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Multicomponent reactions for the synthesis of new 3′-indolyl substituted heterocycles under microwave irradiation

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Abstract

A series of polysubstituted (3′-indolyl)pyrazolo[3,4-*b*]pyridine and (3′-indolyl)benzo[*h*]quinoline derivatives were synthesized via one-pot multicomponent reactions of aldehydes, 3-cyanoacetyl indoles with 5-aminopyrazol or naphthylamine under microwave irradiation. Particularly valuable features of this method include high yields of products, broad substrate scope, short reaction time and straightforward procedure.

Keywords: Indole; Heterocycle; Multicomponent reactions; Microwave irradiation

Indole moiety has been found in various pharmacologically and biologically active compounds.[1] Many indole alkaloids are recognized as one of the rapidly growing groups of marine invertebrate metabolites for their broad spectrum of biological properties.[2] For example, five novel indole alkaloids,[3] meridianins A–E, have been isolated from the tunicate Splidium meridiaum. They show cytotoxicity toward murine tumor cell lines and have potent inhibition against several protein kinases.[4]

Along with these, the substitution at 3-position of the indole ring can take place by connecting an extra heterocyclic ring, such as imidazole (topsentins[5] and nortopsentins[6]), dihydroimidazole (discodermindole[7]), oxazole (martefrgin,[8] amazol[9]), oxadiazine (alboinon[10]), maliemide (didemidines[11]), and piperazine (dragmacidon[12]). These 3-substituted indoles represent a promising structural class of marine alkaloids and therefore, are interesting synthetic targets (Fig. 1).

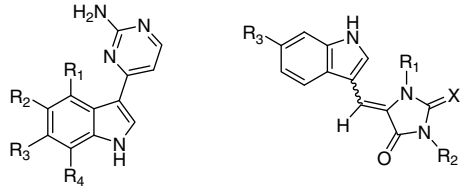

Fig. 1. Examples of 3′-indolyl substituted heterocycles.

However, the methods for synthesis of these important compounds often suffer from tedious synthetic routes, long reaction time, drastic reaction conditions, as well as narrow application scope of substrates. In addition, to the best of our knowledge, there have been few reports about synthesis of indole derivatives including pyrazolo[3,4-*b*]pyridine moieties. While, pyrazolo[3,4-*b*]pyridines are also attractive targets in organic synthesis due to their interesting biological and pharmacological properties such as vasodialotors, hypoglycemic, anti-inflammatory, analgesic, and anti-pyritic activities.[13]

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Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry.[14] The strategies of MCRs offer significant advantages over conventional linear-type syntheses for their high degree of atom economy, convergence, ease of execution, excellent yields and broad application characters, which are particularly useful to generate diverse chemical libraries of 'drug-like' molecules for biological screening.[15]

Recently, we described a new and efficient synthesis of 3-(2-furanyl)indole derivative by three-component reactions of isocyanides, 3-cyanoacetyl indole, and aromatic aldehydes in good yields (Scheme 1).[16]

Due to our interest in the multicomponent syntheses and in continuation to our work on the synthesis of indole derivatives,[17] herein, we reported a simple and facile protocol for the synthesis of a series of indole derivative-incorporated pyrazolo[3,4-*b*]pyridine units.

The target compounds 4-substituted-6-(1*H*-indol-3-yl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile **4** were synthesized by one-pot reactions of 3-cyanoacetyl indoles **1**, aldehydes **2** and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **3** under microwave irradiation conditions (Scheme 2).

In our initial study, various reaction conditions including solvents and temperatures were tested in the one-pot three-component synthesis of **4a** under MW irradiation. Among different polar solvents, such as ethanol, acetic acid, glycol, DMF and water, the best yield was found when glycol was employed (Table 1, entries 1–5, 9 and 11).

To further optimize the reaction temperature, the reactions were carried out at temperatures ranging from 90 to 160 °C. It was found that, as the reaction temperature was increased, the yield of **4a** was improved and the reaction time was shortened. The yields plateaued when temperature was further increased to 150 and 160 °C (Table 1, entries 5–10). Therefore, 150 °C was chosen as the reaction temperature for all further microwave-assisted reactions.

Under these optimal microwave experimental conditions (150 °C, glycol), a series of new 3′-indolyl substituted heterocycles, with which a 3′-indolyl group binding in position 6 of the pyrazolo[3,4-*b*]pyridine nucleus were synthesized in good yields. The results were summarized in Table 2.

