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Facile and efficient synthesis of a new class of bis(3′-indolyl)pyridine derivatives via one-pot multicomponent reactions

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Abstract

A series of 4-aryl-3,5-dicyano-2,6-di(3′-indolyl)pyridine derivatives were synthesized via a one-pot multicomponent reaction of aromatic aldehydes, 3-cyanoacetyl indoles, and ammonium acetate under microwave irradiation. Particularly valuable features of this method include high yields of products, broad substrate scope, short reaction time, and straightforward procedure.

Keywords: Bisindole; 3,5-Dicyanopyridine; Multicomponent reactions; Microwave irradiation

1. Introduction

Indole moiety has been found in a wide variety of pharmacologically and biologically active compounds.[1] Many bisindole alkaloids are recognized as one of the rapidly growing groups of sponge metabolites because of their broad spectrum of biological properties.[2–5] For example, Nortopsentins A–C, having 2,4-bis(3′-indolyl)-imidazole moieties, exhibit in vitro cytotoxicity against P388 cells;[6] Hamacanthin B, having a characteristic 3,5-bis(3′-indolyl)pyrazinone skeleton, exhibits cytotoxic activities against a wide range of human tumor cell lines with GI50 values at micromolar concentration.[7] Moreover, a very interesting group of these bisindole derivatives incorporated a five- or six-membered heterocyclic ring between the two indole rings, such as 2,5-bis(3′-indolyl)pyrazine,[8] 2,4-bis(3′-indolyl)thiazole,[9] 2,4-bis(3′-indolyl)pyrimidine,[10] and 2,5-bis(3′-indolyl)thiophene,[11] demonstrate strong inhibitory effects against a variety of tumor cell lines, including leukemia, non-small cell lung cancer, ovarian cancer, colon cancer, renal cancer, and breast cancer (Fig. 1).

Although these classes of alkaloids are interesting from both the structural and biological points of view, only very small amounts of the biologically active substances have been isolated from the natural materials. And the methods for the synthesis of these important compounds often suffer from tedious synthetic routes, long reaction time, drastic reaction conditions, as well as narrow scope of substrates.

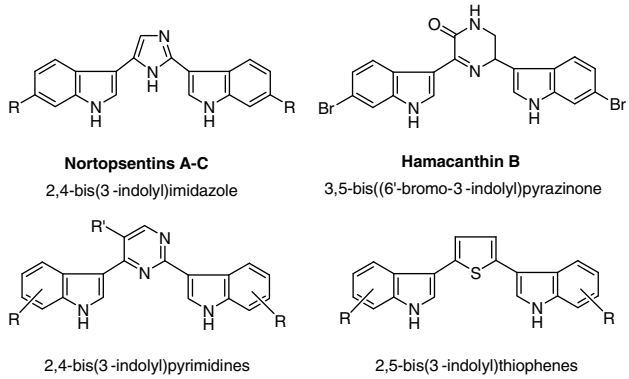

Fig. 1. Representatives of bisindole heterocyclic compounds.

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In addition, to the best of our knowledge, there have been few reports about the synthesis of bisindole derivatives incorporated pyridine moieties.

Recently, multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry.[12] The strategies of MCRs offer significant advantages over conventional linear-type syntheses for their high degree of atom economy, convergence, ease of execution, and broad applications characters. MCRs are particularly useful to generate diverse chemical libraries of 'druglike' molecules for biological screening.[13]

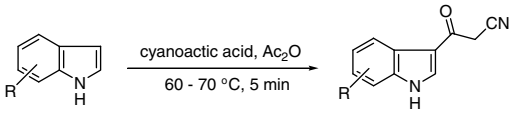
In our previous researches, we had synthesized a series of bis(indolyl)methanes (BIAs), which have shown some potential biological activities under different conditions.[14] As our continuous interest in the synthesis of indole derivatives,[15] guided by the observation that the presence of two or more different heterocyclic moieties in a single molecule often remarkably enhances the biocidal profile, we investigated a simple and efficient protocol for the synthesis of a series of bisindoles derivatives containing 3,5-dicyanopyridine units, which have also attracted great interest in medicinal and optical fields.[16]

2. Results and discussion

Compounds such as 3-cyanoacetyl indoles **1** were previously prepared by Kreher and Wagner[17] and recently by Bergman[18] via a new facile approach starting from indoles and cyanoacetic acid (Scheme 1).

