

TMSCl-Catalyzed synthesis of substituted quinolines from arylimines and enolizable aldehydes

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Abstract

Some substituted quinolines were effectively synthesized utilizing chlorotrimethylsilane (TMSCl) as efficient promoter in the cyclization addition of enolizable aldehydes to arylimines under an air atmosphere in DMSO. The clean, mild and ecofriendly process with high yields and a simple workup of the desired compounds are attractive features of the reaction which enables a facile preparation of the quinoline ring.

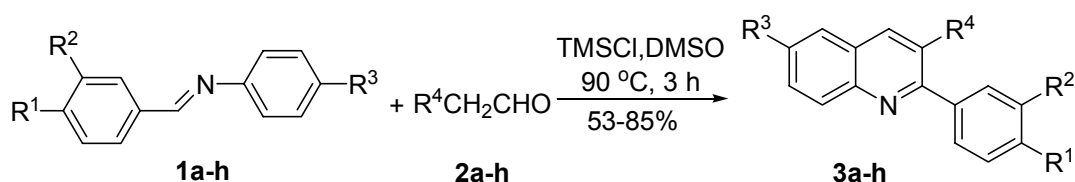
Keywords: Substituted quinoline, TMSCl, arylimine, enolizable aldehyde, synthesis

Introduction

The quinoline nucleus is present in several natural compounds and pharmacologically active substances displaying a broad range of biological activity. Often the type and degree of substitution of the quinoline ring has a profound effect on the biological activity of a given substrate. The substituted quinolines and their derivatives have been found to possess anti-inflammatory, antimalarial, antihypertensive, antibacterial, antiasthmatic, antiprotozoan, antituberculosis, anticancer activity and act as well as tyrosine kinase inhibiting agent, liver X receptor agonist, anti-HIV agent.¹⁻¹⁵ In addition to the synthetic building blocks, variously substituted quinolines and their derivatives have been employed in heterocyclic chemistry.⁶ Therefore, it is of importance to develop novel preparations for substituted quinolines. Although previous syntheses for substituted quinolines such as the Knorr synthesis (acid-catalysis),¹⁶ Skraup, Döbner-von Miller, Conrad-Limpach, Friedlaender and Pfitzinger syntheses are still considered as the most useful,¹⁷⁻²⁴ they require harsh reaction conditions and the yields are unsatisfactory in most cases. Recently, more and more new simple and elegant syntheses of substituted quinolines have been described.²⁵⁻³⁸ Among these methods, the procedure using a

HCl-DMSO system seems to be a very practical method for substituted quinolines starting from imines and carbonyl compounds.³⁴

In view of the remarkable importance from the pharmacological, industrial and synthetic point, the development of new synthetic approaches using mild reaction conditions remains an active research field. Chlorotrimethylsilane (TMSCl) has been used as a mild and efficient promoter for various organic reactions.³⁹⁻⁴³ It has also been reported as a mild useful and inexpensive Lewis acid catalyst for the synthesis of biologically important compounds.⁴⁴⁻⁴⁶ In continuation of our interest in TMSCl-promoted syntheses of nitrogen-containing heterocyclic compounds,⁴⁷ herein we report a simple, highly efficient and environmentally friendly process for the preparation of biologically important quinolines from arylimines and enolizable aldehydes using TMSCl as a Lewis acid catalyst (Scheme 1).



Enter	Imines (1) R ¹ /R ² /R ³	Aldehydes (2) R ⁴	Quinolines (3) Yield (%)
a	H/H/CH ₃ O	(CH ₃) ₂ CH	85
b	H/H/CH ₃ O	PhCH ₂	84
c	H/H/CH ₃ O	n-C ₅ H ₁₁	80
d	H/H/CF ₃	C ₂ H ₅	53
e	H/H/H	CH ₃	68
f	H/H/H	n-C ₆ H ₁₃	72
g	CH ₃ /CH ₃ /Br	n-C ₈ H ₁₇	69
h	H/H/CH ₃ O	C ₂ H ₅	57

