Synthesis of substituted quinolines from arylamines and aldehydes via tandem reaction promoted by chlorotrimethylsilane

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Substituted quinolines were effectively synthesised by utilising chlorotrimethylsilane (TMSCl) as an efficient catalyst in the cyclisation condensation of aromatic amines and enolisable aldehydes via a tandem process in air and DMSO. The clean, mild reaction conditions, operational simplicity and high yields were attractive features of the reaction which enables a facile preparative procedure for building the quinoline ring.

Keywords: substituted quinolines, TMSCl, enolisable aldehydes, cyclisation reaction

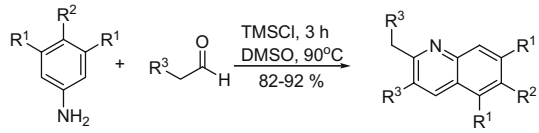
Substituted quinolines and their derivatives are a very important class of heterocyclic compounds which have been used widely as antiinflammatory agents, antimalarial, antihypertensive, antibacterial, antiasthamatic, antiprotozoan, antituberculosis, tyrosine kinase inhibiting agents, liver × receptor agonists, anti-HIV, and anticancer activity.[1-8] Furthermore they had important roles as versatile building blocks for the synthesis of natural products and nano and mesostructures with enhanced electronic and photonic properties.[9] In addition to the medicinal applications, substituted quinolines have been employed in the bioorganic and bioorganometallic research.[10] Studies of their properties and synthesis have attracted considerable attention from medicinal and synthetic organic chemists.

Many substituted quinolines have been synthesised by various conventional named routes such as Skraup, Döbner-von Miller, Conrad-Limpach, Friedlaender and Pfitzinger syntheses.[11,12] They are still considered as the most useful methods for preparing quinolines and related bicyclic azaaromatic compounds, although they require harsh reaction conditions and the yields are unsatisfactory in most cases. Recently, in conjunction with the conventional syntheses, more and more new methods of simple and elegant syntheses of substituted quinolines have also been attempted because of facility, efficiency and convenience of formation of quinoline ring system.[13,14] In view of the remarkable importance from pharmacological, industrial and synthetic point, the development of new synthetic approaches using mild reaction conditions remains an active research area.

Trimethylchlorosilane (TMSCl) has been used as a mild and efficient promoter for various organic transformations.[15] It has also been reported as a mild, useful and inexpensive Lewis acid catalyst for one-pot chemoselective multicomponent Biginelli reactions,[16] the biguanide formation with benzylamine and dicyandiamide,[17] and *direct* cross aldol additions and the related Claisen condensation using $TiCl_4/Bu_3N$.[18] In continuation of our efforts to develop new synthetic routes of substituted quinolines, we report here a TMSCl-promoted one-pot synthesis of substituted quinolines from aromatic amines and enolisable aldehydes via Tandem reaction under an air atmosphere (Scheme 1).

Results and discussion

The more classical and convenient synthesis of substituted quinolines was carried out[11-14] by a one-step condensation reaction from the available and inexpensive starting material aromatic amines and enolisable aldehydes in the presence of Lewis acid. Although the role of TMSCl is not completely understood, it may be explained in terms of Lewis acid, which activates the carbonyl group. We thought that it could be applied in the one-step condensation reaction of aromatic amine and enolisable aldehyde. Thus we initiated our studies in a model reaction by subjecting 4-methoxyaniline (**1a**) and isopentanal (**2a**) to TMSCl in DMSO under an air atmosphere at 90 °C, which gave 2-isobutyl-3-isopropyl-6-methoxyquinoline (**3a**) (Table 1).



1a–j **2a–j** **3a–j**

Entry	$ArNH_2$(**R**^{1}/**R**^{2})(**1**)	Aldehydes(**R**^{3})(**2**)	Quinolines (**3**)(%)
a	H / CH_3O	$(CH_3)_2CH$	92
b	CH_3O / H	$(CH_3)_2CH$	86
c	H / Ph	$(CH_3)_2CH$	88
d	H / Ph	$CH_3(CH_2)_3CH_2$	89
e	CH_3O / H	$CH_3(CH_2)_3CH_2$	86
f	H / CH_3O	$PhCH_2$	84
g	CH_3O / H	$PhCH_2$	82
h	H / Ph	$PhCH_2$	86
i	H / CH_3O	$CH_3(CH_2)_3CH_2$	86
j	H / H	CH_3CH_2	83

Scheme1

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Table 1 Effect of the ratio of **1a**/**2a**/TMSCl[a]

Entry	**1a**/**2a**/TMSCl /mol/mol/mol	Quinoline (**3a**)/%
1	1/2/0.01	67
2	1/3/0.01	74
3	1/4/0.01	81
4	1/5/0.01	81
5	1/4/0.02	87
6	1/5/0.02	88
7	1/4/0.03	92
8	1/4/0.05	92

[a]Conditions: DMSO (5 mL), reaction temperature 90 °C, air, 3 h.

