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Rapid microwave-enhanced synthesis of 4-hydroxyquinolinones under solvent-free conditions

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Abstract—3-Aryl-4-hydroxyquinolin-2(1*H*)-ones are potent and selective glycine-site NMDA receptor antagonists of pharmaceutical interest. A novel microwave-enhanced synthesis of such quinolinones under solvent-free conditions has been developed. The quinolinones are easily obtained in a one-pot procedure as a result of the formal amidation of a malonic ester derivative with an aniline and subsequent cyclisation of the intermediate malondianilides.

Microwave irradiation of organic reactions has rapidly gained in popularity as it accelerates a variety of synthetic transformations.[1,2] Solventless procedures[3] without the use of supporting reagents are particularly eco-friendly. Herein, we report the first microwave enhanced formation of 3-aryl-4-hydroxyquinolin-2(1*H*)-ones from anilines and malonic ester derivatives using solvent-free conditions without the need to add supported reagents. This microwave-enhanced reaction that normally requires many hours at reflux temperatures in a high boiling organic solvent (e.g. diphenyl ether) under classical conditions[4] or the addition of methane sulfonic acid/phosphorus pentoxide mixtures was found to be completed in 15 minutes in a microwave. In general, the work-up conditions consist of simple filtration as we often observed product precipitation from the reaction mixture during the microwave reactions.

4-Hydroxyquinolin-2(1*H*)-ones have attracted considerable interest for various pharmacological targets including glycine NMDA receptor antagonists[5–7] and serotonin (5-HT_3) receptor antagonists.[8] In addition, 3-aryl-4-hydroxyquinolin-2(1*H*)-ones have recently been found[9] to serve as key intermediates in the synthesis of non-peptide GnRH (Gonadotropin releasing hormone) receptor antagonists. Such compounds are of interest for the treatment of sex hormone related conditions.

Our synthetic procedure involves the irradiation of a mixture of the aniline compound and malonic ester starting material in a microwave oven. Preliminary optimisation of reaction conditions was performed using 3-chloroaniline and diethyl phenylmalonate

Table 1. General synthesis of 4-hydroxyquinolin-2(1*H*)-ones produced via Scheme 1

Entry	R[a]	R[1]	R[2]	Yield[b] (%)
1[7,10–14]	H	H	Ph	83
2	2-Cl	H	Ph	0
3[12,15,16]	2-OMe	H	Ph	45
4	2-CF_3	H	Ph	0
5[4,5,12]	3-Cl	H	Ph	81
6[12,14–16]	3-OMe	H	Ph	92
7[12]	3-F	H	Ph	52
8[4,12]	3-CF_3	H	Ph	13
9[14]	4-Cl	H	Ph	72
10[12,14–16]	4-OMe	H	Ph	40
11	4-CF_3	H	Ph	0
12[10,12,13,17–19]	H	CH_3	Ph	79
13[12]	H	*n*-C_4H_9	Ph	57
14[20]	H	Cyclohexyl	Ph	8
15[12]	2-$CH_2CH_2CH_2$-		Ph	88
16[7]	3-Cl	H	4-OCH_3-C_6H_4	94
17[7]	3-Cl	H	4-CH_3-C_6H_4	78
18[5]	3-Cl	H	3-OPh-C_6H_4	25
19[21]	3-Cl	H	3-Thienyl	45

[a] The aniline substitution pattern is indicated.
[b] All yields refer to isolated pure products.

Keywords: anilides; MDL-104,653; microwave heating; quinolinones.
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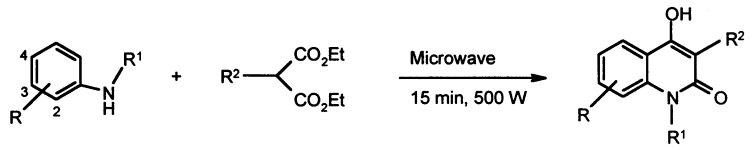
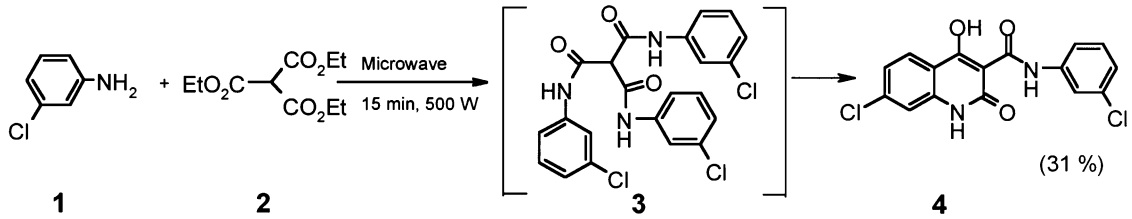


Scheme 1.



Scheme 2.

