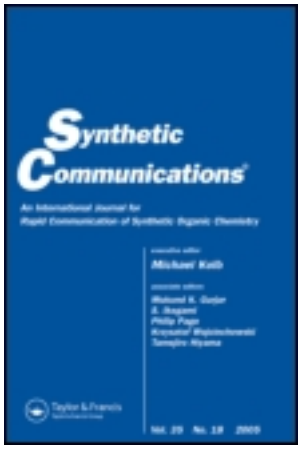

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Silica-Gel-Catalyzed Efficient Synthesis of Quinoxaline Derivatives Under Solvent-Free Conditions

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SILICA-GEL–CATALYZED EFFICIENT SYNTHESIS OF QUINOXALINE DERIVATIVES UNDER SOLVENT-FREE CONDITIONS

Ganesh Chandra Nandi, Subhasis Samai, Ram Kumar, and M. S. Singh

Faculty of Science, Department of Chemistry, Banaras Hindu University, Varanasi, India

Quinoxaline derivatives have been prepared in good to excellent yields using silica gel as catalyst from various 1,2-diketones and 1,2-diamines under solvent-free conditions for the first time. The advantages of this method are short reaction time, reaction simplicity, convenient workup procedure, and purification of compounds by a nonchromatographic method.

Keywords: 1,2-Diamines; 1,2-diketones; quinoxaline; silica gel

The quinoxaline and its derivatives constitute a very important, privileged class of nitrogen-containing heterocyclic compounds that shows various biological activities such as antiviral,[1] anti-inflammatory, antiprotozoal,[2] antihelmintic,[3] anticancer,[4] antimalarial,[5] and antidepressant[6] activities. Quinoxaline derivatives are present in different antibiotics such as echinomycin, levomycin, and actinoleutin,[7] which inhibit the growth of Gram-positive bacteria. Beside its biological activities, it is used in the synthesis of organic semiconductors,[8] dyes,[8c] and electroluminescent materials.[9] Over the years, numerous synthetic strategies have been developed for the preparation of quinoxaline derivatives. Among them, the most common methods are the condensation of the 1,2-diketones and 1,2-aryldiamines at refluxing temperature in ethanol, benzene, or in acetic acid.[10] Different catalysts have also been used for the synthesis of quinoxaline moieties such as iodine,[11] polyaniline sulfate salt,[12] montmorillonite K-10,[13] $InCl_3$,[14] $MnCl_2$,[15] $CuSO_4 \cdot 5H_2O$,[16] Zn/L-proline,[17] ceric ammonium nitrate (CAN),[18] iodoxybenzoic acid (IBX),[19] $Ga(OTf)_3$, and NH_4X.[20] Beside these condensation methods, oxidative coupling of epoxides and ene-1,2-diamines catalyzed by Bi(0),[21] heteroannulation of nitroketene N,S-aryliminoacetals with $POCl_3$,[22] from α-hydroxy ketones via a tandem oxidation process using $Pd(OAc)_2$ or $RuCl_2$-$(PPh_3)_3$-TEMPO,[23] as well as MnO_2[24] have been reported. Moreover, quinoxaline derivatives have also been prepared without any catalyst under microwave heating.[25]

