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A multi-component reaction for the synthesis of N-substituted furo[3,4-*b*]quinoline derivatives under microwave irradiation

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Abstract—A series of new N-substituted furo[3,4-*b*]quinoline derivatives were synthesized via a three-component reaction of an aldehyde, an enamineone and tetronic acid in glacial acetic acid under microwave irradiation without a catalyst. This new protocol has the advantages of shorter time, higher yields, lower cost and broader substrate scope, as well as easier operation.

Multi-component reactions (MCRs) play an increasingly important role in organic and medicinal chemistry for their high degree of atom economy, convergence, productivity, ease of execution, excellent yields and broad applications in combinatorial chemistry.[1] The microwave (MW) assisted organic synthesis has been a topic of continued studies as it could lead to higher yields of pure products, easier operation and shorter reaction time as compared to the traditional heating methods.[2] Use of MW irradiation for the formation of carbon–heteroatoms, especially carbon–nitrogen bonds, has been reported.[3]

Tetronic acid derivatives and their metabolites are interesting because of their antibiotic,[4,5] anticoagulant,[6] antiepileptic,[7] antifungal,[8] insecticidal,[9] analgesic[10] and anti-inflammatory activities.[11] Recently, these compounds have also been reported as HIV-1 protease inhibitors.[12]

Podophyllotoxin is an antitumour lignan that inhibits microtubule assembly.[13] Attempts to use it for the treatment of human neoplasia were mostly unsuccessful and were complicated by side effects. Extensive structural modifications have been performed in order to obtain more potent and less toxic anticancer agents.[14] Among them, 4-aza-podophyllotoxin derivatives, which were reported as powerful DNA topoisomerase inhibitors have recently attracted much attention. For example, Takeya and co-workers[15] reported the synthesis of aza-podophyllotoxin (Fig. 1) via condensation, cyclization and reduction. This method was less efficient. Tratrat et al.[16] also reported the synthesis of aza-podophyllotoxin by one-pot reaction of aldehyde, tetronic acid and aniline in refluxing ethanol with the limitation that aniline must be substituted in the *meta*-position by electron-donating groups. The action mechanism of aza-podophyllotoxin is entirely different from that of the parent natural podophyllotoxin, which suggests that the substitution of carbon atom at position 4 of podophyllotoxin by nitrogen atom would bring about great changes in the biological profile. In view of the important biological properties of the aza-podophyllotoxin derivatives, the modifications on the scaffold of aza-analogue may also bring significant changes in pharmacological activities, which have not been reported.

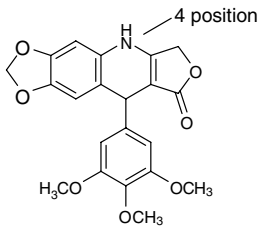

Figure 1. Structure of aza-podophyllotoxin.

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In order to get the new derivatives with furo[3,4-*b*]quinoline motif, we herein described a facile MCR consisting of aldehyde **1**, tetronic acid **2** and enamineone[17] **3** in glacial acetic acid under microwave irradiation without using a catalyst (Scheme 1).

Choosing an appropriate solvent is of crucial importance for successful MW promoted synthesis in view of a rapid rise of temperature in the reaction mixture. In order to search for the optimum solvent, the MW assisted reaction of 4-bromophenyl aldehyde **1b**, tetronic acid **2** and 3-(*p*-tolylamino)-5,5-dimethylcyclohex-2-enone **3** was examined using water, glycol, DMF, glacial acetic acid and ethanol as solvent, respectively, at 80 °C. All the reactions were carried out at the maximum power of 300 W. The results are summarized in Table 1.

It is shown in Table 1 that the reaction with glacial acetic acid as solvent resulted in the most excellent yield and shortest reaction time. Therefore, acetic acid was chosen as the solvent of this reaction.

To optimize the reaction temperature, the reaction of 4-bromophenyl aldehyde **1b**, tetronic acid **2**, 3-(*p*-tolylamino)-5,5-dimethylcyclohex-2-enone **3** was carried out using glacial acetic acid as solvent at temperatures ranging from 70 to 120 °C, with an increment of 10 °C each time. The results are shown in Table 2.