Scheme 1

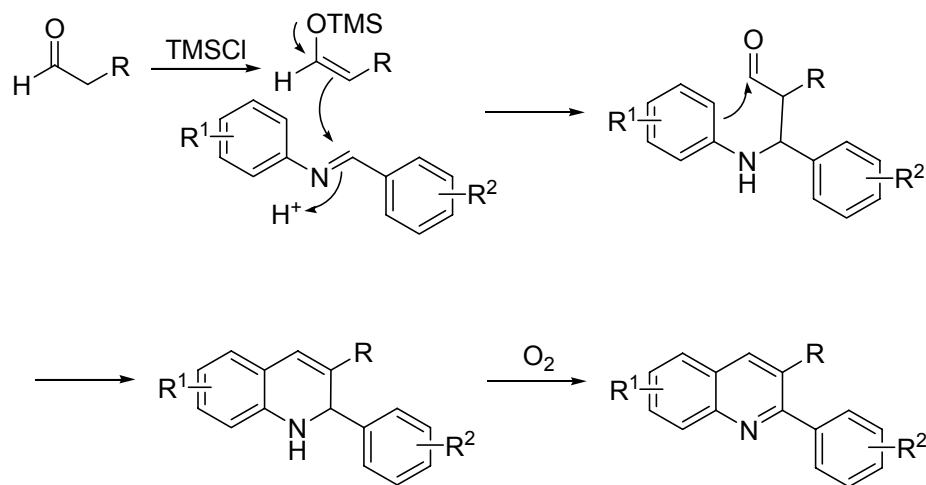
Results and Discussion

According to the classical methods, we firstly prepared the starting arylimines (**1a-h**) from aryl amines and aromatic aldehydes in ethanol. The subsequent cyclization reaction with enolizable aldehydes yielded the substituted quinolines. In a preliminary experiment, stirring a solution of imine **1a**, 3-methylbutanal (**2a**), and TMSCl (10 mol %) was stirred in DMSO under an air atmosphere at 90 °C for 3 h and afforded 3-isopropyl-6-methoxy-2-phenylquinoline (**3a**) in 85% isolated yield. The product **3a** was fully characterized by spectroscopic analyses.

Structural and chemical data of the product **3a** are given in the experimental section. IR spectra of the products showed a C=N stretching band at about 1624 cm^{-1} . In the ^1H NMR spectra, C₄-H, C₅-H, C₇-H and C₈-H protons of the quinoline ring were observed as singlet at 8.02; doublet at 7.10, 7.32 and 8.00 ppm, respectively. The protons belonging to the aromatic ring and the substituents were observed according to the expected chemical shift values.

We observed that TMSCl promotes the cyclization reaction as an effective Lewis acid. In order to optimize the reaction conditions, the solvent in the reaction of imine **1a** and 3-methylbutanal (**2a**) in the presence of TMSCl was varied. Among the solvents tested, DMSO gave the best result. The result showed that CH₃CN, ClCH₂CH₂Cl, DMF, THF, or DMSO gave the product **3a** in 61%, 58%, 79%, 81% and 85% yield, respectively. Furthermore, the reaction time and the catalyst concentration could be reduced to 3 h and 10 mol %, respectively. Thus, with these results in hand and under the optimized reaction conditions, we synthesized the substituted quinolines (**3a-h**) by cyclization of a variety of imines and enolizable aldehydes under an air atmosphere. (Scheme 1)

The mechanism for the conversion of the imine and the enolizable aldehyde to a quinoline can be tentatively explained as shown in Scheme 2. A β -amino aldehyde is preformed by direct-Mannich reaction of the silyl enol ether and the imine,⁴⁸ followed by subsequent cyclization and aromatization under air.³⁴ The air oxygen apparently acts as an effective oxidant for the aromatization of the hydroquinoline.³⁴



Scheme 2. Plausible reaction mechanism.

