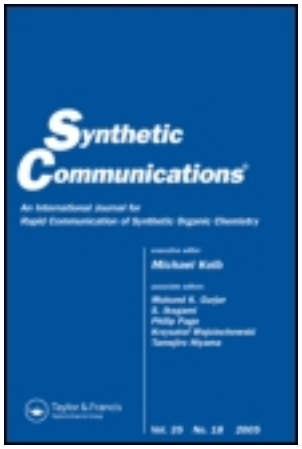

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Unexpected and Green Synthesis of Azapodophyllotoxin Derivatives via Microwave-Assisted Multicomponent Reactions in Ammonia Water

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UNEXPECTED AND GREEN SYNTHESIS OF AZAPODOPHYLLOTOXIN DERIVATIVES VIA MICROWAVE-ASSISTED MULTICOMPONENT REACTIONS IN AMMONIA WATER

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An unexpected and green synthesis of azapodophyllotoxin derivatives was realized via microwave-assisted multicomponent reactions of dimedone, tetronic acid, and aromatic aldehydes in ammonia water. This protocol has the advantages of environmental friendliness, short reaction time, good yields, low cost, and easy operation.

Keywords: Azapodophyllotoxin; green synthesis; microwave irradiation; water

INTRODUCTION

In recent years, microwave-assisted synthesis in water as solvent has been investigated because it combines the two prominent green chemistry principles of ''safer solvents'' and ''energy efficiency.''[1] Besides the general advantages of water and microwave irradiation (MWI),[2] several important benefits are expected when combining them together.[3] In addition, multicomponent reactions (MCRs) occupy an outstanding position in organic and medicinal chemistry by virtue of their intrinsic atom economy and selectivity, simple procedures and equipment, time and energy savings, and environmental friendliness.[4] Thus, it goes without saying that the use of water as a nontoxic reaction medium, together with the employment of energy-efficient microwave heating and atom-economical MCRs, must be a synergistic and effective green strategy of synthesis in the sense that the combination offers greater potential than the three parts in isolation.

Azapodophyllotoxin (Fig. 1) derivatives are well-known anticancer agents[5] that also have cardiotonic,[6] inotropic,[7] pesticidal,[8] potassium channel opening,[9] and calcium channel agonistic[10] activities. Moreover, more potent and less toxic azapodophyllotoxin derivatives with antitumor activities have also been obtained

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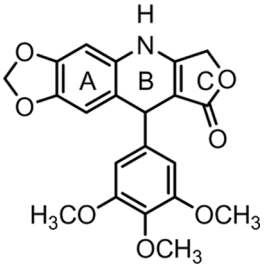


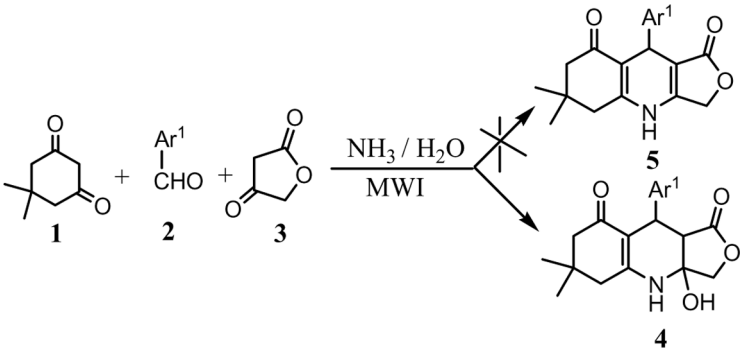
Figure 1. Structure of azapodophyllotoxin.

by extensive structural modifications.[11] However, most modifications were performed on rings B and C (Fig. 1), and the modifications on ring A were not well documented.

As a continuation of our efforts on structural modifications of azapodophyllotoxin[12] and synthesis of bioactive heterocyclic compounds with a green approach,[13] herein we report an unexpected and green synthesis of novel azapodophyllotoxin derivatives **4** instead of the desired products **5** via microwave-assisted, four-component reactions of dimedone **1**, aromatic aldehydes **2**, and tetronic acid **3** in ammonia water (Scheme 1).

