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Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 16 (2006) 2925–2928

New potential biologically active compounds: Design and an efficient synthesis of N-substituted 4-aryl-4,6,7,8-tetrahydroquinoline-2,5(1*H*,3*H*)-diones under microwave irradiation

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Received 5 January 2006; revised 20 February 2006; accepted 1 March 2006
Available online 24 March 2006

Abstract—A series of N-substituted 4-aryl-4,6,7,8-tetrahydroquinoline-2,5(1*H*,3*H*)-diones were synthesized through a rapid one-pot four-component reaction under microwave irradiation. The method has the advantages of excellent yields (82–96%) and short reaction time (4–9 min). We provide new series of potential biologically active compounds for biomedical screening.

Various quinolone derivatives are known[1] to display interesting biological properties ranging from microbial activity to cytotoxicity. As a member of the quinolone family, 4-aryl-quinoline-2(1*H*)-ones are modulators of the large-conductance, calcium-activated potassium (Maxi-K and BK) channels and are potentially useful in the treatment of diseases which arise from dysfunction of cellular membrane polarization and conductance.[2] Extensive interest in the synthesis of new drugs based on 4-aryl-quinoline-2(1*H*)-one moiety continues to increase.

It is well known that N-substituted-2-quinolone, compared with parent nucleus, possesses significant differences in pharmacological activities, for example substituted *N*-phenyl-2-quinolones represent the structural basis of many biologically active compounds, such as protein kinase inhibitors, immunomodulators, anti-ulcer agents, hypoglycemics, farnesyl transferase inhibitors, and antiviral agents.[3] Since the synthesis of 4-aryl-1,2,3,4,5,6,7,8–octahydroquinoline-2,5-diones has been reported by Suarez[4] and us,[5] a question that arose was whether slight modification on the nitrogen of the octahydroquinoline-2,5-dione may bring significant changes in pharmacological activities and may provide new classes of biologically active compounds for biomedical screening.

However, the introduction of a functional group to the nitrogen atom of the octahydroquinoline-2,5-dione has seldom been reported and so far only the introduction of an aromatic ring to the nitrogen of the octahydroquinoline-2,5-dione has been investigated.[6] As a consequence, the interest of further investigations is needed in order to provide vast new compounds with peculiar properties for biomedical screening.

The diversity generating potential of multicomponent reactions (MCRs) has been recognized and their utility in preparing libraries to screen for functional molecules is well appreciated.[7–9] Microwave irradiation of organic reactions has rapidly gained popularity as it accelerates a variety of synthetic transformations.[10] The microwave-enhanced procedures without the use of catalyst are particularly eco-friendly and the protocol has the advantages of short reaction time and high yield.[11]

In connection with our previous studies, we describe here a facile MCR of aldehydes, Meldrum's acid, dimedone, and different amines in 95% ethanol without catalyst under microwave conditions[12] to afford a new series

Keywords: Quinolone; Microwave irradiation; Potential biologically active; Biomedical screening.
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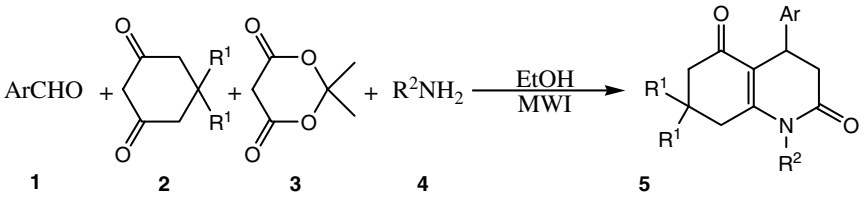
doi:10.1016/j.bmcl.2006.03.011



1 2 3 4 5

Scheme 1. Synthetic route of 4-aryl-2-quinolone derivatives **5**.

of heterocyclic compounds, the N-substituted 4-aryl-tetrahydroquinoline-2,5-dione derivatives (Scheme 1).

