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Microwave assisted synthesis of 4-quinolones and N,N′-diarylureas

Abstract: 4-Quinolinones are an important class of alkaloids, widely used as conventional drugs to treat various infectious diseases. In this study, we report the synthesis of 4-quinolones in one step, under microwave irradiation and with diphenyl ether as a solvent, using ethyl acetoacetate and electron rich anilines. When anilines containing alkyl or electron withdrawing substituents were employed, only N,N′-diarylureas were obtained in moderate to good yields.

Keywords: 4-Quinolinones; microwave; N,N′-diarylureas.

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1 Introduction

4-Quinolinones an important class of alkaloids, are widely used as conventional drugs to treat various infectious diseases [1, 2]. They are the first choice of chemotherapeutic agents for the treatment of a broad range of bacterial infections, and play a pivotal role in the development of new inhibitors [3, 4]. Continuous modifications in the basic structure of quinolones have increased their antibacterial spectrum and potency, making them useful for the treatment of urinary, systemic and respiratory tract infections, resulting in second, third and fourth-generation quinolone antibiotics, which are currently on the market [5]. Besides the antibacterial activity, several reports have shown the antiparasitic activity of 4-quinolinones [6–11]. The toxicity of 4-quinolinones is comparable to other commonly used antimicrobial agents; therefore, they can be considered well-tolerated [12].

Despite the importance of the 4-quinolinone scaffold, several synthetic methods have already been reported in literature, e.g., condensation of o-nitroacetophenone with *N,N*-dimethylformamide dimethyl acetal, yielding enaminones, which are submitted to reductive cyclization under catalytic transfer hydrogenation conditions [13]. In a similar way, 4-quinolines **1** can also be obtained from anilines and β-ketoester, furnishing the corresponding ethyl β-anilinocrotonates **2**, which undergo intramolecular cyclization under reflux of diphenyl ether [14] or microwave irradiation (Scheme 1) [15].

Since the appearance of the first article on the application of microwaves for chemical synthesis in polar solvents [16], the approach has blossomed into a useful technique for a variety of applications in organic synthesis and functional group transformations. The focus has lately shifted to less cumbersome solvent-free methods, wherein the neat reactants, often in the presence of mineral oxides or supported catalysts, undergo facile reactions to provide high yields of pure products, thus eliminating or minimizing the use of organic solvents [17].

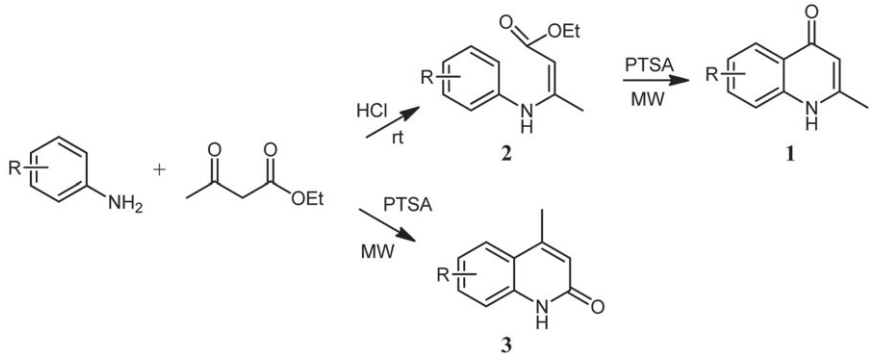
Varma and Saini reported the conversion of 2′-aminochalcones to 2-aryl-1,2,3,4-tetrahydro-4-quinolones under mild and solvent-free conditions, on a montmorillonite K 10 clay surface and under microwave irradiation [18].

Darque et al. synthesized bent and linear tricyclic quinolinones by a two step method involving microwave irradiation and evaluated their biological properties [19]. Recently, we reported the synthesis of 4-quinolinones from 2′-aminoacetophenone and acyl chlorides. The corresponding acylated 2′-aminoacetophenones were submitted to microwave irradiation in the presence of potassium *terc*-butoxide (tBuOK) furnishing the 2-substituted-4-quinolinones [20].

