this transformation using lanthanide triflates as catalysts.[6] These procedures do not require the isolation of unstable imines prior to the reactions, but metal triflates are strongly acidic and highly expensive, and so the development of neutral alternatives like ionic liquids would extend the scope of this useful transformation to synthesize functionalized quinoline derivatives.

Room temperature ionic liquids, especially those based on the 1-*n*-alkyl-3-methylimidazolium cation, have shown great promise as an attractive alternative to conventional solvents. They are non-volatile, recyclable, non-explosive, easy to handle, thermally robust, and in addition they are compatible with various organic compounds and organometallic reagents.[7] Indeed, ionic liquids are good solvents for transition-metal complexes in many homogeneously catalyzed reactions such as hydrogenation, hydroformylation, epoxidation, allylation, the Heck reaction, and Suzuki cross coupling reactions.[8] In many cases the products are weakly soluble in the ionic phase so that the catalyst can be separated by simple extraction. Because of the great potential of room temperature ionic liquids as environmentally benign media for catalytic processes, much attention is currently focused on organic reactions catalyzed by ionic liquids. Several organic reactions promoted by ionic liquids have been reported with high performance.[9] This has offered some evidence that using ionic liquids as promoters for those traditionally acid-base catalyzed synthetic reactions may not only be possible but also practical and even highly efficient. In addition, improved *endo*-selectivity and enhanced reaction rates are the remarkable features observed in Diels–Alder reactions in ionic liquids.[10] However, there are no examples of the use of ionic liquids as promoters for the imino-Diels–Alder reaction.

2. Results and discussion

In view of the emerging importance of ionic liquids as novel reaction media, we wish to report the use of ionic liquids as promoters for the synthesis of tetrahydroquinolines. The treatment of benzaldehyde and aniline with 2,3-dihydrofuran in 1-butyl-3-methylimidazolium tetrafluoroborate ionic liquid afforded the corresponding furanoquinolines **3** in 92% yield (Scheme 1).

Keywords: Diels–Alder reaction; ionic liquids; Lewis acids.

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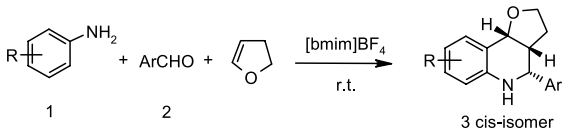


Scheme 1.

Several aldimines (formed in situ from aromatic aldehydes and anilines in ionic liquids) reacted smoothly with 2,3-dihydrofuran in 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4 medium to afford the corresponding furano[3,2-*c*]quinolines in 85–92% yield. In all cases, the products were obtained exclusively as *endo*-isomers **3** whereas under conventional conditions, the products were obtained as a mixture of *endo*- and *exo*-isomers favoring the *endo*-diastereomer.[5b] However, 3,4-dihydro-2*H*-pyran reacted efficiently with imines in the presence of [bmim]BF_4 ionic solvent to produce pyrano[3,2-*c*]quinolines **4** and **5** in excellent yields (Scheme 2).

In the case of 3,4-dihydropyran, the products were obtained as a mixture of 4 *endo*- and 5 *exo*-isomers, favoring *endo*-diastereomers 4, as observed by others in most of the Povarov imino-Diels–Alder reactions.[4–6] In all cases, the reactions proceeded smoothly at ambient temperature with high selectivity. However, in the absence of ionic liquids, the reaction did not yield any product even after a long reaction time (15–20 h). Enhanced reaction rates, excellent yields, and high *cis*-selectivity are the features observed in these ionic solvents. All products were characterized by ^{1}H NMR, IR and mass spectroscopic data. The reactions of various aldehydes, amines and cyclic enol ethers were examined in hydrophilic 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) and hydrophobic 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) ionic liquids. Among these ionic liquids, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) was found to be superior in terms of yields and reaction rates. The advantage of the use of ionic liquids as novel reaction medium for this transformation is that these ionic solvents were easily recovered after the reaction and reused in subsequent reactions. Since the products were weakly soluble in the ionic phase, they were easily separated by simple extraction with ether. The rest of the viscous ionic liquid was thoroughly washed with ether and was recycled after drying at 80°C under vacuum in each cycle. Second and third runs using recovered ionic liquid afforded similar yields to those obtained in the first run. No decrease in yield was observed in runs carried out using recycled ionic liquid and furthermore the products obtained were of the same purity as in the first run. Furthermore, we have performed the reactions in polar organic solvents such as DMF and *N*-methylpyrrolidine to compare the efficiency of ionic liquids. The reactions did not proceed in these solvents even under heating conditions (75–80°C).

