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Three Component One-Pot Synthesis of 1-Aryl-4-benzo[*f*]quinoline Derivatives in Glycerol

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A series of 1-aryl-1,2-dihydrobenzo[*f*]quinolin-3(4*H*)one derivatives were synthesized by one-pot muticomponent reaction of Meldrum's acid with benzaldehyde, naphthalene-2-amine in glycerol. Glycerol, a new green organic solvent, it not only acts as a catalyst but also as a recyclable solvent by significantly enhancing the intramolecular cyclization. When compared with classical methods, this method has the advantages of milder reaction conditions, good yields, easy processing and environmental benignity. All compounds were characterized by elemental analysis, FT-IR and ^{1}H NMR spectra.

Keywords: One-pot synthesis, Benzo[*f*]quinoline derivatives, Glycerol.

INTRODUCTION

As a organic reaction medium, the exploration of glycerol is still very limited, but because of its physical and chemical properties of low toxicity, non-corrosibility, non-combustibility, involatile and wide liquid range, glycerol rightly meet the most requirements of ideal green solvents[1]. It was shown[2,3] that glycerol, as reaction medium, can not only increase the reaction rate, but also improve the reaction selectivity. Because of glycerol's lower solubility in non-polar organic solvents and miscible with water, the separation of the products can be realized by organic solvent extraction method or water washing.

Quinoline is a kind of benzopyridine compound with six-membered nitrogen-fused heterocycle. A further combination with aromatic rings or heterocycles makes it become aza-polycyclic compounds like naphthyridine and acridine, which have conjugated structure with rigid plane. Its strong fluorescence and various bioactivities can act as embedded molecule into DNA, fluorescent probe and drug synthesis, *etc*., which has a broad application in medicine and molecular biology[4,5]. Its multi-hydroxy homologs that contain non-planar structure and active carbonyl groups make this kind of compounds possible when further application is used in material science and life science, especially as new synthesized drugs. The application of nitrogen-fused heterocycles has been promising in the aspect of sterilization, antimalaria and anti-neoplasm[6-8].

There have been some reports on the syntheses of 1-aryl-1,2-dihydrobenzo[*f*]quinolin-3(4*H*)one derivatives, such as two-component reaction[9,10]. Zhang *et al.*[11] have completed the synthesis of these compounds by a three-component one-pot reaction at refluxing temperature catalyzed by triethylbenzylammonium chloride (TEBA) in water. Although water is low cost and facile, as well as environmental benignity, most of organic compounds are hydrophobe and triethylbenzylammonium chloride still has some environmental problems, so these disadvantages limited the applied scope of reaction in water.

Recently, we have reported the synthesis of benzo[*f*]quinoline derivatives in PEG-400 media by one-pot reaction and have gotten good results[12]. In this communication, we report a simple and effective method for synthesis of a series of quinoline derivatives by one-pot multicomponent reaction of Meldrum's acid (**1**) with benzaldehyde (**2**), naphthalene-2-amine (**3**) in glycerol media. 1-Aryl-1,2-dihydrobenzo[*f*]-quinolin-3(4*H*)-one derivatives (**4**) were obtained in high yields (Fig. 1).

EXPERIMENTAL

All reagents were obtained commercially and used without further purification. Meldrum's acid **1** were synthesized according to the literature methods[13]. Melting points were measured on an XT-4 electrothermal micromelting-point apparatus and the thermometer was uncorrected. C, H and N analyses were obtained using an Elemental Vario-EL automatic elemental

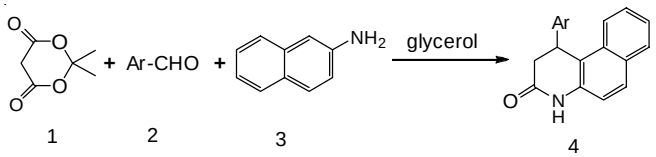

Fig. 1. One-pot synthesis of 1-aryl-1,2-dihydrobenzo[*f*]quinolin-3(4*H*)one derivatives

analysis instrument. FT-IR spectra were recorded using KBr pellets on a Digilab Merlin FT-IR spectrophotometer. ^{1}H NMR spectra were recorded, on a Varian Mercury plus-400 instrument using DMSO or $CDCl_3$ as solvents and TMS as internal standard.