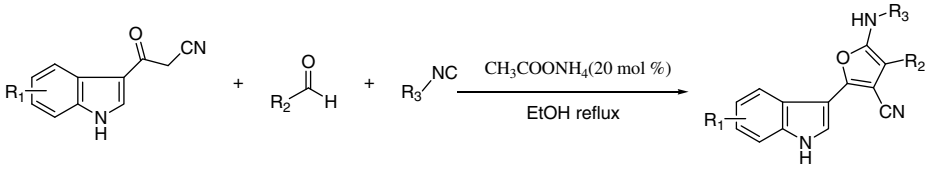
Table 1
Optimization of reaction conditions of compound **4a**[a]

Entry	Solvent[b]	*T* (°C)	Time (min)	Yield[c]
1	H_2O	90	20	None
2	EtOH	90	20	32
3	HOAc	90	15	50
4	DMF	90	15	42
5	Glycol	90	15	57
6	Glycol	110	12	65
7	Glycol	130	10	72
8	Glycol	140	9	78
9	Glycol	150	8	85
10	Glycol	160	8	84
11	EtOH	150	12	75

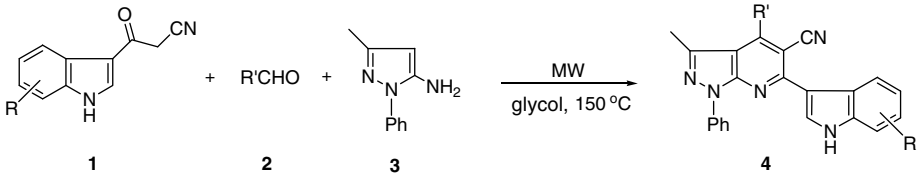
[a] The reaction was carried out under MW.
[b] The amount of solvent was 2 mL.
[c] Isolated yields.

As shown in Table 2, this protocol can be applied not only to aromatic aldehydes with either electron-withdrawing groups or electron-donating groups, but also to heterocyclic and aliphatic aldehydes. Furthermore, a series of substituted 3-cyanoacetyl indoles were used in this reaction, which all gave excellent results. We have also observed delicate electronic effects: that is, arylaldehydes with electron-withdrawing groups reacted rapidly and gave higher yields; while substitutions of electron-rich groups on the benzene ring, as well as heterocyclic and aliphatic aldehydes, required longer reaction times and got lower yields. This was probably due to the decreased reactivities.

Although the detailed mechanism of the above reaction remains to be fully clarified, according to the literatures,[18] compound **4** could be formed from the intermediate **5** via Michael addition reaction with 5-aminopyrazol **3** followed by intramolecular cyclization and elimination. Intermediate **5** could be prepared by condensation of 3-cyanoacetyl indole **1** and aldehyde **2** (see Scheme 3).



Scheme 1.

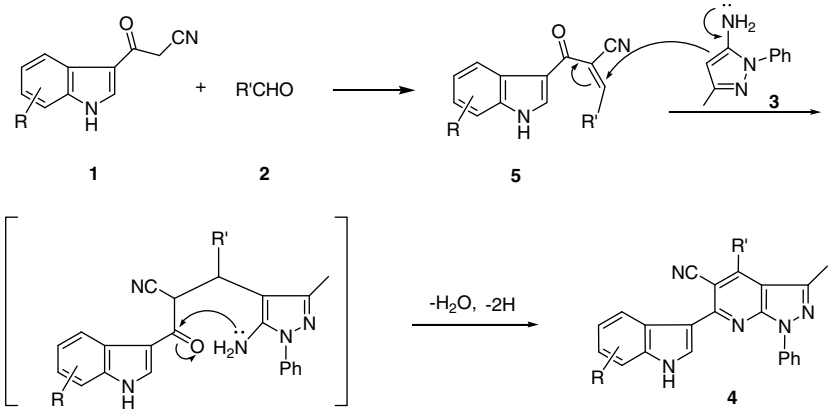


Scheme 2.

