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Multistep soluble polymer-supported, microwave-assisted synthesis of quinoxalines

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A multistep liquid-phase, polymer-supported, microwave-assisted synthesis of quinoxalines on polyethylene glycol, PEG-4500, is demonstrated. The usage of microwave energy to accelerate organic reactions reduces reaction time from hours (under reflux) to only minutes. The solution-phase chemistry on soluble polyethylene glycol, PEG, support facilitates the use of microwave energy (since PEG easily absorbs microwaves) and avoids the silica gel chromatography purifications of intermediate compounds, supporting parallel, combinatorial, and ultimately automated syntheses.

Keywords: quinoxalines; microwave organic synthesis; liquid-phase synthesis; polymer-supported synthesis

Introduction

Liquid-phase synthesis on soluble polymer supports is a growing field in combinatorial chemistry [1–3]. Besides the advantages of solid-phase chemistry (use of excess reagents and simple isolation and purification), it has the advantages of solution chemistry conventional analysis. Polyethylene glycol, PEG, is successful as a polymer support and as a delivery vehicle for many low-molecular-weight drugs, polypeptides, and oligonucleotides [4–5]. Conjugation to PEG increases water solubility and retention time and protects drugs against degrading enzymes. Using microwave energy and water-soluble substrate-PEG conjugates permit the use of water-based organic transformations.

Nitrogen, oxygen, and sulfur containing heterocyclic compounds are key building blocks used to develop medicinally and biologically active compounds. They are predominant among all types of pharmaceuticals and agrochemical products. Heterocyclic compounds also have many industrial uses as components in dyes, antioxidants, polymers, bases, and ligands [6]. Quinoxaline nitrogen heterocycles exhibit a broad spectrum of activities, including antimicrobial, antidiabetic, and antitumor activities [7]. Quinoxalines are also used in materials science as dyes, efficient electroluminescent materials, and organic semiconductors [8].

Enormous numbers of classical synthetic methods of quinoxalines are reported [9]. In a combinatorial chemistry approach, two libraries of quinoxalines were successfully produced via solid-phase syntheses on Rink amide and Wang resins [10,11]. Ecofriendly syntheses of quinoxalines utilizing Nano-BF_3.SiO_2 catalyst [12], zirconium (IV) oxide chloride octahydrate catalyst [13], and catalytic magnetic Fe_3O_4 nanoparticles in water [14] were reported. Green syntheses of quinoxalines, using PEG-400 [15], PEG-600/water [16], and PEG-400/microwave irradiation [17,18] were reported. Recently, an efficient ecofriendly synthesis of biologically active quinoxalines using easily recyclable TiO_2/SO_4^{2-} and microwave irradiation was reported [19–21].

Results and discussion

The present work demonstrates an efficient synthesis of quinoxalines on a PEG-4500 soluble polymer support under microwave irradiation (Figure 1). For simplicity, commercially available 3,4-dinitrobenzoic acid was chosen as the starting material because it possesses a carboxyl group that can be hooked to the hydroxyl termini of PEG-4500, and two adjacent *nitro* groups that can be reduced to the desired 1,2-diamine. Esterification of 2,3-dinitrobenzoic acid to PEG-4500 under open-vessel microwave conditions, afforded the PEG-Substrate conjugate **1** in only 20 minutes. Catalytic hydrogenation reduction of the dinitro, conjugate **1** did not form the desired diamine **2**, instead, partial reduction products were observed by NMR. Reduction of the two nitro groups was successful using excess ammonium formate and catalytic 10% palladium/carbon under open-vessel microwave irradiation for only 7 minutes. The reaction of the 1,2-diamine, **2** and α-diketones was carried out in 9:1 methanol/acetic acid under microwave irradiation in a closed vessel for only 10 minutes. It was easy to monitor this sequence of reactions, using ^{1}H NMR by tracking the position of the aromatic