Finally, the efficiency of various quaternary ammonium salts was studied. The three-component condensation was not successful when *n*-tetrabutyl ammonium chloride (*n*-Bu_4NCl) or 1-*n*-butyl-3-methylimidazolium chloride (BMImCl) was used as reaction media. This indicated that both cation and anion played an important role as the promoter in this transformation.

3. Conclusion

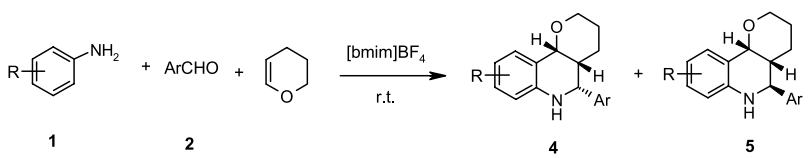
In summary, the paper describes a novel and efficient method for the synthesis of pyrano- and furanoquinolines using ionic liquids as promoters. The simple experimental and product isolation procedures combined with ease of recovery and reuse of this novel reaction media is expected to contribute to the development of green and waste free chemical process for the synthesis of tetrahydroquinolines of biological importance. The use of ionic liquids as promoters for this transformation allows the use of moisture sensitive and heavy metal Lewis acids to be avoided.

4. Experimental

1-Butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) and 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) ionic liquids were prepared according to the procedures reported in the previous literature.[11] Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. CHN analyses were recorded on a Vario EL analyzer.

4.1. General procedure for the synthesis of pyrano- and furanoquinolines

A mixture of aldehyde (1 mmol), aryl amine (1 mmol), and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran (2 mmol) in 1-butyl-3-methylimidazolium tetrafluoroborate or 1-butyl-3-methylimidazolium hexafluorophosphate (1 mL) was stirred at ambient temperature for an appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (3×10 mL). The combined ether extracts were concentrated in vacuo and the resulting product was directly charged on small silica gel column and eluted with a mixture of ethyl acetate/*n*-hexane (2:8) to afford pure quinoline. The rest of the viscous ionic liquid was further washed with ether and dried at 80°C under reduced pressure to retain its activity in subsequent runs.



Scheme 2.

Table 1. [bmim] BF_4,-ionic liquid promoted synthesis of pyrano- and furano-quinolines

Entry	R	Ar	Enol ether	Reaction	Yield (%)[a]	*endo*/*exo*[b]
a	H	C_8H_5		3.5	92	–
b	4-MeO	H		3.0	90	–
c	H	$4\text{-}FC_8H_4$		3.5	89	–
d	4-Me	$4\text{-}ClC_6H_4$		3.0	92	–
e	H	$4\text{-}MeOC_6H_4$		2.5	90	–
f	4-MeO	$4\text{-}FC_8H_4$		4.0	87	–
g	3,5-$(MeO)_2$	$4\text{-}FC_8H_4$		3.5	85	–
h	H	C_8H_5		3.0	91	90:10
I	H	$4\text{-}FC_8H_4$		3.5	89	85:15
j	2-Me	C_8H_5		2.5	90	80:20
k	4-MeO	C_8H_5		3.0	87	87:13
l	4-F	C_6H_5		3.5	89	85:15
m	1-Naphthyl	C_6H_5		4.0	85	80:20
n	1-Naphthyl	$4\text{-}FC_8H_4$		4.5	80	75:25

All products were characterized by ^1H NMR, IR and mass spectra.
[a] Isolated and unoptimized yields.
[b] *endo*/*exo*-isomers were separated by column chromatography.