General synthetic procedure for compounds (4a-i): A mixture of meldrum's acid **1** (2 mmol), aromatic aldehyde **2** (2 mmol), naphthalene-2-amine **3** (2 mmol) in glycerol (2 g) was stirred for 12-16 h at 110 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered and the precipitate was washed with water. The crude products were purified by recrystallization from ethanol (95 %) to give products **4a-i**.

1-Phenyl-1,2-dihydrobenzo[*f*]quinolin-3(4*H*)one (4a): Yield: 81 %, m.p. 257-259 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ): 2.65 (d, *J* = 16.0 Hz, 1H, CH_2), 3.20 (dd, *J* = 16.0, 7.6 Hz, 1H, CH_2), 5.05 (d, *J* = 7.6 Hz, 1H, CH), 7.12 (d, *J* = 8.0 Hz, 1H, ArH), 7.24-7.35 (m, 4H, ArH), 7.43-7.50 (m, 3H, ArH), 7.64 (d, *J* = 8.0 Hz, 1H, ArH), 7.89-7.96 (m, 2H, ArH), 10.45 (s, 1H, NH). IR (KBr, ν_{max}, cm^{-1}): 3196, 3061, 2938, 1685 cm^{-1}. Anal. Calcd for $C_{19}H_{15}NO$: C 83.49, H 5.53, N 5.12; found C 83.63, H 5.57, N 5.17.

1-(4-Chlorophenyl)-1,2-dihydrobenzo[*f*]quinolin-3(4*H*)one (4b): Yield: 85 %, m.p. 243-244 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ): 2.53 (d, *J* = 16.8. Hz, 1H, CH_2), 3.19 (dd, *J* = 16.8 Hz, 8.0 Hz, 1H, CH_2), 5.02 (d, *J* = 4.4 Hz, 1H, CH), 7.15 (d, *J* = 8.4 Hz, 2H, ArH), 7.24-7.32 (m, 4H, ArH), 7.46 (t, *J* = 7.6 Hz, 1H, ArH), 7.82 (t, *J* = 7.6 Hz, 1H, ArH), 7.86-7.90 (m, 2H, ArH), 10.46 (s, 1H, NH). IR (KBr, ν_{max}, cm^{-1}): 3196, 3080, 3048, 2942, 2909, 1679 cm^{-1}. Anal. Calcd for $C_{19}H_{14}NOCl$: C 74.15, H 4.58, Cl 11.52, N 4.55; found C 74.32, H 4.55, Cl 11.57, N 4.52.

1-(2,4-Dichlorophenyl)-1,2-dihydrobenzo[*f*]quinolin-3(4*H*)one (4c): Yield: 83 %, m.p. 269-270 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ): 2.55 (d, *J* = 16.4 Hz, 1H, CH_2) 3.27 (dd, *J* = 16.4, 7.6 Hz, 1H, CH_2), 5.31 (d, *J* = 7.6 Hz, 1H, CH), 7.09 (d, *J* = 8.4, 1H, ArH), 7.16 (d, *J* = 8.4, 1H, ArH), 7.24-7.31 (m, 2H, ArH), 7.42-7.50 (m, 1H, ArH), 7.59-7.64 (m, 1H, ArH), 7.73 (s, 1H, ArH), 7.86-7.96 (m, 2H, ArH), 10.52 (s, 1H, NH). IR (KBr, ν_{max}, cm^{-1}): 3167, 3078, 3046, 2949, 2923, 1684. Anal. Calcd for $C_{19}H_{13}NOCl_2$: C 66.68, H 3.83, N 4.09; found C 66.53, H 3.87, N 4.12.

1-(4-Bromophenyl)-1,2-dihydrobenzo[*f*]quinolin-3(4*H*)one (4d): Yield: 82 %, m.p. 245-246 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ): 2.63 (d, *J* = 16.0 Hz, 1H, CH_2), 3.18 (dd, *J* = 16.0, 7.2 Hz, 1H, CH_2), 5.02 (d, *J* = 7.2 Hz, 1H, CH), 7.07 (d, *J* = 8.0 Hz, 2H, ArH), 7.22-7.35 (m, 4H, ArH), 7.49 (t, 1H, ArH), 7.86 (d, *J* = 8.8 Hz, 1H, ArH), 7.82-7.89 (m, 2H, ArH), 10.43 (s, 1H, NH). IR (KBr, ν_{max}, cm^{-1}): 3198, 3076, 3043, 2967, 2912, 1679. Anal. Calcd for $C_{19}H_{14}NOBr$: C 64.79, H 4.01, Br 22.69, N 3.98; found C 64.61, H 4.04, Br 22.66, N 3.83.