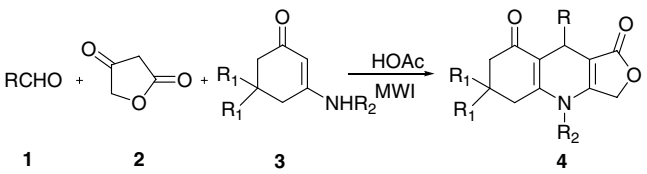
We found that the yield of product **4b** was improved and the reaction time was shortened as the temperature was increased from 70 to 100 °C. The yield plateaued when the temperature was further increased to 110 and 120 °C. Therefore, the most suitable reaction temperature should be 100 °C.

The power of microwave irradiation was optimized by carrying out the same reaction for synthesizing **4b** at 50, 100, 150, 200, 250 and 300 W, respectively, using glacial acetic acid as a solvent at 100 °C (Table 3).

When the power was at 50–150 W, the time taken for the temperature to reach 100 °C was too long. Microwave irradiation at 200 W gave the highest yield. Therefore, microwave power of 200 W was chosen as the optimum power.

Under these optimized reaction conditions, a series of furo[3,4-*b*]quinoline derivatives **4** were synthesized. The results are summarized in Table 4.

To examine the efficiency and the applicability of this new three-component cyclocondensation reaction, a series of different aldehydes and enamineones were tested in glacial acetic acid. As shown in Table 4, this protocol could be applied not only to the aromatic aldehydes with either electron-withdrawing groups or electron-donating groups, but also to heterocyclic and aliphatic aldehydes. Furthermore, it was particularly noteworthy that the protocol could be applied to aromatic amine, aliphatic amine, alicyclic amine and aminoacetic acid, which highlighted the wide scope of this three-component condensation. Cyclohexane-1,3-dione and dimedone were used in this reaction, which all got excellent results. Therefore, we concluded that the electronic nature of the substituents of aldehydes and enamineones has no significant effect on this reaction.



Scheme 1.

Table 1. Solvent optimization for the synthesis of **4b** under MWI at 80 °C

Entry	Solvent	Power (W)	Time (min)	Yield (%)
1	HOAc	300	10	84
2	Glycol	300	12	60
3	Water	300	15	60
4	DMF	300	14	57
5	EtOH	300	15	50

Table 2. Temperature optimization for the synthesis of **4b** under MWI in glacial acetic acid

Entry	T (°C)	Power (W)	Time (min)	Yield (%)
1	70	300	12	78
2	80	300	10	84
3	90	300	8	93
4	100	300	5	97
5	110	300	6	96
6	120	300	5	97

Table 3. Power optimization for the synthesis of **4b** under MWI at 100 °C in glacial acetic acid

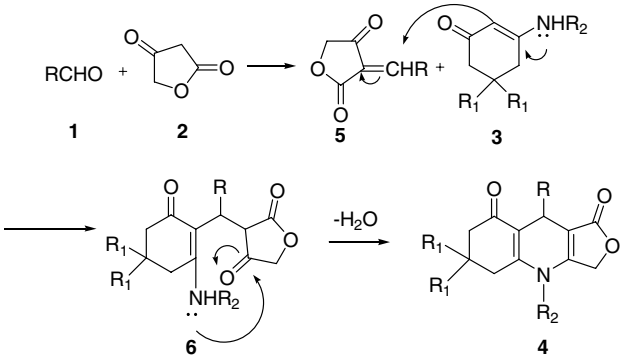
Entry	Power (W)	Time (min)	Yield (%)
1	50	10	82
2	100	10	90
3	150	10	93
4	200	10	95
5	250	10	92
6	300	10	91

Moreover, we performed the synthesis of **4** under both MWI and classical heating conditions at 100 °C. The reactions were efficiently promoted by MWI and the reaction time was strikingly shortened to 5–9 min from 3 to 5 h required under traditional heating conditions and the yields were increased to 90–98% from 37% to 56%. Therefore, microwave irradiation exhibited several advantages over the conventional heating by significantly reducing the reaction time and dramatically improving the reaction yield owing to a specific nonthermal microwave effect.

Although the detailed mechanism of the above reaction remains to be fully clarified, the formation of N-substituted furo[3,4-*b*]quinoline derivatives could be explained by a possible reaction sequence presented in Scheme 2.

