J IRAN CHEM SOC (2012) 9:535–543
DOI 10.1007/s13738-011-0066-z

ORIGINAL PAPER

Synthesis of camphorquinoxaline and quinoxaline derivatives over metal oxides as catalyst

Mona Hosseini-Sarvari

Received: 4 June 2011 / Accepted: 2 November 2011 / Published online: 13 January 2012

Abstract Under solvent-free conditions, the synthesis of camphorquinoxaline and quinoxaline derivatives catalyzed by various solid metal oxides (ZnO, TiO_2, ZrO_2, MgO, acidic and basic Al_2O_3, and CaO) and salts (K_2CO_3, $CaCO_3$) is described. In the cases of ZnO, TiO_2, and ZrO_2, the catalysts can be recovered and reused several times without losing activity.

Keywords Camphorquinoxaline · Camphorquinone · Metal oxide · Quinoxaline · Solvent-free

Introduction

Camphorquinone (CQ) is used as a simple precursor for preparing certain stereoisomer derivatives such as oximes, diols, keto-and aminoalcohols, and is used as a ligand in asymmetric catalysts [1, 2]. The combination of CQ and amine is very valuable for preparing *N*-containing camphor derivatives. 1,2-Diamines, which are widely used in medicinal chemistry to synthesize heterocyclic systems and as chelating agent [3], can immediately introduce nitrogen via a nucleophilic addition reaction to CQ without forming any intermediate. Moreover, the combination of CQ and amines has been used widely as a photoinitiator/co-initiator system and their optically active derivatives are important for asymmetric synthesis [4–8].

Quinoxaline and its derivatives, which have broad biological activities, are used as antibiotic, antiviral, anticancer, and kinase inhibition and antibacterial agents [9–13]. Several studies on the synthesis and investigation of the biological activity of quinoxaline derivatives have been published [14–28]. Nevertheless, a few reported methods exist for the synthesis of camphorquinoxaline [29].

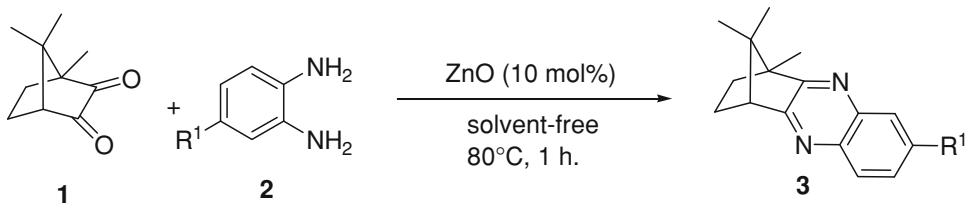
In recent years, metal oxides play an important role in organic synthesis [30–37]. The catalysis by metal oxides has been extensively studied by many researchers because of the catalytic efficiency and multifunctional activities of these metal oxides in several industrial processes [38–42]. Recently, our research group has reported many organic synthetic reactions on the metal oxide active surface [30–35]. Most of these reported reactions proceed rapidly, under mild conditions, with high chemo-, and regioselectivity, and simple work-up compared to similar reaction procedures. These observations prompted me to examine the catalytic efficiency of them for the synthesis of a new series of camphorquinolxalines **3** under solvent-free conditions (Scheme 1).

Experimental

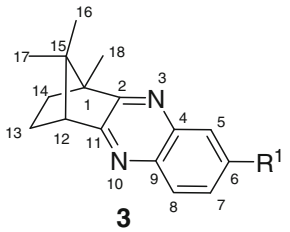
^{1}H NMR and ^{13}C NMR spectra were measured on Bruker Advance DPX FT 250 and 62.9 MHz spectrometry with TMS as an internal standard. IR spectra were obtained on a Perkin–Elmer or FTIR-800 instruments. Mass spectra were obtained on a Shimadzu GCMS0QP 1000EX at 20 and/or 70 eV. Elemental analyses were performed on Thermo Finnigan, Flash EA 1112 series microanalyzer by the head of the CHN lab.

M. Hosseini-Sarvari (✉)
Department of Chemistry, Shiraz University,
Shiraz 71545, Islamic Republic of Iran
e-mail: hossaini@shirazu.ac.ir

Scheme 1 Synthesis of camphorquinoxaline **3** using metal oxides as catalyst



General procedure for synthesis camphorquinoxalines **3**



(±) CQ **1** (1 mmol), and diamine (1 mmol) were added to ZnO (10 mol%, 0.008 g) and the mixture was heated in an oil bath at 80 °C for 1 h. Then EtOAc (2 × 20 mL) was added to the reaction mixture and separate the catalyst by centrifuge. Recrystallization from hexane afforded camphorquinoxalines **3**. The structure of the products was confirmed by NMR, IR, and mass spectra.