The results (Table 1) show that a number of different aldehydes including electrophilic, electron-donating, and hetero-aromatic aldehydes were allowed to participate in the reaction. It is particularly noteworthy that the protocol can be applied for different amines (including aliphatic and alicyclic amines) but also for aromatic amines which highlight the wide scope of this four-component condensation. For comparison, we performed the reaction for synthesizing **5b** under both MWI (78 °C) and classical heating mode by ethanol refluxing. As a result, we found that the reaction was efficiently promoted by MWI and the reaction time was strikingly shortened to 15 min from 3 h required in traditional heating condition and the yields were remarkably increased to 80% from 56%. When the temperature was increased from 78 to 90 °C under microwave irradiation, we found that the yield was increased and the time was shortened. In order to search for the optimized condition for its reaction, we tested various temperatures. We found that the reaction performed at 100 °C furnished the best result.

Due to Meldrum's acid's $pK_a = 9.9$ and dimedone's $pK_a = 11.5$, the activity of methylene of Meldrum's acid is stronger than that of dimedone's.[4] So this reaction may occur via a condensation, addition, cyclization, and elimination mechanism (Scheme 2). The condensation between aldehyde **1** and Meldrum's acid **3** gave intermediate **6**. Michael addition between **6** and **7**, obtained from dimedone **2** and amine **4**, furnished **8**. The intermediate **8** isomerized to **9**, which further isomerized to **10**. Intramolecular cyclodehydration of the intermediate **10** released acetone and carbon dioxide, and gave compound **5**. In order to confirm the proposed mechanism, we proceeded with the reaction of **6a** and **7a** in ethanol under similar condition (Scheme 3). To our delight, we achieved identical results and obtained the target compound **5a**. Consequently, our proposed mechanism may be rational.

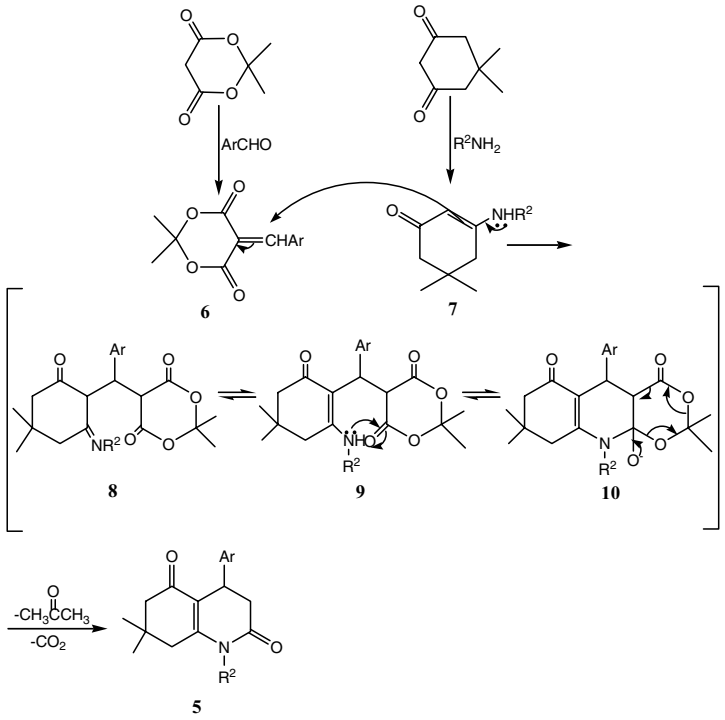
In this reaction, a small detail should bring to attention. The boiling points of methylamine and cyclopropylamine are 48 and 49 °C, respectively. They are easy to volatilize and the yields were greatly influenced. So we convert them into hydrochloride salt and then add NaOAc to liberate the free amines.

All the products were characterized by IR, ^{1}H NMR analysis. Furthermore, the structures of **5a**[13] (Fig. 1) and **5o**[14] (Fig. 2) were confirmed by an X-ray crystallographic analysis.[15].

