HETEROCYCLES, Vol. 83, No. 10, 2011, pp. 2289 - 2298. © 2011 The Japan Institute of Heterocyclic Chemistry
Received, 22nd June, 2011, Accepted, 25th July, 2011, Published online, 4th August, 2011
DOI: 10.3987/COM-11-12289

EFFICIENT ONE-POT SYNTHESIS OF 2-ALKYLQUINOLINES UNDER SOLVENT-FREE CONDITIONS USING SULFONIC ACID FUNCTIONALIZED IONIC LIQUID AS A RECOVERABLE AND REUSABLE CATALYST

Min Zhang,[1*] Biao Xiong,[1] Ting Wang,[1] Yu-Qiang Ding,[1*] and Li Wang[2]

[1]School of Chemical and Materials Engineering and [2]School of Food Science and Technology in Jiangnan University, 1800 Lihu Road, Wuxi, Jiangsu Province, 214122, People's Republic of China. E-mail: zm31289@yahoo.com.cn

Abstract - Sulfonic acid functionalized ionic liquid (FIL-A) was firstly used as a recoverable and reusable catalyst for the synthesis of 2-alkylquinoline derivatives from simple and readily available alkylaldehydes and arylamines. The method has the advantages of simple experimental procedure, easy recovery and reuse of catalyst, solvent-free and mild reaction conditions, excellent functional group tolerance, etc. which makes it a highly practical and environmentally benign pathway for the synthesis of 2-alkylquinolines.

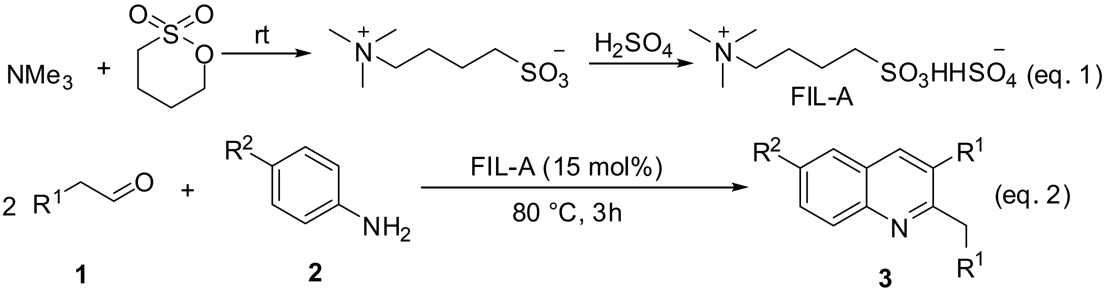
INTRODUCTION

During the past decade, the applications of functionalized ionic liquids (FILs) or so-called "task-specific ionic liquids" (TSILs)[1] have attracted considerable attention due to its notable advantages such as low volatility and toxicity, high thermal and chemical stability, excellent dissolving ability. The use of FILs as reaction medium may offer the potentials for developing highly efficient synthetic methods and avoiding solvent emission and catalyst recycling problems.[2]

Drawing from the significant virtues of FILs and our recently reported method on *p*-toluenesulfonic acid-mediated quinoline formation,[3] we were therefore interested in applying sulfonic acid functionalized ionic liquid as a reusable catalyst in the synthesis of 2-alkylquinolines. 2-alkylquinolines and its analogues constitute a significant important class of nitrogen-containing heterocycles, and they have shown a broad spectrum of biological and pharmaceutical activities such as deacetylase inhibitor,[4] antileishmanial,[5] antimalarial,[6] antidepressant,[7] etc. In addition, 2-alkylquinolines also serve as valuable building blocks for manufacturing functionalized materials,[8] chemosensors,[9] dyes and pigments.[10]