Table 4. Synthesis of **4** under microwave irradiation[18]

Entry	R	R_1	R_2	Time (min)	Yield (%)	Mp (°C)
4a	4-$CH_3OC_6H_4$	CH_3	4-$CH_3C_6H_4$	5	97	256–257
4b	4-BrC_6H_4	CH_3	4-$CH_3C_6H_4$	6	96	269–270
4c	3-$NO_2C_6H_4$	CH_3	4-$CH_3C_6H_4$	5	97	232–233
4d	Thiophen-2-yl	CH_3	4-$CH_3C_6H_4$	6	96	>300
4e	4-ClC_6H_4	CH_3	C_6H_5	8	98	260–261
4f	4-$CH_3OC_6H_4$	CH_3	C_6H_5	5	95	258–259
4g	3-$NO_2C_6H_4$	CH_3	C_6H_5	5	93	293–294
4h	$CH_3CH_2CH_2CH_2$	CH_3	C_6H_5	7	90	250–251
4i	4-ClC_6H_4	CH_3	4-ClC_6H_4	8	96	>300
4j	4-BrC_6H_4	CH_3	4-ClC_6H_4	6	96	>300
4k	4-BrC_6H_4	CH_3	Cyclopropyl	6	95	286–287
4l	C_6H_5	CH_3	Cyclopropyl	8	94	287–288
4m	4-$CH_3OC_6H_4$	CH_3	Cyclopropyl	8	93	268–269
4n	3-$NO_2C_6H_4$	CH_3	Cyclopropyl	5	93	272–273
4o	4-BrC_6H_4	CH_3	CH_2COOH	6	94	>300
4p	3-$NO_2C_6H_4$	CH_3	CH_2COOH	7	97	>300
4q	4-ClC_6H_4	CH_3	CH_3	8	90	232–233
4r	4-ClC_6H_4	H	4-$CH_3C_6H_4$	5	95	274–275
4s	C_6H_5	H	4-$CH_3C_6H_4$	9	92	280–281
4t	4-$CH_3OC_6H_4$	H	4-$CH_3C_6H_4$	8	95	254–255
4u	Thiophen-2-yl	H	4-$CH_3C_6H_4$	9	93	250–251
4v	4-BrC_6H_4	H	C_6H_5	8	92	280–281
4w	4-FC_6H_4	H	C_6H_5	8	92	257–258
4x	C_6H_5	H	C_6H_5	7	90	275–276
4y	4-BrC_6H_4	H	Cyclopropyl	6	92	228–229
4z	4-ClC_6H_4	H	Cyclopropyl	7	93	210–211
4aa	4-ClC_6H_4	H	CH_2COOH	9	92	289–290
4bb	4-ClC_6H_4	H	4-ClC_6H_4	7	93	227–228



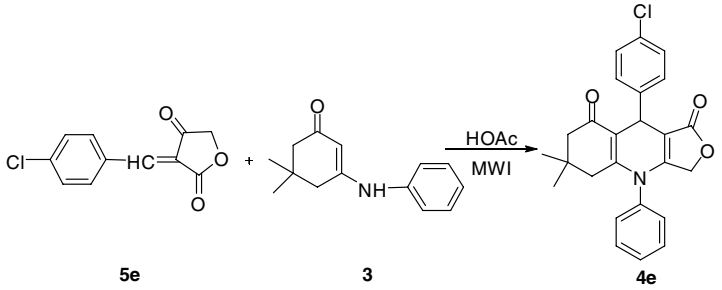
Scheme 2.

Compound **4** may be synthesized via sequential condensation, addition, cyclization and elimination. The condensation between aldehyde **1** and tetronic acid **2** gave intermediate **5**. Michael addition between **5** and **3** furnished **6**, which upon intermolecular cyclization and dehydration gave rise to **4**.

To test the proposed mechanism, we carried out the reaction of **5e** and **3** in glacial acetic acid under similar conditions. The target compound **4e** was obtained with yield similar to the one-pot reaction. The fact supported the proposed mechanism (Scheme 3).

In this study, all the products were characterized by IR spectra, ^1H NMR data and elemental analyses. Furthermore, the structure of **4d** was established by an X-ray crystallographic analysis.[19] The molecular structure of **4d** is shown in Figure 2.

In conclusion, we developed a sequential three-component reaction of an aldehyde, tetronic acid and an enamineone in a small amount of glacial acetic acid under microwave irradiation. Particularly valuable



Scheme 3.