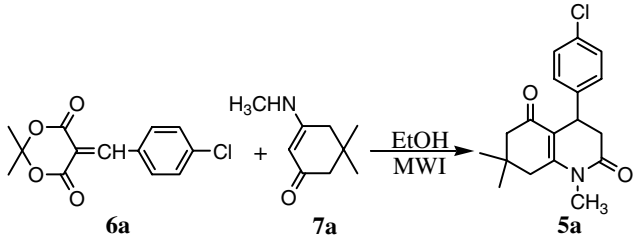
In summary, we have developed a sequential four-component reaction of aldehydes, Meldrum's acid, dimedone, and amines in a small amount of 95% ethanol by employing microwave irradiation. In addition, high yields of the products, short reaction times, ease of work-up, and low-cost[16] make the above method advantageous in comparison to the traditional heating method. This reaction realized the introduction of functional group on the nitrogen of octahydroquinolone

Table 1. Synthesis of **5** under microwave irradiation

Compound	Ar	R^1	R^2	Time (min)	Yield (%)	Mp (°C)
5a	4-Cl–C_6H_4	CH_3	CH_3	4	95	175.4–176.0
5b	4-OCH_3–C_6H_4	CH_3	CH_3	8	95	127.3–128.0
5c	4-F–C_6H_4	CH_3	CH_3	5	96	166.6–167.1
5d	4-Br–C_6H_4	CH_3	CH_3	6	96	207.1–207.8
5e	3-NO_2–C_6H_4	CH_3	CH_3	7	93	126.2–127.0
5f	C_6H_5	CH_3	CH_3	6	92	152.0–153.0
5g	2,4-Cl_2–C_6H_3	CH_3	CH_3	7	90	125.8–127.4
5h	4-CH_3–C_6H_4	CH_3	CH_3	6	92	196.0–197.0
5i	3,4-$(OCH_3)_2$–C_6H_3	CH_3	CH_3	9	82	198.3–199.8
5j	2-Thiofuran	CH_3	CH_3	7	85	128.0–129.0
5k	4-F–C_6H_4	H	Cyclopropyl	4	92	154.1–155.0
5l	4-ClC_6H_4	CH_3	Cyclopentyl	6	90	143.0–144.6
5m	4-BrC_6H_4	CH_3	Cyclopentyl	7	89	157.9–158.5
5n	C_6H_5	CH_3	Cyclopentyl	6	88	132.2–133.2
5o	4-F–C_6H_4	CH_3	Cyclopentyl	8	92	131.9–132.7
5p	2-ClC_6H_4	CH_3	Cyclopentyl	9	85	164.3–165.1
5q	4-BrC_6H_4	CH_3	Cyclohexyl	7	92	163.0–164.1
5r	2,4-$Cl_2C_6H_3$	CH_3	4-$CH_3C_6H_4$	5	90	206.1–207.2



Scheme 2.



Scheme 3. Synthetic route of compound **5a** yield, 96%; time, 3 min.

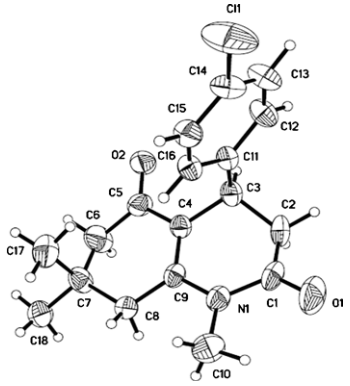


Figure 1. The structure of **5a**.

derivatives. The new series of N-substituted 4-aryl-4,6,7,8-tetrahydroquinoline-2,5(1*H*,3*H*)-diones may prove to be of biological interest and provide new classes of biologically active compounds for biomedical screening.

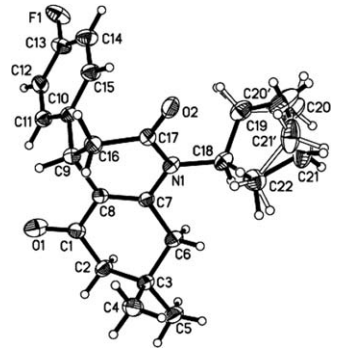


Figure 2. The structure of **5o**.

Crystallographic data for the structures of **5a** and **5o** reported in this letter have been deposited at the Cambridge Crystallographic Data Center as supplementary publication with No. CCDC-290312, CCDC-294134, respectively. Copies of available material can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0) 1223336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgments

We thank the National Science Foundation of China (No. 20372057), Natural Science Foundation of the Jiangsu Province (No. BK 2001142), the Natural Science Foundation of Jiangsu Education Department (No. 01KJB150008), and the Key Laboratory of Chemical Engineering and Technology of the Jiangsu

Province Open Foundation (No. KJS02060) for financial support.