Table 2
Synthesis of **4** under microwave irradiation and conventional heating at 150 °C

Entry	Product	R′	R	Time		Yield[a] (%)		Mp (°C)
				MW[b] (min)	CH[c] (h)	MW[b]	CH[c]	
1	**4a**	4-ClC_6H_4	H	8	10	87	72	>300
2	**4b**	C_6H_5	H	10	11	82	70	>300
3	**4c**	2-ClC_6H_4	H	10	12	80	65	>300
4	**4d**	2-BrC_6H_4	H	10	12	82	72	>300
5	**4e**	3-BrC_6H_4	H	9	10	86	72	284–286
6	**4f**	3-$NO_2C_6H_4$	H	8	8	85	74	276–277
7	**4g**	4-$NO_2C_6H_4$	H	8	8	85	75	>300
8	**4h**	4-FC_6H_4	H	6	8	88	73	>300
9	**4i**	4-$CH_3C_6H_4$	H	10	9	76	69	296–297
10	**4j**	4-$CH_3OC_6H_4$	H	12	10	78	68	274–275
11	**4k**	4-OHC_6H_4	H	12	11	80	71	>300
12	**4l**	4-OH-3-$OCH_3C_6H_3$	H	12	11	80	72	>300
13	**4m**	2-Thienyl	H	13	14	75	65	>300
14	**4n**	2-Pyridyl	H	14	14	70	60	>300
15	**4o**	*n*-Propyl	H	15	16	74	62	297–299
16	**4p**	*n*-Butyl	H	15	16	67	60	275–276
17	**4q**	4-ClC_6H_4	2-CH_3	7	8	88	75	298–299
18	**4r**	4-ClC_6H_4	4-CH_3	8	8	83	73	>300
19	**4s**	4-ClC_6H_4	7-CH_3	8	8	75	68	>300
20	**4t**	4-ClC_6H_4	2-Ph	8	8	86	72	198–200

[a] Isolated yields.
[b] The time and yields under microwave irradiation (MW) conditions.
[c] The time and yields under conventional heating (CH) conditions.



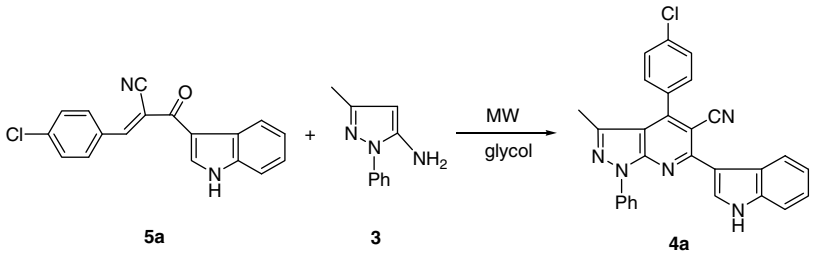
Scheme 3.

Evidence supporting this proposed mechanism came from the observation that the intermediate **5** can be isolated from the reaction, and when **5a** was prior prepared[19] and subsequently reacted with **3** under the same condition, the expected product **4a** was obtained in a yield similar to that obtained in one-pot reaction (Scheme 4).

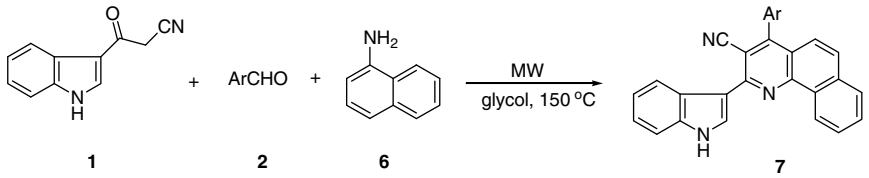
Moreover, the synthesis of **4** was performed under both MW and classical heating at 150 °C. The reactions were efficiently promoted by MW with increased yields, and the reaction times were strikingly shortened to minutes from hours required under traditional heating. Therefore, microwave irradiation exhibited several advantages over the conventional heating by significantly reducing the reaction time and improving the reaction yield, owing to a specific nonthermal microwave effect.

To further expand the scope of the present method, the replacement of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine with naphthylamine was examined. Under the above-optimized MW conditions, the reactions were performed smoothly and a variety of the desired products 2-(1*H*-indol-3-yl)-4-arylbenzo[*h*]quinoline-3-carbonitrile **7** were obtained in moderate to good yields (Scheme 5 and Table 3). However, when this three-component reaction was carried out in oil bath condition, only little amount of desired product **7** was isolated (yield: <20%), accompanied by large amount of condensation product **5** in 70% yield.