The target compounds 4-aryl-3,5-dicyano-2,6-di(1*H*-indol-3-yl)-pyridine were synthesized by one-pot reactions of aldehydes, 3-cyanoacetyl indoles, and ammonium acetate under microwave irradiation conditions (Scheme 2).

Choosing an appropriate solvent is of crucial importance for the successful microwave-assisted synthesis. In our initial studies, different organic solvents, such as ethanol, glycol, acetic acid, DMF, and mixed HOAc/glycol were tested in the synthesis of **3a** under MW irradiation



1

Scheme 1.

Table 1
Solvent optimization for the synthesis of **3a** under MW[a]

Entry	Solvent	Time (min)	Yield[b] (%)
1	EtOH[c]	20	Trace
2	HOAc	18	67
3	DMF	18	50
4	Glycol	18	65
5	HOAc/glycol(1:1)	16	73
6	HOAc/glycol(1:2)	15	78
7	HOAc/glycol(1:3)	15	70
8	HOAc/glycol(2:1)	16	71

[a] The reaction was carried out under MW at 100 °C and 200 W.
[b] Isolated yields.
[c] The temperature was set at 80 °C.

conditions. All the reactions were carried out at a power of 200 W. The results are summarized in Table 1.

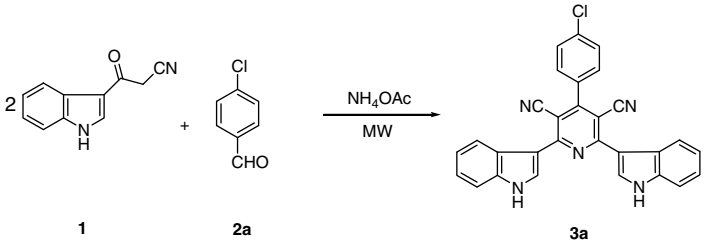
As shown in Table 1, the reaction in the mixed HOAc/glycol (the preferred volume ratio: 1:2) gave the best result (Table 1, entry 6).

We also carried out the reaction at different temperatures ranging from 100 to 160 °C, as well as different MW powers from 100 to 300 W, respectively. The yield of product **3a** was increased and the reaction time was shortened when the temperature and power were increased. Microwave irradiation at 140 °C and 250 W gave the highest yield.

Under these optimized conditions (140 °C, 250 W, and HOAc/glycol (V/V: 1:2) as solvent), a series of 4-aryl-3,5-dicyano-2,6-di(1*H*-indol-3-yl)-pyridine derivatives **3** were synthesized (Scheme 3). The results are summarized in Table 2.

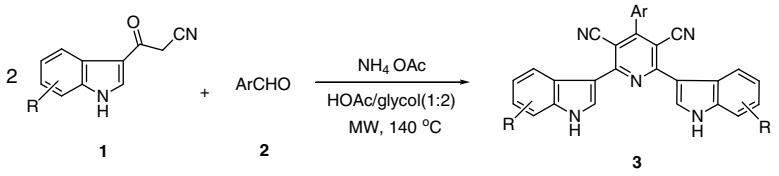
To examine the efficiency of this new multicomponent reaction, a series of different aldehydes and indoles were employed. As shown in Table 2, this protocol can be applied not only to aromatic aldehydes with either electron-withdrawing groups (such as nitro or halide groups) or electron-donating groups (such as hydroxyl or alkoxyl group), but also to heterocyclic aldehydes. Furthermore, a series of different substituted 3-cyanoacetyl indoles were used in this reaction, all of which gave excellent results. However, when aliphatic aldehydes were used in the reactions, we failed to get the expected products.