4.1.1. 3a: *cis*-4-Phenyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]-quinoline. White solid, mp 93–95°C (lit,[5b] mp 95°C); ^1H NMR ($CDCl_3$): δ 1.55 (m, 1H), 2.25 (m, 1H), 2.75 (m, 1H), 3.80 (m, 3H), 4.70 (d, 1H, J=2.8 Hz), 5.25 (d, J=8.0 Hz, 1H), 6.58 (d, J=8.0 Hz, 1H), 6.80 (t, J=8.0 Hz, 1H), 7.05 (t, J=8.0 Hz, 1H), 7.35–7.55 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 24.5, 45.8, 57.3, 66.6, 75.9, 114.9, 119.0, 122.5, 126.3, 127.6, 128.2, 128.6, 130.0, 142.3, 144.8. EIMS: *m*/*z*: 251 M^+, 220, 206, 174, 130, 91. IR (KBr): ν_{max}: 3348, 2975, 2855, 1615, 1480, 1070 cm^{-1}. Anal. calcd for $C_{17}H_{17}NO$ (251.32): C, 81.24; H, 6.82; N, 5.57. Found: C, 81.26; H, 6.83; N, 5.58.

4.1.2. 3b: *cis*-8-Methoxy-4-phenyl-2,3,3a,4,5,9b-hexahydro furo[3,2-*c*]quinoline. Pale yellow solid, mp 132–133°C (lit,[5b] mp 132–133°C); ^1H NMR ($CDCl_3$): δ 1.55 (m, 1H), 2.20 (m, 1H), 2.75 (m, 1H), 3.65–3.85 (m, 3H), 3.78 (s, 3H), 4.62 (d, J=2.8 Hz, 1H), 5.22 (d, J=8.0 Hz, 1H), 6.50 (d, J=8.6 Hz, 1H), 6.74 (dd, J=8.6, 2.8 Hz, 1H), 6.94 (d, J=2.8 Hz, 1H), 7.25–7.45 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 24.3, 45.8, 55.7, 57.9, 66.7, 76.3, 113.8, 115.9, 116.3, 123.5, 126.5, 127.4, 128.6, 139.0, 142.5, 153.0. EIMS: *m*/*z*: 281 M^+, 236, 206, 160, 141, 115, 91, 41. IR (KBr): ν_{max}: 3305, 2975, 2875, 1605, 1510, 1225, 1058 cm^{-1}. Anal. calcd for $C_{18}H_{19}NO_2$ (281.35): C, 76.84; H, 6.81; N, 4.98. Found: C, 76.86; H, 6.83; N, 4.99.

4.1.3. 3c: *cis*-4-(4-Fluorophenyl)-2,3,3a,4,5,9b-hexahydro furo[3,2-*c*]quinoline. White solid, mp 173–175°C; ^1H NMR ($CDCl_3$): δ 1.50 (m, 1H), 2.10–2.15 (m, 1H), 2.60–2.80 (m, 1H), 3.65–3.80 (m, 3H), 4.64 (d, J=2.5 Hz, 1H), 5.20 (d, J=8.0 Hz, 1H), 6.50 (d, J=8.0 Hz, 1H), 6.78 (t, J=8.0 Hz, 1H), 7.05 (m, 3H), 7.30 (m, 1H), 7.40 (m,2H). EIMS: *m*/*z*: 269 M^+, 240, 224, 198, 174, 130, 117, 77, 39. IR (KBr): ν_{max}: 3315, 2976, 2880, 1606, 1508, 1223, 1155, 1059 cm^{-1}. Anal. calcd for $C_{17}H_{16}FNO$ (269.31): C, 75.82; H, 5.99; F, 7.05; N, 5.20. Found: C, 75.85; H, 6.00; F, 7.07; N, 5.22.

4.1.4. 3d: *cis*-4-(4-Chlorophenyl)-8-methyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline. White solid, mp 148–149°C; ^1H NMR ($CDCl_3$): δ 1.50 (m, 1H), 2.20 (m, 1H), 2.35 (s, 3H), 2.64 (m, 1H), 3.60 (brs, NH, 1H), 3.72 (m, 1H), 3.80 (m, 1H), 4.60 (d, J=2.1 Hz, 1H), 5.20 (d, J=8.0 Hz, 1H), 6.50 (d, J=8.0 Hz, 1H), 6.85 (dd, J=8.0, 2.1 Hz, 1H), 7.10 (d, J=2.1 Hz, 1H), 7.35 (d, J=8.0 Hz, 2H), 7.40 (d, J=8.0 Hz, 2H). EIMS: *m*/*z*: 299 M^+, 254, 188, 160, 144, 115, 77. IR (KBr): ν_{max}: 3345, 2991, 2878, 1610, 1493,

1145, 1031 cm^{-1}. Anal. calcd for $C_{18}H_{18}NClO$ (299.79): C, 72.11; H, 6.05; N, 4.67; Cl, 11.83. Found: C, 72.14; H, 6.09; N, 4.68; Cl, 11.89.