In this study, the products were characterized by melting point, IR, NMR and HRMS spectral data. Furthermore, the structures of **4c** and **7d** were established by X-ray crystallographic analysis (Figs. 2 and 3).[20]



Scheme 4.



Scheme 5.

Table 3
Synthesis of **7** under microwave irradiation

Product	Ar	Time (min)	Yield[a] (%)	Mp (°C)
7a	C_6H_5	12	67	>300
7b	4-ClC_6H_4	12	72	>300
7c	4-BrC_6H_4	14	70	>300
7d	4-$CH_3C_6H_4$	15	72	>300
7e	3-BrC_6H_4	15	68	>300

[a] Isolated yields.

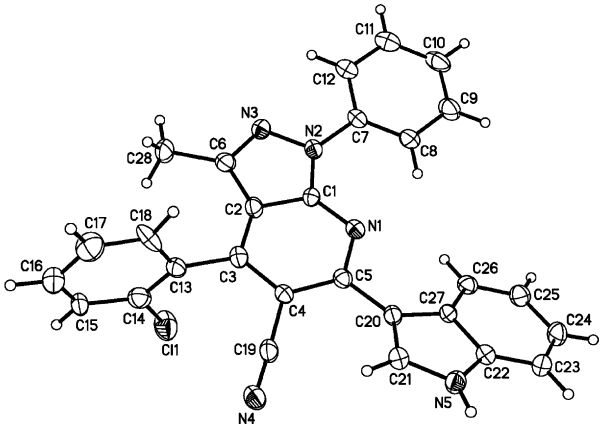


Fig. 2. The crystal structure of **4c**.

In summary, we have demonstrated a simple and efficient approach for synthesis of highly functionalized indole derivatives via one-pot three-component reactions. This method incorporates both indole and pyrazolo[3,4-*b*]pyridine or benzo[*h*]quinoline moieties into a single molecule. In view of those molecules having either functionality, these novel compounds may potentially have enhanced biological activities.

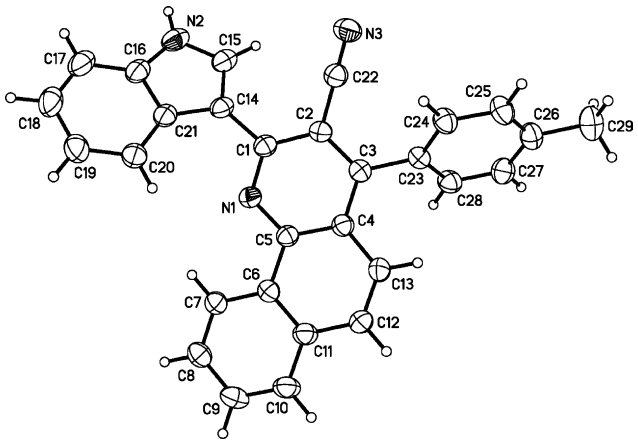


Fig. 3. The crystal structure of **7d**.