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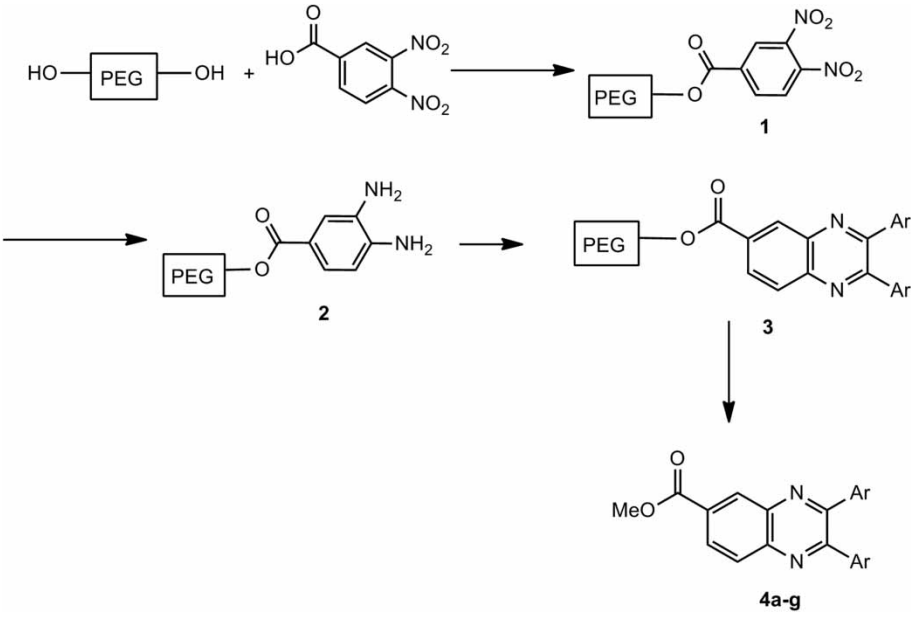


Figure 1. Liquid phase synthesis of quinoxalines.

protons that change from the PEG-dinitrosubstrate, conjugate **1** to the PEG-diamine, substrate **2** and then to respective PEG-quinoxalines **3**. Finally, cleavage of the quinoxaline product from the PEG support was successful using sodium methoxide in methanol. The suppression of reaction time from hours to minutes and the elimination of chromatography purification, minimizing the quantities of organic solvents used, make this method more environment friendly than conventional syntheses and opens the door to parallel and combinatorial syntheses.

Experimental

Chemicals were purchased from various suppliers, including Sigma Aldrich and TCI America. ^{1}H NMR spectra were recorded using a Bruker Avance 400 MHz spectrometer with tetramethylsilane as the internal standard. Mass spectra were recorded using a Bruker Esquire-3000 ESI-MS. HR mass spectra were measured at Mass Spectrometry & Proteomics Facility, Ohio State University at Columbus, Ohio. The microwave irradiation experiments were undertaken in a focused microwave CEM Discover reactor fitted with a rotational system and an IR detector of temperature.

Synthesis of conjugate 1

A 100 mL round-bottomed flask fitted with a reflux condenser was charged with PEG-4500 (5.00 g, 1.11 mmol), 3,4-dinitrobenzoic acid (1.40 g, 6.66 mmol), N,N'-Dicyclohexylcarbodiimide (1.37 g, 6.66 mmol), and 4-dimethylaminopyridine (0.22 mmol, 27 mg) and dry dichloromethane (40 mL). The flask was subjected to microwave irradiation (open-vessel mode, 80 w) for 15 minutes, cooled at 0°C for 30 minutes and then filtered to remove dicyclohexyl urea. Cold ether (400 mL) was added to precipitate the PEG-substrate, conjugate **1** as a yellowish powder. The precipitate was isolated by filtration and washed with cold ether (yield, 4.86 g).

Synthesis of conjugate 2

To a solution of conjugate **1** (1.30 g, 0.29 mmol) and ammonium formate (366 mg, 5.80 mmol) in methanol (20 mL) was added 10% palladium/carbon (184 mg, 0.087 mmol). The mixture was subjected to microwave irradiation (open-vessel mode, 80 w, 7 minutes). It was filtered over a bed of cellite. Methanol was removed under reduced pressure, and the residue was dissolved in toluene (10 mL) and filtered to remove any insoluble ammonium formate. Cold ether was added to precipitate the PEG-diaminosubstrate, conjugate **2** as a white precipitate (yield 0.98 g)

General procedure for the synthesis of conjugates 3, and cleavage of quinoxalines 4

A CEM designed 10 mL pressure-rated vial was charged with PEG-diaminosubstrate, **2** (300 mg, 0.17 mmol), the respective α-diketones (0.35 mmol), and 9:1 MeOH/AcOH (3 mL). The mixture was irradiated in a CEM Discover Focused Synthesizer (150 w, 130°C, 200 psi, 8 minutes). The mixture was

cooled to room temperature by passing compressed air through the microwave cavity for 2 minutes. It was poured into cold ether (40 mL) and the formed precipitate filtered, washed with ether, and air dried to give **3**. A solution of **3** in NaOMe/MeOH (1 M, 2 mL) was left to stand at room temperature for overnight. Cleaved quinoxalines **4** were precipitated, filtered, and washed with methanol. They were purified by passing through a short column eluted with 10% ethyl acetate/dichloromethane (Table 1).