*1,15,15-Trimethyl-3,10-diazatetracyclo [10.2.1.0^{2,11}.0^{4,9}] pentadeca-2,4(9),5,7,10-pentaene (**3a**)*

Yellow solid; yield 98%; mp 68–70 (69–70 °C) [29]; (KBr) 2,968, 2,854, 1,650, 1,481 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.50 (3H, s, Me), 0.98 (3H, s, Me), 1.24–1.33 (5H, m, Me and H-13$_{endo}$, H-14$_{exo}$), 1.89–2.01 (1H, m, H-14$_{endo}$), 2.13–2.23 (1H, m, H-13$_{exo}$), 2.94 (1H, d, $J = 5.6$ MHz, H-12), 7.50–7.54 (2H, m, H-5,8), 7.86–7.94 (2H, m, H-6,7); δ_C (62.9 MHz, $CDCl_3$) 165.3(C-2), 163.6 (C-11), 141.4 (C-9), 141.2 (C-4), 128.7 (C-5), 128.5 (C-8), 128.0 (C-7), 127.9 (C-6), 54.0 (C-12), 53.6 (C-15), 53.1 (C-1), 31.7 (C-14), 24.5 (C-13), 20.2 (C-16), 18.4 (C-17), 9.9 (C-18). Anal. Calcd. for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; Found: C, 80.54; H, 7.53; *m/z* 238 [MH+]; HRMS (ESI) calcd for $C_{16}H_{18}N_2$ (MH+) 238.147, found 238.141.

*1,7,15,15-Tetramethyl-3,10-diazatetracyclo [10.2.1.0^{2,11}.0^{4,9}] pentadeca-2,4(9),5,7,10-pentaene (**3b**)*

Yellow solid; yield 98%; mp 72–74 °C; (KBr) 2,953, 2,847, 1,652, 1,465 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.88 (3H, s, Me), 0.96 (3H, s, Me), 1.09 (3H, s, Me), 1.58–1.66 (2H, m, H-13$_{endo}$, H-14$_{exo}$), 1.83 (1H, m, H-14$_{endo}$), 2.03–2.05 (1H, m, H-13exo), 2.15 (3H, s, Me), 2.88 (1H, d, $J = 4.65$ MHz, H-12), 6.09 (1H, d, $J = 9.50$ MHz, H-7), 6.30 (1H, s, H-5), 6.82 (1H, d, $J = 7.75$ MHz, H-8); δ_C (62.9 MHz, $CDCl_3$) 171.2(C-2), 160.2 (C-11), 148.5 (C-9), 145.0 (C-4), 130.6 (C-6), 119.5 (C-7), 110.3 (C-8), 107.3 (C-5), 58.0 (C-12), 50.1 (C-15), 44.5 (C-1), 30.1 (C-14), 24.3 (C-13), 20.8 (C-16), 17.5 (C-PhMe), 16.9 (C-17), 9.0 (C-18); Anal. Calcd for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; Found: C, 80.80; H, 7.87; *m/z* 252 [MH+]; HRMS (ESI) calcd for $C_{17}H_{20}N_2$ (MH+) 252.1626, found 252.1617.

*Phenyl[1,15,15-trimethyl-3,10-diazatetracyclo [10.2.1.0^{2,11}.0^{4,9}] pentadeca-2,4(9),5,7,10-pentaene-6-yl] methanone (**3c**)*

Yellow solid; yield 95%; mp 104–106 °C; (KBr) 2,962, 2,849, 1,663, 1,461 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.38 (3H, s, Me), 0.87 (3H, s, Me), 1.12–1.23 (5H, m, Me and H-13$_{endo}$, H-14$_{exo}$), 1.77–1.87 (1H, m, H-14$_{endo}$), 2.03–2.11 (1H, m, H-13$_{exo}$), 2.81–2.86 (1H, m, H-12), 7.21–7.38 (3H, m, COPh-H), 7.60 (2H, d, $J = 8.1$ Hz, COPh-H), 7.85–7.91 (2H, m, H-5,7), 8.14 (1H, d, $J = 10.4$ Hz, H-8); δ_C (62.9 MHz, $CDCl_3$) 195.9 (C–CO), 165.7(C-2), 164.8 (C-11), 143.6 (C-9), 140.5 (C-4), 137.4 (C-1′), 136.7 (C-6), 132.5 (C-2′,6′), 131.9 (C-5′), 131.7 (C-7), 130.0 (C-4′,6′), 128.9 (C-8), 128.3 (C-5), 54.2 (C-12), 53.8 (C-15), 53.1 (C-1), 31.6 (C-14), 24.4 (C-13), 20.3 (C-16), 18.4 (C-17), 9.9 (C-18); Anal. Calcd for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48; Found: C, 80.51; H, 6.32; *m/z* 342 [MH+]; HRMS (ESI) calcd for $C_{23}H_{220}N_2O$ (MH+) 342.1732, found 342.1724.

*1,15,15-Trimethyl-7-nitro-3,10-diazatetracyclo [10.2.1.0^{2,11}.0^{4,9}] pentadeca-2,4(9),5,7,10-pentaene (**3d**)*

Yellow solid; yield 95%; mp 154–156 °C; (KBr) 2,954, 2,850, 1,653, 1,464, 1,567, 1,385 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.86 (3H, s, Me), 0.99 (3H, s, Me), 1.03 (3H, s, Me), 1.37–1.57 (2H, m, H-13$_{endo}$, H-14$_{exo}$), 1.81–1.90 (1H, m, H-14$_{endo}$), 2.07–2.11 (1H, m, H-13$_{exo}$), 2.56 (1H, d, $J = 5.12$, H-12), 8.05 (1H, m, H-7), 8.34 (1H, m, H-8), 8.85 (1H, m, H-5); δ_C (62.9 MHz, $CDCl_3$) 167.3(C-2), 165.6 (C-11), 148.2 (C-6), 147.2 (C-9), 145.3 (C-4), 130.6 (C-8), 128.6 (C-5), 121.9 (C-7), 54.0 (C-12), 53.5 (C-15), 53.2 (C-1), 31.8 (C-14), 24.3 (C-13), 20.5 (C-16), 18.7 (C-17), 9.8 (C-18); Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; Found: C, 67.71; H, 5.91; *m/z* 283 [MH+]; HRMS (ESI) calcd for $C_{16}H_{17}N_3O_2$ (MH+) 283.1321, found 283.1313.