The results (Table 1) showed that the best results were obtained using 3.0 mol% catalyst in the ratio of 1/4 and excessive TMSCl was not necessary.

In order to optimise other reaction conditions, reaction temperature, solvents and reaction time were measured. As shown in Table 2 and Table 3, the reaction gave a satisfactory yield in DMSO under an air atmosphere at 90 °C for 3 h.

Thus, with these results in hand, we synthesised substituted quinolines (**3a–j**) by one-pot condensation reaction of aromatic amines and enolisable aldehydes under the optimum reaction conditions (Scheme 1).

The mechanism for the conversion of imine and enolisable aldehyde to a quinoline can be explained tentatively as in Scheme 2. A β-amino aldehyde is preformed by direct-Mannich reaction of silyl enol ether and imine, followed by subsequent cyclisation and aromatisation under air.[19] Oxygen in the air apparently acts as an effective oxidant for aromatisation of hydroquinoline.[20]

In summary, we have developed a new and efficient procedure to substituted quinolines from available aromatic amines and enolisable aldehydes under an air atmosphere in DMSO at 90 °C for 3 h. A catalytic amount of TMSCl (3.0 mol%) effectively initiates the reaction in a one-pot tandem process to yield the products in 82–92%. The procedure offers several advantages including mild reaction conditions, operational simplicity, inexpensive reagents, short reaction time and high yields of products.

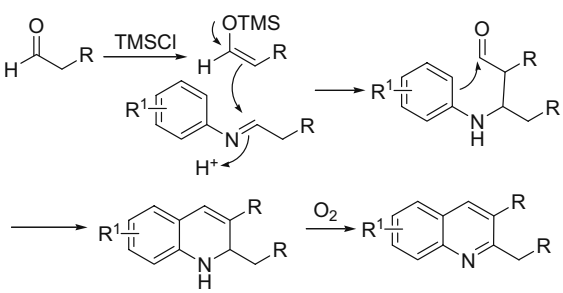
Experimental

Elemental analytical data were obtained by using a model 240 elementary instrument, IR spectra were measured with a model 408 IR spectrometer, ^{1}H NMR and ^{13}C NMR spectra were recorded on a JNM-90Q spectrometer by using TMS as an internal standard ($CDCl_3$ as solvent).

Table 2 Effect of the temperature and solvent[a]

Entry	Solvent	Temperature/°C	Quinoline **3a**/%
1	THF	70	78
2	C_6H_6	80	85
3	DMF	80	83
4	DMSO	80	86
5	DMSO	90	92
6	DMSO	100	91

[a]Conditions: **1a/2a**/TMSCl: 1/4/0.03 (mol/mol/mol), air, 3 h.



Scheme 2 Plausible reaction mechanism.

Table 3 Effect of the reaction time[a]

Entry	Time/h	Quinoline **3a**/%
1	1.5	67
2	2.0	78
3	3.0	92
4	3.5	92

[a]Conditions: **1a/2a**/TMSCl: 1/4/0.03 (mol/mol/mol), DMSO, 90 °C, air.

General procedure for one-pot synthesis of substituted quinolines from arylamines and aldehydes via Tandem reaction promoted by chlorotrimethylsilane.

TMSCl (0.1303 g, 1.2 mmol) was added to a mixture of aldehyde (16 mmol) and substituted aniline (4 mmol) in DMSO (5 mL) at room temperature. The resulting mixture was stirred at 90 °C for 3 h under an air atmosphere. After the mixture was cooled to room temperature, it was poured to 10% sodium carbonate and was extracted with ethyl acetate (3 × 15 mL), then the organic phase was washed with water and brine, dried over Na_2SO_4. Removal of solvent, the residue was purified by column chromatography (silica gel, EtOAc/CH_2Cl_2: 1/20) to yield product (**3a–i**).

