An Efficient and Clean Synthesis of Indeno[1,2-*b*]pyrazolo[4,3-*e*]-pyridin-5(1*H*)-one Derivatives under Microwave Irradiation in Water

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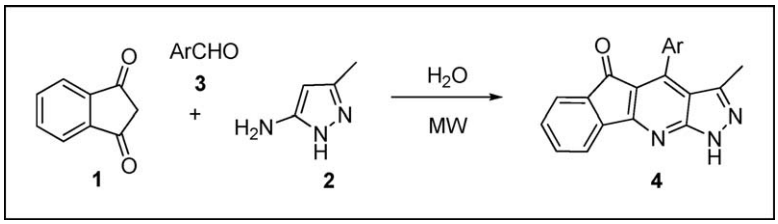

A series of new indeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one derivatives were synthesized by three-component reactions of 1,3-indandione, 3-methyl-1*H*-pyrazol-5-amine, and aldehyde in water under microwave irradiation without any catalyst.

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INTRODUCTION

Many recent efforts were made to make organic synthesis eco-friendlier. In this way, usual but hazardous volatile organic solvents were replaced with water and/or conventional heating was substituted by microwave irradiation (MW). Green chemistry is brewing which protects the environment, not by cleaning it up, but by inventing new chemistry and new chemical processes that prevent pollution [1]. In essence, it prompts the chemical and pharmaceutical manufacturer to consider how human life is impacted after these chemicals are generated and introduced into their society [2]. Thus, it has become clear that the combined approach of microwave heating and aqueous medium offers a nearly synergistic strategy in the sense that the combination in itself offers greater potential than the two parts in isolation [3].

Now, with growing concern over the environmental impact of chemicals, cleaner green reaction conditions in organic reaction have been advocated. Multicomponent reactions, an important class of organic tandem reactions, are one-pot processes with at least three components to form a single product, which incorporates most or even all of atoms of the starting materials [4]. Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding complicated purification operations and allowing savings both of solvents and of reagents.

Six-membered nitrogen-containing heterocycles, especially onychine derivatives (Fig. 1) are abundant in nature and exhibit diverse and important biological properties [5]. Indenopyridines [6], as a member of this family exhibit cytotoxic [7], phosphodiesterase inhibitory [8], adenosine A2a receptor antagonistic [9], antiinflammatory/antiallergic [10], coronary dilating [11], and calcium modulating activities [12]. The synthesis of these molecules has attracted considerable attention [13]. Shi *et al.* [14] reported the reaction of 5-amino-3-methyl-1-phenylpyrazole with arylaldehyde and 1,3-indandione to give indeno[2,1-*e*]pyrazolo derivatives in ionic liquid with the disadvantage of long time and pollution to the environment. Considering the significance of this kind of organic molecules, a more efficient and environmental friendly approach would be established to synthesis the set of onychine derivatives so as to provide candidate compounds for bioassay and enrich compound libraries. As the continuation of our research devoted to the development of green organic chemistry by performing reactions under using water conditions [15], we describe the synthesis of indeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-ones in water under microwave irradiation without catalyst (Scheme 1).

RESULTS AND DISCUSSION

Choosing an appropriate solvent is of crucial importance for successful microwave-promoted synthesis in

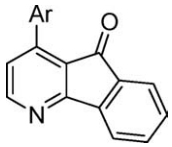


Figure 1. Structure of oychine.

view of a rapid rise of temperature in the reaction mixture. To search for the optimal solvent, the reaction of 1,3-indandione **1**, 3-methyl-1*H*-pyrazol-5-amine **2** and *p*-chlorobenzaldehyde **3a** were examined by using solvents of ethanol, DMF, ethylene glycol, acetic acid, and water, respectively. All the reactions were carried out at 120°C with the maximum power of 250 W and the results are summarized in Table 1. As shown in Table 1, the reaction in water resulted in higher yields and shorter reaction time than others. So water was chosen as the appropriate solvent.

Moreover, to further optimize the reaction temperature, the synthesis of **4a** was performed in water at the temperatures ranging from 100 to 140°C in the increment of 10°C each time at the maximum power of 250 W. As illustrated in Table 2, when the temperature was increased from 100 to 130°C, the yield of **4a** was obviously improved from 50 to 83%. However, no significant increase in the yield of **4a** was observed as the reaction temperature was further raised to 140°C. Therefore, the temperature of 130°C was chosen for all further microwave-assisted reactions.

