Amberlyst-15-catalyzed Novel Synthesis of Quinoline Derivatives in Ionic Liquid

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In recent years, ionic liquids have attracted much attention as useful synthetic solvents. Compared with classical molecular solvents, the ionic liquids are environmentally benign reaction media. A variety of quinoline derivatives have been synthesized under ionic liquid conditions using Amberlyst-15 as catalyst.

Keywords: Ionic liquid; Amberlyst-15; Quinoline.

INTRODUCTION

Room temperature ionic liquids (RTIL) are liquids that are composed entirely of ions. In fact, ionic liquids can now be produced which remain liquid at room temperature and below (even as low as -90 °C) and appear to be undemanding and inexpensive to manufacture.[1] Ionic liquids offer an attractive alternative to conventional organic liquids for clean synthesis, as they are easy to recycle, lack flammability, and possess effectively no vapour pressure. Compared with classical molecular solvents, the ionic liquids are environmentally benign reaction media.[2] To date, some of the more important reactions have been carried out and investigated in ionic liquids, for example, Friedel-Crafts reaction,[3] alkoxycarbonylation,[4] hydrogenation,[5] Diels-Alder reaction,[6] Wittig reaction,[7] Heck reaction,[8] Trost-Tsuji coupling,[9] ring-closing metathesis (RCM),[10] Suzuki cross-coupling,[11] Fischer indole synthesis,[12] 1,3-dipolar cycloaddition reaction,[13] Beckmann rearrangement,[14] the Knoevenagel and Robinson annulation reactions,[15] etc.

Recently, the use of ion exchange resins in organic synthesis has received great attention.[16] Amberlyst-15[17-18] is a porous sulfonated polystyrene resin that serves as an excellent source of strong acid in nonaqueous media (Fig. 1). It has been used in various catalyzed reactions, e.g., esterification, etherification, oxidation, hydration of olefins, condensation, cyclization and electrophilic aromatic substitution. It is easy to measure, safe to use, and readily removed at the end of the reaction. An additional advantage is that the catalyst can be regenerated and used several times. We report here using Amberlyst-15 as catalyst to synthesize quinolines *via* Friedländer reaction in ionic liquid.[19]

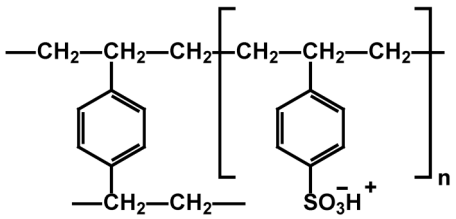

Fig. 1

RESULTS AND DISCUSSION

Treatment of 2-aminobenzophenone (**1**) and aryl ketones (**2**) with Amberlyst-15 as catalyst in ionic liquid 1-*n*-butyl-3-methylimidazolium hexafluorophoaphate, [Bmin][PF_6] at 80 °C for 3 h caused cyclodehydration to give quinolines (**3**) in good yields (Scheme I). The results are given in Table 1. When the reaction is conducted in a conventional solvent, such as acetonitrile, the preparation of 2,4-diphenylquinoline (**3a**) needs refluxing for 10 h.[20]

The ionic liquid [Bmin][PF_6] can be typically recovered by extracting out the product first and filtering the suspension followed by vacuum drying. The recovered solvent can be reused without loss of activity.

In summary, our results herein demonstrate that the use of 2-aminobenzophenone and arylketones in ionic liquid [Bmim][PF_6] can be performed rapidly for Friedländer reaction to prepare quinoline derivatives using Amberlyst-15 as catalyst. The ionic liquid plays the dual role of sol-