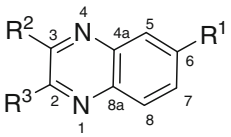
*1,15,15-Trimethyl-3,5,10-triazatetracyclo [10.2.1.0^{2,11}.0^{4,9}] pentadeca-2,4(9),5,7,10-pentaene (**3e**)*

Yellow solid; yield 95%; mp 83–85 °C; (KBr) 2,962, 2,854, 1,662, 1,458 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.63 (3H, s, Me), 1.13 (3H, s, Me), 1.40–1.48 (5H, m, Me and H-13$_{endo}$, H-14$_{exo}$), 2.05–2.09 (1H, m, H-14$_{endo}$), 2.28 (1H, m, H-13$_{exo}$), 2.80 (1H, d, J = 5.41 MHz, H-12), 7.60 (1H, m, H-8), 8.36 (1H, m, H-7), 8.95 (1H, m, H-6); δ_C (62.9 MHz, $CDCl_3$) 169.2 (C-2), 167.3 (C-11), 166.7 (C-9), 165.0 (C-4), 150.9 (C-6), 137.5 (C-8), 123.5 (C-7), 54.3 (C-12), 53.7 (C-15), 53.0 (C-1), 31.6 (C-14), 24.4 (C-13), 20.2 (C-16), 18.4 (C-17), 9.9 (C-18); Anal. Calcd for $C_{15}H_{17}N_3$: C, 75.28; H, 7.16; Found: C, 75.11; H, 7.09; *m/z* 239 [MH+]; HRMS (ESI) calcd for $C_{15}H_{17}N_3$ (MH+) 239.1422, found 239.1412.

*1,15,15-Trimethyl-3,10-diazatetracyclo [10.2.1.0^{2,11}.0^{4,9}] pentadeca-2,10-diene (**3f**)*

Yellow solid; yield 95%; mp 50–52 °C; (KBr) 2,960, 2,851, 1,650, 1,447 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.40 (3H, s, Me), 0.56 (3H, s, Me), 0.65 (3H, s, Me), 1.39 (8H, m, H-5-8), 1.87–1.94 (3H, m, H-13$_{endo}$, H-14$_{exo,\ endo}$), 2.26–2.28 (2H, m, H-4,9), 2.57 (1H, m, H-13exo), 2.99 (1H, d, J = 5.52 MHz, H-12); δ_C (62.9 MHz, $CDCl_3$) 169.1(C-2), 168.0 (C-11), 61.8 (C-4), 61.7 (C-9), 59.0 (C-12), 52.7 (C-15), 52.2 (C-1), 33.9 (C-5,8), 30.4 (C-14), 25.7 (C-13), 22.9 (C-6,7), 20.3 (C-16), 17.4 (C-17), 9.7 (C-18); Anal. Calcd for $C_{16}H_{24}N_2$: C, 78.64; H, 9.90; Found: C, 78.52; H, 9.81; *m/z* 244 [MH+]; HRMS (ESI) calcd for $C_{16}H_{24}N_2$ (MH+) 244.1939, found 244.1930.

General procedure for synthesis quinoxalines **5**



5

The required 1,2-diketone compound **4** (1 mmol), and diamines **2** (1 mmol) were added to ZnO (10 mol%, 0.008 g) and the mixture was heated in an oil bath at 80 °C. The progress of the reaction was monitored by TLC (eluent: EtOAc/*n*-hexane, 20:80). After the reaction was completed, EtOAc (2 × 20 mL) was added to the reaction mixture and separated the catalyst by centrifuge. The organic solvent was removed under reduced pressure and quinoxaline was obtained. The crude product was purified by column chromatography (eluent 95:5 hexane/EtOAc). The structure of the products was confirmed by NMR, IR, and mass spectra and comparison with authentic samples obtained commercially or prepared by reported methods.

*2,3-Diphenylquinoxaline (**5a**)*

White solid; yield 98%; mp 127–129 °C (130–131 °C) [14]; δ_H (250 MHz $CDCl_3$) 7.23–7.25 (6H, m, Ar–H), 7.40–7.44 (4H, m, Ar–H), 7.64–7.67 (2H, m, Ar–H), 8.075 (2H, m, Ar–H); δ_C (62.9 MHz, $CDCl_3$) 153.4, 141.2, 139.0, 129.8, 129.1, 129.0, 128.8, 128.5.

*6-Methyl-2,3-diphenylquinoxaline (**5b**)*

White solid; yield 65%; mp 115–117 °C (115–117 °C) [14]; δ_H (250 MHz, $CDCl_3$) 2.56, (3H, s, Me), 7.28–7.32 (6H, m, Ar–H), 7.50–7.56 (4H, m, Ar–H), 7.96 (1H, s, Ar–H), 8.04 (1H, s, Ar–H), 8.26 (1H, s, Ar–H); δ_C (62.9 MHz, $CDCl_3$) 153.2, 152.5, 141.3, 140.4, 139.2, 134.8, 132.2, 130.3, 129.9, 129.0, 128.6, 128.2, 21.9 (Some of the peaks were overlap).