Conclusions

In summary, an efficient methodology for the synthesis of substituted quinolines was developed which allows obtaining the desired compounds in high yields (53-85 %). Firstly, a variety of imines were prepared by condensing the appropriate aromatic amines with benzaldehyde

derivatives using the classical method. Then, the substituted quinolines were synthesized by the TMSCl-promoted cyclization addition of enolizable aldehydes to imines in DMSO under an air atmosphere. The optimized reaction conditions of the TMSCl-promoted cyclization were studied and used for the preparation of all targeted compounds.

Experimental Section

General Procedures. Elemental analytical data were obtained using a model 240 elementary instrument, IR spectra were measured with a model 408 infrared spectrometer (Shimadzu Corporation, Japan), ¹H-NMR and ¹³C-NMR spectra were recorded on a JNM-90Q Spectrometer (Bruker Corporation, Germany) by using TMS as an internal standard (CDCl₃ as solvent).

General procedure for the synthesis of substituted quinolines from arylimines and enolizable aldehydes promoted by chlorotrimethylsilane

To a mixture of aldehyde (3 mmol) and arylimine (2 mmol) in DMSO (5 mL) was added TMSCl (22.0 mg, 0.2 mmol) at room temperature. The resulting mixture was stirred at 90 °C for 3 h. After the mixture was cooled to room temperature, it was poured into 10% of sodium carbonate and was extracted with ethyl acetate (3×10 mL), then the organic phase was washed with water and brine, dried over Na₂SO₄. After removal of the solvent, the residue was purified by column chromatography (silica gel, EtOAc/CH₂Cl₂: 1/30) to yield the product (**3a-h**).

3-Isopropyl-6-methoxy-2-phenylquinoline (3a).²⁸ Solid (needles); mp 115-116 °C (EtOAc/Hexanes); IR (KBr, cm⁻¹): 2963, 2870, 2834, 1624, 1598, 1489, 1384, 1350, 1227, 1028, 831, 701; ¹H NMR (CDCl₃, 300 MHz, ppm) δ 8.02 (s, 1H; C₄-H), 8.00 (d, *J* = 9.3 Hz, 1H; C₈-H), 7.53-7.42 (m, 5H; Ph-), 7.32 (dd, *J* = 9.0, 3.0 Hz, 1H; C₇-H), 7.10 (d, *J* = 2.7 Hz, 1H; C₅-H), 3.94 (s, 3H; -OCH₃), 3.23 (m, 1H; ArCH(CH₃)₂), 1.24 (d, *J* = 6.9 Hz, 6H; ArCH(CH₃)₂); ¹³C NMR (CDCl₃, 75 MHz, ppm) δ 157.9 (C₂ or C₆), 157.7 (C₆ or C₂), 142.3 (C₃), 141.1 (C₉), 140.6 (Ph-), 131.5 (C₄), 130.7 (C₁₀), 128.9(2XC) (Ph-), 128.8 (Ph-), 128.2(2XC) (Ph-), 127.8 (C₈), 121.6 (C₇), 104.5 (C₅), 55.5 (-OCH₃), 29.2 (ArCH(CH₃)₂), 24.1(2XC) (ArCH(CH₃)₂); Anal.Calcd. for C₁₉H₁₉NO: C, 82.28; H, 6.90; N, 5.05; Found: C, 82.13; H, 6.62; N, 4.88.

