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Abstract: A simple and efficient method was developed for the synthesis of 4-quinolone-3-carboxylic esters and 4-quinolone-3-carbonitriles under microwave (MW) activation using anilines and acrylates as materials. All reactions demonstrated the benefits of microwave reactions: convenient operation, short reaction time, and good yields.

Keywords: Microwave, 4-quinolone, synthesis

INTRODUCTION

The synthesis of substituted 4-quinolones has been of considerable interest to organic and medicinal chemists for many years as a large number of natural products[1,2] and drugs[3,4] contain these heterocyclic cores. Many compounds that possess a 4-quinolone-3-carboxylic acid fragment have been synthesized and evaluated as potential antibacterial agents during the past thirty years,[5,6] and many different substituted quinoline-3-carbonitriles have also been synthesized as the key

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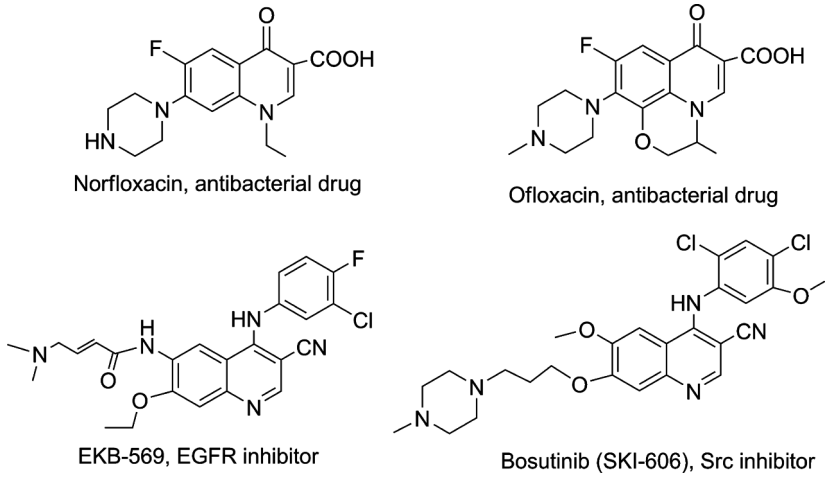


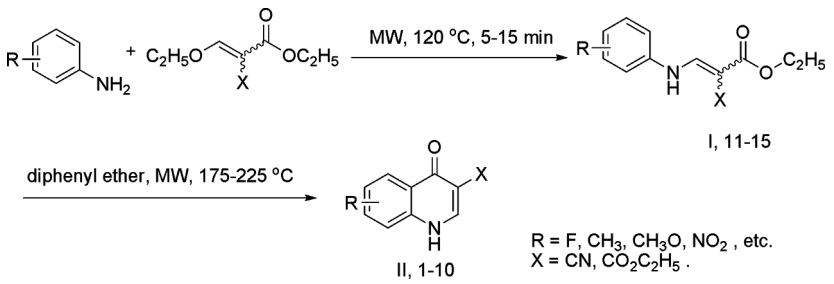
Figure 1. Some quinoline core drugs and drug candidates.

intermediates of protein tyrosine kinase inhibitors, anticancer drugs, in recent years (Fig. 1).[7]

As already described,[8] the 4-quinolone ring construction was generally synthesized by a Gould–Jacobs reaction. This method involved thermal cyclization of aniline derivatives to 4-quinolones under extremely harsh conditions. Reactions were typically carried out in mineral oil, dowtherm, or diphenyl ether at 250°C or greater. The severe reaction conditions made the preparation of the 4-quinolone products difficult. Thus, many different methods have been developed for the synthesis of 4-quinolones.[9–14] However, most of these methods are not satisfactory in terms of yields, reaction conditions, and operational simplicity. For this reason, a simple, general, and efficient procedure for the synthesis of these important heterocyclic compounds is urgently needed.[8–14]

RESULTS AND DISCUSSION

Nowadays, there is an increasing environment need for clean and efficient organic synthesis to replace the traditional synthetic methods. The microwave (MW)–catalyzed reactions have many advantages, and so we report here a convenient procedure under MW irradiation conditions for the synthesis of substituted 4-quinolones. All reactions were carried out using a CEM monomode MW synthesizer with a CEM Discover System workstation.



Scheme 1. Convenient MW-assisted synthesis of 4-quinolones derivatives.

This procedure included two continuous reactions (Scheme 1). The first reaction led to a condensation intermediate **I** in short time under MW irradiation using the readily available aniline and acrylate as raw materials. Most anilines and acrylates ($X = CO_2C_2H_5$, EMME; $X = CN$, 2-cyano-3-ethoxyacrylic acetate) used were liquid at room temperature or had low melting points, and the reaction could be carried out in a solvent-free environment without using poisonous condensation solvents such as benzene or toluene. The power of the CEM MW synthesizer was 30–50 W, the reaction temperature was 120°C, and the pressure within the reaction tube was less than 30 bar. This reaction had a good yield, generally greater than 95%.