RESULTS AND DISCUSSION

Initially, the microwave-assisted, four-component reaction of dimedone **1** (1 mmol), aromatic aldehyde **2a** (1 mmol), tetronic acid **3** (1 mmol), and excess ammonia water (1 mL) was employed to prepare the desired compound **5a**. Surprisingly, the spectroscopic data indicated this product was not the expected compound **5a** but rather another unexpected compound, **4a**, which was established on the basis of its spectroscopic data. In the ^{1}H NMR spectra, the two singlets at δ 7.79 and δ 6.20 were assigned to the protons of NH and OH group, which were further comfirmed by D_2O exchange. The two doublets with coupling constant of 8.4 Hz at δ 7.24 and δ 7.19 were assigned to the protons of *p*-chlorophenyl group. Another



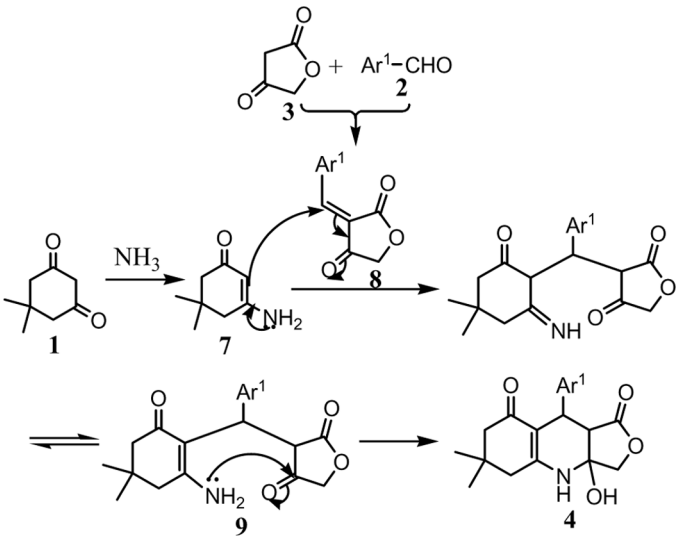
Scheme 1. The unexpected synthesis of azapodophyllotoxin derivatives.

Table 1. Synthesis of **4** in water under MWI

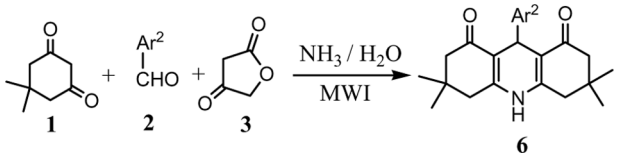
Entry	4	Ar^1	Time (min)	Yield (%)	Mp (°C)
1	**4a**	4-ClC_6H_4	5	87	265–266
2	**4b**	4-FC_6H_4	7	85	260–261
3	**4c**	4-BrC_6H_4	6	88	261–262
4	**4d**	C_6H_5	10	81	268–269

two singlets at δ 4.20 and δ 3.20 were assigned to the two tertiary protons. The dimedone skeleton was confirmed by two multiples in the range of δ 2.28–2.39 and δ 1.98–2.19, assigned to the protons of two CH_2, as well as two singlets at δ 1.03 and δ 0.94, designated as two methyl groups in dimedone skeleton. Another two doublets with coupling constant of 8.4 Hz at δ 4.15 and δ 4.04 were assigned to the protons of CH_2 in the skeleton of tetronic acid. The infrared (IR) spectrum of compound **5a** showed strong absorption at 3302 cm^{-1} due to the NH group and broad absorption in the range of 2900–3200 cm^{-1} due to the OH group. The strong absorption at 1757 cm^{-1} was assigned to the C=O group and that in the range of 1400–1600 cm^{-1} was designated to the phenyl group. Besides, the structure of this unexpected compound **4a** was also confirmed by high-resolution mass spectrometry (HRMS), electrospray ionization (ESI).

Then we performed the reaction of dimedone **1** (1 mmol), aromatic aldehyde **2b–d** (1 mmol), tetronic acid **3** (1 mmol), and excess ammonia water in the same reaction conditions. Similarly, the unexpected products **4** instead of desired products **5** were afforded. As shown in Table 1, a series of novel azapodophyllotoxin derivatives **4** were successfully synthesized with good yields within a short reaction time via microwave-assisted MCR in ammonia water.



Scheme 2. The reasonable mechanism of the unexpected reaction.