Owing to its useful functions, there has been an increasing demand for developing highly efficient methods to synthesize 2-alkylquinoline derivatives. To date, except the well-established name reactions (such as Skraup,[11] Friedländer,[12] Combes[13] and Doebner-Von Miller reactions[14]) and related improved methodologies,[15] a variety of recent examples have also showed elegant pathways for elaboration of 2-alkylquinolines.[16] However, some of these methods still suffer from the limitations such as harsh reaction conditions, limited substrate scope, low product yields, poor chemo-selectivity or regioselectivity, usage of volatile organic solvent, multistep manipulations, etc. Notably, the cross-coupling reaction of two molecules of alkylaldehydes with one molecule of arylamine provides an attractive pathway for synthesis of 2-alkylquinoline derivatives.[3,17] However, the employed catalysts in such a reaction are generally difficult to be recovered. In the context of these synthetic problems, the search for an effective catalytic system along with eco-compatible preparation of 2-alkylquinolines from readily available starting materials is of significant importance.

Herein, we report a sulfonic acid functionalized ionic liquid A (FIL-A) catalyzed method for the synthesis of 2-alkylquinolines from readily available alkylaldehydes **1** and arylamine **2** (Scheme 1, eq. 2). FIL-A featuring a *n*-butyl sulfonic acid group in tri-methyl-ammonium cation (Scheme1, FIL-A) was prepared initially according to the protocols reported recently (Scheme 1, eq. 1).[18] To the best of our knowledge, such a methodology has not been reported in spite of its importance as described above.



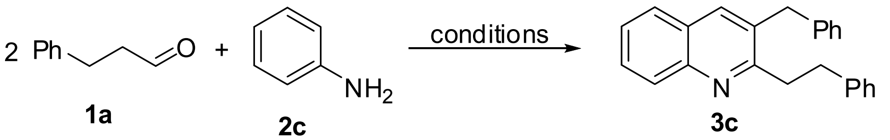
Scheme 1. Synthesis of sulfonic acid FIL-A and its application in the synthesis of 2-alkylquinoline **3**

RESULTS AND DISCUSSION

In order to formulate an effective conversion system, the synthesis of 3-benzyl-2-phenethylquinoline **3c** from 3-phenylpropanal **1a** and aniline **2c** was chosen as a model reaction to evaluate the influence of different catalyst loadings initially. The reaction was conducted at 80 °C for 3 hours under solvent-free conditions by introducing 10 mol% of FIL-A, a 72% GC yield was detected (Table 1, entry 1); Further test of different catalyst loadings showed that 15 mol% of FIL-A was sufficient to promote the reaction (Table 1, entry 2). The combination of 15 mol% of FIL-A with several conventional organic solvents also showed to be effective in the formation of product **3** (Table 1, entry 3), but the reaction efficiency is relatively lower than that of solvent-free conditions. Reaction under catalyst-free conditions failed to yield the expected product even after a prolonged reaction time (Table 1, entry 4). Decreasing the reaction temperature from 80 °C to 60 °C required longer reaction time to give a desired product yield (Table 1, entry 5). Thus, the optimized reaction conditions are summarized as: 15 mol% of FIL-A catalyst loading, solvent-free conditions, and at 80 °C.

With the availability of optimal reaction conditions in hand, we tried to recover and reuse the FIL-A catalyst. After completion of the reaction for the first run, diethylether was added to the reaction mixture to extract the product, then the remaining oil catalyst was recovered after removal of residual solvent under vacuum, and it was reused in the next run without further purification. This procedure was repeated 8 times and the results were outlined in Table 1 (entry 6). The detected GC yields were close in the previous 6 cycles, and subsequently a gradual decrease of yields was observed in the two latter-cycles. This phenomenon might be attributed to the negative effect of accumulated water generating from the reactions or partial catalyst decomposition from the seventh cycle. Hence the catalyst could be effectively recycled for at least 6 times without any loss of activity.

Table 1. Screening optimized conditions for the synthesis of **3c**[a] and investigation on reuse of catalyst



Entry	Catalyst loading (mol%)	Solvent	Yield %[b]
1	10	-	72
2	5, 8, 15, 20	-	58, 59, 86, 85
3	15	1,4-dioxane, MeCN, EtOH, $(CH_2Cl)_2$	85, 68, 79, 57
4	-	-	Not found[c]
5	15	-	82[d]
6	15	-	(86, 85, 84, 85, 84, 86, 71, 63)[e]

[a] Reaction conditions: unless otherwise stated, **1a** (2.4 mmol, 321.6 mg) and aniline **2c** (1 mmol, 93 mg) along with FIL-A (0.15 mmol, 43.8 mg) were stirred in a open schlenk tube equipped with circulating cooling water at 80 °C for 3 h.