Methyl-2,3-diphenylquinoxaline-6-carboxylate, ***4a*** *[22]*
^{1}H NMR (400 MHz, CDCl3): δ = 8.92 (dd, J = 1.2, 0.4 Hz, 1*H*), 8.39 (dd, *J* = 8.8, 2.0 Hz, 1*H*), 8.24 (dd, *J* = 8.8, 0.4 Hz, 1*H*), 7.52 (m, 4*H*), 7.42 (m, 4*H*), 4.01 (s, 3*H*). ^{13}C NMR (100 MHz): δ = 166.4, 155.2, 154.4, 143.2, 140.4, 138.7, 138.6, 132.0, 131.2, 129.9, 129.8, 129.3, 129.2, 129.1, 129.0, 128.4, 52.7. MS-ESI (m/z), 341($M^+ + 1$).

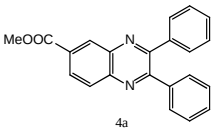
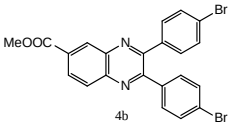
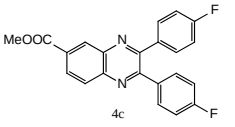
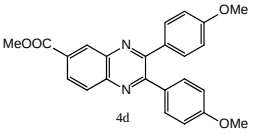
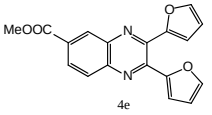
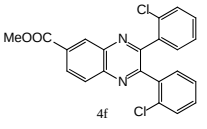
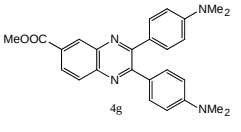
Methyl-2,3-di(4-bromophenyl)quinoxaline-6-carboxylate, ***4b***
^{1}H NMR (400 MHz, CDCl3): δ = 8.87 (d, *J* = 1.2 Hz, 1*H*), 8.39 (dd, *J* = 8.8, 2.0 Hz, 1*H*), 8.24 (dd, *J* = 8.8 Hz, 1*H*), 7.58 (m, 4*H*), 7.39 (m, 6*H*), 4.00 (s, 3*H*). ^{13}C NMR (100 MHz): δ = 166.2, 153.5, 152.9, 143.2, 140.4, 137.3, 131.8, 131.4, 129.9, 129.4, 124.3, 124.1, 52.7 MS-EI: 497 (M + H). HRMS (EI): calcd. for $C_{22}H_{14}Br_2N_2NaO_2$ (M + Na) 518.9320, found 518.9318.

Methyl-2,3-di (4-difluorophenyl)quinoxaline-6-carboxylate, ***4c***
^{1}H NMR (400 MHz, CDCl3): δ = 8.88 (d, *J* = 1.6 Hz, 1*H*), 8.38 (dd, *J* = 8.8, 2.0 Hz, 1*H*), 8.20 (dd, *J* = 8.4, 0.4 Hz, 1*H*), 7.54 (m, 4*H*), 7.01 (m, 4*H*), 4.01 (s, 3*H*). ^{13}C NMR (100 MHz): δ = 166.3, 164.7, 164.6, 153.8, 153.1, 143.0, 141.1, 134.5, 134.4, 131.9, 131.9, 131.8, 131.7, 131.6, 129.7, 129.3, 52.7. MS-EI: 377 (M + H). HRMS (EI): calcd. for $C_{22}H_{14}F_2N_2NaO_2$ (M + Na) 399.0921, found 399.0918.