Nadaraj and Selvi [15] reported that only 2-quinolone derivatives **3** are produced in one step under microwave irradiation using a domestic oven, from anilines and β-ketoester without solvent. Furthermore, Sapkal et al. described a $NaHSO_4/SiO_2$-catalyzed solvent-free synthesis of 2-methylquinolin-4(1H)-one derivatives **1** under microwave irradiation [21].

2 Experimental

Unless otherwise noted, all commercially available reagents were purchased from Aldrich Chemical Co (St. Louis, MO, USA). Reagents and solvents were purified when necessary according to the usual procedures described in the literature. ^1H and ^{13}C NMR spectra were recorded on



Scheme 1

a Bruker ARX-400 (400 and 100 MHz, respectively). The IR spectra refer to films and were measured on a Bomem M102 spectrometer. Mass spectra were recorded on a Shimadzu GCMS-QP5000. Elemental analyses were performed on a Fisons EA 1108 CHNS-O. Analytical thin-layer chromatography was performed on a 0.25 µm film of silica gel containing the fluorescent indicator UV_{254} supported on an aluminum sheet (Sigma-Aldrich). Flash column chromatography was performed using silica gel (Kieselgel 60, 230–400 mesh, E. Merck, Darmstadt, Germany). Gas chromatography was performed in a Shimadzu GC-17A, with H_2 as carrier and using a DB-5 column. Melting points were performed in Microquimica MQAPF – 301. Reactions were irradiated in a focused microwave oven CEM Discover.

3 General procedure

A mixture of aniline (1 eq), ethyl acetoacetate (1 eq), acetic acid (0.01 eq), in diphenyl ether (1 ml) was irradiated with microwave at 300 W in an open flask. The reaction development was carefully accompanied. It was observed that the temperature varied (see Tables 1–3) for 3–5 min, and then became stable. Then the reaction mixture was allowed to cool, and the resulting precipitate was washed with hexane, ethyl acetate, and methanol. The organic phase was concentrated to give the product.

6-methoxy-2-methylquinolin-4(1*H*)-one (1a) [21]: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.33 (s, 3H), 3.82 (s, 3H), 5.87 (s, 1H), 7.25 (dd, 1H, *J* 2.91, 6.25 Hz), 7.44–7.46 (m, 2H), 11.54 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 19.5, 56.4, 99.3, 100.2, 111.0, 114.9, 126.7, 133.9, 148.5, 157.8, 170.4. IR (ν_{max},KBr): 520.7, 567.0, 829.3, 1033.7, 1081.9, 1178.4, 1222.7, 1299.9, 1384.7, 1471.5, 1510.1, 1552.5, 1596.9, 1618.1, 2983.6, 2991.3, 3105.1, 3253.6 cm^{-1}.

5,7-dimethoxy-2-methylquinolin-4(1*H*)-one (1b) [22]: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.18 (s, 3H), 3.72 (s, 3H), 3.78 (s, 3H), 5.64 (s, 1H), 6.23 (d, 1H, *J* 2.08 Hz), 6.42 (d, 1H, *J* 2.08 Hz), 11.09 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 18.6, 55.2, 55.5, 91.2, 93.9, 110.2, 112.9, 144.2, 146.5, 160.8, 161.5, 176.6.

6-methyl-[1,3]dioxolo[4,5-g]quinolin-8(5*H*)-one (1c) [23]: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.27 (s, 3H), 5.81 (s, 1H), 6.10 (s, 2H), 6.90 (s, 1H), 7.32 (s, 1H), 11.44 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 18.1, 92.7, 98.1, 98.4, 107.0, 124.4, 139.0, 146.6, 150.0, 152.2, 174.6. IR (ν_{max},KBr): 561.2, 578.6, 829.3, 937.3, 1045.3, 1213.1, 1261.3, 1413.7, 1475.4, 1523.6, 1622.0, 2771.5 cm^{-1}.

5,7-difluoro-2-methylquinolin-4(1*H*)-one (1d): ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.27 (s, 3H), 5.82 (s, 1H), 6.97–7.04 (m, 2H), 11.64 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 19.5, 99.0, 100.1, 105.0, 117.2, 146.3, 147.0, 158.9, 159.4, 161.4, 162.1, 175.2.