Scheme 3. The unexpected synthesis of products **6**.

The structures of all these novel compounds were established on the basis of their spectroscopic data and HRMS.

Although the detailed mechanism of the reaction remains to be fully clarified, the formation of **4** could be explained by a reaction sequence presented in Scheme 2. First, the condensation of tetronic acid **3** and aromatic aldehyde **2** gives intermediate **8**. Then, the intermediate **8** undergoes Michael addition with enamine **7** (formed from the condensation of dimedone **1** with ammonia) to give an open-chain intermediate **9**, which is subsequently cyclized to afford the final product **4**.

However, when the aromatic aldehydes with electron-donating groups such as alkoxyl group were employed using the same reaction conditions, another unexpected product, **6**, was were afforded (Scheme 3, Table 2), which implied that tetronic acid did not take part in the reactions at all.

This result indicated that the electronic nature of the substituents on aldehydes has significant effect on this reaction. However, the reason is still unclear, which should be investigated in further research.

CONCLUSION

In brief, we have realized an unexpected and green synthesis of novel azapodophyllotoxin derivatives via microwave-assisted MCRs of dimedone, tetronic acid, and aromatic aldehyde in ammonia water. This protocol has the prominent advantages of environmental friendliness, short reaction time, good yields, low cost, and easy operation. At the same time, this facile synthesis can not only offer a green synthetic strategy to heterocyclic compounds with biological significance but also enrich the investigation of microwave-assisted MCRs in water.

EXPERIMENTAL

Microwave irradiation was carried out in a monomodal Emrys Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined on an XT5

Table 2. Synthesis of **6** in water under MWI

Entry	**6**	Ar^2	Time (min)	Yield (%)	Mp (°C)
1	**6a**	4-$(CH_3)_2NC_6H_4$	6	83	264–266
2	**6b**	3,4-$(CH_3O)_2C_6H_3$	5	87	258–260
3	**6c**	3,4-$(OCH_2O)C_6H_3$	6	84	323–325
4	**6d**	4-$CH_3OC_6H_4$	8	82	269–271

apparatus and are uncorrected. IR spectra were recorded on a Fourier transform (FT)–IR Tensor 27 spectrometer. ^{1}H NMR spectra were measured on a DPX 400 spectrometer operating at 400 MHz, using dimethyl sulfoxide (DMSO-d_6) as solvent and tetramethylsilane (TMS) as an internal standard. HRMS (ESI) was determined by MicroTOF-QII HRMS/MS instrument (Bruker).

General Procedure for the Synthesis of Compounds 4 and 6 Under Microwave Irradiation

Typically, in a 10-mL Emrys reaction vial, dimedone **1** (1 mmol), aromatic aldehyde **2** (1 mmol), tetronic acid **3** (1 mmol), and excess ammonia water (1 mL) were mixed and then capped. The mixture was irradiated at maximum power of 200 W (initial power 100 W) and 90°C for a given time. The reaction mixture was cooled to room temperature, poured into water, and filtered to give the crude product, which was further purified by recrystallization from ethanol (EtOH) to give pure product **4** or **6**.

Data

9-(4-Chlorophenyl)-3a,4,6,7,9,9a-hexahydro-3a-hydroxy-6,6-dimethylfuro[3,4-*b*]quinoline-1,8(3*H*,5*H*)-dione (4a). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.79 (s, 1H, NH), 7.24 (d, 2H, $J = 8.4$ Hz, ArH), 7.19 (d, 2H, $J = 8.4$ Hz, ArH), 6.20 (s, 1H, OH), 4.20 (s, 1H, CH), 4.15 (d, 1H, $J = 8.4$ Hz, CH_{2a}), 4.04 (d, 1H, $J = 8.4$ Hz, CH_{2b}), 3.20 (s, 1H, CH), 2.28–2.39 (m, 2H, CH_2), 1.98–2.19 (m, 2H, CH_2), 1.03 (s, 3H, CH_3), 0.94 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3302, 3136, 2958, 2929, 2914, 2870, 1757, 1572, 1517, 1474, 1419, 1401, 1371, 1264, 1182, 1125, 1092, 1025, 827, 701, 666. HRMS (ESI) m/z: calc. for $C_{19}H_{20}ClNO_4$: 362.1154 $[M + H]^+$; found: 362.1159 $[M + H]^+$.