[b] GC yields of **3c** with hexadecane as internal standard.

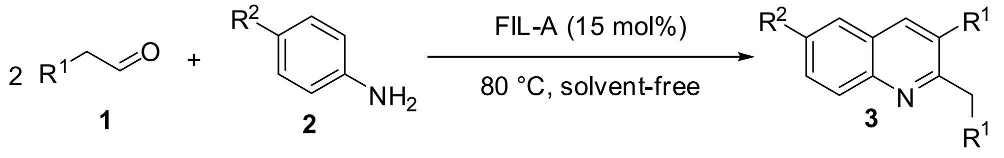
[c] The reaction was carried out for 24 h.

[d] The reaction was carried out at 60 °C for 6 h.

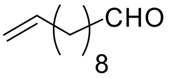
[e] GC yields are with respect to catalyst reused from the first to the eighth cycle respectively.

Subsequently, we tested the generality of this synthetic method under optimized reaction conditions. Various alkylaldehydes **1** and arylamines **2** bearing electron withdrawing groups (such as halide) or electron releasing groups (such as CH_3, CH_3O) were employed for 2-alkylquinoline syntheses. As shown in Table 2, all the reactions proceeded smoothly and yielded the expected products in good to excellent isolated yields. Notably, minor by-products such as mono- and dialkylated anilines were also formed in the reactions,[17] which could lead to the decrease of product yields (see entries 1, 8 and 9 in Table 2). It was found that substituents on the benzene ring of arylamines had significant influence on the reaction efficiency. The electron rich ones gave faster reactions and completed the conversion of starting materials in three hours (Table 2, entries 1, 2, 5, 8, 10), and it might be attributable to the enhanced nucleophilicity of arylamines favors the formation of products. The halide-containing products have the potentials for further functionalization by classical cross-coupling reactions (Table 2, entries 4, 7, 8, 9, 12). Products **3j**, **3k**, **3l** containing two terminal vinyl groups have the potentials for preparation of macrocyclic compounds or long chain polymers via intra- or intermolecular olefin metathesis (Table 2, entries 10-12).[19] Notably, undec-10-enal **1e** is renewable resource existing in castor oil, the conversion of this natural product into quinoline products exhibits one of its applications. Interestingly, various functional groups could be selectively introduced into the quinoline skeleton by mediating appropriate alkylaldehydes or arylamines using this FIL-A catalyzed methodology (Table 2).

Table 2. Efficient one-pot synthesis of 2-alkylquinoline derivatives[a]



Entry	Aldehyde **1**	Amine **2**	Reaction Time (h)	Product **3**[b], Yield %[c]
1	**1a**:R^1 = $PhCH_2$	**2a**: R^2 = OMe	3	**3a**, 72
2	**1a**	**2b**: R^2 = Me	3	**3b**, 81
3	**1a**	**2c**: R^2 = H	3	**3c**, 78
4	**1a**	**2d**: R^2 = Br	3	**3d**, 78
5	**1b**: R^1 = Ph	**2a**	3	**3e**, 80
6	**1b**	**2b**	5	**3f**, 76
7	**1b**	**2e**: R^2 = Cl	5	**3g**, 73
8	**1c**: R^1 = 4-Br-C_6H_4	**2b**	3	**3h**, 51
9	**1d**: R^1 = Et	**2d**	5	**3i**, 66