1,3-bis(4-fluorophenyl)urea (3a) [24]: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.07–7.13 (m, 4H); 7.41–7.47 (m, 4H) 8.67 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): 115.1, 115.3, 119.9, 120.0, 135.9, 152.6, 156.1, 158.5.IR (ν_{max},KBr): 516.8, 653.8, 831.2, 1211.2, 1512.0, 1573.8, 1631.6, 3292.2 cm^{-1}.

1,3-bis(2-bromophenyl)urea (3b) [25]: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.14–7.31 (m, 6H); 7.83 (t, 2H, *J* 1.66 Hz); 8.93 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): 111.1, 114.9, 124.2, 129.1, 131.2, 142.2, 148.5.IR (ν_{max},KBr): 522.6, 684.6, 788.8, 1226.6, 1286.4, 1475.4, 1546.8, 1581.5, 1635.5, 3288.3 cm^{-1}.

1,3-bis(4-*n*-propylphenyl)urea (3c) [26]: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.94 (t, 6H, *J* 7.39 Hz), 1.57 (sex, 4H, *J* 7.39 Hz), 2.59 (t, 4H, *J* 7.39 Hz), 7.00 (ddd, 2H, *J* 1.09, 2.47, 6.43 Hz), 7.12–7.18 (m, 4H), 7.64–7.66 (m, 2H), 8.12 (s, 2H).

Table 1 Conditions employed in the microwave assisted reactions.

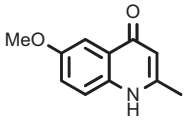
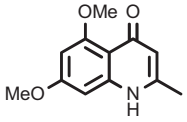
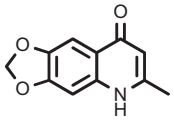
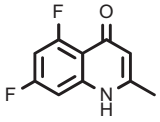
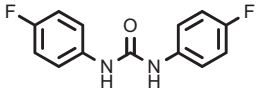
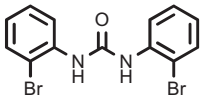
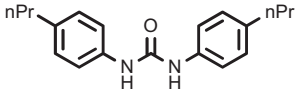
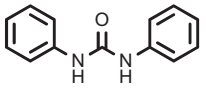
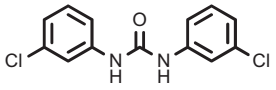
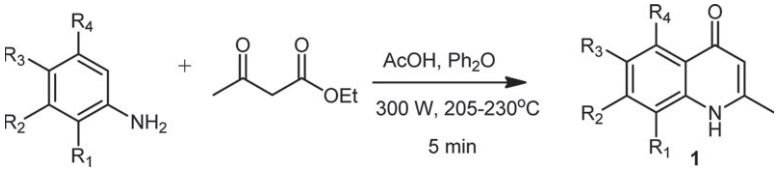
Entry	Aniline	Ethyl acetoacetate (mmol)	Time (min)	Temperature (°C)	Product	Yield (%)
1	4-methoxy	0.81	5	220	 **1a**	75
2	3,5-dimethoxy	0.70	5	215	 **1b**	71
3	3,4-methylenedioxy	0.73	5	230	 **1c**	62
4	3,5-difluoro	0.90	5	205	 **1d**	25
5	4-fluoro	0.85	3	235	 **3a**	82
6	2-bromo	0.87	4	220	 **3b**	73
7	4-n-propyl	0.74	3	250	 **3c**	85
8	–	0.70	5	242	 **3d**	76
9	3-chloro	0.78	4	240	 **3e**	58

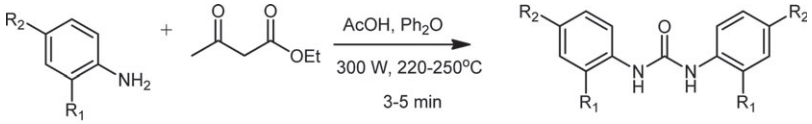
Table 2 Synthesis of 4-quinolinones.