9-(4-Fluorophenyl)-3a,4,6,7,9,9a-hexahydro-3a-hydroxy-6,6-dimethylfuro[3,4-*b*]quinoline-1,8(3*H*,5*H*)-dione (4b). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.81 (s, 1H, NH), 7.36 (d, 2H, $J = 8.4$ Hz, ArH), 7.20 (d, 2H, $J = 8.4$ Hz, ArH), 6.23 (s, 1H, OH), 4.20 (s, 1H, CH), 4.17 (d, 1H, $J = 8.4$ Hz, CH_{2a}), 4.04 (d, 1H, $J = 8.4$ Hz, CH_{2b}), 3.21 (s, 1H, CH), 2.30–2.41 (m, 2H, CH_2), 2.00–2.16 (m, 2H, CH_2), 1.03 (s, 3H, CH_3), 0.93 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3303, 3145, 2958, 2930, 2917, 2874, 1759, 1576, 1519, 1420, 1403, 1371, 1265, 1181, 1125, 1073, 1021, 826, 697, 665. HRMS (ESI) m/z: calc. for $C_{19}H_{20}FNO_4$: 346.1450 $[M + H]^+$; found: 346.1455 $[M + H]^+$.

9-(4-Bromophenyl)-3a,4,6,7,9,9a-hexahydro-3a-hydroxy-6,6-dimethylfuro[3,4-*b*]quinoline-1,8(3*H*,5*H*)-dione (4c). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.79 (s, 1H, NH), 7.40 (d, 2H, $J = 8.4$ Hz, ArH), 7.19 (d, 2H, $J = 8.4$ Hz, ArH), 6.20 (s, 1H, OH), 4.18 (s, 1H, CH), 4.15 (d, 1H, $J = 8.4$ Hz, CH_{2a}), 4.04 (d, 1H, $J = 8.4$ Hz, CH_{2b}), 3.20 (s, 1H, CH), 2.31–2.39 (m, 2H, CH_2), 1.98–2.05 (m, 2H, CH_2), 1.03 (s, 3H, CH_3), 0.94 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3302, 3142, 2959, 2929, 2913, 2869, 1757, 1573, 1518, 1417, 1398, 1371, 1264, 1182, 1124, 1024, 824, 688, 661, 586. HRMS (ESI) m/z: calc. for $C_{19}H_{20}BrNO_4$: 406.0649 $[M + H]^+$; found: 406.0653 $[M + H]^+$.

3a,4,6,7,9,9a-Hexahydro-3a-hydroxy-6,6-dimethyl-9-phenylfuro[3,4-*b*]quinoline-1,8(3*H*,5*H*)-dione (4d). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.74 (s, 1H, NH), 7.09–7.24 (m, 5H, ArH), 6.10 (s, 1H, OH), 4.23 (s, 1H, CH), 4.14 (d, 1H, $J = 8.4$ Hz, CH_{2a}), 4.03 (d, 1H, $J = 8.4$ Hz, CH_{2b}), 3.20 (s, 1H, CH), 2.28–2.39 (m, 2H, CH_2), 2.00–2.10 (m, 2H, CH_2), 1.05 (s, 3H, CH_3), 0.95 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3294, 3137, 2956, 2928, 2872, 1755, 1574, 1518, 1472, 1402, 1369, 1267, 1185, 1127, 1027, 761, 700, 648, 586. HRMS (ESI) m/z: calc. for $C_{19}H_{21}NO_4$: 328.1544 $[M + H]^+$; found: 328.1549 $[M + H]^+$.

9-(4-(Dimethylamino)phenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (6a). Mp 264–266°C (lit. 264–266°C).[14]

3,4,6,7-Tetrahydro-9-(3,4-dimethoxyphenyl)-3,3,6,6-tetramethylacridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (6b). Mp 258–260°C (lit. 258–260°C).[14]

9-(Benzo[*d*][1,3]dioxol-5-yl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (6c). Mp 323–325°C. (lit. 324–326°C).[14]

3,4,6,7-Tetrahydro-9-(4-methoxyphenyl)-3,3,6,6-tetramethylacridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (6d). Mp 269–271°C. (lit. 269–270°C).[14]

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