In addition, the same temperature was applied to the synthesis of **3f** in HOAc/glycol under classical heating conditions. After refluxing for 12 h, the desired product **3f** was obtained in 47% yield, accompanied by the non-aromatized



1 2a 3a

Scheme 2.



Scheme 3.

Table 2
Synthesis of 3 under microwave irradiation at 140 °C and 250 W

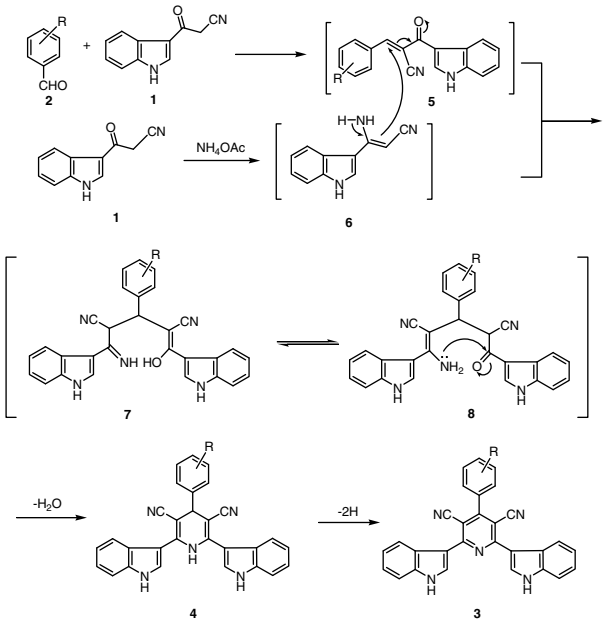
Entry	Product	Ar	R	Time (min)	Yield[a] (%)	Mp (°C)
1	**3a**	4-ClC_6H_4	H	12	85	>300
2	**3b**	C_6H_5	H	14	81	>300
3	**3c**	2-ClC_6H_4	H	15	83	>300
4	**3d**	3-BrC_6H_4	H	12	86	>300
5	**3e**	4-$CH_3C_6H_4$	H	15	76	>300
6	**3f**	4-$CH_3OC_6H_4$	H	13	80	>300
7	**3g**	3-$NO_2C_6H_4$	H	15	78	299–300
8	**3h**	4-$NO_2C_6H_4$	H	15	82	>300
9	**3i**	4-OHC_6H_4	H	12	83	>300
10	**3j**	3,4-$OCH_2OC_6H_3$	H	15	77	>300
11	**3k**	4-OH–3-$OCH_3C_6H_3$	H	13	79	285–287
12	**3l**	2-Thienyl	H	16	71	247–248
13	**3m**	4-ClC_6H_4	2-Ph	15	80	>300
14	**3n**	4-ClC_6H_4	4-CH_3	15	78	>300
15	**3o**	4-ClC_6H_4	5-CH_3	15	75	>300
16	**3p**	4-ClC_6H_4	7-CH_3	15	86	>300

[a] Isolated yields.