Scheme I

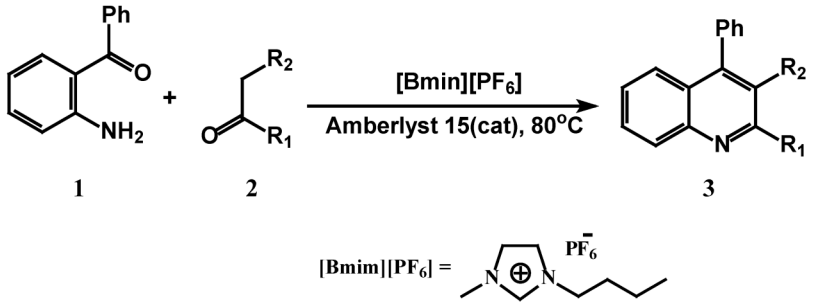

Table 1. Synthesis of quinoline derivatives

Entry	Product	R_1	R_2	Yield (%)
1	**3a**	Ph	H	78
2	**3b**	4-MeC_6H_4	H	73
3	**3c**	4-$MeOC_6H_4$	H	75
4	**3d**	4-FC_6H_4	H	77
5	**3e**	4-ClC_6H_4	H	80
6	**3f**	4-BrC_6H_4	H	82
7	**3g**	2-Furyl	H	72
8	**3h**	2-Thienyl	H	76
9	**3i**	4-$NO_2C_6H_4$	H	84
10	**3j**	Ph	CH_3	81
11	**3k**	Ph	Ph	76

vent and promoter. Separation of products from the ionic liquids is very straightforward, as is recycling of the ionic liquid.

EXPERIMENTAL SECTION

All melting points are uncorrected. The IR spectra were recorded on a Shimadzu IR-27 G spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity Plus 400 MHz. Chemical shifts (δ) were measured in ppm with respect to TMS. MS were obtained on a JEOL JMS D-300 instrument.

Typical procedure for the preparation of 2,4-diphenylquinoline (3a)

To a solution of acetophenone (**2a**) (120 mg, 1.0 mmol) and 2-aminobenzophenone (197 mg, 1.0 mmol) in [Bmin][PF_6] (2 mL) was added Amberlyst-15 (100 mg, 0.5 mmole), and the mixture was stirred at 80 °C for 3 h and filtered after cooling. Subsequently, the filtrate was extracted with ethyl acetate. The organic layer was washed with saturated $NaCl_{(aq)}$, dried over $MgSO_4$, then concentrated under reduced pressure and the residue was chromatographed on silica gel eluting with ethyl acetate-hexane (1:5) to give **3a**. mp 110-111 °C (Lit.[21], mp 112-113 °C). IR (KBr) ν: 3050, 1584, 1541 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.45-7.59 (m, 9H), 7.74 (ddd, *J* = 1.2, 6.8, 15.2 Hz, 1H), 7.83 (s, 1H), 7.92 (dd, *J* = 0.8, 8.4 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 2H), 8.26 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 119.3, 125.6, 125.7, 126.3, 127.5, 128.4, 128.5, 128.8, 129.3, 129.4, 129.5 130.0, 138.3, 139.6, 148.7, 149.1, 156.8. MS (EI) *m/z*: 281 (M^+), 280, 202, 176, 139, 125.

2-(4-Methylphenyl)-4-phenylquinoline (3b)

mp 95-96 °C (Lit.[22], mp 116-117 °C). IR (KBr) ν: 3049, 1624, 1548 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.43 (s, 3H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.44-7.58 (m, 6H), 7.71-7.75 (m, 1H), 7.81 (s, 1H), 7.89 (dd, *J* = 1.0, 8.0 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 2H), 8.23 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.3, 119.1, 125.5, 125.6, 126.0, 127.3, 128.3, 128.5, 129.3, 129.5, 129.9, 136.7, 138.4, 139.3, 148.7, 148.9, 156.7. MS (EI) *m/z* : 295 (M^+), 294, 202, 145, 139.

2-(4-Methoxyphenyl)-4-phenylquinoline (3c)

mp 78-79 °C (Lit.[21], mp 77-79 °C). IR (KBr) ν: 1736 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.89 (s, 3H), 7.06 (ddd, *J* = 2.6, 2.6, 9.2 Hz, 2H), 7.44-7.58 (m, 6H), 7.69-7.75 (m, 1H), 7.79 (s, 1H), 7.89 (ddd, *J* = 0.8, 0.8, 8.4 Hz, 1H), 8.19 (ddd, *J* = 2.4, 2.4, 9.2 Hz, 2H), 8.24 (ddd, *J* = 0.6, 0.8, 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 55.3, 114.1, 118.8, 125.4, 125.5, 125.9, 128.3, 128.5, 128.8, 129.4, 129.5, 129.8, 130.1, 132.0, 137.4, 138.4, 148.7, 149.0, 156.3, 160.8. MS (EI) *m/z*: 311 (M^+), 310, 268, 267, 140, 139, 132.