This condensation was followed by a cyclization reaction also under MW irradiation in diphenyl ether.[15] The handling of this reaction was convenient, and the brown solid product could be easily recovered by filtration from diphenyl ether and washing with petroleum ether and ethyl acetate twice. Ten different 4-quinolone derivatives (compounds **1**–**10**) were synthesized by this method, and most examples got good yields. The reaction conditions and results are listed in Table 1.

A further one-pot, solvent-free procedure including both reaction steps was also evaluated in the MW irradiation environment, but the transformation rate was not as high. The raw materials disappeared, and the 4-quinolones partly formed, but some products charred even though the reactions were under an N_2 atmosphere. Perhaps because of the high melting points of all 4-quinolone compounds, they would precipitate from the melting condensation intermediates at the reaction temperature and adhere to the surface of reaction tubes when generated. As the solid product increased, the nonhomogeneous phase turned complex and was partly carbonized.

Table 1. Results of MW-assisted cyclization reactions of 4-quinolone derivatives

Compounds (II)	R	X	T (°C)	t (min)	Yield (%)[a]	Traditional cyclization yields (%)[b]
1	H	CN	175	15	58.2	44.5
2	4-Me	CN	235	8	56.6	46.3
3	3-MeO-4-Me	CN	210	30	55.1	38.5
4	3-*i*PrO-4-Me	CN	230	30	76.5	42.0
5	3-*i*PrO-4-MeO	CN	225	30	94.3	40.5
6	3-Cl-4-F	CN	210	20	75.6	46.0
7	2,3,4-Trifluoro	CN	200	20	74.2	48.2
8	H	$CO_2C_2H_5$	190	25	82.8	75.0
9	3-Cl-4-F	$CO_2C_2H_5$	190	25	81.3	72.5
10	2,3,4-Trifluoro	$CO_2C_2H_5$	190	25	85.7	74

[a]All microwave-catalyzed reactions were performed with a CEM microwave synthesizer, and the power used in the reactions was 280 W.

[b]The conventional yields were obtained after thermal cyclization reactions at 250–280°C over 4–10 h.

CONCLUSION

In conclusion, this work demonstrates an easy and convenient method for synthesizing 4-quinolone-3-carboxylic esters and 4-quinolone-3-carbonitriles under MW irradiation. The solvent-free method for the condensation step proved to be more efficient and friendlier to the environment than the classical procedures because it avoids using organic solvents during the reactions. The MW-assisted cyclization reactions take place at relatively low temperatures and with in short times compared to the classical methods. This method also simplifies the handling of the reactions and gets good yields of 4-quinolone derivatives.

EXPERIMENTAL

All purchased starting materials and reagents were used without further purification unless noted. ^{1}H NMR spectra were recorded on an ACF-300 or an ACF-500 Bruker instrument. Chemical shifts are expressed in parts per million (ppm, d units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br s (broad singlet). Mass spectra (MS) were recorded

on Shimadzu GC-MS 2010 (EI) or a Mariner Mass Spectrum (ESI) instruments.

General Procedure for the Condensation Reaction

Both aniline (3 mmol) and acrylates (3 mmol) were put into a 10-ml CEM reaction tube sealed by the rubber stopper. Then MW irradiation was carried out for 5–15 min at 120°C. After that, the tube cooled and a light yellow solid formed in the reaction tube. The crude product was recrystallized by dehydrated alcohol, and then the white solid was formed.

Data for Compounds 11–15

2-Cyano-3-(3-isopropoxy-4-methylphenylamino)-acrylic Acid Ethyl Ester (**11**)

Mp 138°C; MS m/z 288.1; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.30 (m, 9H), 2.08 (s, 3H), 4.21 (m, 2 H), 4.55 (m, 1H), 6.88 (m, 2H), 7.02 (s, 1H), 8.29 (d, $J = 14$ Hz, 1H), 10.68 (bs, 1H).

2-Cyano-3-(3-isopropoxy-4-methoxyphenylamino)-acrylic Acid Ethyl Ester (**12**)

Mp 122–124°C; MS m/z 304.1; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.29 (s, 3H), 1.30 (s, 3H), 1.31 (s, 3H), 4.22–4.24 (m, 2H), 4.48–4.50 (m, 1H), 6.56–6.57 (m, 1H), 6.79–6.81 (d, $J = 7$ Hz, 1H), 7.67–7.69 (d, $J = 13$Hz, 1H), 10.58 (s, 1H).

2-Cyano-3-(2,3,4-trifluorophenylamino)-acrylic Acid Ethyl Ester (**13**)

Mp 118°C; MS m/z 270.1; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28–1.33 (t, 3H), 4.22–4.29 (q, 2H), 6.83–7.03 (m, 2H), 7.69–7.73 (d, $J = 13$ Hz, 1H), 10.79 (b, 1H).