Methyl-2,3-di(4-methoxyphenyl)quinoxaline-6-carboxylate, ***4d***
^{1}H NMR (400 MHz, CDCl3): δ = 8.84(d, J = 1.6 Hz, 1*H*), 8.31 (dd, *J* = 8.8, 1.6 Hz, 1*H*), 8.15 (d, *J* = 8.8 Hz, 1*H*), 7.52 (m, 4*H*), 6.91 (m, 4*H*), 4.01 (s, 3*H*), 3.85 (s, 6*H*). ^{13}C NMR (100 MHz): δ = 166.5, 160.6, 160.4, 154.7, 154.0, 143.0, 140.2, 131.6, 131.3, 131.2, 131.1, 131.0, 130.7, 129.1, 113.8, 55.1, 52.7. MS-EI: 401 (M + H). HRMS (EI): calcd. for $C_{24}H_{20}N_2NaO_4$ (M + Na) 423.1321, found 423.1333.

Methyl-2,3-di(2-furyl)quinoxaline-6-carboxylate, ***4e*** *[23]*
^{1}H NMR (400 MHz, CDCl3): δ = 8.85(d, J = 1.6 Hz, 1*H*), 8.34 (dd, *J* = 8.8, 1.6 Hz, 1*H*), 8.17 (d, *J* = 8.8 Hz, 1*H*), 7.65 (ddd, *J* = 5.2, 1.6, 0.8 Hz, 2*H*), 6.76 (dd, *J* = 5.2, 1.6 Hz, 2*H*), 6.60 (m, 2*H*), 4.02 (s, 3*H*). ^{13}C NMR (100 MHz): δ = 166.1, 150.6, 143.9, 143.3, 142.6, 139.7, 131.8, 131.3, 129.9, 129.3, 114.3, 113.5, 112.1, 112.0, 52.7. MS-ESI: 321($M^+ + 1$).

Table 1. Melting points and yields for quinoxalines **4a-g.**

Run	Product	Yield[a] (%)	MP (°C)
1	 4a	30	144–145[b]
2	 4b	34	193–194
3	 4c	38	188–189
4	 4d	26	163–164
5	 4e	28	164–165[c]
6	 4f	36	183–184
7	 4g	31	193–195

[a]Over the four steps, based on PEG-4500.
[b]Known compound [22], no mp reported.
[c]Known compound [23], no mp reported.

Methyl-2,3-di(2-chlorophenyl)quinoxaline-6-carboxylate, ***4f***

^{1}H NMR (400 MHz, CDCl3): δ = 8.97(d, J = 1.6 Hz, 1*H*), 8.46 (dd, *J* = 8.9, 1.4 Hz, 1*H*), 8.29 (d, *J* = 6.4 Hz, 1*H*), 7.48 – 7.25 (m, 8*H*). ^{13}C NMR (100 MHz): δ = 166.1, 154.4, 153.7, 143.1, 140.5, 136.9, 136.8, 132.9, 132.1, 131.8, 131.3, 131.1, 130.4, 130.1, 130.0, 129.7, 129.6, 126.4, 52.7. MS-EI: 409 (M + H). HRMS (EI): calcd. for $C_{22}H_{14}Cl_2N_2NaO_2$ (M + Na) 431.0330, found 431.0326.

Methyl-2,3-bis(4-dimethylaminophenyl)quinoxaline-6-carboxylate, ***4g***

^{1}H NMR (400 MHz, CDCl3): δ = 8.87(d, J = 1.5 Hz, 1*H*), 8.34 (dd, *J* = 8.2, 1.3 Hz, 1*H*), 8.15 (d, *J* = 8.1 Hz, 1*H*), 7.55 (m, 4*H*), 6.8 (m, 4*H*), 4.03 (s, 3*H*), 3.91 (s, 6*H*). 3.89 (s, 6*H*). ^{13}C NMR (100 MHz): δ = 166.5, 160.6, 160.5, 154.7, 154.0, 143.1, 140.3, 132.4, 132.3, 131.7, 131.4, 131.3, 130.7, 129.2, 129.1, 113.6, 110.9, 55.7, 55.3, 52.6. MS-EI: 427 (M + H). HRMS (EI): calcd. for $C_{26}H_{27}N_4O_2$ (M + H), 427.2134, found, 427.2156.

Conclusion

Multistep microwave-assisted synthesis of quinoxalines on soluble PEG-4500 polymer support is presented. A sequence of microwave-assisted esterification, reduction, and condensation is demonstrated. In each step, the product is separated simply by precipitation, filtration, and washing. This work demonstrates the validity of liquid-phase, polymer-supported synthesis in combination with microwave energy to carry out multistep synthesis in a convenient and efficient way, paving the way to a more environment friendly, automated, parallel, and combinatorial chemistry approaches.

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