3-Benzyl-6-methoxy-2-phenylquinoline (3b). Solid (needles); mp 116-118 °C (EtOAc/Hexanes); IR (KBr, cm⁻¹): 1622, 1599, 1489, 1380, 1228, 1028, 832, 699; ¹H NMR (CDCl₃, 300 MHz, ppm) δ 8.02 (d, *J* = 9.3 Hz, 1H; C₈-H), 7.79 (s, 1H; C₄-H), 7.50-7.39 (m, 5H; Ph-), 7.32 (dd, *J* = 9.3, 3.0 Hz, 1H; C₇-H), 7.27-7.18 (m, 3H; C₆H₅CH₂-), 7.02-6.98 (m, 3H; C₅-H and C₆H₅CH₂-), 4.10 (s, 2H; C₆H₅CH₂-), 3.88 (s, 3H; -OCH₃); ¹³C NMR (CDCl₃, 75 MHz, ppm) δ 158.8 (C₂ or C₆), 157.7 (C₆ or C₂), 140.8 (C₃), 140.6 (C₉), 139.0 (Ph-), 136.2 (Ph-), 131.5 (C₄), 130.0 (C₁₀), 129.6(2XC) (Ph-), 129.0(2XC) (Ph-), 128.6(2XC) (Ph-), 128.2(2XC) (Ph-), 127.8 (C₈), 126.4 (Ph-), 125.3 (Ph-), 121.6 (C₇), 104.9 (C₅), 55.5 (ArOCH₃), 43.0 (C₆H₅CH₂-); Anal.calcd. for C₂₃H₁₉NO: C, 84.89; H, 5.89; N, 4.30; Found: C, 84.73; H, 5.65; N, 4.16.

6-Methoxy-3-pentyl-2-phenylquinoline (3c).³⁴ Oil; IR (neat, cm^{-1}): 2927, 2858, 1624, 1598, 1489, 1381, 1225, 1029, 830, 700; ^1H NMR (CDCl_3 , 300 MHz, *ppm*) δ 7.92 (d, $J = 9.6$ Hz, 1H; $\text{C}_8\text{-H}$), 7.82 (s, 1H; $\text{C}_4\text{-H}$), 7.45-7.28 (m, 5H; Ph-), 7.22 (dd, $J = 9.3, 6.6$ Hz, 1H; $\text{C}_7\text{-H}$), 6.96 (d, $J = 3.0$ Hz, 1H; $\text{C}_5\text{-H}$), 3.82 (s, 3H; ArOCH_3), 2.64 (t, $J = 7.8$ Hz, 2H; $\text{ArCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.43 (m, 2H; $\text{ArCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.12 (m, 4H; $\text{ArCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.72 (t, $J = 4.2$ Hz, 3H; $\text{ArCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3 , 75 MHz, *ppm*) δ 158.2 (C_2 or C_6), 157.7 (C_6 or C_2), 142.5 (C_3), 141.1 (C_9), 134.5 (Ph-), 134.2 (C_4), 130.7 (C_{10}), 128.8(2XC) (Ph-), 128.5 (Ph-), 128.1(2XC) (Ph-), 127.8 (C_8), 121.4 (C_7), 104.4 (C_5), 55.4 (ArOCH_3), 32.7, 31.4, 30.2, 22.2, 13.8 ($\text{ArCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$); Anal. calcd. for $\text{C}_{21}\text{H}_{23}\text{NO}$: C, 82.58; H, 7.59; N, 4.59; Found: C, 82.43; H, 7.65; N, 4.56.

3-Ethyl-2-phenyl-6-(trifluoromethyl)quinoline (3d).⁴⁹ Oil; IR (neat, cm^{-1}): 2930, 2860, 1626, 1590, 1453, 1376, 1220, 1020, 830; ^1H NMR (CDCl_3 , 300 MHz, *ppm*) δ : 8.49 (d, $J = 9.0$ Hz, 1H; $\text{C}_8\text{-H}$), 8.28 (s, 1H; $\text{C}_4\text{-H}$), 8.20 (d, $J = 1.8$ Hz, 1H; $\text{C}_5\text{-H}$), 7.88 (dd, $J = 9.0, 1.8$ Hz, 1H; $\text{C}_7\text{-H}$), 7.60 (m, 5H; Ph-), 2.28 (q, $J = 7.2$ Hz, 2H; ArCH_2CH_3), 1.27 (t, $J = 7.2$ Hz, 3H; ArCH_2CH_3); ^{13}C NMR (CDCl_3 , 75 MHz, *ppm*) δ : 160.6 (C_2), 148.2 (C_9), 139.0 (C_4), 138.0 (C_3), 137.2 (Ph-), 129.8 (C_6), 129.6(2XC) (Ph-), 127.9 (Ph-), 127.6(2XC) (Ph-), 127.0 (C_8), 126.4 (C_7), 126.0 (C_5), 125.0 (C_{10}), 120.8 (CF_3), 24.9 (ArCH_2CH_3), 16.8 (ArCH_2CH_3). Anal. calcd for $\text{C}_{18}\text{H}_{14}\text{F}_3\text{N}$: C, 71.75; H, 4.68; N, 4.65. Found: C, 71.68; H, 4.82; N, 4.40.