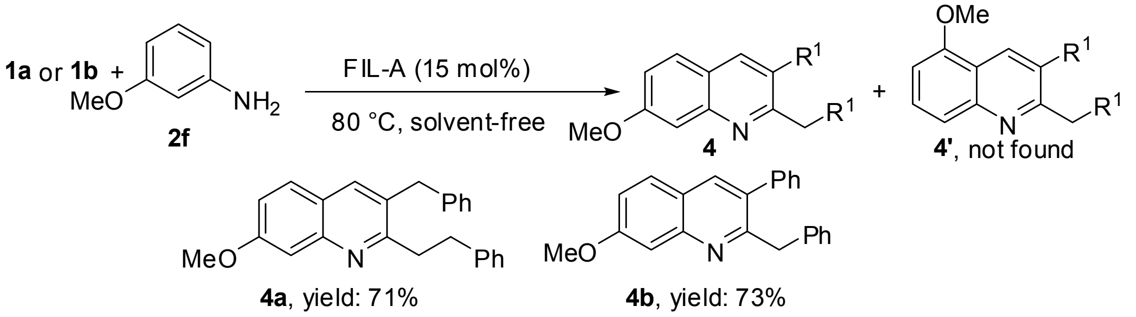
10	**1e**: 	**2a**	3	**3j**, 85
11	**1e**	**2c**	3	**3k**, 85
12	**1e**	**2d**	3	**3l**, 83

[a] Reaction conditions: The mixture of aldehyde **1** (2.4 mmol), arylamine **2** (1 mmol,) and FIL-A (0.15 mmol, 43.8 mg) was stirred in a open schlenk tube equipped with circulating cooling water at 80 °C for appropriate reaction time according table 2.

[b] Known compounds were compared with related references, the IR, ^{1}H NMR spectra were found to be identical with the one described in reference.[3]

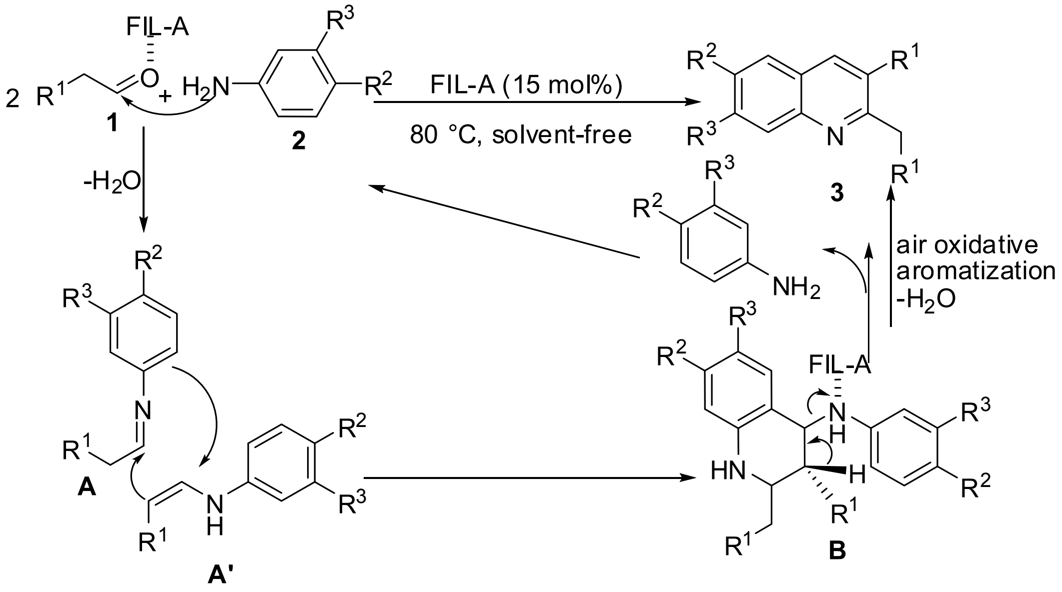
[c] Isolated yield after flash chromatography.

m-Anisidine **2f** was then employed to investigate the regioselectivity of the reaction. In which could lead to two possible regioisomers **4**, **4'** (Scheme 2). However, product **4** was obtained exclusively, and the cyclization reaction occurs at less steric hindered position of the aryamine. It shows that the steric factor is a major contributor to site the regioselectivity in the reactions. And trisubstituted quinoline **4a** and **4b** were obtained in 71%, 73% isolated yields respectively.