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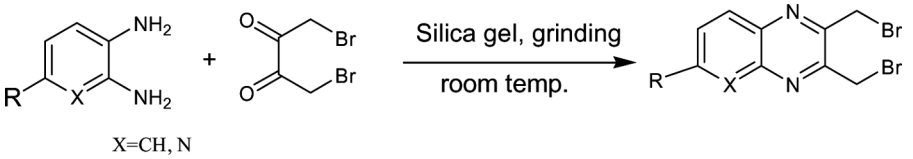
Most of these methods suffer from one or more drawbacks such as high temperature, poor yield, long reaction time, use of hazardous solvent, critical product isolation procedure, and use of expensive catalysts, so a generalized method still remains an ongoing challenge. In recent days, solvent-free syntheses have attracted the attention of chemists because they are environmentally benign processes. As part of our continued interest[26] in the development of solvent-free synthesis, herein we report a new synthetic strategy for the preparation of quinoxaline derivatives catalyzed by silica gel under solvent-free conditions. Silica gel has been effectively used in organic synthesis not only as a simple medium but also as a mild acid catalyst or as an accelerator. It is easily separable from the product because of its insolubility in organic solvents. Previously, silica gel has been used in many reactions such as selective allylation of aldehyde with tetrabutyltin,[27] selective C-S bond formation, and synthesis of benzochromene.[28] Silica-gel-supported catalysts such as $SiO_2/FeCl_3$, SiO_2/BF_3, $SiO_2/NaHSO_4$, and SiO_2/H_2SO_4[29] have also been widely used in various kinds of organic transformations. It is inexpensive, ecofriendly, and easily available and can be easily separated out from the product.

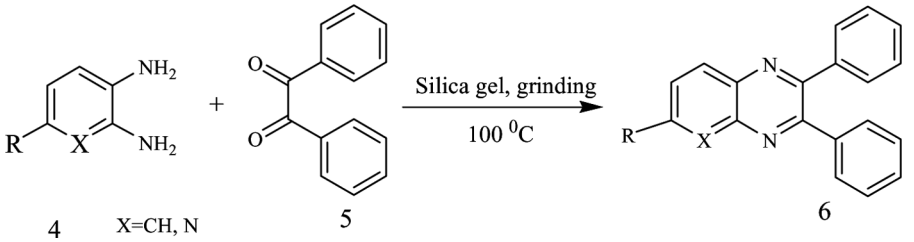
RESULTS AND DISCUSSION

The new synthetic routes to quinoxaline derivatives are outlined in Schemes 1 and 2. The reactions of 1,2-diketones and 1,2-diamines were carried out in the presence of silica gel via a grinding process. The reaction proceeds at room temperature (Scheme 1) or under heating (Scheme 2), depending upon the nature of the 1,2-diketones. To realize the generality and versatility of the reaction condition, different substituted 1,2-diamines and aliphatic as well as aromatic 1,2-diketones were taken. For optimization of the reaction condition, silica gel was taken in different ratios, and it was observed that for 1 mmol of the reactant 1.0 g silica gel provides the maximum yield in the shortest time. Use of less than 1.0 g silica gel for 1 mmol of the reactant requires a longer time to complete for both the methods. As shown in Table 1, when 1,4-dibromo-2,3-butanedione is treated with various 1,2-diamines, all reactions proceeded efficiently at room temperature and the desired quinoxalines were obtained in excellent yields within short reaction times. However, the corresponding quinoxaline unit of 2,3-diaminopyridine (Table 1, entry 3f) is obtained in less yield (30%).

When benzil was used as 1,2-diketone (Scheme 2), the progress of the reaction was slow. Even after 1 h of grinding, the reaction was not complete and only 30% conversion to product was achieved. Then the reaction mixture was heated at 100°C for the stipulated time to get the quinoxaline derivatives in good yields. The results obtained are given in detail in Table 2. Whether the substituent is



Scheme 1. Synthesis of quinoxalines from 1,4-dibromo-2,3-diketone with 1,2-diamines.



Scheme 2. Synthesis of quinoxalines from benzil with 1,2-diamines.

electron-withdrawing or electron-donating in the 1,2-diamine does not affect the yield, which is an advantage of the reaction.