4.1.5. 3e: *cis*-4-(4-Methoxyphenyl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline. Pale yellow solid, mp 155–156°C; ^1H NMR ($CDCl_3$): δ 1.58 (m, 1H), 2.20 (m, 1H), 2.70 (m, 1H), 3.70–3.80 (m, 3H), 3.85 (s, 3H), 4.62 (d, J=2.2 Hz, 1H), 5.22 (d, J=8.0 Hz, 1H), 6.54 (d, J=8.0 Hz, 1H), 6.78 (t, J=8.0 Hz, 1H), 6.90 (t, J=8.0 Hz, 1H), 7.05 (d, J=8.0 Hz, 2H), 7.40 (m, 3H). EIMS: m/z: 281 M^+, 252, 236, 224, 167, 155, 141, 121, 91, 69, 43. IR (KBr): ν_{max}: 3340, 2990, 2870, 1605, 1520, 1135 cm^{-1}. Anal. calcd for $C_{18}H_{19}NO_2$ (281.35): C, 76.84; H, 6.81; N, 4.98. Found: C, 76.87; H, 6.86; N, 4.99.

4.1.6. 3f: *cis*-4-(4-Fluorophenyl)-8-methoxy-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline. White solid, mp 136–138°C; ^1H NMR ($CDCl_3$): δ 1.35–1.55 (m, 1H), 2.10–2.25 (m, 1H), 2.60–2.75 (m, 1H), 3.60–3.80 (m, 3H), 3.76 (s, 3H), 4.62 (d, J=2.8 Hz, 1H), 5.20 (d, J=8.0 Hz, 1H), 6.45 (d, J=8.4 Hz, 1H), 6.68 (dd, J=8.4, 2.8 Hz, 1H), 6.92 (d, J=2.8 Hz, 1H), 7.00–7.10 (m, 2H), 7.20–7.30 (m, 2H). EIMS: m/z: 299 M^+, 272, 255, 205, 150, 109, 77, 43. IR (KBr): ν_{max}: 3014, 1662, 1577, 1503, 1220, 1036 cm^{-1}. Anal. calcd for $C_{18}H_{18}FNO_2$ (299.34): C, 72.22; H, 6.06; F, 6.35; N, 4.68. Found: C, 72.24 %; H, 6.07 %; F, 6.37%; N, 4.70%.

4.1.7. 3g: *cis*-4-(4-Fluorophenyl)-7,9-dimethoxy-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline. White solid, mp 80–82°C; ^1H NMR ($CDCl_3$): δ 1.60–1.65 (m, 1H), 2.20–2.25 (m, 1H), 2.75–2.85 (m, 1H), 3.60–3.85 (m, 3H), 3.68 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.78 (d, J=2.8 Hz, 1H), 5.40 (d, J=8.0 Hz, 1H), 6.20 (m, 1H), 6.60 (m, 1H), 7.05 (m, 2H), 7.40 (m, 2H). EIMS: m/z: 329 M^+, 314, 285, 254, 190, 149, 133, 109, 71, 43. IR (KBr): ν_{max}: 3305, 2985, 2880, 1615, 1500, 1225, 1035 cm^{-1}. Anal. calcd for $C_{19}H_{20}FNO_3$ (329.36): C, 69.29; H, 6.12; F, 5.77; N, 4.25. Found: C, 69.31; H, 6.14; F, 5.79; N, 4.26.

