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PAPER

A new rapid multicomponent domino reaction for the formation of functionalized benzo[*h*]pyrazolo[3,4-*b*]quinolines†

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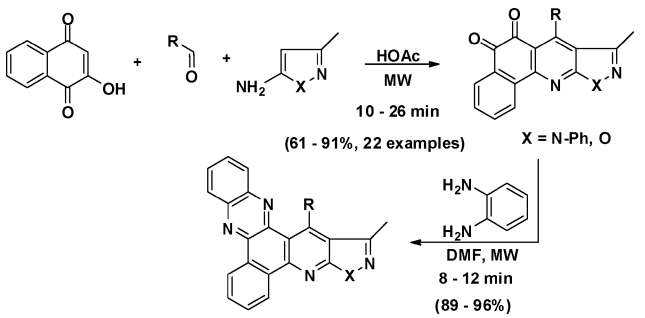
A new multicomponent domino reaction for rapid and regioselective synthesis of highly functionalized benzo[*h*]pyrazolo[3,4-*b*]quinolines has been established. The reaction can be conducted by using readily available and inexpensive substrates under microwave irradiation within short periods of 10–26 min. Good to excellent chemical yields (61–91%) and complete regioselectivity have been achieved for 22 examples. Tedious work-up procedure can be avoided due to the direct precipitation of products from the reaction solution. The resulting benzoquinolines have been readily converted into quinoxaline-fused benzo[*h*]isoxazolo[5,4-*b*]quinoline analogues by treating with benzene-1,2-diamine under microwave irradiation. The structural assignment has been ambiguously confirmed by X-ray analysis. A new mechanism has been proposed for this new multicomponent domino process.

Introduction

Assembly of molecular complexity and diversity from readily available starting materials in regard to economic and environmental aspects constitutes a great challenge in modern organic chemistry.[1–4] For this purpose, multicomponent domino reactions (MDRs) has become increasingly useful tools for the synthesis of chemically and biologically important compounds because of their atom-, structure-, bond-forming economy and green chemistry characteristic.[4–5] These reactions can avoid time-consuming and costly processes for purification of various precursors and tedious steps of protection and deprotection of functional groups.[6] Therefore, the development of new regio- and stereoselective domino reactions is a continuing challenge at the forefront of modern organic chemistry.

In the past several years, our group and others have developed various multicomponent domino reactions that can provide easy access to functionalized multiple heterocycles.[7–10] Among these reactions is a four-component domino process for concise synthesis of multi-functionalized quinazoline derivatives.[7a] The reaction can be easily performed by simply mixing readily available starting materials, aromatic aldehydes, cyclopentanone and cyanoacetamide with K_2CO_3 in ethylene glycol under microwave (MW) irradiation. Furthermore, we have also found that when aliphatic aldehydes were employed to replace their aromatic counterparts, the reaction proceeded along another pathway leading to the formation of multi-functionalized tricyclo[6.2.2.$0^{1,6}$]dodecanes.[7b]

During our continuous efforts on searching for useful multicomponent domino reactions,[7–9] we now found a new regioselective multicomponent domino annulation which provides an easy access to benzo[*h*]pyrazolo[3,4-*b*]quinolines and their derivatives. This reaction was achieved by reacting aldehydes, pyrazol- or isoxazolo-amines and 2-hydroxy-1,4-naphthoquinone under microwave irradiation (MW) in the absence of strong acids or metal catalysts/promoters (Scheme 1). The resulting benzoquinolines has been reacted with benzene-1,2-diamine to give polycyclic heteroaromatics, quinoxaline-fused benzo[*h*]isoxazolo[5,4-*b*]quinolines.



Scheme 1

It is well-known that the quinoline subunit plays a prominent role in organic and medicinal chemistry; and they exist in a wide variety of naturally occurring compounds and rationally designed pharmaceutical agents (*e.g.*, quinine, camptothecin).[11] Quinolines are integral to a large number of drug substances with activities including antimalarial, antiinflammatory, antineoplastic, antifungal, antiseptic/antiinfective, and analgesic properties.[12] Therefore,

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Table 1 Optimization for the Synthesis of **4a** under microwave irradiation

Entry	Solvent	T/°C	Time (min)	Yield (%)
1	—	100	10	13
2	EtOH	100	10	40
3	Glycol	100	10	56
4	AcOH	100	10	84
5	DMF	100	10	65
6	1,4-Dioxane	100	10	57

the development of new methods for their syntheses has been an area of ongoing interest.[13] Surprisingly, to the best of our knowledge, an efficient domino approach to fused benzo[*h*]pyrazolo[3,4-*b*]quinoline and benzo[h]isoxazolo[5,4-*b*]quinoline derivatives, containing a naphthoquinone unit, has not been well documented. In this paper, we would like to report the new reaction for their syntheses.