1-(4-Fluorophenyl)-1,2-dihydrobenzo[*f*]quinolin-3(4*H*)one (4e): Yield: 85 %, m.p. 254-256 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ): 2.67(d, *J* = 16.0 Hz, 1H, CH_2), 3.19 (dd, *J* = 16.0, 7.6 Hz, 1H, CH_2), 5.06 (d, *J* = 7.6 Hz, 1H, CH), 7.08 (d, *J* = 8.0 Hz, 2H, ArH), 7.08 (d, *J* = 8.0 Hz, 1H, ArH), 7.26 (d, *J* = 8.0 Hz, 2H, ArH), 7.33-7.49 (m, 2H, ArH), 7.67-7.79 (m, 1H, ArH), 7.85-7.92 (m, 2H, ArH), 10.46 (s, 1H, NH). IR (KBr, ν_{max}, cm^{-1}): 3204, 3068, 2995, 2908, 1679. Anal. Calcd for $C_{19}H_{14}NOF$: C 78.33, H 4.84, N 4.81; found C 78.54, H 4.79, N 4.83.

1-(4-Methoxyphenyl)-1,2-dihydrobenzo[*f*]quinolin-3(4*H*)one (4f): Yield: 84 %, m.p. 241-242 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ): 2.67 (d, *J* = 16.4 Hz, 1H, CH_2), 3.14 (dd, *J* = 16.4, 7.2 Hz, 1H, CH_2), 3.72 (s, 3H, CH_3), 4.98 (d, *J* = 7.2 Hz, 1H, CH), 6.86 (d, *J* = 8.8 Hz, 2H, ArH), 7.05 (d, *J* = 8.8 Hz, 2H, ArH), 7.28 (d, *J* = 8.8 Hz, 2H, ArH), 7.33-7.41 (m, 1H, ArH), 7.45-7.52 (m, 1H, ArH), 7.84 (d, *J* = 8.8 Hz, 1H, ArH), 7.88 (d, *J* = 8.8 Hz, 2H, ArH), 10.37 (s, 1H, NH). IR (KBr, ν_{max}, cm^{-1}): 3203, 3086, 2994, 2952, 2906, 1686. Anal. Calcd for $C_{20}H_{17}NO_2$: C 79.19, H 5.65, N 4.62; found C 79.05, H 5.62, N 4.57.

1-(2-Nitrophenyl)-1,2-dihydrobenzo[*f*]quinolin-3(4*H*)one (4g): Yield: 83 %, m.p. 244-246 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ): 2.61 (d, *J* = 16.8 Hz, 1H, CH_2), 3.38 (dd, *J* = 16.4, 8.0 Hz, 1H, CH_2), 5.46 (d, *J* = 5.2 Hz, 1H, CH), 6.84 (d, *J* = 4.0 Hz, 1H, ArH), 7.31-7.56 (m, 6H, ArH), 7.85-7.91 (m, 3H, ArH), 10.8 (s, 1H, NH). IR (KBr, ν_{max}, cm^{-1}): 3215, 3079, 2989, 2944, 1678. Anal. Calcd for $C_{19}H_{14}N_2O_3$: C 79.69, H 4.43, N 8.80; found C 71.53, H 4.41, N 8.83.

1-(3-Nitrophenyl)-1,2-dihydrobenzo[*f*]quinolin-3(4*H*)one (4h): Yield: 86 %, m.p. 270-271 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ): 2.66 (d, *J* = 16.4 Hz, 1H, CH_2), 3.26 (dd, *J* = 16.0, 7.2 Hz, 1H, CH_2), 5.31 (d, *J* = 4.40 Hz, 1H, CH), 7.33-7.58 (m, 5H, ArH), 7.84-8.13 (m, 5H, ArH), 10.56 (s, 1H, NH). IR (KBr, ν_{max}, cm^{-1}): 3198, 3086, 2992, 2933, 1686. Anal. Calcd for $C_{19}H_{14}N_2O_3$: C 79.69, H 4.43, N 8.80; found C 71.57, H 4.46, N 8.83.