4.1.8. 4h: *cis*-5-Phenyl-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinoline. White solid, mp 129–130°C (lit,[5b] mp 128.8–131°C); ^1H NMR ($CDCl_3$): δ 1.25 (m, 1H), 1.50–1.70 (m, 3H), 2.15–2.20 (m, 1H), 3.40 (dt, 1H, J=11.3, 2.4 Hz), 3.55 (dd, 1H, J=11.3, 2.4 Hz), 3.80 (brs, 1H, NH), 4.70 (d, J=2.7 Hz, 1H), 5.30 (d, J=5.6 Hz, 1H), 6.55 (d, J=8.0 Hz, 1H), 6.78 (t, J=8.0 Hz, 1H), 7.05 (t, J=7.8 Hz, 1H), 7.25–7.45 (m, 6H); ^{13}C NMR ($CDCl_3$) δ: 18.2, 25.7, 39.0, 59.3, 60.7, 72.8, 114.4, 118.0, 120.4, 126.9, 127.5, 127.7, 128.0, 128.4, 141.2, 145.2. EIMS: m/z: 265 M^+, 234, 220, 194, 129, 117, 91, 77. IR (KBr): ν_{max}: 3340, 2970, 2850, 1610, 1490, 1090 cm^{-1}. Anal. calcd for $C_{18}H_{19}NO$ (265.35): C, 81.48; H, 7.22; N, 5.28. Found: C, 81.50; H, 7.24; N, 5.30.

4.1.9. 5h: *trans*-5-Phenyl-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinoline. Pale yellow oil, ^1H NMR ($CDCl_3$): δ 1.25–1.60 (m, 3H), 1.80–1.90 (m, 1H), 2.00–2.10 (m, 1H), 3.75 (dt, 1H, J=11.5, 2.5 Hz), 4.00–4.10 (m, 2H), 4.40 (d, J=2.5 Hz, 1H), 4.75 (d, J=10.8 Hz, 1H), 6.50 (d, J=8.0 Hz, 1H), 6.70 (t, J=7.5 Hz, 1H), 7.10 (t, J=7.5 Hz, 1H), 7.25 (d, J=8.0 Hz, 1H), 7.40–7.55 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 22.3, 24.4, 39.3, 55.0, 69.2, 74.5, 114.2, 117.4, 120.5, 127.7, 127.9, 128.5, 129.4, 130.9, 142.2, 144.5. IR (KBr): ν_{max}: 3325, 2941, 2864, 1607, 1482, 1088 cm^{-1}. Anal. calcd for $C_{18}H_{19}NO$ (265.35): C, 81.48; H, 7.22; N, 5.28. Found: C, 81.51; H, 7.23; N, 5.32.

4.1.10. 4i: *cis*-5-(4-Fluorophenyl)-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinoline. White solid, mp 174–175°C; ^1H NMR ($CDCl_3$): δ 1.30 (m, 1H), 1.45–1.60 (m, 3H), 2.12 (m, 1H), 3.40 (dt, J=11.5, 2.5 Hz, 1H), 3.56 (dd, J=11.5, 2.5 Hz, 1H), 3.75 (brs, 1H, NH), 4.65 (d, J=2.7 Hz, 1H), 5.28 (d, J=5.7 Hz, 1H), 6.52 (d, J=8.0 Hz, 1H), 6.75 (dd, J=8.0, 2.5 Hz, 1H), 7.05 (m, 3H), 7.40 (m, 3H). EIMS: m/z: 283 M^+, 239, 225, 198, 150, 148, 91. IR (KBr): ν_{max}: 3325, 2945, 2860, 1608, 1490, 1252, 1081 cm^{-1}. Anal. calcd for $C_{18}H_{18}FNO$ (283.34): C, 76.30; H, 6.40; F, 6.71; N, 4.94. Found: C, 76.32; H, 6.44; F, 6.72; N, 4.95.

4.1.11. 5i: *trans*-5-(4-Fluorophenyl)-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinoline. White solid, mp 143–144°C; ^1H NMR ($CDCl_3$): δ 1.30–1.35 (m, 1H), 1.40–1.45 (m, 1H), 1.60–1.70 (m, 1H), 1.75–1.85 (m, 1H), 2.05 (m, 1H), 3.70 (dt, J=11.5, 2.5 Hz, 1H), 3.95 (brs, 1H, NH), 4.10 (d, J=2.5 Hz, 1H), 4.35 (d, J=2.7 Hz, 1H), 4.70 (d, J=10.8 Hz, 1H), 6.48 (d, J=8.0 Hz, 1H), 6.68 (dd, J=8.0, 2.5 Hz, 1H), 7.05 (m, 3H), 7.18 (m, 1H), 7.38 (m, 2H). IR (KBr): ν_{max}: 3327, 2950, 2870, 1610, 1495, 1250, 1089 cm^{-1}. Anal. calcd for $C_{18}H_{18}FNO$ (283.34): C, 76.30; H, 6.40; F, 6.71; N, 4.94. Found: C, 76.33; H, 6.42; F, 6.73; N, 4.96.