Based on these optimized conditions [water, 130°C], the reactions proceeded smoothly. A series of compounds **4** were synthesized with this simple procedure. The results were summarized in Table 3 and the results indicated that aromatic aldehydes bearing either electron withdrawing or electron donating functional groups, such as chloro, nitro, bromo, or methyl are suitable for the reaction.

A tentative mechanism for the formation of products **4** is outlined in Scheme 2, which proceeded *via* a reaction sequence of condensation, addition, cyclization, dehydration, and aromatization. First, the condensation of 1,3-indandione **1** and aldehyde **3** gave the intermediate product **5**. The addition of **2** to **5** then furnished the intermediate product **7**, which cylices to dihydropyrine **9** and subsequently dehydrogenated to afford the fully aromatized compound **4**.

Scheme 1

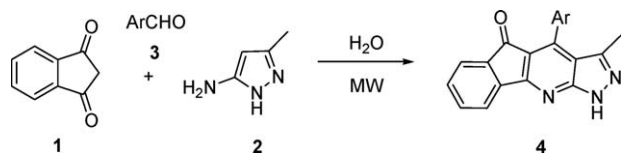


Table 1

Solvent optimization for the synthesis of **4a**.

Entry	Solvent	Time (min)	Yield (%)
1	EtOH	13	40
2	DMF	18	trace
3	Glycol	12	50
4	HOAc	10	70
5	Water	10	77

All the products were characterized by IR, ^{1}H NMR, and HRMS (ESI).

In summary, we demonstrated an efficient and clean route for the one-pot, three-component synthesis of highly functionalized indeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one derivatives in good yields. This method has the obvious advantages on short reaction time, high yield, operational simplicity, and environmental friendliness. Besides, this method may provide a shortcut for further investigations on the pharmacological activities of this type of compounds as important and novel onychine analogues.

EXPERIMENTAL

Microwave irradiation was carried out in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in XT5 apparatus and are uncorrected. IR spectra were recorded on a FTIR-Tensor 27 spectrometer. ^{1}H NMR spectra were measured on a DPX 400 spectrometer operating at 400 MHz, using DMSO-d_6 as solvent and TMS as internal standard. HRMS (ESI) was determined by using micrOTOF-QII HRMS/MS instrument (BRUKER).

General procedure for the synthesis of compounds 4 with microwave irradiation. Typically, a mixture of aromatic 1,3-indandione **1** (1.0 mmol), 3-methyl-1*H*-pyrazol-5-amine **2** (1.0 mmol), aldehyde **3** (1.0 mmol), and water (2.0 mL) was added to the reaction vessel of the monomodal Emrys™ Creator microwave synthesizer and allowed to react under MW at 250 W power (initial power 100 W) and 130°C for several minutes. Upon completion, monitored by TLC, the reaction vessel was cooled to room temperature. The solid compound was collected by filtration and recrystallized from EtOH (95%) to give pure azapodophyllotoxin derivatives **4**.

Table 2

Temperature optimization for the synthesis of **4a**.

Entry	T (°C)	Time (min)	Yield (%)
1	100	12	50
2	110	12	55
3	120	10	77
4	130	8	83
5	140	8	81

Table 3

Synthesis of products **4**.

Entry	4	Ar	Time (min)	Yield (%)	Mp (°C)
1	**4a**	4-ClC_6H_4	8	83	>300
2	**4b**	4-BrC_6H_4	10	80	>300
3	**4c**	4-$CH_3C_6H_4$	8	77	>300
4	**4d**	2-ClC_6H_4	10	79	209–210
5	**4e**	3-$NO_2C_6H_4$	7	80	243–244
6	**4f**	3,4-$(CH_3O)_2C_6H_3$	8	77	245–246
7	**4g**	C_6H_5	10	78	258–259
8	**4h**	3,4,5-$(CH_3O)_3C_6H_2$	10	76	240–242
9	**4i**	Thien-2-yl	13	77	263–264