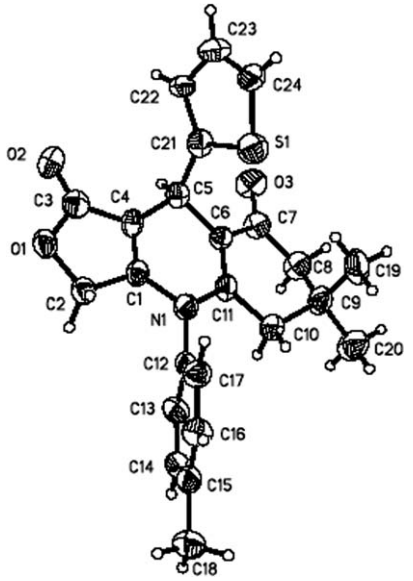


Figure 2. ORTEP diagram of **4d**.

features of this method include excellent yields of products, shorter reaction time and easier operation. This reaction realized the modification on the scaffold of aza-podophyllotoxin. The new series of N-substituted furo[3,4-*b*]quinoline derivatives may provide new classes of biologically active compounds for biomedical screening. This work is currently in progress and the results will be reported in due course.

Acknowledgements

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18. The general procedure for **4** was as follows: All reactions were performed in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Typically, in a 10-mL Emrys™ reaction vial, aldehyde **1** (1 mmol), tetronic acid **2** (1 mmol), enamineone **3** (1 mmol) and glacial acetic acid (2 mL) were mixed and then capped. The mixture was irradiated at 200 W at 100 °C for a given time. The reaction mixture was cooled to room temperature and poured into water (50 mL), filtered to give the crude product, which was further purified by recrystallization from EtOH to give pure N-substituted furo[3,4-*b*]quinoline derivatives **4**. All products were characterized by IR spectra, ^{1}H NMR data and elemental analyses. Compound **4b**: Mp: 269–270 °C; ^{1}H NMR: δ 7.48 (d, 2H, $J =$ 8.0 Hz, ArH), 7.45–7.36 (m, 4H, ArH), 7.30 (d, 2H, $J = 8.0$ Hz, ArH), 4.75 (s, 1H, CH), 4.55–4.52 (m, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.23–2.19 (m, 2H, CH_2), 2.08–