*(2,3-Diphenyl-6-quinoxalinyl)(phenyl)methanone (**5c**)*

Gray solid; yield 95%; mp 143–145 °C (140–142 °C) [16]; δ_H (250 MHz, $CDCl_3$) 7.24–7.48 (15H, m, Ar–H), 7.80 (1H, d, J = 8.3 Hz, Ar–H), 8.17 (1H, d, J = 8.9 Hz, Ar–H), 8.43 (1H, s, Ar–H); δ_C (62.9 MHz, $CDCl_3$) 195.5, 155.0, 154.4, 142.9, 140.1, 138.6, 138.2, 137.1, 134.8, 132.7, 132.4, 130.1, 129.8, 129.6, 129.2, 129.0, 128.5 (Some of the peaks were overlap).

*6-Nitro-2,3-diphenylquinoxaline (**5d**)*

Yellow solid; yield 60%; mp 192–194 °C (193–194 °C) [15]; δ_H (250 MHz, $CDCl_3$) 7.33–7.43 (6H, m, Ar–H), 7.53–7.58 (4H, m, Ar–H), 8.30 (1H, d, J = 9.1 MHz, Ar–H), 8.50 (1H, d, J = 6.6 MHz, Ar–H), 9.06 (1H, s, Ar–H); δ_C (62.9 MHz, $CDCl_3$) 156.2, 155.6, 147.8, 143.5, 139.9, 138.1, 138.0, 130.7, 129.8, 128.4, 125.6, 123.2 (Some of the peaks were overlap).

*2,3-Diphenylpyrido[2,3-b]pyrazine (**5e**)*

Yellow solid; yield 65%; mp 151–143 °C; δ_H (250 MHz, $CDCl_3$) 7.22–7.28 (7H, m, Ar–H), 7.44–7.63 (4H, m, Ar–H), 8.39 (1H, s, Ar–H), 9.06 (1H, s, Ar–H); δ_C (62.9 MHz, $CDCl_3$) 156.2, 154.6, 154.0, 149.7, 138.4, 138.0, 136.1, 130.2, 129.7, 129.4, 129.2, 128.3, 128.1, 125.2 (Some of the peaks were overlap); Anal. Calcd for $C_{19}H_{13}N_3$: C, 80.54; H, 4.62; Found: C, 80.42; H, 4.51; *m/z* 283 [MH+].

*2,3-Diphenyl-4a,5,6,7,8,8a-hexahydroquinoxaline (**5f**)*

Yellow solid; yield 95%; mp 167–169 °C (168–170 °C) [14]; δ_H (250 MHz, $CDCl_3$) 1.42–1.48 (4H, m, –CH_2C$\underline{H_2}$ C$\underline{H_2}$$CH_2$-, H-6,7), 1.88–1.92 (2H, m, –$CH_2CH_2CH_2$C$\underline{H_2}$–,

H-5), 2.48–2.54 (2H, m, –$C\underline{H}_2CH_2CH_2CH_2$–, H-8), 2.82–2.86 (2H, m, H-4a, 8a), 7.22–7.29 (6H, m, Ar–H), 7.38–7.41 (4H, m, Ar–H); δ_C (62.9 MHz, $CDCl_3$) 159.6, 137.7, 129.2, 128.0, 59.5, 33.5, 25.4 (Two peaks were overlap).

*2,3-Dimethyiquinoxaline (**5g**)*

Yellow solid; yield 98%; mp 101–103 °C (105.5–105.3 °C) [17]; δ_H (250 MHz, $CDCl_3$) 2.35 (6H, s, Me), 7.31 (2H, m, Ar–H), 7.65 (2H, m, Ar–H); δ_C (62.9 MHz, $CDCl_3$) 153.3, 140.9, 128.7, 128.1, 22.5; Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; Found: C, 75.84; H, 6.28; *m/z* 158 [MH+].

*6-Methy-2,3-dimethyiquinoxaline (**5h**)*

Yellow solid; yield 95%; mp 52–54 °C; δ_H (250 MHz, $CDCl_3$) 2.50 (3H, s, -Me), 2.71 (6H, s, -Me), 7.89 (1H, d, $J = 8.5$ MHz, H-8), 8.33 (1H, d, $J = 9.7$ MHz, H-7), 8.54 (1H, s, H-5); δ_C (62.9 MHz, $CDCl_3$) 156.2, 155.6, 143.4, 141.7, 138.3, 129.2, 125.1, 122.5, 23.2, 22.5; 21.9; Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; Found: C, 76.67; H, 6.92; *m/z* 172 [MH+].

*(2,3-Dimethyi-6-quinoxalinyl)(phenyl)methanone (**5i**)*

Yellow solid; yield 95%; mp 90–93 °C; (KBr) 3,056, 2,921, 1,664, 1,542, 1,344, 768, 696 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 2.51 (3H, s, Me), 2.54 (3H, s, Me), 7.18–7.30 (3H, m, Ar–H), 7.61–7.65 (2H, m, Ar–H), 7.83–7.95 (2H, m, H-5,7), 8.12 (1H, s, H-8); δ_C (62.9 MHz, $CDCl_3$) 195.9, 155.7, 154.8, 142.9, 140.0, 137.3, 137.2, 132.6, 131.6, 130.0, 129.3, 128.4, 128.1, 23.3, 23.2; Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; Found: C, 77.71; H, 5.25; *m/z* 262 [MH+].