4-(4-chlorophenyl)-3-methylindeno[1,2-b]pyrazolo[4,3-e]pyridin-5(1H)-one (4a). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 13.78 (s, 1H, NH), 7.65 (d, 2H, J = 6.8 Hz, ArH), 7.40 (t, 1H, J = 7.6 Hz, ArH), 7.34–7.28 (m, 3H, ArH), 7.23 (t, 2H, J = 8.4 Hz, ArH), 7.19 (d, 1H, J = 6.8 Hz, ArH), 1.87 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3197, 3056, 2882, 1717, 1698, 1559, 1542, 1491, 1436, 1363, 1340, 1290, 1245, 1185, 1130, 1082, 989, 811, 777, 709. HRMS (ESI) *m/z*: calc. for $C_{20}H_{13}ClN_3O$: 346.0742 $[M+H]^+$, found: 346.0793 $[M+H]^+$.

4-(4-bromophenyl)-3-methylindeno[1,2-b]pyrazolo[4,3-e]pyridin-5(1H)-one (4b). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 13.80 (s, 1H, NH), 7.91 (d, 1H, J = 7.2 Hz, ArH), 7.73, (d, 4H, J = 8.4 Hz, ArH), 7.61–7.54 (m, 3H, ArH), 7.49 (d, 3H, J = 8.0 Hz, ArH), 1.94 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3198, 3056, 2994, 1712, 1684, 1594, 1536, 1491, 1432, 1338, 1302, 1256, 1208, 1183, 1115, 1071, 995, 811, 762, 730. HRMS (ESI) *m/z*: calc. for $C_{20}H_{13}BrN_3O$: 390.0237 $[M+H]^+$, found: 390.0212 $[M+H]^+$.

3-methyl-4-p-tolylindeno[1,2-b]pyrazolo[4,3-e]pyridin-5(1H)-one (4c). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 13.74 (s, 1H, NH), 7.88 (d, 1H, J = 7.2 Hz, ArH), 7.71, (t, 1H, J = 7.2 Hz, ArH), 7.58–7.51 (m, 2H, ArH), 7.39 (d, 2H, J = 8.0 Hz, ArH), 7.33 (d, 2H, J = 8.0 Hz, ArH), 2.44 (s, 3H, CH_3), 1.92 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3190, 3048, 2962, 1710, 1612,1562, 1511, 1475, 1449, 1338, 1300,1255, 1207, 1179, 1116, 1072, 987, 809, 786, 733. HRMS (ESI) *m/z*: calc. for $C_{21}H_{16}N_3O$: 326.1288 $[M+H]^+$, found: 326.1317 $[M+H]^+$.

4-(2-chlorophenyl)-3-methylindeno[1,2-b]pyrazolo[4,3-e]pyridin-5(1H)-one (4d). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 13.87 (s, 1H, NH), 7.94 (d, 1H, J = 7.6 Hz, ArH), 7.76, (t, 1H, J = 7.6 Hz, ArH), 7.67 (d, 1H, J = 7.6 Hz, ArH), 7.62–7.57 (m, 3H, ArH), 1.86 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3153, 3109, 2997, 1714, 1602, 1572, 1550, 1473, 1439, 1340, 1303, 1280, 1251, 1183, 1155, 1060, 991, 807, 752, 711. HRMS (ESI) *m/z*: calc. for $C_{20}H_{13}ClN_3O$: 346.0742 $[M+H]^+$, found: 346.0744 $[M+H]^+$.

3-methyl-4-(3-nitrophenyl)indeno[1,2-b]pyrazolo[4,3-e]pyridin-5(1H)-one (4e). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 13.87 (s, 1H, NH), 8.43 (d, 2H, J = 9.2 Hz, ArH), 8.04 (d, 1H, J = 7.6 Hz, ArH), 7.93 (d, 1H, J = 7.2 Hz, ArH), 7.85 (t, 1H, J = 7.6 Hz, ArH), 7.77–7.73 (m, 1H, ArH), 7.62–7.55 (m, 2H, ArH), 1.94 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3190, 3117, 2990, 1754, 1634, 1599, 1504, 1488, 1457, 1385, 1300, 1294, 1236, 1177, 1120, 1070, 985, 800, 765, 713. HRMS (ESI) *m/z*: calc. for $C_{20}H_{13}N_4O_3$: 357.0979 $[M+H]^+$, found: 357.1005 $[M+H]^+$.