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12. All microwave reactions were performed on an Emrys Optimizer (Personal Chemistry, Available from: <http://www.personalchemistry/>).
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15. The single-crystal growth was carried out in ethanol at room temperature. X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Semens P4 diffractometer. Crystal data for **5a**: $C_{18}H_{20}ClNO_2$, yellow, crystal dimension $0.29 \times 0.25 \times 0.17$ mm, orthorhombic, space group Pca2(1), $a = 17.492(3)$, $b = 9.805(2)$, $c = 9.634(2)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 1652.3(7)$ Å^3, $M_r = 317.80$, $Z = 4$, $Dc = 1.278$ g/cm^3, $\lambda = 0.71073$ Å, μ(Mokα) = 0.238 mm^{-1}, $F(000) = 672$, $R_1 = 0.0591$, $wR_2 = 0.1491$. Crystal data for **5o**: $C_{22}H_{26}FNO_2$, yellow, crystal dimension $0.28 \times 0.26 \times 0.24$ mm, monoclinic, space group P2(1)/*n*, $a = 10.3031(16)$, $b = 10.7991(17)$, $c = 17.207(3)$ Å, $\alpha = \gamma = 90°$, $\beta = 101.942(3)°$, $V = 1873.1(5)$ Å^3, $M_r = 355.44$, $Z = 4$, $Dc = 1.260$ g/cm^3, $\lambda = 0.71073$ Å, μ(Mokα) = 0.087 mm^{-1}, $F(000) = 760$, $R_1 = 0.0447$, $wR_2 = 0.1011$.
16. The general procedure is represented below: All reactions were performed in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. In a 10 mL Emrys™ reaction vial, aldehyde (2 mmol), Meldrum's acid (2 mmol), dimedone (2 mmol), and amine (2 mmol) in 95% ethanol (5 mL) were mixed and then capped. The mixture was irradiated for 4–9 min at 200 W power and 100 °C. The reaction mixture was cooled to room temperature and the solid product was filtered, and then washed with ether. It was recrystallized by DMF and dried to give the pure product. All products are characterized by IR and ^{1}H NMR spectral data. Spectra of five compounds are summarized as follows:
Compound **5a**. Mp: 175.4–176.0 °C; IR (KBr, ν, cm^{-1}): 2962, 2896, 1690, 1619, 1487, 1459, 1301, 1198, 1107, 838; ^{1}H NMR (DMSO-d_6) (δ, ppm): 7.31 (d, 2H, $J = 8.4$ Hz, ArH), 7.12 (d, 2H, $J = 8.4$ Hz, ArH), 4.17 (t, 1H, $J = 7.2$ Hz, CH), 3.13 (s, 3H, NCH_3), 2.96 (dd, 1H, $J = 16.0$ Hz, $J = 7.6$ Hz, $NCOCH_2$), 2.84 (dd, 1H, $J = 17.6$ Hz, $J = 8.0$ Hz, $NCOCH_2$), 2.62 (d, 1H, $J = 16.0$ Hz, $^8CH_2$), 2.53 (d, 1H, $J = 16.4$ Hz, $^8CH_2$), 2.29 (d, 1H, $J = 16.0$ Hz, $COCH_2$), 2.17 (d, 1H, $J = 16.0$ Hz, $COCH_2$), 1.09 (s, 3H, CH_3), 1.07 (s, 3H, CH_3).