In conclusion, we have developed a facile and efficient method for the synthesis of quinoxalines by the reaction of 1,2-diketones and 1,2-diamino compounds in the presence of silica gel under solvent-free conditions. The method is equally

Table 1. Reaction of 1,4-dibromo-2,3-diketone with 1,2-diamines

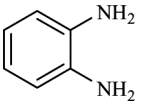
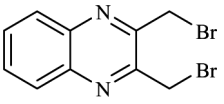
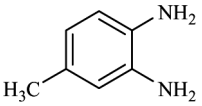
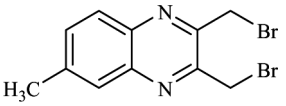
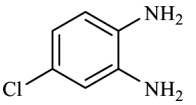
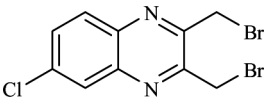
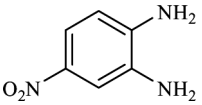
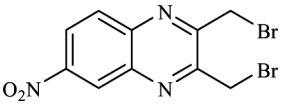
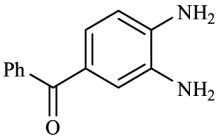
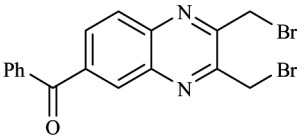
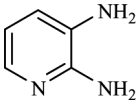
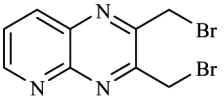
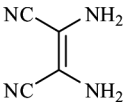
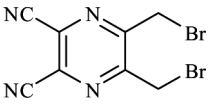
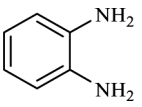
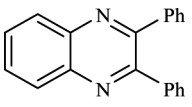
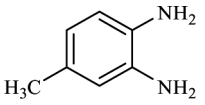
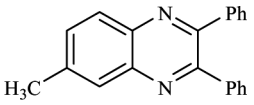
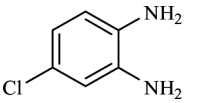
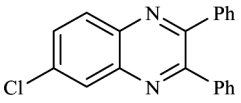
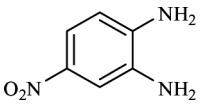
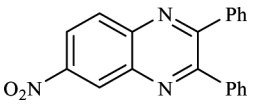
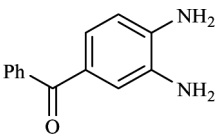
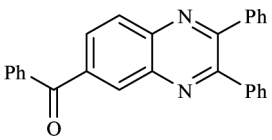
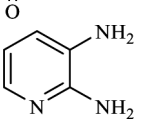
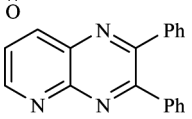
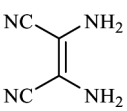
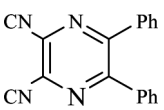
Entry	1,2-Diamine	Product	Time (min)	Yield (%)
3a			20	85
3b			17	87
3c			20	80
3d			20	83
3e			20	84
3f			20	30
3g			25	83

Table 2. Reaction of benzil with 1,2-diamines

Entry	1,2-Diamine	Product	Time (min)	Yield (%)
6a			45	94
6b			60	96
6c			45	88
6d			65	97
6e			70	97
6f			45	83
6g			75	80

efficient for aromatic, aliphatic, and heterocyclic diamines and also for both aromatic and aliphatic diketonic compounds. Both the electron-withdrawing and electron-donating substituent in the 1,2-diamine shows equal ease in this transformation. The advantages of this new strategy are short reaction time, excellent yield, low cost, reaction simplicity, and purification of compounds by nonchromatographic methods. Finally, it is in agreement with the green chemistry protocols.

EXPERIMENTAL

General

All reagents were purchased from Merck, Aldrich, CDH, and Fluka and used without further purification. The silica gel G used as catalyst for thin-layer chromatography (TLC) was obtained from Merck. NMR spectra were recorded on a Jeol AL 300 Fourier transform (FT) NMR spectrometer. The infrared (IR) spectra were recorded on a Varian 3100 FT-IR spectrophotometer. CHN analyses

were performed on an Exeter Analytical model CE-400 CHN analyzer. All the reactions were monitored by TLC using precoated sheets of silica gel G/UV-254 0.25 mm thick (Merck 60 F_{254}). Melting points were determined with a Buchi B-540 melting-point apparatus and are uncorrected.