2-(4-Fluorophenyl)-4-phenylquinoline (3d)

mp 63-64 °C. IR (KBr) ν: 3056, 1593, 1546 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.19-7.24 (m, 2H), 7.47-7.57 (m, 6H), 7.72-7.76 (m, 1H), 7.78 (s, 1H), 7.91 (dd, *J* = 1.0, 8.4 Hz, 1H), 8.18-8.24 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 115.4, 115.7, 118.7, 125.5, 126.2, 128.3, 128.4, 129.2, 129.3, 129.4, 129.5, 129.8, 135.5, 135.6, 138.1, 148.6, 149.1, 155.5, 162.4. MS (EI) *m/z*: 299 (M^+), 298, 220, 202,

201, 139, 125. Anal. Calcd for $C_{12}H_{14}NF$: C, 84.26, H, 4.71, N, 4.68; Found: C, 84.39, H, 4.54, N, 4.53.

2-(4-Chlorophenyl)-4-phenylquinoline (3e)

mp 104-105 °C (Lit.[23], mp 106 °C). IR (KBr) ν: 3055, 1589, 1542 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.47-7.57 (m, 8H), 7.74-7.77 (m, 1H), 7.79 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 8.14-8.18 (m, 2H), 8.23 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 118.6, 125.6, 125.7, 126.5, 128.4, 128.6, 128.8, 128.9, 129.5, 129.6, 130.0, 136.5, 137.9, 138.2, 148.7, 149.4, 155.4. MS (EI) *m/z*: 317 (M^++2), 315 (M^+), 314, 220, 202, 176, 139.

2-(4-Bromophenyl)-4-phenylquinoline (3f)

mp 111-112 °C (Lit.[24], mp 128-129 °C). IR (KBr) ν: 3029, 1584, 1539 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.48-7.57 (m, 6H), 7.64-7.67 (m, 2H), 7.73-7.87 (m, 2H), 7.91 (dd, *J* = 1.0, 8.4 Hz, 1H), 8.08-8.11 (m, 2H), 8.24 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 118.7, 123.8, 125.5, 125.7, 126.4, 128.4, 128.5, 129.0, 129.4, 129.6, 130.0, 131.8, 138.1, 138.3, 148.6, 149.3, 155.3. MS (EI) *m/z*: 361 (M^++2), 360 (M^++1), 359 (M^+), 279, 278, 202, 139.

2-(2-Furyl)-4-phenylquinoline (3g)

mp 98-99 °C (Lit.[22], mp 109-111 °C). IR (KBr) ν: 3060, 1594, 1546 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 6.60 (dd, *J* = 1.6, 3.6 Hz, 1H), 7.25 (m, 1H), 7.43-7.57 (m, 6H), 7.63 (dd, *J* = 0.6, 1.8 Hz, 1H), 7.74 (ddd, *J* = 1.0, 6.8, 8.4 Hz, 1H), 7.78 (s, 1H), 7.87 (dd, *J* = 1.2, 8.4 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 110.1, 112.1, 117.6, 125.6, 125.7, 126.1, 128.3, 128.4, 129.4, 129.5, 129.8, 138.0, 144.0, 148.4, 148.5, 148.9, 153.6. MS (EI) *m/z*: 271 (M^+), 270, 243, 242, 241, 120.

4-Phenyl-2-(2-thienyl)quinoline (3h)

mp 92-93 °C (Lit.[22], mp 89-92 °C). IR (KBr) ν: 3054, 1585, 1543 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.16 (dd, *J* = 3.8, 5.0 Hz, 1H), 7.42-7.57 (m, 7H), 7.68-7.74 (m, 3H), 7.84 (dd, *J* = 0.8, 8.4 Hz, 1H), 8.16 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 117.8, 125.6, 125.7, 125.8, 126.0, 128.0, 128.4, 128.5, 128.6, 129.4, 129.5, 129.6, 138.0, 145.3, 148.5, 148.7, 151.7. MS (EI) *m/z*: 287 (M^+), 286, 253, 202, 200.