*6-Nitro-2,3-dimethylquinoxaline (**5j**)*

Yellow solid; yield 85%; mp 62–64 °C; (KBr) 3,026, 2,935, 1,554, 1,524, 1,341 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 2.71 (6H, s, Me), 7.99 (1H, d, $J = 8.6$ MHz, H-8), 8.30 (1H, d, $J = 9.1$ MHz, H-7), 8.74 (1H, s, H-5); δ_C (62.9 MHz, $CDCl_3$) 157.2, 156.2, 143.6, 142.6, 139.8, 129.8, 124.8, 122.3, 23.2, 22.5; Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; Found: C, 59.02; H, 4.37; *m/z* 203 [MH+].

*2,3-Dimethylpyrido[2,3-b]pyrazine (**5k**)*

Yellow solid; yield 95%; mp 73–75 °C; δ_H (250 MHz, $CDCl_3$) 2.72 (3H, s, Me), 2.76 (3H, s, Me), 7.55–7.60 (1H, m, Ar–H), 8.30 (1H, m, Ar–H), 8.99 (1H, m, Ar–H); δ_C (62.9 MHz, $CDCl_3$) 157.3, 155.0, 153.4, 152.5, 137.3, 135.8, 124.2, 23.4, 22.9; Anal. Calcd for $C_9H_9N_3$: C, 67.90; H, 5.70; Found: C, 67.82; H, 5.63; *m/z* 159 [MH+].

*2,3-Dimethyl-4a,5,6,7,8,8a-hexahydroquinoxaline (**5l**)*

Yellow solid; yield 90%; mp 128–130 °C; δ_H (250 MHz, $CDCl_3$) 1.18–1.28 (8H, m, H-5,6,7,8), 1.93 (6H, s, 2Me), 2.46 (2H, m, H-4a, 8a); δ_C (62.9 MHz, $CDCl_3$) 159.4, 46.2, 30.5, 21.6, 15.3; Anal. Calcd for $C_{10}H_{16}N_2$: C, 73.13; H, 9.82; Found: C, 73.01; H, 9.74; *m/z* 164 [MH+].

Results and discussion

Activity of various metal oxides and salts catalysts

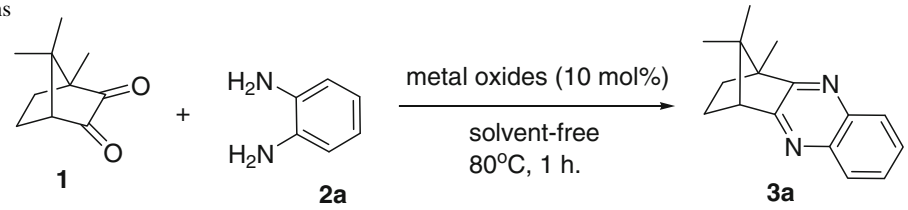
At first, the activity of various metal oxides and salt catalysts in the reaction between (±) CQ **1** and 1,2-phenyldiamine **2a** has been examined. The reaction was carried out under solvent-free conditions for 1 h at 80 °C in mole ratio 1:1 of the substrates. The results are summarized in Table 1.

It is shown that chosen metal oxides and salts are active catalysts for the reaction studying particularly, ZnO, and acidic alumina. Among the catalysts, CaO, K_2CO_3, and $CaCO_3$ show lower activity as compared with other oxide catalysts. It is interesting to note that the order for the activity of the metal oxides and salts catalysts is quite similar to that for their acidic strengths, which are expected to play important roles in the condensation reaction. Moreover, two kinds of alumina (basic and acidic) give practically little different results. The acidic alumina shows much higher activity in the condensation reaction than the basic ones. The catalytic activity of metal oxides and salts in synthesis of camphorquinoxaline **3a** was further compared with the value from previous reported literature. Previously, Adamenko et al. [29] reported that camphorquinoxaline **3a** was obtained by the reaction of CQ with phenyldiamine in 50–70% yields by using solvents such as methanol and acetic acid at 65–118 °C for a very long period of reaction times (30 h). However, herein we are reported that ZnO catalyzed such reaction and the camphorquinoxaline **3a** was obtained in 98% yields after 1 h under solvent-free conditions. Thus, these metal oxides and salts are specific active surfaces for effecting the reaction between (±) CQ and phenyldiamine.

Reusability of the catalyst

Reusability of the metal oxides and salts was studied through a condensation reaction of CQ (**1**) with phenyldiamine **2a**. For all cases after completion of the reaction (monitored by TLC), ethylacetate was added to the reaction mixture and centrifuged until the catalyst was deposited at

Table 1 The reaction of (±) CQ **1** with 1,2-phenyldiamine **2a** in the presence of metal oxides or metal salts as catalyst at 80 °C in 1 h under solvent-free conditions



Entry	Active surface (10 mol%)	Isolated yield (%)
1	ZnO	98
2	TiO_2	95
3	ZrO_2	95
4	MgO	90
5	Acidic-Al_2O_3	98
6	Basic-Al_2O_3	90
7	CaO	75
8	K_2CO_3	75
9	$CaCO_3$	80

the bottom of the centrifuge tube. The deposited catalyst was washed with ethylacetate two to three times to complete removal of organic residuals, dried in an oven at 100–120 °C for 5–6 h, and then the catalyst was reused for the same reaction. It was shown that only ZnO, TiO_2, and ZrO_2 could be recovered and reused. In the cases of the other metal oxides and salts (MgO, Aluminas, CaO, K_2CO_3, and $CaCO_3$), the amount of catalysts was extremely decreased after first reaction and cannot be recovered for further catalytic reaction cycles. In the cases of ZnO, TiO_2, and ZrO_2, the results indicate these catalysts have a same activity on recycling. The results of the reusability of these oxides are listed in Table 2.