2.02 (m, 2H, CH_2), 0.92 (s, 3H, CH_3), 0.84 (s, 3H, CH_3). IR: (KBr, ν, cm^{-1}): 3447, 2956, 1750, 1683, 1547, 1541, 1511, 843. Anal. Calcd for $C_{26}H_{24}BrNO_3$: C, 65.28; H, 5.06; N, 2.93. Found C, 65.32; H, 5.02; N, 2.91. Compound **4f**: Mp: 258–259 °C; ^{1}H NMR: δ 7.59–7.54 (m, 5H, ArH), 7.24 (d, 2H, $J = 8.4$ Hz, ArH), 6.85 (d, 2H, $J = 8.4$ Hz, ArH), 4.72 (s, 1H, CH), 4.59–4.47 (m, 2H, CH_2), 3.72 (s, 3H, CH_3), 2.26–2.19 (m, 2H, CH_2), 2.09–2.00 (m, 2H, CH_2), 0.92 (s, 3H, CH_3), 0.85 (s, 3H, CH_3). IR: (KBr, ν, cm^{-1}): 2956, 1737, 1680, 1640, 1579, 1509, 1493, 838, 799, 774. Anal. Calcd for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.06; N, 3.37. Found C, 74.89; H, 6.13; N, 3.41. Compound **4i**: Mp: >300 °C; ^{1}H NMR: δ 7.67–7.59 (m, 4H, ArH), 7.38–7.33 (m, 4H, ArH), 4.76 (s, 1H, CH), 4.63–4.53 (m, 2H, CH_2), 2.26–2.19 (m, 2H, CH_2), 2.09–2.04 (m, 2H, CH_2), 0.93 (s, 3H, CH_3), 0.85 (s, 3H, CH_3). IR: (KBr, ν, cm^{-1}): 2956, 1737, 1680, 1640, 1579, 1509, 1493, 838, 799, 774. Anal. Calcd for $C_{25}H_{21}Cl_2NO_3$: C, 66.09; H, 4.66; N, 3.08. Found C, 66.18; H, 4.59; N, 3.12. Compound **4k**: Mp: 286–287 °C; ^{1}H NMR: δ 7.41 (d, 2H, $J = 8.4$ Hz, ArH), 7.08 (d, 2H, $J = 8.4$ Hz, ArH), 5.27–5.02 (m, 2H, CH_2), 4.67 (s, 1H, CH), 3.05–3.00 (m, 2H, CH_2), 2.75–2.70 (m, 1H, CH), 2.16–2.09 (m, 2H, CH_2), 1.08–1.06 (m, 2H, CH_2), 1.04 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.00–0.90 (m, 2H, CH_2). IR: (KBr, ν, cm^{-1}): 2954, 1776, 1676, 1573, 1480, 838, 799, 774. Anal. Calcd for $C_{22}H_{22}BrNO_3$: C, 61.69; H, 5.18; N, 3.27. Found C, 61.75; H, 5.09; N, 3.18. Compound **4o**: Mp: >300 °C; ^{1}H NMR: δ 13.55 (s, 1H, COOH), 7.42 (d, 2H, $J = 8.4$ Hz, ArH), 7.22 (d, 2H, $J = 8.4$ Hz, ArH), 5.07–4.85 (m, 2H, CH_2), 4.65 (s, 1H, CH), 4.48 (s, 2H, CH_2), 2.68–2.45 (m, 2H, CH_2), 2.24–2.05 (m, 2H, CH_2), 1.02 (s, 3H, CH_3), 0.90 (s, 3H, CH_3). IR: (KBr, ν, cm^{-1}): 3321, 2956, 1737, 1680, 1640, 1579, 1509, 1493, 838, 799, 774. Anal. Calcd for $C_{21}H_{20}BrNO_5$: C, 56.52; H, 4.52; N, 3.14. Found C, 56.45; H, 4.61; N, 3.22. Compound **4t**: Mp: 254–255 °C; ^{1}H NMR: δ 7.44–7.39 (m, 4H, ArH), 7.24 (d, 2H, $J = 8.4$ Hz, ArH), 6.84 (d, 2H, $J = 8.4$ Hz, ArH), 4.75 (s, 1H, CH), 4.42–4.59 (m, 2H, CH_2), 3.72 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.28–2.23 (m, 2H, CH_2), 2.19–2.14 (m, 2H, CH_2), 1.91–1.69 (m, 2H, CH_2). IR: (KBr, ν, cm^{-1}): 2940, 2921, 2834, 1744, 1682, 1608, 1511. Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N, 3.49. Found C, 74.65; H, 5.81; N, 3.52. Compound **4w**: Mp: 257–258 °C; ^{1}H NMR: 7.58–7.52 (m, 5H, ArH), 7.40–7.36 (m, 2H, ArH), 7.13–7.08 (m, 2H, ArH), 4.82 (s, 1H, CH), 4.60–4.50 (m, 2H, CH_2), 2.34–2.28 (m, 2H, CH_2), 2.25–2.15 (m, 2H, CH_2), 1.91–1.71 (m, 2H, CH_2). IR: (KBr, ν, cm^{-1}): 3059, 2952, 2894, 1744, 1684, 1639, 1599, 1508. Anal. Calcd for $C_{23}H_{18}FNO_3$: C, 73.59; H, 4.83; N, 3.73. Found C, 73.52; H, 4.95; N, 3.80. Compound **4y**: Mp: 228–229 °C; ^{1}H NMR: δ 7.40 (d, 2H, $J = 8.0$ Hz, ArH), 7.09 (d, 2H, $J = 8.0$ Hz, ArH), 5.26–5.00 (m, 2H, CH_2), 4.68 (s, 1H, CH), 3.13–3.05 (m, 2H, CH_2), 2.86–2.79 (m, 1H, CH), 2.34–2.25 (m, 2H, CH_2), 1.97–1.94 (m, 2H, CH_2), 1.08–1.00 (m, 2H, CH_2), 0.94–0.88 (m, 2H, CH_2). IR: (KBr, ν, cm^{-1}): 3097, 2930, 1751, 1674, 1633, 1567, 1507, 1483. Anal. Calcd for $C_{20}H_{18}BrNO_3$: C, 60.01; H, 4.53; N, 3.50. Found C, 60.11; H, 4.46; N, 3.48.

19. Crystal data for **4d**: $C_{24}H_{23}NO_3S$, red, crystal dimension $0.32 \times 0.21 \times 0.18$ mm, Monoclinic, space group c_2/c, $a = 26.12(2)$ Å, $b = 12.566(11)$ Å, $c = 15.496(11)$ Å, $\alpha = \gamma = 90°$, $\beta = 122.43(5)°$, $V = 4293(6)$ Å^3, $M_r = 405.49$, $Z = 8$, $D_c = 1.255$ Mg/m^3, $\lambda = 0.71073$ Å, μ(Mo K_α) = 0.175 mm^{-1}, $F(0\,0\,0) = 1712$, $1.85° < \theta < 25.01°$, $R = 0.0769$, $wR_2 = 0.1905$, $S = 0.920$, largest diff. Peak and hole: 0.228 and −0.375 e/Å^3. Crystallographic data for the structure of **4d** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-609065.