1-(4-Nitrophenyl)-1,2-dihydrobenzo[*f*]quinolin-3(4*H*)one (4i): Yield: 84 %, m.p. 257-258 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ): 2.65 (d, *J* = 16.4 Hz, 1H, CH_2), 3.42 (dd, *J* = 16.4, 7.6 Hz, 1H, CH_2), 5.51 (d, *J* = 5.2 Hz, 1H, CH), 6.85 (d, *J* = 8.4 Hz, 2H, ArH), 7.12-7.35 (m, 4H, ArH), 7.34 (t, *J* = 7.6 Hz, 1H, ArH), 7.76 (d, *J* = 7.6 Hz, 1H, ArH), 7.90-8.07 (m, 2H, ArH), 10.58 (s, 1H, NH). IR (KBr, ν_{max}, cm^{-1}): 3205, 3069, 2995, 2939, 1682. Anal. Calcd for $C_{19}H_{14}N_2O_3$: C 79.69, H 4.43, N 8.80; found C 71.57, H 4.41, N 8.76.

RESULTS AND DISCUSSION

We tried the synthesis of **4a** with reactive substrates of aromatic aldehyde, naphthalene-2-amine and Meldrum's acid under different reaction conditions. It was indicated that the yield of 1-phenyl-1,2-dihydrobenzo[*f*]quinolin-3(4*H*)one (**4a**) was been effected by the time and temperature of reaction. The yield was better at higher temperature than that under the conditions of lower temperature and short time. Thereby, we deduced that the desired 1-phenyl-1,2-dihydrobenzo[*f*]quinolin-3(4*H*)one (**4a**) can be obtained at 81 % yield in glycerol for 16 h. In addition, the yield will increase gradually with the

increase of the temperature of reaction, the maximal yield was obtained at 110 °C.

To validate the feasibility of the reaction, we chose different aromatic aldehyde derivatives to react with naphthalene-2-amine and Meldrum's acid, respectively (Table-1). The results show that all reactions have good yields whether benzaldehyde or benzaldehyde substituted by substitutents in the *ortho*, *meta* and *para* positions, which are either electron-withdrawing groups (such as halide) or electron-donating groups (such as alkoxyl group). The influence brought by electronic effect of the substitutents, was not too great for the yields of reactions. It indicated that the experimental conditions have excellent selectivity, we did not obtain the *bis*-substituted products.

TABLE-1
SYNTHESIS OF 1-ARYLBENZO[*f*]QUINOLINE DERIVATIVES **4** IN GLYCEROL AT 110 °C

Product	Ar	Time (h)	Yield (%)
4a	C_6H_5	16	81
4b	4-ClC_6H_4	12	85
4c	2,4-$Cl_2C_6H_3$	13	83
4d	4-BrC_6H_4	12	82
4e	4-FC_6H_4	12	85
4f	4-$CH_3OC_6H_4$	15	84
4g	2-$NO_2C_6H_4$	14	83
4h	3-$NO_2C_6H_4$	14	86
4i	4-$NO_2C_6H_4$	13	84

Reaction conditions: **1** (2 mmol), **2** (2 mmol), **3** (2 mmol), glycerol (2 g)

In summary, This work describes an efficient and environmentally friendly approach for the one-pot multicomponent synthesis of 1-aryl-1,2-dihydrobenzo[*f*]quinolin-3(4*H*)-one derivatives in glycerol. The present method offers attractive features such as excellent yields, simple reaction conditions, environmentally benign and easily work up. Moreover, glycerol not only acts as a catalyst but also as a clean solvent by significantly enhancing the intramolecular cyclization.

The conceivable reaction mechanism for compound **4** had been previously described[12].

Conclusion

A series of 1-aryl-1,2-dihydrobenzo[*f*]quinolin-3(4*H*)one derivatives were synthesized by three-component one-step reaction in glycerol. Compared with the traditional two-component method, this method has the advantages of milder reaction conditions, good yields, easy processing and environmental benignity, *etc*. Compared to the reaction in water by noxious catalyzer (such as triethylbenzylammonium chloride), glycerol is more environmental friendliness, because the dual role of glycerol as reaction solvent and catalyst and glycerol can be recycled. Compared with the one-pot reaction in PEG-400, this method could significantly shorten the reaction time, improve the yield and product separation is more convenient and even the reaction solvent is low-cost and easily accessible. A simple and green but effective synthesis of benzo-[*f*]quinoline derivatives using glycerol as reaction medium is reported.

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