Therefore, on the basis of these results, and in order to generalize the procedure, ZnO was chosen as effective catalyst for the reaction between (±) CQ **1** and other diamines **2** to synthesis a novel series of camphorquinoxaline derivatives. The results are summarized in Table 3.

According to Table 3, all of the condensation reaction between (±) CQ and diamines were completed within 1 h. The reactions are clean, the conversion of substrates (determined by GC) being 100% and no chromatographic separation is necessary to get the spectra-pure compounds except in a some cases where some starting materials remained, the conversion being less than 100%. It was found that aromatic and aliphatic diamines could react with CQ. Reaction of aromatic diamines bearing both electron-donating and withdrawing groups proceeded rapidly to give the corresponding camphorquinoxaline compounds in excellent yields (Entries 2–4). Furthermore, in the case of heterocyclic diamine (Entry 5), the reaction shows excellent result.

Due to the high efficiency of this condensation reaction, I expected that the newly developed procedure would serve as extremely useful and quick synthesis route to obtain quinoxaline derivatives. In this context, and after the successful synthesis of camphorquinoxalines **3**, the condensation reaction between other 1,2-diketones and diamines using ZnO as catalyst was explored (Scheme 2). The reactions afforded the quinoxaline derivatives **5** in good to excellent yields. These results are shown in Table 4.

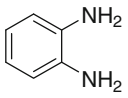
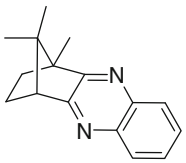
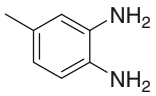
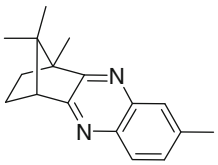
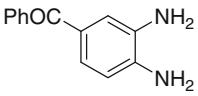
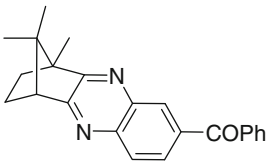
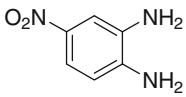
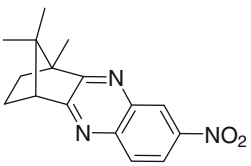
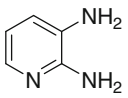
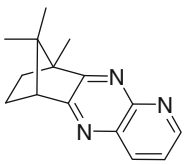
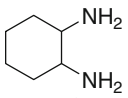
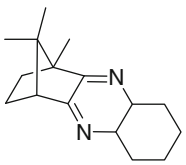
Results in Table 4 was shown that electron-donating groups on the phenyl ring of 1,2-diamines favored the

Table 2 Reusability of the metal oxides catalysts in synthesis of **3a**

Entry	Catalyst	Reusability			
		Catalytic runs	(±) CQ (mmol)	Catalyst (mg)	Yield (%)[a]
1	ZnO	Fresh	5	41	98
		1	4	32.5	98
		2	3	24.4	96
		3	2	16.3	96
2	TiO_2	Fresh	5	40	95
		1	4	32	95
		2	3	24	93
		3	2	16	92
3	ZrO_2	Fresh	5	62	95
		1	4	49.3	94
		2	3	37	94
		3	2	25	92

[a] Isolated yield

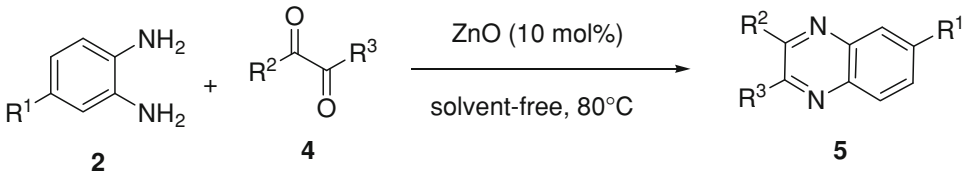
Table 3 Synthesis of novel camphorquinoxaline derivatives using metal oxides (10 mol%) as catalyst under solvent-free conditions at 80 °C in 1 h

Entry	Diamine	Product	Catalyst	Yield (%)[a]
1	 **2a**	 **3a**	ZnO	98
			TiO_2	95
			ZrO_2	95
			MgO	90
			Acidic-Al_2O_3	98
			Basic-Al_2O_3	90
2	 **2b**	 **3b**	ZnO	98
			TiO_2	96
			ZrO_2	96
			MgO	95
			Acidic-Al_2O_3	98
			Basic-Al_2O_3	95
3	 **2c**	 **3c**	ZnO	95
			TiO_2	90
			ZrO_2	90
			MgO	87
			Acidic-Al_2O_3	93
			Basic-Al_2O_3	90
4	 **2d**	 **3d**	ZnO	95
			TiO_2	90
			ZrO_2	90
			MgO	88
			Acidic-Al_2O_3	90
			Basic-Al_2O_3	88
5	 **2e**	 **3e**	ZnO	95
			TiO_2	90
			ZrO_2	90
			MgO	90
			Acidic-Al_2O_3	95
			Basic-Al_2O_3	89
6	 **2f**[b]	 **3f**	ZnO	95
			TiO_2	90
			ZrO_2	90
			MgO	90
			Acidic-Al_2O_3	95
			Basic-Al_2O_3	90