3-Methyl-2-phenylquinoline (3e)²⁹ Pale yellow oil; IR (neat, cm^{-1}): 2912, 2844, 1626, 1592, 1452, 1366, 1224, 1020, 832; ^1H NMR (CDCl_3 , 300 MHz, *ppm*) δ : 8.16 (d, $J = 8.5$ Hz, 1H; $\text{C}_8\text{-H}$), 7.93 (s, 1H; $\text{C}_4\text{-H}$), 7.71 (d, $J = 8.4$ Hz, 1H; $\text{C}_5\text{-H}$), 7.60 (m, 1H; $\text{C}_7\text{-H}$), 7.56 (m, 2H; Ph-), 7.41 (m, 4H; $\text{C}_6\text{-H}$ and Ph-), 2.41 (s, 3H; Ar-CH_3); ^{13}C NMR (CDCl_3 , 75 MHz, *ppm*) δ : 160.4 (C_2), 147.1 (C_9), 140.2 (Ph-), 136.6 (C_4), 129.3 (C_3), 129.0(2XC) (Ph-), 128.7 (C_7), 128.3 (C_8), 128.1 (C_5), 127.9 (Ph-), 127.4(2XC) (Ph-), 126.5 (C_6), 126.1 (C_{10}), 20.2 (Ar-CH_3); Anal. calcd for $\text{C}_{16}\text{H}_{13}\text{N}$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.60; H, 5.72; N, 6.42.

3-Hexyl-2-phenylquinoline (3f). Oil; IR (neat, cm^{-1}): 2924, 2850, 1619, 1590, 1486, 1455, 1422, 778, 700; ^1H NMR (CDCl_3 , 300 MHz, *ppm*) δ : 8.17 (d, $J = 8.4$ Hz, 1H; $\text{C}_8\text{-H}$), 8.00 (s, 1H; $\text{C}_4\text{-H}$), 7.83 (d, $J = 8.0$ Hz, 1H; $\text{C}_5\text{-H}$), 7.66 (m, 1H; $\text{C}_7\text{-H}$), 7.45-7.58 (m, 6H; $\text{C}_6\text{-H}$ and $\text{C}_6\text{H}_5\text{-}$), 2.74 (t, $J = 8.1$ Hz, 2H; $\text{Ar-CH}_2\text{CH}_2(\text{CH}_2)_3\text{CH}_3$), 1.50-1.57 (m, 2H; $\text{Ar-CH}_2\text{CH}_2(\text{CH}_2)_3\text{CH}_3$), 1.16-1.27 (m, 6H; $\text{Ar-CH}_2\text{CH}_2(\text{CH}_2)_3\text{CH}_3$), 0.90 (t, $J = 7.2$ Hz, 3H; $\text{Ar-(CH}_2)_5\text{CH}_3$); ^{13}C NMR (CDCl_3 , 75 MHz, *ppm*) δ : 160.7 (C_2), 146.4 (C_9), 140.4 (Ph-), 135.6 (C_4), 133.8 (C_3), 129.0 (C_7), 128.7(2XC) (Ph-), 128.5 (C_8), 128.3 (C_5), 128.0 (Ph-), 127.4(2XC) (Ph-), 126.5 (C_6), 126.2 (C_{10}), 32.6 ($\text{Ar-CH}_2\text{CH}_2(\text{CH}_2)_3\text{CH}_3$), 31.4, 30.0, 29.4, 22.2, 14.0 ($\text{Ar-(CH}_2)_5\text{CH}_3$); Anal. calcd for $\text{C}_{21}\text{H}_{23}\text{N}$: C, 87.15; H, 8.01; N, 4.84. Found: C, 87.00; H, 7.88; N, 4.61.