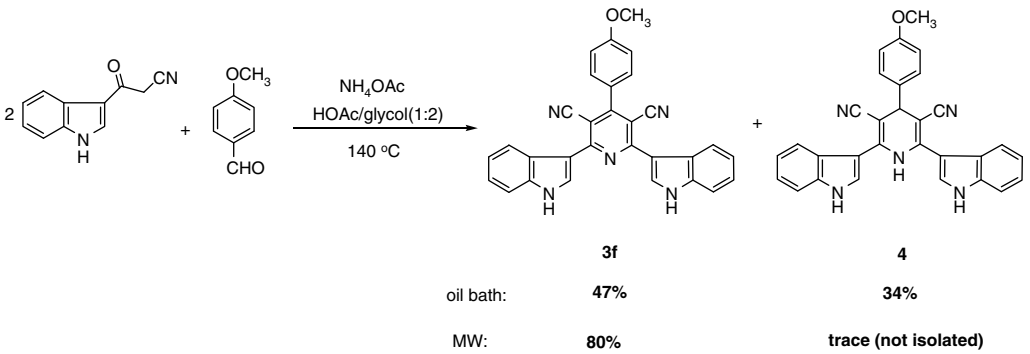
compound 4-(4-chlorophenyl)-3,5-dicyano-1,4-dihydro-2,6-di(1*H*-indol-3-yl)pyridine (**4**, yield: 34%). However, under microwave irradiation condition, the yield of **3f** was up to 80% (Table 2, entry 6), and only trace amount of **4** was detected (Scheme 4). Therefore, microwave irradiation exhibited several advantages over the conventional heating by significantly reducing the reaction times and improving the reaction yields, as well as the purity of products, owing to a specific non-thermal microwave effect.

Although the detailed mechanism of the above reaction remains to be fully clarified, the formation of 2,6-di(indol-3-yl)pyridine derivatives could be explained by a possible reaction procedure presented in Scheme 5. Compounds **3** may be synthesized via sequential condensation, addition, cyclization, and elimination. First, the condensations between 3-cyanoacetyl indoles **1** with aldehydes **2**, and 3-cyanoacetyl indoles **1** with ammonium acetate could form intermediates **5** and **6**, respectively. Michael addition between **5** and **6** could give intermediate **7**, which could isomerize to intermediate **8**. Intramolecular condensation of **8** could afford the compound **4**, which could be oxidized to afford the fully aromatized product **3** (Scheme 5). This type of de-hydrogenation is well precedented.[19]

In this study, all the products were characterized by melting point, IR, NMR, and HRMS spectral data.[20]



Scheme 5.



Scheme 4.

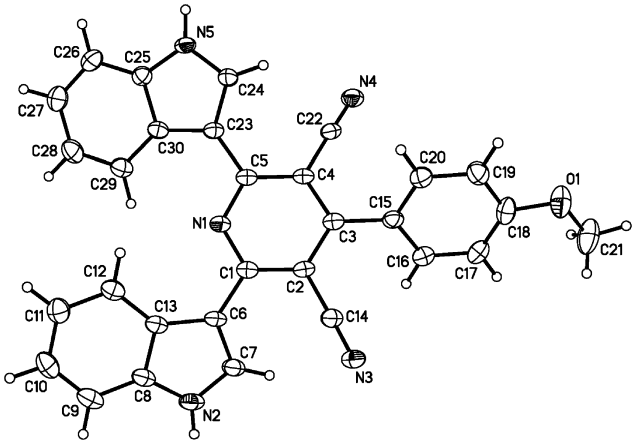


Fig. 2. The crystal structure of **3f**.

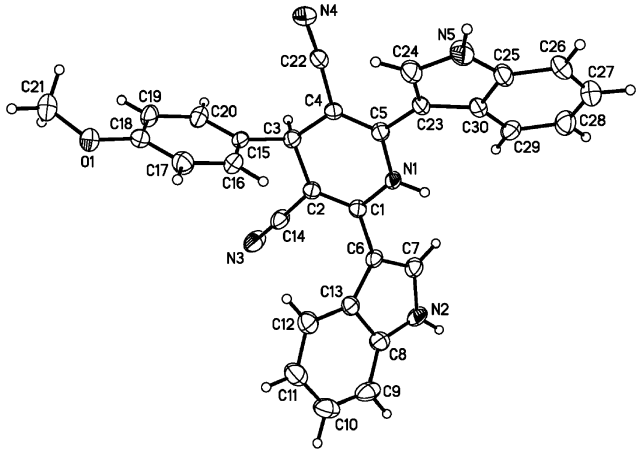


Fig. 3. The crystal structure of **4**.