2-Isobutyl-3-isopropyl-6-methoxyquinoline (**3a**): White solid; m.p. 58–60 °C (EtOAc/Hexanes); IR (KBr, cm^{-1}) 1624, 1599, 1567, 1492, 1465, 1383, 1226, 1032, 830; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 7.90 (d, J = 9.3 Hz, 1H), 7.85 (s, 1H), 7.28 (dd, J = 2.7 Hz and 0.6 Hz, 1H), 7.02 (d, J = 3.0 Hz, 1H), 3.90 (s, 3H), 3.30 (m, 1H), 2.88 (d, J = 7.5 Hz, 2H), 2.23 (m, 1H), 1.32 (d, J = 6.9 Hz, 6H), 0.98 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 157.7, 156.9, 142.2, 140.7, 130.3, 129.7, 127.9, 120.7, 104.4, 55.1, 43.7, 29.1, 28.5, 23.6(2C), 22.4(2C). Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.13; H, 8.82; N, 5.40%.

2-Isobutyl-3-isopropyl-5,7-dimethoxyquinoline (**3b**): White solid; m.p. 64–65 °C (EtOAc/Hexanes); IR (KBr, cm^{-1}) 1622, 1598, 1576, 1492, 1454, 1382, 1258, 1205, 1056, 831; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.25 (s, 1H), 6.96 (d, J = 1.8 Hz, 1H), 6.43 (d, J = 2.1 Hz, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.29 (m, 1H), 2.88 (d, J = 7.5 Hz, 2H), 2.23 (m, 1H), 1.32 (d, J = 6.9 Hz, 6H), 0.99 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 161.0, 160.4, 155.6, 148.1, 137.5, 126.2, 115.4, 99.1, 97.1, 55.5, 55.4, 44.1, 29.4, 28.7, 24.0(2C), 22.5(2C). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.16; H, 8.82; N, 4.61%.

2-Isobutyl-3-isopropyl-6-phenylquinoline (**3c**): Oil; IR (neat, cm^{-1}) 1597, 1578, 1482, 1463, 1382, 1053, 837; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.18 (d, J = 9.0 Hz, 1H), 7.98 (s, 1H), 7.92 (d, J = 2.1 Hz, 1H), 7.86 (dd, J = 6.4 Hz and 1.8 Hz, 1H), 7.68 (d, J = 7.2 Hz, 2H), 7.45 (t, J = 7.5 Hz, 2H), 7.34 (t, J = 7.5 Hz, 1H), 3.33 (m, 1H), 2.94 (d, J = 6.9 Hz, 2H), 2.30 (m, 1H), 1.33 (d, J = 6.9 Hz, 6H), 1.01 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 160.7, 145.5, 141.1, 140.7, 138.2, 131.6, 128.9 128.8(2C), 128.0, 127.4, 127.3, 127.2(2C), 124.8, 44.1, 29.2, 28.7, 23.8(2C), 22.6(2C). Anal. Calcd for $C_{22}H_{25}N$: C, 87.08; H, 8.30; N, 4.62. Found: C, 87.16; H, 8.02; N, 4.60%.

2-Hexyl-3-pentyl-6-phenylquinoline (**3d**): Oil; IR (neat, cm^{-1}) 3060, 3032, 2955, 2926, 2857, 1682, 1598, 1578, 1483, 1465, 1377, 1354, 910, 836, 760, 697; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.07. (d, J = 9.3 Hz, 1H), 7.90–7.85(m, 3H), 7.72–7.70 (m, 2H), 7.50–7.45 (m, 2H), 7.39–7.37 (m, 1H), 2.98 (t, J = 8.1 Hz, 2H), 2.78 (t, J = 8.1 Hz, 2H), 1.83–1.68 (m, 4H), 1.48–1.33 (m, 10H), 0.96–0.88 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 162.3, 145.9, 140.7, 138.2, 134.9, 134.5, 128.9, 128.8(2C), 127.9, 127.4(2C), 127.3(2C), 124.6, 35.9, 32.3, 31.7(2C), 30.1, 29.6, 29.5, 22.6, 22.5, 14.0, 13.9; Anal. Calcd for $C_{26}H_{33}N$: C, 86.85; H, 9.25; N, 3.90. Found: C, 86.73; H, 9.12; N, 3.70%.

2-Hexyl-3-pentyl-5,7-dimethoxyquinoline (**3e**): Oil; IR (neat, cm^{-1}) 3000, 2924, 2857, 1623, 1578, 1493, 1452, 1390, 1360, 1203, 1152, 1048, 830; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.12. (s, 1H), 6.96. (d, J = 2.1 Hz, 1H), 6.43. (d, J = 2.1 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 2.92 (t, J = 7.8 Hz, 2H), 2.73 (t, J = 7.8 Hz, 2H), 1.79–1.64 (m, 4H), 1.49–1.32 (m, 10H), 0.95–0.87 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 162.3, 160.3, 155.5, 148.5, 130.9, 129.6, 115.3, 99.1, 97.2, 55.6, 55.5, 35.9, 32.3, 31.7, 30.6, 29.8, 29.6(2C), 22.6, 22.5, 14.0, 13.9; Anal. Calcd for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68; N, 4.08. Found: C, 76.73; H, 9.72; N, 3.90%.