6-Bromo-2-(3,4-dimethylphenyl)-3-octylquinoline (3g). White solid, mp 102-103 °C (Et_2O -hexanes); IR (KBr, cm^{-1}): 2954, 2918, 2858, 1680, 1590, 1464, 1454; ^1H NMR (CDCl_3 , 300 MHz, *ppm*) δ : 8.02 (d, $J = 8.4$ Hz, 1H; $\text{C}_8\text{-H}$), 7.92 (d, $J = 1.8$ Hz, 1H; $\text{C}_5\text{-H}$), 7.88 (s, 1H; $\text{C}_4\text{-H}$), 7.72 (dd, $J = 8.1, 1.8$ Hz, 1H; $\text{C}_7\text{-H}$), 7.27 (s, 1H; 2- $\text{C}_2\text{-H}$), 7.24 (m, 2H; 2- $\text{C}_5\text{-H}$ and 2- $\text{C}_6\text{-H}$), 2.78 (t, $J = 8.1$ Hz, 2H; $-\text{CH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$), 2.33 (s, 6H; 2X CH_3), 1.50-1.57 (m, 2H; $-\text{CH}_2\text{CH}_2(\text{CH}_2)_5\text{CH}_3$), 1.19-1.26 (m, 10H; $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.87 (t, $J = 6.9$

Hz, 3H; $-(\text{CH}_2)_7\text{CH}_3$); ^{13}C NMR (CDCl_3 , 75 MHz, ppm) δ : 161.2 (C_2), 145.0 (C_9), 138.0 (C_4), 136.8 (2- C_3), 136.4 (2- C_4), 135.1 (2- C_1), 134.4 (C_7), 131.6 (C_8), 131.0 (2- C_2), 129.6 (C_5), 129.2 (C_3), 128.9 (2- C_5), 128.4 (2- C_6), 126.0 (C_{10}), 119.8 (C_6), 32.6, 31.8, 30.4, 29.6, 29.1, 29.0, 22.5, 19.6, 19.1, 14.0 ($-\text{CH}_2\text{CH}_3$); Anal. Calcd for $\text{C}_{25}\text{H}_{30}\text{NBr}$: C, 70.75; H, 7.12; N, 3.30. Found: C, 70.59; H, 7.00; N, 3.06.

3-Ethyl-6-methoxy-2-phenylquinoline (3h). White solid, mp 70-72 °C (Et_2O -hexanes); IR (KBr, cm^{-1}): 2920, 2842, 1677, 1588, 1450; ^1H NMR (CDCl_3 , 300 MHz, ppm) δ : 8.00 (d, $J = 9.3$ Hz, 1H; $\text{C}_8\text{-H}$), 7.83 (s, 1H; $\text{C}_4\text{-H}$), 7.47-7.29 (m, 5H; $\text{C}_6\text{H}_5\text{-}$ or $\text{C}_7\text{-H}$), 7.22 (m, 1H; $\text{C}_6\text{H}_5\text{-}$ or $\text{C}_7\text{-H}$), 7.04 (m, 1H; $\text{C}_5\text{-H}$), 3.80 (s, 3H; $-\text{OCH}_3$), 2.61 (m, 2H; $-\text{CH}_2\text{CH}_3$), 1.24 (t, $J = 6.9$ Hz, 3H; $-\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3 , 75 MHz, ppm) δ : 160.2 (C_2), 157.0 (C_6), 142.0 (C_9), 140.0 (Ph-), 134.4 (C_4), 134.1 (C_8), 131.0 (C_3), 128.9(2XC) (Ph-), 128.4 (Ph-), 179.0(2XC) (Ph-), 126.9 (C_{10}), 119.8 (C_7), 105.0 (C_5), 55.4 ($-\text{OCH}_3$), 32.6 ($-\text{CH}_2\text{CH}_3$), 14.0 ($-\text{CH}_2\text{CH}_3$); Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{NO}$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.12; H, 6.48; N, 5.43.

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