Compound	R_1	R_2	R_3	R_4	Temperature (°C)	Yield (%)[1]
1a	H	H	OMe	H	210	75
1b	H	OMe	H	OMe	205	71
1c	H	OCH_2CH_2O	$R_2=R_3=OCH_2CH_2O$	H	205	62
1d	H	F	H	F	230	25

[1]Isolated yield after purification by filtration.

Table 3 Synthesis of *N,N′*-diarylureas.



3

Compound	R_1	R_2	Time (min)	Temperature (°C)	Yield (%)[1]
3a	H	F	5	240	82
3b	H	Br	5	250	73
3c	H	^{n}Pr	3	220	85
3d	H	H	3	235	76
3e	Cl	H	5	250	58

[1]Isolated yield after purification by filtration.

^{13}C NMR (100 MHz, DMSO-d_6): 13.7, 22.5, 32.8, 123.3, 123.4, 126.0, 129.2, 133.1, 136.7, 153.5.IR (ν_{max},KBr): 748.3, 1120.5, 1245.9, 1448.4, 1552.5, 1585.3, 1639.3, 2869.8, 2931.5, 2960.5, 3305.7 cm^{-1}.

1,3-diphenylurea (3d) [24]: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.07–7.14 (m, 5H); 7.44–7.49 (m, 5H); 8.69 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): 118.2, 120.0, 127.8, 135.9, 152.6.IR ($\nu_{max,}$KBr): 520.7, 613.3, 752.1, 954.6, 1162.9, 1294.1, 1361.6, 1452.2, 1483.1, 1581.5, 1614.3, 1647.0, 3338.5 cm^{-1}.

1,3-bis(3-chlorophenyl)urea (3e): ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.02 (dt, 2H, *J* 1.67, 7.29 Hz), 7.25–7.32 (m, 4H); 7.69 (t, 2H, *J* 1.80 Hz); 8.95 (s, 2H). ^{13}C NMR(100 MHz, DMSO-d_6): 117.2, 120.6, 121.6, 124.5, 130.6, 133.0, 141.0, 152.1.IV ($\nu_{max,}$KBr): 570.8, 823.5, 1029.9, 1180.3, 1243.9, 1328.8, 1456.1, 1510.1, 1541.0, 1606.5, 1650.9, 1689.5, 3276.8 cm^{-1}.

4 Results and discussion

Based on previous results, we decided to reinvestigate the one-step synthesis of 4-quinolinones from substituted anilines and ethyl acetoacetate, using Ph_2O and acetic acid under microwave irradiation. Employing electron donor substituted anilines, 4-quinolones **1** were obtained in good isolated yield after irradiation for 5 min at 205–240°C using 300 W of potency (Table 2). By using, 2,4-difluoraniline, the corresponding 4-quinolinone was obtained in only a 25% yield.

When the reaction of 4-methoxyaniline with ethyl acetoacetate in acetic acid was carried out without solvent, the corresponding 2-quinolinone was obtained in 58% isolated yield, as reported by Nadaraj and Selvi [15].

Surprisingly, with alkyl or electron withdrawing substituents as halogens, *N,N′*-diarylureas **3** were formed in moderate to good yields (Table 3). Sarveswari and Raja reported the synthesis of *N,N′*-diarylureas under microwave irradiation, using a domestic microwave oven, in solvent free conditions [27]. The proposed mechanism for the *N,N′*-diarylureas is the formation of acetoacetanilides as intermediates which react with a second equivalent of aniline, followed by the loss of acetone. Phenyl thiazolylurea derivatives have been reported as inhibitors of murine receptor A and B [28]. Some substituted ureas are used as antidiabetics and tranquilizing drugs, antioxidants in gasoline, corrosion inhibitors and herbicides [29].

5 Conclusion

This study showed that 4-quinolones are produced in one step, under microwave irradiation and with diphenyl ether as solvent, using two different β-ketoesters only, with electron rich anilines. When other anilines were employed, *N,N′*-diarylureas were obtained in moderate to good yields.

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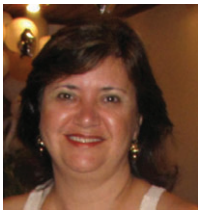

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