General Procedure for Preparation of Quinoxaline Derivatives (3a–g)

A mixture of 1,2-dicarbonyl (1 mmol), 1,2-diamine (1 mmol), and 1.0 g of silica gel were taken in a mortar and ground with a pestle thoroughly at room temperature for 15 min. After the completion of the reaction, $CHCl_3$ was added to dissolve the product. Silica gel was filtered off, and the solvent was evaporated under vacuum to give the crude products, which were crystallized from ethanol. The products have been characterized by spectral and elemental analysis.

Physical and Spectral Data of the Products

2,3-Bis-bromomethyl-quinoxaline (3a). Mp 153 °C. IR (KBr) ν_{max} (cm^{-1}): 3053, 2924, 1610, 1125. ^1H NMR (300 MHz, $CDCl_3$): δ 8.08 (dd, $J = 3.6$ Hz, 6.3 Hz, 2H), 7.81 (dd, $J = 3.6$ Hz, 6.3 Hz, 2H), 4.92 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.7, 141.4, 130.8, 128.9, 30.4. Anal. calcd. for $C_{10}H_8Br_2N_2$: C, 38.01; H, 2.55, N, 8.87. Found: C, 38.10; H, 2.65; N, 8.92.

2,3-Bis(bromomethyl)-6-methylquinoxaline (3b). Mp 126–127 °C. IR (KBr) ν_{max} (cm^{-1}): 3055, 2925, 1612, 1341, 1120, 698. ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, $J = 8.7$ Hz, 1H), 7.83 (s, 1H), 7.63 (d, $J = 8.7$ Hz, 1H), 4.90 (s, 4H), 2.59 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.5, 149.6, 141.6, 141.5, 139.9, 133.1, 128.4, 127.7, 30.6, 30.5, 21.8. Anal. calcd. for $C_{11}H_{10}Br_2N_2$: C, 40.03; H, 3.05; N, 8.49. Found: C, 39.85; H, 2.91; N, 8.15.

2,3-Bis-bromomethyl-6-chloro-quinoxaline (3c). Mp 150–151 °C. IR (KBr) ν_{max} (cm^{-1}): 3051, 2924, 1590. ^1H NMR (300 MHz, $CDCl_3$): δ 8.07 (s, 1H), 8.01 (d, $J = 8.7$ Hz, 1H), 7.75 (d, $J = 8.7$ Hz, 1H), 4.89 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.8, 150.9, 141.7, 139.9, 136.8, 131.8, 130.1, 127.9, 30.1, 30.0. Anal. calcd. for $C_{10}H_7Br_2ClN_2$: C, 34.27, H, 2.01, N, 7.99. Found: C, 34.30; H, 2.12; N, 8.09.

2,3-Bis-bromomethyl-6-nitro-quinoxaline (3d). Mp 116–117 °C. IR (KBr) ν_{max} (cm^{-1}): 3056, 1603, 1180. ^1H NMR (300 MHz, $CDCl_3$): δ 8.97 (s, 1H), 8.57 (d, $J = 9.0$ Hz, 1H), 8.24 (d, $J = 9.3$ Hz, 1H), 4.94 (s, 2H), 4.93 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0, 153.3, 148.3, 143.7, 140.3, 130.7, 125.2, 124.1, 29.6, 29.5. Anal. calcd. for $C_{10}H_7Br_2N_3O_2$: C, 33.27; H, 1.95; N, 11.64. Found: 33.20; H, 1.92; N, 11.65.