3-Benzyl-6-methoxy-2-phenethylquinoline (**3f**): Needle solid; m.p. 142–144 °C (EtOAc/hexanes); IR (KBr, cm^{-1}): 1624, 1606, 1493, 1467, 1451, 1363, 1226, 1187, 1123, 1030, 835, 702; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 7.96 (d, J = 9.0 Hz, 1H), 7.63 (s, 1H), 7.33–7.09 (m, 11H), 6.97 (d, J = 2.1 Hz, 1H), 3.91 (s, 2H), 3.89 (s, 3H), 3.17 (m, 2H), 3.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 158.2, 157.1, 142.7, 141.9, 139.2, 135.0, 132.5, 129.8, 128.8(2C), 128.5(2C), 128.4(2C), 128.1(2C), 127.8, 126.3, 125.7, 121.2, 104.6, 55.2, 38.4, 37.2, 35.1; Anal. Calcd for $C_{25}H_{23}NO$: C, 84.95; H, 6.56; N, 3.96. Found: C, 84.83; H, 6.42; N, 3.88%.

3-Benzyl-5,7-dimethoxy-2-phenethylquinoline (**3g**): Oil; IR (neat, cm^{-1}) 1623, 1600, 1577, 1494, 1452, 1389, 1361, 1204, 1153, 1127, 1047, 831; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.14. (s, 1H), 7.29–7.07 (m, 10H), 7.02 (s, 1H), 6.46 (m, 1H), 4.03 (s, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 3.14 (m, 2H), 2.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 161.8, 160.8, 155.7, 149.0, 142.0, 140.0, 131.6, 128.96, 128.62(2C), 128.50(2C), 128.46(2C), 128.26(2C), 126.2, 125.8, 115.4, 99.1, 97.6, 55.6, 55.2, 38.7, 37.7, 35.5; Anal. Calcd for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65. Found: C, 81.73; H, 6.42; N, 3.90%.

3-Benzyl-2-phenethyl-6-phenylquinoline (**3h**): Needle solid; m.p. 171–172 °C (EtOAc/Hexanes); IR (KBr, cm^{-1}): 1599, 1578, 1495, 1485, 1451, 1429, 1355, 1178, 835, 755, 729; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.13 (d, J = 8.7 Hz, 1H), 7.90 (dd, J = 8.7 and 1.8 Hz, 1H), 7.85 (d, J = 1.5 Hz, 1H), 7.73 (s, 1H), 7.67 (d, J = 7.5 Hz, 2H), 7.44 (t, J = 7.2 Hz, 2H), 7.37–7.08 (m, 11H), 4.03 (s, 2H), 3.24–3.19 (m, 2H), 3.10–3.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 161.1, 146.3, 141.9, 140.5, 139.2, 138.5, 136.4, 132.9, 128.99, 128.90(3C), 128.82(2C), 128.65(2C), 128.52(2C), 128.40, 128.30(2C), 127.5, 127.3(2C), 126.5, 125.9, 124.8, 38.6, 37.6, 35.2; Anal. Calcd for $C_{30}H_{25}N$: C, 90.19; H, 6.31; N, 3.51. Found: C, 90.01; H, 6.42; N, 3.48%.

2-Hexyl-6-methoxy-3-pentylquinoline (**3i**): Oil; IR (neat, cm^{-1}) 1625, 1604, 1567, 1492, 1464, 1380, 1360, 1226, 1164, 1034, 830; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 7.91. (d, J = 9.0 Hz, 1H), 7.71. (s, 1H), 7.26 (m, 1H), 6.96 (m, 1H), 3.85 (s, 3H), 2.92 (t, J = 7.8 Hz, 2H), 2.73 (t, J = 7.8 Hz, 2H), 1.82–1.61 (m, 4H), 1.46–1.32 (m, 10H), 0.94–0.87 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 159.5, 157.0, 142.5, 134.2, 133.6, 129.9, 127.9, 120.6, 104.5, 55.2, 35.6, 32.3, 31.7(2C), 30.1, 29.6, 29.5, 22.5, 14.0, 13.9; Anal. Calcd for $C_{21}H_{31}NO$: C, 80.46; H, 9.97; N, 4.47. Found: C, 80.53; H, 9.73; N, 4.30%.