Furthermore, the structures of **3f** and **4** were confirmed by X-ray crystallographic analysis (Figs. 2 and 3).[21]

3. Conclusion

In summary, we have demonstrated a simple and efficient approach to bis(3′-indolyl)pyridine derivatives by multicomponent reactions of aldehydes, 3-cyanoacetyl indoles, and ammonium acetate under microwave irradiation conditions. This method incorporates both bisindole and 3,5-dicyanopyridine moieties into a single molecule. In view of those molecules having either functionality, these novel compounds may potentially have enhanced biological activity and optical property. Further work is in progress in our laboratories.

Acknowledgments

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20. Typical experimental procedure: Preparation of compound **3a** by microwave irradiation.The reaction was performed in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. In a 10 mL Emrys™ reaction vial, 3-cyanoacetyl indole (2 mmol), 4-chlorobenzaldehyde (1 mmol), ammonium acetate (5 mmol), and acetic acid (0.5 mL), glycol (1.0 mL) were mixed and then capped. The mixture was irradiated for the given time at a power of 250 W and 140 °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 and washed with EtOH (95%). The product was purified by recrystallization from EtOH–DMF (1:1) to afford (**3a**): *4-(4-chlorophenyl)-2,6-di(1H-indol-3-yl)pyridine-3,5-dicarbonitrile*: 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 12.16 (br s, 2H, NH), 8.52 (s, 2H, Indolyl-H), 8.37 (d, $J = 8.0$ Hz, 2H, Indolyl-H), 7.83 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.75 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.58 (d, $J = 8.0$ Hz, 2H, Indolyl-H), 7.26 (t, $J = 7.6$ Hz, 2H, Indolyl-H), 7.08 (t, $J = 7.6$ Hz, 2H, Indolyl-H); ^{13}C NMR (75 MHz, DMF-d_7): δ 159.2, 158.7, 137.5, 132.3, 132.2, 131.2, 126.6, 123.3, 122.9, 121.4, 118.3, 116.3, 116.0, 113.6, 112.6, 100.3; HRMS [Found: *m*/*z* 469.1080 (M^+), calcd for $C_{29}H_{16}N_5Cl$: M, 469.1094].

Preparation of compound **4** by conventional heating.A mixture containing 3-cyanoacetyl indole (2 mmol), anisaldehyde (1 mmol), ammonium acetate (5 mmol), and acetic acid (0.5 mL), glycol (1.0 mL) was introduced into a 25 mL reaction vial and stirred at 140 °C (oil bath temperature) for the given time. When the reaction was complete (TLC), the reaction mixture was allowed to cool to room temperature. The solid was filtered and washed with water and EtOH (95%). The product was purified by column chromatography (silica gel, 200–300 mesh, PE–acetone, 4:1) to give compounds **3f** and **4**.

4-(4-Methoxyphenyl)-1,4-dihydro-2,6-di(1H-indol-3-yl)pyridine-3,5-dicarbonitrile (**4**): Light yellow solid; mp: >300 °C; IR (KBr): *v* 3310, 3249, 3056, 2932, 2215, 1606, 1512, 1435, 1258, 1034, 741 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.80 (br s, 2H, NH), 9.82 (br s, 1H, NH), 7.94 (s, 2H, Indolyl-H), 7.55–7.58 (m, 6H, ArH + Indolyl-H), 7.48 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.18 (d, $J = 8.4$ Hz, 2H, Indolyl-H), 7.16 (d, $J = 8.4$ Hz, 2H, Indolyl-H), 4.55 (s, 1H, CH), 3.81 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.2, 158.7, 143.6, 137.3, 135.9, 129.9, 128.2, 124.9, 121.9, 120.7, 119.9, 114.3, 112.1, 107.4, 81.5, 55.1, 41.9; HRMS [found: *m*/*z* 467.1754 (M^+), calcd for $C_{30}H_{21}N_5O$: M, 467.1746].

21. Crystallographic data for the structures of **3f** and **4** reported in this paper have been deposited at the Cambridge Crystallographic Data Centre with No. CCDC 632750 and 632751, respectively.