(2,3-Bis-bromomethyl-quinoxalin-6-yl)-phenyl-methanone (3e). Mp 120–121 °C. IR (KBr) ν_{max} (cm^{-1}): 3052, 1654, 1600, 1438. ^1H NMR (300 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.25–8.17 (m, 2H), 7.88 (d, $J = 7.2$ Hz, 2H), 7.68–7.51 (m, 3H), 4.94 (s, 2H), 4.92 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.3, 152.6, 152.0, 143.1, 140.6, 139.2, 136.8, 133.0, 131.8, 130.7, 130.0, 129.5, 128.5, 30.0. Anal. calcd. for $C_{17}H_{12}Br_2N_2O$: C, 48.60; H, 2.88; N, 6.67. Found: C, 48.62; H, 2.98; N, 6.53.

2,3-Bis-bromomethyl-pyrido[2,3-b]pyrazine (3f). Mp 106–107 °C. IR (KBr) ν_{max} (cm^{-1}): 3052, 1592, 1542. ^1H NMR (300 MHz, $CDCl_3$): δ 9.18 (d, $J = 8.1$ Hz, 1H), 8.49 (d, $J = 8.1$ Hz, 1H), 7.81 (dd, $J = 3.3$ Hz, 7.5 Hz, 1H), 4.97 (s, 2H), 4.95 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.1, 152.0, 149.8, 141.2, 141.0, 135.2, 123.5, 31.0, 30.9. Anal. calcd. for $C_9H_7Br_2N_3$: C, 34.10; H, 2.23; N, 13.26. Found: C, 34.08; H, 2.15; N, 13.22.

5,6-Bis-bromomethyl-pyrazine-2,3-dicarbonitrile (3g). Mp 107 °C. IR (KBr): ν_{max} (cm^{-1}): 2240, 1742, 1383. ^1H NMR (300 MHz, $CDCl_3$): δ 4.74 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 131.8, 112.2, 30.9. Anal. calcd. for $C_8H_4Br_2N_4$: C, 30.41; H, 1.28; N, 17.73. Found: C, 30.45; H, 1.39; N, 17.92.

General Procedure for Preparation of Quinoxaline Derivatives (6a–g)

A mixture of 1,2-dicarbonyl (1 mmol), 1,2-diamine (1 mmol), and 1.0 g of silica gel were taken in a mortar and ground with a pestle thoroughly at room temperature for 1 h. Then the reaction mixture was heated at 100 °C for 1 h. $CHCl_3$ was added to dissolve the product, silica gel was filtered off, and the solvent was evaporated under vacuum to obtain the crude products, which were crystallized from ethanol. The products have been characterized by spectral and elemental analyses.

Physical and Spectral Data of the Products

2,3-Diphenyl-quinoxaline (6a). Mp 130–131 °C. IR (KBr) ν_{max} (cm^{-1}): 3055, 2925, 1546, 1344, 767. ^1H NMR (300 MHz, $CDCl_3$): δ 8.20 (dd, $J = 3.6$ Hz, 6.3 Hz, 2H), 7.79 (dd, $J = 3.6$ Hz, 6.3 Hz, 2H), 7.53–7.50 (m, 4H), 7.35–7.33 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4, 141.1, 139.0, 129.9, 129.8, 129.1, 128.7, 128.2. Anal. calcd. for $C_{20}H_{14}N_2$: C, 85.08; H, 5.00; N, 9.92. Found: C, 84.95; H, 4.82; N, 9.75.

6-Methyl-2,3-diphenyl-quinoxaline (6b). Mp 115–116 °C. IR (KBr) ν_{max} (cm^{-1}): 3051, 2921, 1690, 1621, 1503. ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, $J = 8.4$ Hz, 1H), 7.84 (s, 1H), 7.68 (dd, $J = 3.6$ Hz, 6.3 Hz, 1H), 7.53–7.50 (m, 4H), 7.34–7.26 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.8, 153.0, 143.1, 138.9, 138.5, 138.0, 134.4, 130.9, 130.4, 129.9, 129.7, 129.0, 128.1, 126.2, 126.0, 21.9. Anal. calcd. for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45. Found: C, 85.19; H, 5.34; N, 9.72.