2-(4-Nitrophenyl)-4-phenylquinoline (3i)

mp 156-157 °C (Lit.[24], mp 162-163 °C). IR (KBr) ν: 3055, 1588, 1547 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.52-7.58 (m, 6H), 7.77-7.81 (m, 1H), 7.86 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 8.37-8.42 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 119.0, 120.8, 123.3, 123.9, 125.7, 126.0, 127.2, 128.1, 128.2, 128.6, 129.3, 129.4, 130.0, 130.2, 130.9, 137.8, 145.3, 148.2, 148.7, 149.8, 153.9. MS (EI) *m/z*: 326 (M^+), 325, 280, 278, 202, 176, 139.

3-Methyl-2,4-diphenylquinoline (3j)

mp 134-135 °C (Lit.[25], mp 145-146 °C). IR (KBr) ν: 3048, 1609, 1568 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.17 (s, 3H), 7.32-7.34 (m, 2H), 7.40-7.58 (m, 8H), 7.62-7.68 (m, 3H), 8.20 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.5, 115.8, 126.1, 126.5, 126.9, 127.7, 127.9, 128.0, 128.2, 128.4, 128.6, 128.8, 129.2, 129.3, 137.5, 141.3, 146.1, 147.6, 160.6. MS (EI) *m/z*: 295 (M^+), 294, 217, 189, 139.

2,3,4-Triphenylquinoline (3k)

mp 190-191 °C (Lit.[26], mp 189-190 °C). IR (KBr) ν: 3052, 1603, 1547 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 6.88-6.91 (m, 2H), 6.99-7.02 (m, 3H), 7.14-7.16 (m, 2H), 7.21-7.23 (m, 3H), 7.26-7.31 (m, 3H), 7.38-7.40 (m, 2H), 7.46 (ddd, *J* = 1.2, 6.8, 8.4 Hz, 1H), 7.59 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.74 (ddd, *J* = 1.2, 6.8, 8.4 Hz, 1H), 8.28 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 126.2, 126.4, 126.5, 127.1, 127.2, 127.4, 127.5, 127.6, 129.2, 129.5, 129.8, 130.1, 131.2, 132.8, 136.8, 138.2, 141.0, 147.2, 147.5, 158.8. MS (EI) *m/z*: 357 (M^+), 356, 278, 176, 171.

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REFERENCES

1. (a) Welton, T. *Chem. Rev*. **1999**, *99*, 2071. (b) Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed*. **2000**, *39*, 3772.
2. (a) Zhang, S.; Zhang, Q.; Zhang, Z. C. *Ind. Eng. Chem. Res*. **2004**, *43*, 614. (b) Esser, J.; Wasserscheid, P.; Jess, A. *Green Chem*. **2004**, *6*, 316. (c) Wang, Y.; Li, H. R.; Wang, C. M.; Hui, J. *Chem. Commun*. **2004**, 1938. (d) Gmouh, S.; Yang, H.; Vaultier, M. *Org. Lett*. **2003**, *5*, 3365.
3. (a) Surette, J. K. D.; Green, L.; Singer, R. D. *Chem. Commun*. **1996**, 2753. (b) Boon, J. A.; Levisky, J. A.; Pflug, J. L.; Wilkes, J. S. *J. Org. Chem*. **1986**, *51*, 480. (c) Adams, C. J.; Earle, M. J.; Roberts, G.; Seddon, K. R. *Chem. Commun*. **1998**, 2097. (d) Stark, A.; MacLean, B. L.; Singer, R. D. *J. Chem. Soc. Dalton Trans*. **1999**, 63.
4. Zim, D.; de Souza, R. F.; Dupont, J.; Monteiro, A. L. *Tetrahedron Lett*. **1998**, *39*, 7071.
5. (a) Dyson, P. J.; Ellis, D. J.; Parker, D. G.; Welton, T. *Chem. Commun*. **1999**, *25*. (b) Monteiro, A. L.; Zinn, F. K.; de Souza, R. F.; Dupont, J. *Tetrahedron: Asymmetry* **1997**, *8*, 177. (c) Fisher, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahe-*

dron Lett. **1999**, *40*, 793. (d) Adams, C. J.; Earle, M. J.; Seddon, K. R. *Chem. Commun*. **1999**, 1043. (e) Einloft, J. E. L.; de Souza, R. F. Dupont, J. *Polyhedron* **1996**, *15*, 1217.