Scheme 2. Regioselective synthesis of trisubstituted quinolines

The proposed mechanism for this cyclization reaction is illustrated in Scheme 3 based on the reported exampls.[17,20,21] Aldehyde **1** activated by the functionalized sulfonic acid group in cation of FIL-A condenses with aniline 2, and gives imine **A** and its tautomer enamine **A'** initially. Then mutual nucleophilic addition of **A** and **A'** results in a tetrahydroquinoline intermediate B. The final quinoline product is formed by FIL-A promoted aniline elimination and air oxidative aromatization of **B** (Scheme 3). Alternatively, the reaction between two imine **A**, or two enamine **A'**, or a Povarov-type reaction[22] between imine and enol formed from aldehyde leads to the formation of quinoline **3**, could also explain the outcome of the reaction.



Scheme 3. Proposed mechanism for FIL-A catalyzed 2-alkylquinoline synthesis

In conclusion, sulfonic acid functionalized ionic liquid (FIL-A) was firstly used as a recoverable and reusable catalyst for the synthesis of 2-alkylquinoline derivatives from simple and readily available alkylaldehydes and arylamines. With this method, functional groups such as halides, vinyl groups can be selectively introduced into the quinoline skeleton by mediating the reactants. Additionally, unsymmetrical arylamines can be employed for regioselective synthesis of 2-alkylquinolines. The method having the advantages of simple experimental procedure, easy recovery and reuse of catalyst, solvent-free and mild reaction conditions, excellent functional group tolerance makes it a highly practical and environmentally benign pathway for the synthesis of 2-alkylquinolines.

EXPERIMENTAL

All the obtained products were characterized by melting points (mp), ^{1}H-NMR, ^{13}C-NMR, infrared spectra (IR) and Low-, high-resolution mass spectra (MS and HRMS). Melting points were measured on an Electrothemal SGW-X4 microscopy digital melting point apparatus and are uncorrected; IR spectra were recorded on a FTLA2000 spectrometer; ^{1}H-NMR and ^{13}C-NMR spectra were obtained on Bruker-200 and Avance 300. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). EI mass spectra (LRMS) were recorded on an MAT 95XP spectrometer (70 eV, Thermo ELECTRON CORPORATION). ESI high resolution mass spectra (HRMS) were recorded on an Agilent Technologies 6210 TOF LC/MS using H_2O + 0.1% formic acid (10%) and methanol (90%) as eluent. All the chemical reagents were purchased from commercial sources (Alfa, Acros, Aldrich), and used without further purification.

General procedure for synthesis of the quinoline 3a-3l, 4a, and 4b.

A Schlenk tube equipped with a magnetic stirrer bar and also with a provision of circulating cool water was used in the experimentation, the catalyst FIL-A (0.15 mmol, 43.8 mg), arylamine (1 mmol), alkylaldehyde (2.4 mmol) were introduced successively, and the reaction mixture formed a homogeneous system at 80 °C and it was stirred for 3-5 h in an open system. TLC was used to detect the completion of the reaction. After cooling down to room temperature, Et_2O (5 x 15 mL) was added to the reaction mixture to extract the product, the remaining oil FIL-A catalyst could be recycled for the next run after removal of the solvent. The combined organic solvent was evaporated to afford the crude product, it was purified by flash column chromatography on silica, eluting with petroleum ether, ethyl acetate in the ratio of 30: 1, to provide desired quinoline products (isolated yields ranges from 63% to 86%).