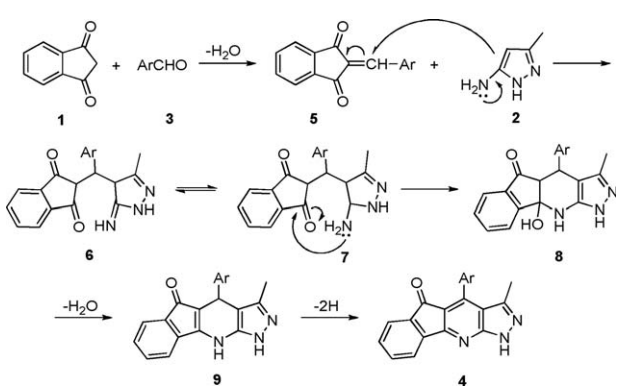
4-(3,4-dimethoxyphenyl)-3-methylindeno[1,2-b]pyrazolo[4,3-e]pyridin-5(1H)-one (4f). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 13.73 (s, 1H, NH), 7.90 (d, 1H, J = 7.2 Hz, ArH), 7.72, (t, 1H, J = 7.2 Hz, ArH), 7.61 (d, 1H, J = 7.2 Hz, ArH), 7.55 (t, 1H, J = 7.6 Hz, ArH), 7.15 (d, 1H, J = 1.2 Hz, ArH), 7.10–7.04 (m, 2H, ArH), 3.86 (s, 3H, CH_3), 3.77 (s, 3H, CH_3), 2.01 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3054, 3001, 2934, 1699, 1608, 1559, 1542, 1490, 1437, 1338, 1309, 1285, 1263, 1169, 1139, 1086, 1025, 801, 766, 726. HRMS (ESI) *m/z*: calc. for $C_{22}H_{18}N_3O_3$: 372.1343 $[M+H]^+$, found: 372.1333 $[M+H]^+$.

3-methyl-4-phenylindeno[1,2-b]pyrazolo[4,3-e]pyridin-5(1H)-one (4g). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 13.77 (s, 1H, NH), 7.91 (d, 1H, J = 7.2 Hz, ArH), 7.73 (t, 1H, J = 7.2, ArH), 7.61–7.48 (m, 8H, ArH), 1.90 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3102, 2994, 1708, 1671, 1592, 1562, 1541, 1498, 1446, 1339, 1305, 1256, 1240, 1189, 1140, 1094, 978, 805, 760, 705. HRMS (ESI) *m/z*: calc. for $C_{20}H_{14}N_3O$: 312.1132 $[M+H]^+$, found: 313.1148 $[M+H]^+$.

3-methyl-4-(3,4,5-trimethoxyphenyl)indeno[1,2-b]pyrazolo[4,3-e]pyridin-5(1H)-one (4h). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 13.76 (s, 1H, NH), 7.91 (d, 1H, J = 7.2 Hz, ArH), 7.73, (t, 1H, J = 7.6 Hz, ArH), 7.62 (d, 1H, J = 6.8 Hz, ArH), 7.56 (t, 1H, J = 7.2 Hz, ArH), 6.83 (s, 2H, ArH), 3.78 (d, 9H, J = 3.2 Hz, CH_3), 1.86 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3193, 3107, 2967, 1709, 1583, 1562, 1504, 1464, 1433, 1344, 1318, 1296, 1250, 1163, 1126, 1005, 967, 809, 777, 729. HRMS (ESI) *m/z*: calc. for $C_{23}H_{20}N_3O_4$: 402.1444 $[M+H]^+$, found: 402.1434 $[M+H]^+$.

3-methyl-4-(thiophen-2-yl)indeno[1,2-b]pyrazolo[4,3-e]pyridin-5(1H)-one (4i). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm):

Scheme 2



13.81 (s, 1H, NH), 7.91–7.86 (m, 2H, ArH), 7.73 (t, 1H, J = 7.6 Hz, ArH), 7.62 (d, 1H, J = 7.2 Hz, ArH), 7.56 (t, 1H, J = 7.2 Hz, ArH), 7.36 (d, 1H, J = 3.6 Hz, ArH), 7.28–7.25 (m, 1H, ArH), 2.04 (s, 3H, CH_3). IR (KBr, ν, cm^{-1}): 3096, 3053, 2983, 1707, 1684, 1590, 1559, 1473, 1435, 1334, 1302, 1252, 1225, 1178, 1130, 1078, 972, 808, 771, 730. HRMS (ESI) *m*/*z*: calc. for $C_{18}H_{12}N_3OS$: 318.0696 $[M+H]^+$, found: 318.0696 $[M+H]^+$.