4.1.12. 4j: *cis*-7-Methyl-5-phenyl-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinoline. White solid, mp 142–143°C (lit,[5b] mp 143–144°C); ^1H NMR ($CDCl_3$): δ 1.25 (m, 1H), 1.35–1.50 (m, 4H), 2.10 (s, 3H), 3.34 (dt, 1H, J=11.3, 2.4 Hz), 3.50 (dd, 1H, J=11.3, 2.4 Hz), 3.55 (brs, 1H, NH), 4.62 (d, J=2.5 Hz, 1H), 5.30 (d, J=5.2 Hz, 1H), 6.70 (t, J=7.8 Hz, 1H), 6.90 (dd, J=7.8, 0.7 Hz, 1H), 7.20–7.40 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 17.4, 18.0, 25.3, 38.6, 59.3, 60.6, 73.4, 117.8, 119.0, 121.6, 125.3, 126.9, 127.5, 128.9, 129.2, 141.0, 143.5. EIMS: m/z: 279 M^+, 260, 220, 184, 155, 144, 104, 91, 65. IR (KBr): ν_{max}: 3345, 2970, 2845, 1610, 1509, 1030 cm^{-1}. Anal. calcd for $C_{19}H_{21}NO$ (279.38): C, 81.68; H, 7.58; N, 5.01. Found: C, 81.70; H, 7.61; N, 5.02.

4.1.13. 5j: *trans*-7-Methyl-5-phenyl-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinoline. White solid, mp 130–131°C (lit,[5b] mp 130–132°C); ^1H NMR ($CDCl_3$): δ 1.25–1.35 (m, 3H), 1.60–1.65 (m, 1H), 1.80–1.85 (m, 1H), 2.10 (s, 3H), 3.70, (dt, 1H, J=11.5, 2.5 Hz), 3.90 (brs, 1H, NH), 4.10 (m, 1H), 4.40 (d, J=2.8 Hz, 1H), 4.78 (d, J=10.5 Hz, 1H), 6.64 (t, J=8.0 Hz, 1H), 7.00 (dd, J=8.0, 1.0 Hz, 1H), 7.10 (dd, J=8.0, 1.0 Hz, 1H), 7.30–7.40 (m, 3H), 7.44 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 17.2, 22.1, 24.3, 38.7, 55.3, 68.7, 74.5, 117.0, 120.0, 121.3, 127.8, 128.0, 128.5, 128.9, 130.5, 142.5, 142.9. IR (KBr): ν_{max}: 3340, 2975, 2840, 1615, 1504, 1085 cm^{-1}. Anal. calcd for $C_{19}H_{21}NO$ (279.38): C, 81.68; H, 7.58; N, 5.01. Found: C, 81.71; H, 7.60; N, 5.03.

4.1.14. 4k: *cis*-9-Methoxy-5-phenyl-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinoline. White solid, mp 145–146°C (lit,[5b] mp 140–144°C); ^1H NMR ($CDCl_3$): δ 1.30–1.60 (m, 4H), 2.15 (m, 1H), 3.42 (m, 1H), 3.58 (m, 1H), 3.60

(brs, 1H, NH), 3.80 (s, 3H), 4.62 (d, J=2.0 Hz, 1H), 5.25 (d, J=5.2 Hz, 1H), 6.50 (d, J=8.2 Hz, 1H), 6.70 (dd, J=8.2, 2.7 Hz, 1H), 7.00 (d, J=2.7 Hz, 1H), 7.30–7.45 (m, 5H). EIMS: *m/z*: 295 M^+, 237, 225, 160, 91. IR (KBr): ν_{max}: 3340, 2970, 2855, 1610, 1520, 1065 cm^{-1}. Anal. calcd for $C_{19}H_{21}NO_2$ (295.38): C, 77.26; H, 7.17; N, 4.74. Found: C, 77.28; H, 7.20; N, 4.77.