[a] Isolated yields

[b] A mixture of isomers (*cis* and *trans*) was used

Scheme 2 Synthesis of quinoxalines **5** using ZnO as catalyst



2 **4** **5**

Table 4 ZnO (10 mol%) catalyzed synthesis of quinoxaline derivatives under solvent-free conditions at 80 °C

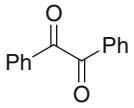
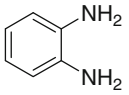
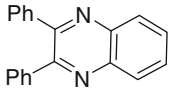
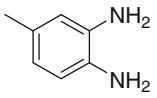
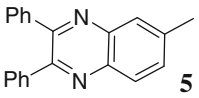
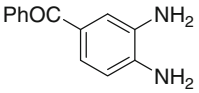
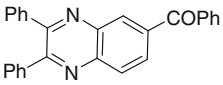
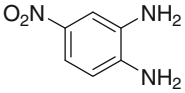
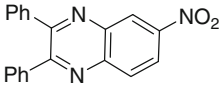
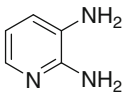
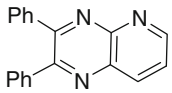
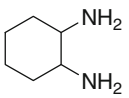
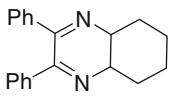
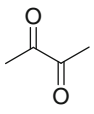
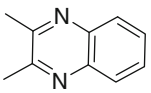
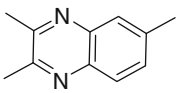
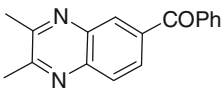
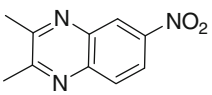
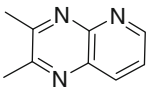
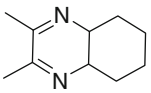
Entry	1,2-Diketone	Diamine	Product	Time (h)	Yield (%)[a]
1		 **2a**	 **5a**	1	98
2	**4a**	 **2b**	 **5 b**	4	80
3	**4a**	 **2c**	 **5c**	6	95
4	**4a**	 **2d**	 **5d**	5	60
5	**4a**	 **2e**	 **5e**	6	65
6	**4a**	 **2f**[b]	 **5f**	4	95
7	 **4b**	**2a**	 **5g**	2	98
8	**4b**	**2b**	 **5h**	1	95
9	**4b**	**2c**	 **5i**	2	95
10	**4b**	**2d**	 **5j**	2	85

Table 4 continued

Entry	1,2-Diketone	Diamine	Product	Time (h)	Yield (%)[a]
11	**4b**	**2e**	 **5k**	2	95
12	**4b**	**2f**[b]	 **5l**	2	90

[a] Isolated yields

[b] A mixture of isomers (*cis* and *trans*) was used

formation of desired products in excellent yields. In contrast, electron-withdrawing groups (especially nitro group) gave lower yields. The reaction of 1,2-cyclohexandiamine **2f** with benzyl **4a** was carried out and gave excellent yield of the corresponding quinoxaline **5f** (Table 4, Entry 6). A comparison of the present protocol, using ZnO, with the most previously known methods clearly was shown that the present protocol is indeed superior to several of the other protocols. In the case of the reaction between 1,2-dialkylketone **4b** and diamines, the corresponding quinoxaline derivatives were obtained in excellent yields (>90%) in short reaction times using ZnO (Entries 7–12). However, most of the other protocols reported in the literature either take longer times for completion, the reactions were carried out in reflux, requires an additive, use organic solvents with generally reduced isolated yields, or were not effective in the case of 1,2-dialkylketones. Thus, this observation was shown that ZnO is a better choice for these reactions.

Conclusions

In conclusion, a novel approach for the synthesis of camphorquinoxaline derivatives on metal oxides and salts active surfaces under solvent-free condition has been generalized for the first time. Metal oxides especially ZnO has been found to be effective for the synthesis of other quinoxaline derivatives. High yields, easy set-up and work-up, no by-product formation, solvent-free and reusability of the catalysts make this method attractive and a useful contribution to the present methodologies.

Acknowledgments We thank the Shiraz University Research Council, and the Iran National Science Foundation (Grant No. 87040564) for financial support.