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REFERENCES AND NOTES

[1] Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice, Oxford University Press: Oxford, 2000.

[2] Wang, X. S.; Zhang, M. M.; Zeng, Z. S.; Shi, D. Q.; Tu, S. T.; Wei, X. Y.; Zong, Z. M. Tetrahedron Lett 2005, 46, 7169.

[3] Cho, C. S.; Kim, J. S.; Oh, B. H.; Kim, T. J.; Shim, S. C.; Yoon, N. S. Tetrahedron 2000, 56, 7747.

[4] (a) Hulme, C.; Gore, V. Curr Med Chem 2003, 10, 51; (b) Orru, R. V. A.; de Greef, M. Synthesis 2003, 1471; (c) Domling, A.; Ugi, I. Angew Chem Int Ed 2000, 39, 3168; (d) Nair, V.; Rajesh, C.; Vinod, A. V.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. Acc Chem Res 2003, 36, 899; (e) Zhu, J. Eur J Org Chem 2003, 7, 1133; (f) Domling, A. Curr Opin Chem Biol 2002, 6, 306.

[5] Strunz, G. M.; Buckingham, J. A. The Alkaloids; Academic Press: New York, 1985, 26, 89.

[6] Manpadi, M.; Uglinskii, P. Y.; Rastogi, S. K. Org Biomol Chem 2007, 5, 3865.

[7] Miri, R.; Javidnia, K.; Hemmateenejad, B.; Azarpira, A.; Amirghofran, Z. Bioorg Med Chem 2004, 12, 2529.

[8] Heintzelman, G. R.; Averill, K. M.; Dodd, J. H. PCT Int Appl WO 2002085894 A1 20021031, 2002; (b) Kim, J. S.; Oh, B. H.; Kim, T. J.; Shim, S. C.; Yoon, N. S. Tetrahedron 2000, 56, 7747.

[9] Heintzelman, G. R.; Averill, K. M.; Dodd, J. H.; Demarest, K. T.; Tang, Y.; Jackson, P. F. US Pat Appl Publ 2004082578 A1 20040429, 2004.

[10] Cooper, K.; Fray, M. J.; Cross, P. E.; Richardson, K. Eur Pat Appl EP 299727 A1 19890118, 1989.

[11] Vigante, B.; Ozols, J.; Sileniece, G.; Kimenis, A.; Duburs, G. U. S. S. R. SU, 794006 19810107, 1989.

[12] Safak, C.; Simsek, R.; Altas, Y.; Boydag, S.; Erol, K. Boll Chim Farm 1997, 136, 665.

[13] (a) Tadic, D.; Cassels, B. K.; Cave', A.; Goulart, M. P. F.; de Oliveira, A. B. Phytochemistry 1987, 26, 1551; (b) Alves, T.; de Oliveira, A. B.; Snieckus, V. Tetrahedron Lett 1988, 29, 2135; (c) Emelen, K. V.; Wit, T. D.; Hoornaert, G. J.; Compernolle, F. Tetrahedron 2002, 58, 4225.

[14] Shi, D. Q.; Yang, F.; Ni, S. N. J Heterocycl Chem 2009, 46, 469.

[15] (a) Tu, S. J.; Cao, X. D.; Hao, W. J.; Zhang, X. H.; Yan, S.; Wu, S. S.; Han, Z. G.; Shi, F. Org Biomol Chem 2009, 7, 557; (b) Tu, S. J.; Zhang, X. H.; Han, Z. G.; Cao, X. D.; Wu, S. S.; Yan, S.; Hao, W. J.; Ma, N. J Comb Chem 2009, 11, 428; (c) Jiang, B.; Cao, L. J.; Tu, S. J.; Zheng, W. R.; Yu, H. Z. J Comb Chem 2009, 11, 612.