3-Ethyl-2-propylquinoline (**3j**): White solid; m.p. 57–58 °C (hexanes); IR (KBr, cm^{-1}) 1624, 1590, 1564, 1492, 1460, 1382, 1032, 790; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 8.00 (d, J = 9.3 Hz, 1H), 7.72 (s, 1H), 7.68 (d, J = 9.0 Hz, 1H), 7.64 (m, 1H), 7.50 (m, 1H), 2.88 (t, J = 7.5 Hz, 2H), 2.58 (m, 2H), 1.63 (m, 2H), 1.23 (t, J = 6.9 Hz, 3H), 1.01 (t, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 160.8, 142.8, 134.0, 132.2, 129.2, 128.0, 127.0, 126.4, 126.0, 39.2, 30.6, 24.8, 15.0, 12.9. Anal. Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.60; N, 7.03. Found: C, 84.19; H, 8.62; N, 7.22%.

We are grateful to the Natural Science Foundation of Education Ministry of Jiangsu, China for financial support. (Grant 07KJB150135)

Received 11 September 2008; accepted 12 December 2008
Paper 08/0165 *doi: 10.3184/030823409X401835*
Published online: 24 February 2009

References

1 Y.L. Chen, K.C. Fang, J.Y. Sheu, S.L. Hsu and C.C. Tzeng, *J. Med. Chem.,* 2001, **44**, 2374.
2 D. Doube, M. Bloun, C. Brideau, C. Chan, S. Desmarais, D. Eithier, J.P. Falgueyeret, R.W. Friesen, M. Girad, Y. Girad, J. Guay, P. Tagari and R.N. Yong, *Bioorg. Med. Chem. Lett.,* 1998, **8**, 1255.
3 O. Bilker, V. Lindo, M. Panico, A.E. Etiene, T. Paxton, A. Dell, M. Rogers, R.E. Sinden and H.R. Morris, *Nature*, 1998, **392**, 289.
4 J.P. Michael, *Nat. Prod. Rep.,* 1997, **14**, 605.
5 A.G. Tempone, A.C.M.P. da Silva, C.A. Brandt, F.S. Martinez, S.E.T. Borborema, M.A.B. da Silveira and H.F. de Andrade, *Antimicrob. Agents Chemother.,* 2005, **49**, 1076.
6 A. Nayyar, A. Malde, R. Jain and E. Coutinho, *Bioorg. Med. Chem.,* 2006, **14**, 847.
7 B. Hu, M. Collini and R. Unwalla, *J. Med. Chem.,* 2006, **49**, 6151.
8 A. Tsotinis, M. Vlachou, S. Zouroudis, A. Jeney, F. Timar, D.E. Thurston and C. Roussakis, *Lett. Drug Des. Discov.,* 2005, **2**, 189.
9 J.P. Michael, *Nat. Prod. Rep.,* 2003, **20**, 476.
10 S.A. Jenekhe, L. Lu and M.M. Alam, *Macromolecules,* 2001, **34**, 7315.
11 K. Nakatani, S. Sando and I. Satio, *Bioorg. Med. Chem.*, 2001, **9**, 2381.
12 B. Jiang and Y.C. Si, *J. Org. Chem*., 2002, **67**, 9449.
13 M.E. Theclitou and L.A. Robinson, *Tetrahedron Lett*., 2002, **43**, 3907.
14 T. Igarashi, T. Inada, T. Sekioka, T. Nakajima and I. Shimizu, *Chem. Lett.*, 2005, **34**, 106.
15 N. Sakai, K. Annaka and T. Konakahara, *J. Org. Chem.,* 2006, **71**, 3653.
16 S.V. Ryabukhin, A.S. Plaskon, E.N. Ostapchuk, D.M. Volochnyuk and A.A. Tolmachev, *Synthesis,* 2007, 417.
17 Y.-l. Zhu, S.-l. Huang and Y.-j. Pan, *Eur. J. Org. Chem.,* 2005, 2354.
18 S. Mayer, D.M. Daigle, E.D. Brown, J. Khatri and M.G. Organ, *J. Comb. Chem.,* 2004, **6**, 776.
19 Y. Yoshida, N. Matsumoto, R. Hamasaki and Y. Tanabe, *Tetrahedron Lett.,* 1999, **40**, 4227.
20 S.-y. Tanaka, M. Yasuda and A. Baba, *J. Org. Chem.,* 2006, **71**, 800.