6-Chloro-2,3-diphenyl-quinoxaline (6c). Mp 122–123 °C. IR (KBr) ν_{max} (cm^{-1}): 3053, 2915, 1599, 1546. ^1H NMR (300 MHz, $CDCl_3$): δ 8.17 (s, 1H), 8.11 (d, $J = 8.7$ Hz, 1H), 7.72 (dd, $J = 2.1$ Hz, 9 Hz, 1H), 7.51–7.49 (m, 4H), 7.35–7.32 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.1, 153.5, 141.3, 139.6, 138.6, 138.5, 135.5, 130.8, 130.3, 129.8, 129.7, 129.0, 128.9, 128.2, 127.9. Anal. calcd. for $C_{20}H_{13}ClN_2$: C, 75.83; H, 4.14; N, 8.84. Found: C, 75.95; H, 4.21; N, 8.85.

6-Nitro-2,3-diphenylquinoxaline (6d). Mp 193–195 °C. IR (KBr) ν_{max} (cm^{-1}): 3031, 2921, 1617, 1497, 1358, 1100, 692, 662. ^1H NMR (300 MHz, $CDCl_3$): δ 9.07 (s, 1H), 8.54 (dd, $J = 2.1$ Hz, 9.0 Hz, 1H), 8.30 (d, $J = 9.0$ Hz, 1H), 7.57–7.54 (m, 4H), 7.42–7.34 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 155.6, 147.8, 143.5, 139.9, 138.0, 137.9, 130.7, 129.8, 129.7, 129.7, 129.5, 128.4, 125.5, 123.2.

Anal. calcd. for $C_{20}H_{13}N_3O_2$: C, 73.38; H, 4.00; N, 12.84. Found: C, 73.45; H, 4.07; N, 12.87.

(2,3-Diphenyl-quinoxalin-6-yl)-phenylmethanone (6e). Mp 147–148 °C. IR (KBr) ν_{max} (cm^{-1}): 3053, 1660, 1600, 1438. ^1H NMR (300 MHz, $CDCl_3$): δ 8.58 (s, 1H), 8.34–8.26 (m, 2H), 8.00 (d, $J = 5.7$ Hz, 2H), 7.70–7.30 (m, 13 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.7, 155.0, 154.5, 142.9, 140.1, 138.6, 138.5, 138.2, 137.1, 132.7, 130.0, 129.8, 129.7, 129.6, 129.2, 129.1, 128.4, 128.3. Anal. calcd for $C_{27}H_{18}N_2O$: C, 83.92; H, 4.69; N, 7.25. Found: C, 84.03; H, 4.81; N, 7.23.

2,3-Diphenyl-pyrido[2,3-b]pyrazine (6f). Mp 144–145 °C. IR (KBr) ν_{max} (cm^{-1}): 3056, 1591, 1545, 1433. ^1H NMR (300 MHz, $CDCl_3$): δ 9.17 (d, $J = 4.2$ Hz, 1H), 8.53 (dd, $J = 1.8$ Hz, 8.4 Hz, 1H), 7.73–7.54 (m, 5H), 7.40–7.30 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 154.6, 154.0, 149.7, 138.4, 138.0, 137.9, 136.0, 130.1, 129.7, 129.3, 129.2, 128.3, 128.0, 125.1. Anal. calcd for $C_{19}H_{13}N_3$: C, 80.54; H, 4.62; N, 14.83. Found: C, 80.59; H, 4.79; N, 14.95.

5,6-Diphenyl-pyrazine-2,3-dicarbonitrile (6g). Mp 209–210 °C. IR (KBr) ν_{max} (cm^{-1}): 3063, 2230, 1675, 1595. ^1H NMR (300 MHz, $CDCl_3$): δ 7.54–7.33 (m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5, 135.1, 131.1, 129.7, 128.8, 128.4, 113.1. Anal. calcd. for $C_{18}H_{10}N_4$: C, 76.58; H, 3.57; N, 19.85. Found: C, 76.69; H, 3.68; N, 19.93.

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