2-Cyano-3-(3-chloro-4-fluorophenylamino)-acrylic Acid Ethyl Ester (**14**)

Mp 114°C; MS m/z 268.1; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25–1.32 (t, 3H), 4.19–4.26 (q, 2H), 6.96–7.08 (m, 2H), 7.19–7.20 (m, 1H), 8.18–8.23 (d, $J = 14$ Hz, 1H), 8.45 (bs, 1H).

2-Cyano-3-(3-methoxy-4-methylphenylamino)-acrylic Acid Ethyl Ester (**15**)

Mp 124°C; MS m/z 260.1; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25–1.32 (t, 3H), 2.11 (s, 3H), 3.78 (s, 3H), 4.19–4.26 (q, 2H), 6.43–6.44 (d, $J = 2$ Hz, 1H), 6.51–6.54 (dd, 1H), 7.03–7.06 (d, $J = 8$ Hz, 1H), 8.29–8.34 (d, $J = 15$ Hz, 1H), 10.67 (b, 1H).

General Procedure for the Cyclization Reaction

The intermediate **I** (1 mmol) and diphenyl ether (8 mL) were put into a 10-mL CEM reaction tube sealed by the rubber stopper. Then MW irradiation was carried out for 15–30 min at 175–225°C. After that, the tube cooled, and there was a brown solid on the inner wall of the tube. The solid was collected by filtration and washed with petroleum ether and ethyl acetate twice. The crude product was further purified by column chromatography with ethyl acetate and methanol.

Data for Compounds 1–10

4-Quinolone-3-carbanitrile (**1**)

Mp > 280°C, (lit.[15] mp 306–308°C); MS m/z 170.1; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.46–7.51 (dd, 1H), 7.62–7.65 (d, 1H), 7.76–7.81 (m, 1H), 8.12–8.15 (m, 1H), 8.73 (s, 1H), 12.81 (bs, 1H).

6-Methyl-4-quinolone-3-carbanitrile (**2**)

Mp > 280°C; MS m/z 184.2; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.43 (s, 3H), 7.55–7.60 (d, $J = 13$ Hz, 2H), 7.93 (s, 1H), 8.68 (s, 1H), 12.75 (bs, 1H).

7-Methoxy-6-methyl-4-quinolone-3-carbonitrile (**3**)

Mp > 280°C; MS m/z 214; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.24 (s, 3H), 4.00 (s, 3H), 6.95 (s, 1H), 7.87 (s, 1H), 8.61 (s, 1H), 12.54 (bs, 1H).

7-Isopropoxy-6-methyl-4-quinolone-3-carbonitrile (**4**)

Mp > 280°C; MS m/z 242.1; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.35 (s, 3H), 1.37 (s, 3H), 2.21 (s, 3H), 4.66–4.68 (m, 1H), 7.00 (s, 1H), 7.87 (s, 1H), 8.60 (s, 1H), 12.46 (bs, 1H).

7-Isopropoxy-6-methoxy-4-quinolone-3-carbonitrile (**5**)

Mp > 280°C; MS m/z 258.1; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.31 (s, 3H), 1.32 (s, 3H), 3.81 (s, 3H), 4.65–4.67 (m, 1H), 7.05 (s, 1H), 7.41 (s, 1H), 8.55 (s, 1H).

6-Fluoro-7-chloro-4-quinolone-3-carbonitrile (**6**)

Mp > 280°C; MS m/z 222.1; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.84–7.86 (d, $J = 6$ Hz, 1H), 7.96–7.99 (d, $J = 9$ Hz, 1H), 8.80 (s, 1H), 12.95 (bs, 1H).

6,7,8-Trifluoro-4-quinolone-3-carbonitrile (**7**)

Mp > 280°C; MS m/z 224.1; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.87–7.95 (dd, 1H), 8.73 (s, 1H).

4-Quinolone-3-carboxylic Acid Ethyl Ester (**8**)

Mp 273–275°C, (lit.[6] mp 275–276°C).

6-Fluoro-7-chloro-4-quinolone-3-carboxylic Acid Ethyl Ester (**9**)

Mp > 280°C, (lit.[16] mp 290–291°C); MS m/z 269.0; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.56–1.58 (t, 3H), 4.71 (q, 2H), 8.35 (s, 1H), 8.37 (s, 1H), 9.36 (1H).

6,7,8-Trifluoro-4-quinolone-3-carboxylic Acid Ethyl Ester (**10**)

Mp 203–205°C, (lit.[16] mp 205–206°C); MS m/z 271.1; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.58–1.59 (t, 3H), 4.74–4.76 (q, 2H), 7.98–8.01 (dd, 1H), 8.78 (s, 1H).

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