References

1. R.E. Lowenthal, S. Masamune, Tetrahedron Lett. **32**, 7373 (1991)
2. J.D. White, D.J. Wardrop, K.F. Sundermann, Org. Synth. **79**, 125 (2002)
3. D. Lucet, T. Le Gall, C. Mioskowski, Angew. Chem. Int. Ed. Engl. **37**, 2580 (1998)
4. H. Shintani, T. Inoue, M. Yamaki, Dent. Mater. **1**, 124 (1985)
5. H.H. Alvim, A.C. Alecio, W.A. Vasconcellos, M. Furlan, J.E. de Oliveira, J.R. Saad, Dent. Mater. **23**, 1245 (2007)
6. Y.L. Bennani, S. Hanessian, Chem. Rev. **97**, 3161 (1997)
7. A. Togni, L.M. Venanzi, Angew. Chem. Int. Ed. Engl. **33**, 497 (1994)
8. K. Tomioka, Synthesis **7**, 541 (1990)
9. C.W. Lindsley, Z. Zhao, W.H. Leister, R.G. Robinson, S.F. Barnett, D. Defeo-Jones, R.E. Jones, G.D. Hartman, J.R. Huff, H.E. Huber, M.E. Duggan, Bioorg. Med. Chem. Lett. **15**, 761 (2005)
10. M. Loriga, S. Piras, P. Sanna, G. Paglietti, Farmaco **52**, 157 (1997)
11. L.E. Seitz, W.J. Suling, R.C. Reynolds, J. Med. Chem. **45**, 5604 (2002)
12. W. He, M.R. Meyers, B. Hanney, A. Spada, G. Blider, H. Galzeinski, D. Amin, S. Needle, K. Page, Z. Jayyosi, H. Perrone, Bioorg. Med. Chem. Lett. **13**, 3097 (2003)
13. Y.B. Kim, Y.H. Kim, J.Y. Park, S.K. Kim, Bioorg. Med. Chem. Lett. **14**, 541 (2004)
14. A. Hasaninejad, A. Zare, R. Mohammadizadeh, M. Shekouhy, ARKIVOC **xiii**, 28 (2008)
15. M.M. Heravi, K. Bakhtiari, M.H. Tehrani, N.M. Javadi, H.A. Oskooie, ARKIVOC **xvi**, 16 (2006)
16. H.R. Darabi, S. Mohandessi, K. Aghapoor, F. Mohsenzadeh, Catal. Commun. **8**, 389 (2007)
17. M.M. Heravi, Kh Bakhtiari, F.F. Bamoharram, M.H. Tehrani, Monatsh. Chem. **138**, 465 (2007)
18. M.M. Heravi, Kh Bakhtiari, H.A. Oskooie, Sh Taheri, Heteroat. Chem. **19**, 218 (2008)
19. M.M. Heravi, Sh Taheri, Kh Bakhtiari, H.A. Oskooie, Catal. Commun. **8**, 211 (2007)
20. M.M. Heravi, M.H. Tehrani, Kh Bakhtiari, H.A. Oskooie, Catal. Commun. **8**, 1341 (2007)
21. H.M. Bachhav, S.B. Bhagat, V.N. Telvekar, Tetrahedron Lett. **52**, 5697 (2011)

22. B. Karami, S. Khodabakhshib, M. Nikroozb, J. Chin. Chem. Soc. **58**, 474 (2011)
23. P. Ghosh, A. Mandal, Adv. Appl. Sci. Res. **2**, 255 (2011)
24. J. Sun, S. Wuc, H.-Y. Chen, F. Gao, J. Liu, L.-N. Ji, Z.-W. Mao, Polyhedron **30**, 1953 (2011)
25. X.-Z. Zhang, J.-X. Wang, L. Bai, Synth. Commun. **41**, 2053 (2011)
26. B. Krishnakumar, M. Swaminathan, J. Organomet. Chem. **695**, 2572 (2010)
27. T. Huang, D. Jiang, J. Chen, W. Gao, J. Ding, H. Wu, Synth. Commun. **41**, 3334 (2011)
28. H.M. Meshram, P. Ramesh, G. Santosh Kumar, B. Chennakesava Reddy, Tetrahedron Lett. **51**, 4313 (2010)
29. E.N. Adamenko, L.L. Frolova, M.V. Panteleeva, A.V. Kuchin, Chem. Nat. Compd. **43**, 59 (2007)
30. M. Hosseini Sarvari, H. Sharghi, J. Org. Chem. **69**, 6953 (2004)
31. M. Hosseini Sarvari, Synthesis 6, 787 (2005)
32. M. Hosseini-Sarvari, H. Sharghi, J. Org. Chem. **71**, 652 (2006)
33. M. Hosseini-Sarvari, Acta Chim. Slov. **54**, 354 (2007)
34. M. Hosseini-Saravri, Synth. Commun. **6**, 832 (2008)
35. M. Hosseini-Sarvari, E. Sodagar, M.M. Doroodmand, J. Org. Chem. **76**, 2853 (2011). and references cited therein
36. R. Grigg, D.M. Cooper, S. Holloway, S. McDonald, E. Millington, M.A.B. Sarker, Tetrahedron **61**, 8677 (2005)
37. B.A. Trofimov, L.N. Sobenina, Z.V. Stepanova, T.I. Vakul'skaya, O.N. Kazheva, G.G. Aleksandrov, O.A. Dyachenko, A.I. Mikhaleva, Tetrahedron **64**, 5541 (2008)
38. H. Wakayama, H. Itahara, N. Tatsuda, S. Inagaki, Y. Fukushima, Chem. Mater. **13**, 2392 (2001)
39. P.D.F. Vernon, M.L.H. Green, A.K. Cheetham, A.T. Ashcroft, Catal. Lett. **6**, 181 (1990)
40. T. Tani, L. Mädler, S.E. Pratsinis, J. Nanoparticle Res.**4**, 337 (2002)
41. C.L. Carnes, K.J. Klabunde, J. Mol. Catal. A Chem. **194**, 227 (2003)
42. S.D. Jackson, J.S.J. Hargreaves, *Metal Oxide Catalysis*, vol. 1 (Wiley-VCH, New York, 2008)