6. (a) Howarth, J.; Hanlon, K.; Fayne, D.; McCormac, P. *Tetrahedron Lett*. **1997**, *38*, 3097. (b) Earle, M.; McCormac, P. B.; Seddon, R. K. *Green Chem*. **1999**, *1*, 23. (c) Huddleston, J. G.; Willauer, H. D.; Swatloski, R. P.; Visser, A. E.; Rogers, R. D. *Chem. Commun*. **1998**, 1765. (d) Song, C. E.; Shim, W. H.; Roh, E. J.; Lee, S.; Choi, J. H. *Chem. Commun*. **2001**, 1122.
7. Boulaire, V. L.; Gree, R. *Chem. Commun*. **2000**, 2195.
8. (a) Calo, V.; Nacci, A.; Lopez, L.; Mannarini, N. *Tetrahedron Lett*. **2000**, *41*, 8973. (b) Xu, L. J.; Chen, W. P.; Xiao, J. L. *Organometallics* **2000**, *19*, 1123. (c) Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B.; Seddon, K. R. *Org. Lett*. **1999**, *1*, 997. (d) Deshmukh, R. R.; Rajagopal, R.; Srinivasan, K. V. *Chem. Commun*. **2001**, 1544. (e) Bohm, V. P. W.; Herrmann, W. A. *Chem. Eur. J*. **2000**, *6*, 1017.
9. de Bellefon, C.; Pollet, E.; Grenouillet, P. *J. Mol. Catal*. **1999**, *145*, 121.
10. (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Buijsman, R. C.; van Vuuren, E.; Sterrenburg, J. G. *Org. Lett*. **2001**, *3*, 3785.
11. Mathews, C. J.; Smith, P. J.; Welton, T. *Chem. Commun*. **2000**, 1249.
12. Rebeiro, G. L.; Khadilkar, B. M. *Synthesis* **2001**, 370.
13. Dubreuil, J. F.; Bazureau, J. P. *Tetrahedron Lett*. **2000**, *41*, 7351.
14. (a) Izumi, Y.; Sato, S.; Urabe, K. *Chem. Lett*. **1983**, 1649. (b) Peng, J.; Deng, Y. *Tetrahedron Lett*. **2001**, *42*, 403.
15. Morrison, D. W.; Forbes, D. C.; James, H. *Tetrahedron Lett*. **2001**, *42*, 6053.
16. Bravo, R. D.; C'anepa, A. S. *Synthetic Comm*. **2002**, *32*, 3675.
17. Richard, A. B.; Henry, D. R. *J. Chem. Edu*. **1990**, *67*, 69.
18. Zhang, X.; Fan, X.; Wang, J.; Li, Y. *J. Chin. Chem. Soc*. **2004**, *51*, 1339.
19. Friedländer, P. *Chem. Ber.* **1882**, *15*, 2572.
20. Skraup, Z. H. *Chem. Ber.* **1880**, *13*, 2086.
21. Leardini, R.; Nanni, D.; Tundo, A.; Zanard, G.; Ruggieri, F. *J. Org. Chem*. **1992**, *57*, 1842.
22. Kobayash, K.; Yoneda, K.; Miyamoto, K.; Morikawa, D.; Konishi, H. *Tetrahedron* **2004**, *60*, 11639.
23. Dorothy, J. P.; Tammy, D. F.; Charles, F. B. *J. Heterocyclic. Chem*. **1981**, *18*, 649.
24. Zhang, X.; Fan, X.; Wang, J.; Li, Y. *J. Chin. Chem. Soc*. **2004**, *51*, 1339.
25. Osborne, A. G.; Ahmet, M. T.; Miller, J. R.; Warmsley, J. F. *Spectrochimica Acta*. **1995**, *51A*, 237.
26. Fehnel, E. A. *J. Heterocyclic. Chem*. **1967**, *4*, 565.