4.1.15. 5k: *trans*-9-Methoxy-5-phenyl-3, 4, 4a, 5, 6, 10b-hexahydro-2*H*-pyrano[3,2-*c*]quinoline. Brown solid, mp 98–99°C (lit,[5b] mp 98–100°C); ^1H NMR ($CDCl_3$): δ 1.24 (m, 1H), 1.40 (m, 1H), 1.60 (m, 1H), 1.70 (m, 1H), 2.00 (m, 1H), 3.50 (m, 1H), 3.60 (s, 3H, OCH_3), 4.00 (m, 2H), 4.30 (d, J=2.7 Hz, 1H), 4.55 (d, J=10.5 Hz, 1H), 6.38 (d, J=8.1 Hz, 1H), 6.60 (dd, J=8.1, 2.7 Hz, 1H), 6.65 (d, J=2.7 Hz, 1H), 7.20–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 22.0, 24.5, 39.0, 55.4, 55.9, 68.5, 74.5, 114.9, 115.5, 116.7, 121.4, 127.9, 128.5, 139.0, 142.4, 152.3. IR (KBr): ν_{max}: 3325, 2965, 2865, 1605, 1515, 1070 cm^{-1}.

4.1.16. 4l: *cis*-9-Fluoro-5-phenyl-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinoline. White solid, mp 174–175°C; ^1H NMR ($CDCl_3$): δ 1.30 (m, 1H), 1.35–1.60 (m, 3H), 2.10 (m, 1H), 3.40 (dt, J=11.5, 2.5 Hz, 1H), 3.58 (dd, J=11.5, 2.5 Hz, 1H), 3.68 (brs, 1H, NH), 4.60 (d, J=2.7 Hz, 1H), 5.20 (d, J=5.7 Hz, 1H), 6.44 (d, J=8.4 Hz, 1H), 6.78 (dd, J=8.4, 2.8 Hz, 1H), 7.10 (d, J=2.8 Hz, 1H), 7.25–7.40 (m, 5H). EIMS: *m/z*: 283 M^+, 239, 225, 198, 150, 148, 91. IR (KBr): ν_{max}: 3326, 2943, 2865, 1608, 1497, 1252, 1089 cm^{-1}. Anal. calcd for $C_{18}H_{18}FNO$ (283.34): C, 76.30; H, 6.40; F, 6.76; N, 4.94. Found: C, 76.35; H, 6.45; F, 6.78; N, 4.95.

4.1.17. 5l: *trans*-9-Fluoro-5-phenyl-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinoline. Pale brown oil; ^1H NMR ($CDCl_3$): δ 1.35 (m, 1H), 1.50 (m, 1H), 1.55–1.65 (m, 1H), 1.75–1.90 (m, 1H), 2.10 (m, 1H), 3.68 (dt, J=11.5, 2.8 Hz, 1H), 3.90 (brs, 1H, NH), 4.10 (d, J=2.8 Hz, 1H), 4.32 (d, J=2.8 Hz, 1H), 4.65 (d, J=10.8 Hz, 1H), 6.45 (d, J=8.4 Hz, 1H), 6.80 (dd, J=8.4, 2.8 Hz, 1H), 6.95 (d, J=2.8 Hz, 1H), 7.30–7.40 (m, 5H). IR (KBr): ν_{max}: 3325, 2945, 2870, 1605, 1495, 1250, 1080 cm^{-1}. Anal. Calcd for $C_{18}H_{18}FNO$ (283.34): C, 76.30; H, 6.40; F, 6.76; N, 4.94. Found: C, 76.33; H, 6.42; F, 6.79; N, 4.96.

4.1.18. 4m: *cis*-12-Phenyl-2,3,4a,11,12,12a-hexahydro-1*H*-benzo[h]pyrano[3,2-*c*]quinoline. Pale brown solid, mp 163–164°C; ^1H NMR ($CDCl_3$): 1.30–1.50 (m, 3H), 1.65 (m, 1H), 2.30 (m, 1H), 3.40 (dt, J=11.5, 2.5 Hz, 1H), 3.62 (dd, J=11.5, 2.5 Hz, 1H), 4.50 (brs, 1H, NH), 4.88 (d, J=2.7 Hz, 1H), 5.50 (d, J=5.7 Hz, 1H), 7.30 (m, 2H), 7.35–7.50 (m, 4H), 7.60 (m, 3H), 7.80 (m, 2H). EIMS: *m/z*: 316 M^+, 256, 206, 180, 155, 141, 115, 69, 43. IR (KBr): ν_{max}: 3375, 2941, 2861, 1667, 1574, 1520, 1465, 1081 cm^{-1}. Anal. calcd for $C_{22}H_{21}NO$ (315.41): C, 83.78; H, 6.71; N, 4.44. Found: C, 83.80; H, 6.75; N, 4.45.