Compound **5k**. Mp: 154.1–155.0 °C; IR (KBr, ν, cm^{-1}): 3041, 2977, 1772, 1656, 1601, 1541, 1507, 1463, 805; ^{1}H NMR (DMSO-d_6) (δ, ppm): 7.08 (d, 2H, $J = 8.4$ Hz, ArH), 7.06 (d, 2H, $J = 8.4$ Hz, ArH), 4.10 (t, 1H, $J = 6.4$ Hz, CH), 3.06 (dd, 1H, $J = 16.0$ Hz, $J = 4.4$ Hz, $NCOCH_2$), 2.87 (dd, 1H, $J = 16.4$ Hz, $J = 6.8$ Hz, $NCOCH_2$), 2.75 (d, 1H, $J = 16.0$ Hz, $^8CH_2$), 2.70 (d, 1H, $J = 16.0$ Hz, $^8CH_2$), 2.57 (d, 1H, $J = 16.8$ Hz, $COCH_2$), 2.41 (d, 1H, $J = 16.0$ Hz, $COCH_2$), 2.35–2.30 (m, 1H, NCH), 2.06–2.01 (m, 2H, $^7CH_2$), 0.98–0.91 (m, 2H, CH_2), 0.61–0.30 (m, 2H, CH_2).
Compound **5m**. Mp: 157.9–158.5 °C; IR (KBr, ν, cm^{-1}): 2960, 2926, 1684, 1646, 1490, 1408, 1366, 844; ^{1}H NMR (DMSO-d_6) (δ, ppm): 7.45 (d, 2H, $J = 8.8$ Hz, ArH), 7.08 (d, 2H, $J = 8.4$ Hz, ArH), 4.19 (t, 1H, $J = 8.0$ Hz, CH), 4.15–4.09 (m, 1H, NCH), 2.99 (dd, 1H, $J = 16.0$ Hz, $J = 7.2$ Hz, $NCOCH_2$), 2.91 (dd, 1H, $J = 16.4$ Hz, $J = 7.2$ Hz, $NCOCH_2$), 2.52 (d, 1H, $J = 11.6$ Hz, $^8CH_2$), 2.39 (d, 1H, $J = 16.4$ Hz, $^8CH_2$), 2.35 (d, 1H, $J = 17.2$ Hz, $COCH_2$), 2.14 (d, 1H, $J = 16.0$ Hz, $COCH_2$), 1.79–1.47 (m, 8H, 4× CH_2), 1.13 (s, 3H, CH_3), 1.04 (s, 3H, CH_3).
Compound **5q**. Mp: 163.0–164.1 °C; IR (KBr, ν, cm^{-1}): 2931, 2850, 1692, 1616, 1486, 1346, 1287, 1086, 982, 840; ^{1}H NMR (DMSO-d_6) (δ, ppm): 7.43 (d, 2H, $J = 8.4$ Hz, ArH), 7.13 (d, 2H, $J = 8.4$ Hz, ArH), 4.49 (t, 1H, $J = 8.0$ Hz, CH), 4.12–4.04 (m, 1H, NCH), 2.97 (dd, 1H, $J = 16.8$ Hz, $J = 7.2$ Hz, $NCOCH_2$), 2.87 (dd, 1H, $J = 16.0$ Hz, $J = 7.2$ Hz, $NCOCH_2$), 2.51 (d, 1H, $J = 5.6$ Hz, $^8CH_2$), 2.49 (d, 1H, $J = 7.2$ Hz, $^8CH_2$), 2.36 (d, 1H, $J = 16.0$ Hz, $COCH_2$), 2.26 (d, 1H, $J = 16.8$ Hz, $COCH_2$), 2.22–2.18 (m, 10H, 5× CH_2), 1.12 (s, 3H, CH_3), 1.04 (s, 3H, CH_3).
Compound **5r**. Mp: 206.1–207.2 °C; IR (KBr, ν, cm^{-1}): 2964, 2872, 1715, 1645, 1622, 1510, 1373, 1265, 1191, 1094, 781, 759; ^{1}H NMR (DMSO-d_6) (δ, ppm): 7.57 (d, 1H, $J = 8.4$ Hz, ArH), 7.42–7.32 (m, 3H, ArH), 7.23 (dd, 2H, $J = 21.6$ Hz, $J = 6.8$ Hz, ArH), 7.03 (d, 1H, $J = 7.2$ Hz, ArH), 4.58 (t, 1H, $J = 7.6$ Hz, CH), 3.33 (dd, 1H, $J = 13.2$ Hz, $J = 3.6$ Hz, $NCOCH_2$), 2.59 (dd, 1H, $J = 16.0$ Hz, $J = 4.0$ Hz, $NCOCH_2$), 2.51 (dd, 1H, $J = 16.0$ Hz, $J = 5.6$ Hz, $^8CH_2$), 2.43 (dd, 1H, $J = 17.6$ Hz, $J = 6.8$ Hz, $^8CH_2$), 2.38 (s, 3H, Ar-CH_3), 2.15 (d, 1H, $J = 16.0$ Hz, $COCH_2$), 1.99 (d, 1H, $J = 17.6$ Hz, $COCH_2$), 1.01 (s, 3H, CH_3), 0.98 (s, 3H, CH_3).