Selected Analytical Data of obtained compounds

3-Benzyl-6-methoxy-2-phenethylquinoline (3a)

Yield: 72%; White solid, mp 136-137 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.01 (d, $J = 9.0$ Hz, 1H), 7.67 (s, 1H), 7.13-7.38 (m, 11H), 7.01 (d, $J = 2.4$ Hz, 1H), 4.08 (s, 2H), 3.93 (s, 3H), 3.18-3.27 (m, 2H), 3.03-3.11 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.9, 157.8, 142.5, 139.8, 135.7, 133.2, 130.4, 129.4, 129.1, 129.0, 128.8, 128.4, 126.9, 126.3, 121.8, 105.1, 55.9, 39.1, 37.9, 35.8; IR (KBr, cm^{-1}) ν_{max} = 3018, 2928, 1624, 1601, 1493, 1450, 1363, 1227, 1123, 1028, 940; MS (EI, *m/z*): 353 $[M]^+$; HRMS (EI): Calcd. for $C_{25}H_{23}NO$ $[M]^+$: 353.18; Found: 353.17792.

3-Benzyl-6-methyl-2-phenethylquinoline (3b)

Yield: 81%; White solid, mp 124-126 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.01 (d, $J = 8.4$ Hz, 1H), 7.70 (s, 1H), 7.51-7.55 (m, 2H), 7.11-7.36 (m, 10H), 4.08 (s, 2H), 3.19-3.28 (m, 2H), 3.03-3.13 (m, 2H), 2.54 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.9, 140.7, 138.1, 134.6, 134.4, 131.1, 129.8, 127.6, 127.3, 127.2, 126.8, 125.8, 125.1, 124.7, 124.6, 37.4, 36.3, 34.1, 20.2; IR (KBr, cm^{-1}) ν_{max} = 3021, 2928, 1601, 1493, 1451, 1355, 1132, 1031, 938; MS (EI, *m/z*): 337 $[M]^+$; HRMS (EI): Calcd. for $C_{25}H_{23}N$ $[M]^+$: 337.18; Found: 337.18301.

3-Benzyl-2-phenethylquinoline (3c)

Yield: 78%; White solid, mp 94-97 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.11 (d, $J = 8.4$ Hz, 1H), 7.66-7.79 (m, 2H), 7.51 (dd, $J = 7.2$ Hz, 1H), 7.12-7.39 (m, 11H), 4.11 (s, 2H), 3.21-3.30 (m, 2H), 3.06-3.14 (m, 2H); ^{13}C NMR (50 MHz, CDCl$_3$): δ 164.9, 142.4, 139.7, 136.9, 132.9, 129.8, 129.3, 129.2, 129.1, 129.0, 128.8, 127.6, 126.9, 126.8, 126.4, 39.1, 38.1, 35.7; IR (KBr, cm^{-1}) ν_{max} = 3060, 2926, 1601, 1493, 1453, 1418, 1074, 1029; MS (EI, *m/z*): 323 [M]$^+$; HRMS (EI): Calcd. for $C_{24}H_{21}N$ [M]$^+$: 323.17; Found: 323.16738.

3-Benzyl-6-bromo-2-phenethylquinoline (3d)

Yield: 78%; White solid, mp 89-91 °C; ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.98 (d, *J* = 9.0 Hz, 1H), 7.89 (d, *J* = 1.8 Hz, 1H), 7.75 (dd, *J* = 2.2 Hz, 1H), 7.65 (s, 1H), 7.10-7.39 (m, 10H), 4.08 (s, 2H), 3.21-3.30 (m, 2H), 3.06-3.14 (m, 2H); ^{13}C NMR (50 MHz, CDCl$_3$): δ 161.7, 145.4, 141.8, 138.8, 135.2, 133.7, 132.2, 130.4, 129.2, 129.0, 128.8, 128.6, 128.4, 128.3, 126.7, 126.0, 119.6, 38.6, 37.6, 35.1; IR (KBr, cm^{-1}) ν_{max} = 3025, 2927, 1595, 1494, 1477, 1453, 1397, 1059, 918; MS (EI, *m/z*): 400 [M]$^+$; HRMS (EI): Calcd. for $C_{24}H_{19}NBr$ [M]$^+$: 400.07; Found: 400.07008.