Acknowledgments

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19. *Typical experimental procedure*:
Preparation of compound **4a** under MW condition: The reaction was performed in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. In a 10 mL Emrys™ reaction vial, 3-cyanoacetyl indole (1 mmol), 4-chlorobenzaldehyde (1 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **3** (1 mmol) and glycol (2 mL) were mixed and then capped. The mixture was irradiated for the given time at the maximum power of 250 W and 150 °C. Upon completion, monitored by TLC, the reaction mixture was allowed to cool to room temperature and then poured into cold water (100 mL). The solid product was filtered, washed with EtOH (95%). The product was purified by recrystallization from EtOH–DMF (1:1) to afford (**4a**). *4-(4-Chlorophenyl)-6-(1H-indol-3-yl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile*: Light yellow solid; mp: >300 °C; IR (KBr): *v* 3303, 3063, 2971, 2199, 1613, 1481, 1304, 1234, 1041, 740 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.92 (br s, 1 H, NH), 8.44–8.45 (m, 2H), 8.27 (d, $J = 8.0$ Hz, 2H), 7.73–7.74 (m, 4H), 7.62 (t, $J = 7.6$ Hz, 2H), 7.56 (d, $J = 8.0$ Hz, 1H), 7.42 (t, $J = 7.2$ Hz, 1H), 7.26 (t, $J = 7.6$ Hz, 1H), 7.20 (t, $J = 7.6$ Hz, 1H), 2.06 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.3, 151.2, 149.9, 143.6, 138.2, 136.3, 134.6, 132.7, 130.8, 129.4, 129.1, 128.5, 126.4, 125.7, 122.6, 121.4, 121.0, 120.9, 118.5, 112.6, 112.1, 111.4, 99.5, 14.3; HRMS found: *m*/*z* 469.1265 (M^+), calcd for $C_{28}H_{18}N_5Cl$: M, 459.1251.
Preparation of compound **4a** under conventional heating condition: An equimolar (1 mmol) mixture of 3-cyanoacetyl indole **1**, aldehyde **2**, and 5-amino-3-methyl-1-phenylpyrazol **3** was subsequently introduced into a 25 mL flask, and stirred in 5 mL glycol at 150 °C (oil bath temperature) for a given time. The subsequent work-up procedure was the same as in the microwave irradiation reactions.
Preparation of compound **5a**. A mixture containing 3-cyanoacetyl indole (1 mmol), 4-chlorobenzaldehyde (1 mmol), and glycol (2.0 mL) was introduced into a 10 mL reaction vial and irradiated at the maximum power of 250 W and 150 °C for 10 min. The reaction mixture was allowed to cool to room temperature. The solid was filtered and washed with water and EtOH (95%) to give pure product **5a**. *3-(4-Chlorophenyl)-2-(1H-indole-3-carbonyl)acrylonitrile*: Yellow solid; mp: 224–225 °C; IR (KBr): *v* 3356, 3175, 3056, 2929, 2221, 1602, 1512, 1489, 1433, 1312, 1234, 1182, 1091, 1013, 867, 823, 751, 645, 527 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 12.39 (br s, 1H, NH), 8.46 (s, 1H, CH), 8.23 (s, 1H, Indolyl-H), 8.17 (d, $J = 6.8$ Hz, 1H, Indolyl-H), 8.05 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.68 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.55 (d, $J = 7.2$ Hz, 1H, Indolyl-H), 7.26–7.31 (m, 2H, Indolyl-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 181.2, 150.6, 136.9, 136.8, 136.3, 131.9, 131.4, 129.3, 126.1, 123.6, 122.5, 121.4, 117.5, 113.5, 112.6, 112.1; HRMS found: *m*/*z* 306.0564 (M^+), calcd for $C_{18}H_{11}N_2OCl$: M, 306.0560.
Preparation of compound **7b**. In a 10 mL Emrys™ reaction vial, 3-cyanoacetyl indole (1 mmol), 4-chlorobenzaldehyde (1 mmol), naphthalen-1-amine **6** (1 mmol) and glycol (2 mL) were mixed and then capped. The mixture was irradiated for the given time at the maximum power of 250 W and 150 °C. Upon completion, monitored by TLC, the reaction mixture was allowed to cool to room temperature and then poured into cold water (100 mL). The solid product was filtered, washed with EtOH (95%). The product was purified by column chromatography (silica gel, 200–300 mesh, PE–acetone, 4:1) to give (**7b**). *4-(4-Chlorophenyl)-2-(1H-indol-3-yl)benzo[h]quinoline-3-carbonitrile*: Brown solid; mp: >300 °C; IR (KBr): *v* 3252, 3058, 2979, 2187, 1608, 1519, 1479, 1399, 1241, 951, 807, 755, 600 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.86 (br s, 1H, NH), 9.35 (d, $J = 10.0$ Hz, 1H), 8.68 (d, $J = 10.4$ Hz, 1H), 8.45 (s, 1H, Indolyl-H), 8.07–8.09 (m, 2H), 7.88–7.90 (m, 4H), 7.33–7.52 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.4, 152.9, 149.8, 138.3, 136.4, 134.8, 132.6, 132.4, 130.6, 129.2, 128.8, 128.5, 127.8, 127.0, 126.8, 126.5, 126.1, 122.9, 122.4, 122.2, 120.7, 119.2, 118.2, 112.2, 111.9, 104.5; HRMS found: *m*/*z* 429.1019 (M^+), calcd for $C_{28}H_{16}N_3Cl$: M, 429.1033.
20. Crystallographic data for the structures of **4a** and **7d** reported in this paper have been deposited at the Cambridge Crystallographic Data Centre with No. CCDC-632865 and 631307, respectively.