4.1.19. 5m: *trans*-12-Phenyl-2,3,4a,11,12,12a-hexahydro-1*H*-benzo[*h*]pyrano[3,2-*c*]quinoline. Pale yellow solid, mp 144–145°C; ^1H NMR ($CDCl_3$): δ 1.38 (m, 1H), 1.55 (m, 1H), 1.68 (m, 1H), 1.80 (m, 1H), 2.20 (m, 1H), 3.75 (dt, J=11.8, 2.8 Hz, 1H), 4.10 (d, J=2.8 Hz, 1H), 4.45 (d, J=2.8 Hz, 1H), 4.70 (brs, 1H, NH), 4.80 (d, J=10.8 Hz, 1H), 7.20–7.25 (m, 2H), 7.30–7.45 (m, 4H), 7.50 (m, 3H), 7.70 (m, 2H). IR (KBr): ν_{max}: 3378, 2945, 2870, 1665, 1575, 1468, 1080 cm^{-1}. Anal. calcd for $C_{22}H_{21}NO$ (315.41): C, 83.78; H, 6.71; N, 4.44. Found: C, 83.81; H, 6.73; N, 4.46.

4.1.20. 4n: *cis*-12-(4-Fluorophenyl)-2,3,4a,11,12,12a-hexahydro-1*H*-benzo[*h*]pyrano[3,2-*c*] quinoline. Brown solid, mp 138–140°C; ^1H NMR ($CDCl_3$): δ 1.20–1.35 (m, 2H), 1.40–1.50 (m, 2H), 2.10 (m, 1H), 3.25 (dt, J=11.5, 2.5 Hz, 1H), 3.50 (dd, J=11.5, 2.5 Hz, 1H), 4.00 (brs, 1H, NH), 4.70 (d, J=2.7 Hz, 1H), 5.40 (d, J=5.7 Hz, 1H), 7.00 (m, 2H), 7.20 (m, 1H), 7.35 (m, 2H), 7.40–7.50 (m, 3H), 7.65 (m, 2H). EIMS: *m/z*: 333 M^+, 274, 238, 220, 180, 155, 141, 119, 69, 57, 43. IR (KBr): ν_{max}: 3370, 2945, 2860, 1665 1570, 1465, 1080 cm^{-1}. Anal. calcd for $C_{22}H_{20}FNO$ (333.40): C, 79.26; H, 6.05; F, 5.70; N, 4.20. Found: C, 79.28; H, 6.07; F, 5.74; N, 4.22.

4.1.21. 5n: *trans*-12-(4-Fluorophenyl)-2,3,4a,11,12,12a-hexahydro-1*H*-benzo[*h*]pyrano[3,2-*c*]quinoline. Brown solid, mp 179–181°C; ^1H NMR ($CDCl_3$): δ 1.30–1.45 (m, 2H), 1.60–1.80 (m, 2H), 2.10 (m, 1H), 3.75 (dt, J=11.5, 2.7 Hz, 1H), 4.10 (d, J=2.7 Hz, 1H), 4.42 (d, J=2.7 Hz, 1H), 4.65 (brs, 1H, NH), 4.80 (d, J=10.8 Hz, 1H), 7.05–7.15 (m, 2H), 7.20–7.40 (m, 4H), 7.45–7.50 (m, 2H), 7.70–7.80 (m, 2H). IR (KBr): ν_{max}: 3378, 2947, 2870, 1668, 1575, 1468, 1081 cm^{-1}. Anal. calcd for $C_{22}H_{20}FNO$ (333.40): C, 79.26; H, 6.05; F, 5.70; N, 4.20. Found: C, 79.27; H, 6.08; F, 5.72; N, 4.23.

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