6-Bromo-3-ethyl-2-propylquinoline (3i)

Yield: 66%; Colorless oil; ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.87-7.91 (m, 2H), 7.77 (s, 1H), 7.64-7.70 (m, 1H), 2.79-3.00 (m, 4H), 1.84 (q, *J* = 8.0 Hz, 2H), 1.34 (t, *J* = 7.4 Hz, 3H), 1.08 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (50 MHz, CDCl$_3$): δ 162.6, 145.0, 136.4, 132.7, 131.9, 131.7, 130.3, 128.9, 128.5, 119.2, 114.2, 37.7, 25.2, 22.6, 14.3, 14.2; IR (KBr, cm^{-1}) ν_{max} = 2963, 1594, 1477, 1377, 1345, 1184, 911; MS (EI, *m/z*): 277 [M]$^+$; HRMS (EI): Calcd. for $C_{14}H_{16}NBr$ [M]$^+$: 277.05; Found: 277.04658.

2-(Dec-9-enyl)-6-methoxy-3-(non-8-enyl)quinoline (3j)

Yield: 85%; Colorless oil; ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.93 (d, *J* = 9.0 Hz, 1H), 7.77 (s, 1H), δ 7.26 (d, *J* = 9.0 Hz, 1H), 7.01 (s, 1H), 6.80 (d, *J* = 9.2 Hz, 1H), 6.61 (d, *J* = 8.8 Hz, 1H), 5.76-5.91 (m, 3H), 4.93-5.06 (m, 6H), 3.93 (s, 3H), 2.95 (t, *J* =8.0 Hz, 2H), 2.78 (t, *J* =8.0 Hz, 2H), 2.06 (m, 4H), 1.19-1,78 (br, 17H); ^{13}C NMR (50 MHz, CDCl$_3$): δ 162.6, 139.9, 139.7, 135.4, 134.7, 129.3, 128.8, 127.6, 127.2, 126.3, 117.6, 114.6, 114.3, 113.2, 59.3, 50.3, 44.6, 36.4, 34.3, 32.5, 30.7, 30.6, 30.5, 30.2, 30.0, 29.9, 29.8, 29.6, 29.3, 29.2, 29.1, 27.6; IR (KBr, cm^{-1}) ν_{max} = 3074, 2925, 1624, 1513, 1493, 1381, 1229, 1165, 1034, 909; MS (EI, *m/z*): 421 [M]$^+$; HRMS (EI): Calcd. for $C_{29}H_{43}NO$ [M]$^+$: 421.33; Found: 421.33444.

3-benzyl-7-methoxy-2-phenethylquinoline (4a)

Yield: 71%; Light yellow oil; ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.71 (s, 1H), 7.12-7.40 (m, 12H), 4.08 (s, 2H), 3.92 (s, 3H), 3.18-3.26 (m, 2H), 3.03-3.12 (m, 2H); ^{13}C NMR (50 MHz, CDCl$_3$): δ159.0, 142.6, 139.8, 135.8, 133.2, 130.4, 129.5, 129.2, 129.0, 128.6, 128.4, 126.9, 126.3, 121.8, 105.6, 55.9, 39.2, 37.9, 35.8; IR (KBr, cm^{-1}) ν_{max} = 2931, 1640, 1599, 1493, 1361, 1227, 1135, 939; MS

(EI, *m/z*): 353 $[M]^+$; HRMS (EI): Calcd. for $C_{25}H_{23}NO$ $[M]^+$: 353.18; Found: 353. 1786.

2-benzyl-7-methoxy-3-phenylquinoline (4b)

Yield: 73%; Light yellow oil; ^1H NMR (200 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 6.89-7.42 (m, 12H), 4.28 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ159.2, 129.6, 128.9, 128.6, 128.5, 128.4, 128.2, 128.1, 127.5, 125.9, 55.6, 42.7; IR (KBr, cm^{-1}) ν_{max} = 2962, 1643, 1592, 1321, 1263, 1180, 909; MS (EI, *m/z*): 325 $[M]^+$; HRMS (EI): Calcd. for $C_{23}H_{19}NO$ $[M]^+$: 325.15; Found: 325. 14662.

ACKNOWLEDGEMENT

The authors thanks “the Fundamental Research Funds for the Central Universities” (JUSRP10905), and the “Start-up grant of Jiangnan University” (1045210372090460) for financial support.

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