(entry 5 in Table 1). Optimal conditions for the synthesis were found to be 15 min reaction time using 500 W of microwave irradiation power. These optimal conditions were then applied for the synthesis of a range of 3-substituted 4-hydroxyquinolinones depicted in Table 1. It is interesting to note that the yield of this reaction strongly depends on the relative amount of the starting materials used (a 2:1 molar ratio of the diethyl phenylmalonate versus 3-chloroaniline gave the optimal yield (81%) of 7-chloro-4-hydroxy-3-phenylquinolin-2(1*H*)-one). The temperature during this particular reaction is approximately 290°C. It is essential to work in an open vessel to enable the formed ethanol to escape from the reaction mixture. In a closed vessel the reaction does not proceed at all. The results in Scheme 1/Table 1 illustrate the scope of this synthetic conversion.

The multi-gram synthesis of 7-chloro-4-hydroxy-3-phenylquinolin-2(1*H*)-one (this compound is known[6] as the glycine NMDA receptor antagonist MDL-104,653) is representative (entry 5 in Table 1). A mixture of 3-chloroaniline (2.10 mL, 20.0 mmol) and diethyl phenylmalonate (8.62 mL, 40.0 mmol) is stirred and irradiated in a microwave oven (Type: Milestone Ethos 900) for 15 min at 500 W power under a gentle stream of nitrogen (in order to effectively remove the formed ethanol during the reaction). The mixture is allowed to attain room temperature and diluted with diethyl ether. The precipitate is collected by filtration and washed with diethyl ether to furnish pure 7-chloro-4-hydroxy-3-phenylquinolin-2(1*H*)-one (4.36 g, 81%) as white crystals.

The results from Table 1 reveal that the microwave-assisted synthesis provides an efficient way to access a variety of 4-hydroxy-3-arylquinolin-2(1*H*)-ones under solvent-free conditions. The results indicate that electron-donating groups on the aniline ring lead to the desired products in high yields. The presence of the electron-withdrawing trifluoromethyl group on the aniline ring has a deactivating effect on the final electrophilic aromatic cyclisation. These reactions (entries 4, 8 and 11, respectively) remain at the intermediate malondianilide stage.

The synthesis of Merck's well known glycine NMDA receptor antagonist L-701,324 (entry 18) is illustrative. L-701,324 could be easily prepared in one step according to our microwave procedure, whereas the reported synthetic procedure[5] comprises several reaction steps.

N-Substituted anilines react nicely, although the sterically bulky cyclohexyl group (entry 14) leads to a low yield. The use of 1,2,3,4-tetrahydroquinoline leads to the formation of 1-hydroxy-2-phenyl-6,7-dihydro-5*H*-benzo[*ij*]quinolizin-3-one[12] in a high yield (entry 15). Disappointingly, diethyl malonate and diethyl alkylmalonates (wherein $R^2 = n$-butyl, *t*-butyl or benzyl) were found not to react with *m*-chloroaniline under these conditions. These findings may be rationalised by invoking the additional degree of conjugation that is present between the 3-aryl group and the quinolin-2(1*H*)-one moiety, which obviously is absent in the case where R^2 is alkyl or benzyl. This phenomenon prompted us to investigate the potential impact of conjugation in more detail. Therefore, we studied the reaction[22] of 3-chloroaniline **1** with triethyl methanetricarboxylate **2**. This reaction gave the formation of **4** in 31% yield (Scheme 2). The formation of **4** is rationalised[4] by initial amidation of **2** to provide the intermediate malontrianilide **3**, followed by cyclisation to give 7-chloro-*N*-(3-chlorophenyl)-1,2-dihydro-4-hydroxy-2-oxo-3-quinoline-carboxamide **4**.[23]

In conclusion, a rapid and practical procedure for the synthesis of 4-hydroxy-3-arylquinolin-2(1*H*)-ones from anilines and malonic ester derivatives under microwave irradiation conditions was developed, which involves solvent-free conditions without the need to add supported reagents.

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20. Selected analytical data for 1-cyclohexyl-4-hydroxy-3-phenylquinolin-2(1*H*)-one: mp 198°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.22–1.34 (m, 1H), 1.40–1.52 (m, 2H), 1.64–1.74 (m, 3H), 1.84–1.92 (m, 2H), 2.50–2.70 (m, 2H), 4.50 (br s, 1H), 7.21 (t, $J=8$ Hz, 1H), 7.28–7.42 (m, 5H), 7.56 (t, $J=8$ Hz, 1H), 7.68 (br s, 1H), 8.25 (d, $J=8$ Hz, 1H), 9.80 (br s, 1H). MS (ESI-): m/z 318. MS (EI): m/z 319, 237. HRMS (EI): calcd for $C_{21}H_{21}NO_2$ (M^+) 319.1572; found 319.1577.
21. Selected analytical data for 7-chloro-4-hydroxy-3-(3-thienyl)quinolin-2(1*H*)-one: mp>300°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.16 (dd, $J=8$ Hz, $J=2$ Hz, 1H), 7.32 (d, $J=2$ Hz, 1H), 7.43–7.46 (m, 2H), 7.73 (m, 1H), 7.97 (d, $J=8$ Hz, 1H), 10.35 (br s, 1H), 11.55 (s, 1H); MS (ESI-): m/z 276. MS (EI): m/z 277. HRMS (EI): calcd for $C_{13}H_8ClNO_2S$ (M^+) 276.9964; found 276.9944.
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