Results and discussion

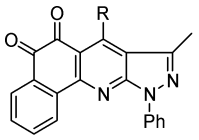
Initially, we conducted this synthesis by reacting 4- fluorobenzaldehyde **1a** with 2-hydroxy-1,4-naphthoquinone **2** and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **3a** to serve as the model case for condition optimization.

As shown in Table 1, the use of acetic acid at 100 °C allowed the direct conversion of 2-hydroxy-1,4-naphthoquinone **2** into the corresponding benzo[*h*]pyrazolo[3,4-*b*]quinoline **4a** in a yield of 84% under microwave irradiation condition (Table 1, entry 4). Other polar solvents, such as ethanol, ethylene glycol, *N*,*N*-dimethylformamide, 1,4-dioxane or solvent-free condition resulted in moderate to poor to modest yields of 13%–65% (Table 1, entries 1–3). The reaction proceeded rapidly to completion within a few minutes at 100 °C. Increasing reaction temperature to 120 °C did not improve chemical yields.

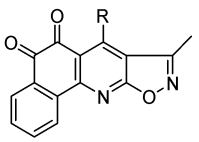
Next, we studied the substrate scope of this reaction by subjecting a series of aromatic aldehydes **1b–k** to the reactions with 2-hydroxy-1,4-naphthoquinone **2** under the optimal condition. As shown in Table 2, the reaction of thiophene-2-carbaldehyde with 2-hydroxy-1,4-naphthoquinone **2** and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine can be finished within 15 min to give thienyl-substituted benzo[*h*]pyrazolo[3,4-*b*]quinoline **4j** in 79% yield. In addition, an aliphatic aldehyde also showed high reactivity under this standard condition providing corresponding benzo[*h*]pyrazolo[3,4-*b*]quinolines in a good yield of 61% (Table 2, entry 11). Similarly, benzoquinoline products, **4b–k**, were produced within 10–26 min in good to excellent yields of 67–91% (Table 2, entries 2–11). Bedsides 3-methyl-1-phenylpyrazol-5-amine (**3a**) substrate, 3-methyl-isoxazol-5-amine (**3b**) was also proven to be suitable for the reaction with 2-hydroxy-1,4-naphthoquinone (**1**) and eleven arylaldehydes bearing electron-withdrawing or electron-donating groups to give the corresponding benzo[*h*]isoxazolo[5,4-*b*]quinoline-5,6-diones (**5a–5k**) in good yields (67–89%) and excellent selectivities (Table 1, entries 12–22). For all these cases, the reaction proceeded rapidly to completion within 10–24 min.

A heteroaromatic substrate (**1j**) was also employed for this reaction to give 2-thienyl-substituted benzo[*h*]isoxazolo[5,4-*b*]quinolines (**5k**) in a yield of 71%. The structural elucidation was unequivocally determined by NMR analysis and X-ray diffraction

Table 2 Regioselective domino synthesis of products **4** and **5** under MW Irradiation



4a-4k



5a-5k

Entry	**4** or **5**	*R*	Time (min)	Yield (%)
1	**4a**	4-Fluorophenyl (**1a**)	10	84
2	**4b**	2-Chlorophenyl (**1b**)	18	82
3	**4c**	3-Bromophenyl (**1c**)	18	89
4	**4d**	3-Nitrophenyl (**1d**)	10	91
5	**4e**	4-Hydroxy-3-nitrophenyl (**1e**)	12	87
6	**4f**	Phenyl (**1f**)	20	83
7	**4g**	4-Methylphenyl (**1g**)	22	84
8	**4h**	4-Methoxyphenyl (**1h**)	20	83
9	**4i**	Benzo[*d*][1,3]dioxol-5-yl (**1i**)	18	86
10	**4j**	2-Thienyl (**1j**)	15	79
11	**4k**	*n*-Butyl (**1k**)	26	61
12	**5a**	4-Fluorophenyl (**1a**)	12	87
13	**5b**	4-Chlorophenyl (**1l**)	14	89
14	**5c**	4-Bromophenyl (**1m**)	15	84
15	**5d**	4-Nitrophenyl (**1n**)	10	88
16	**5e**	3-Nitrophenyl (**1d**)	10	86
17	**5f**	Phenyl (**1f**)	18	78
18	**5g**	4-Methylphenyl (**1g**)	20	82
19	**5h**	3,4-Dimethoxyphenyl (**1o**)	24	74
20	**5i**	Benzo[*d*][1,3]dioxol-5-yl (**1p**)	20	79
21	**5j**	4-Dimethylaminophenyl (**1q**)	24	67
22	**5k**	Thien-2-yl (**1j**)	22	71

of single crystals that were obtained by slowly evaporating solvent from the solution containing benzo[*h*]pyrazolo[3,4-*b*]quinolines **4h** (Fig. 1).

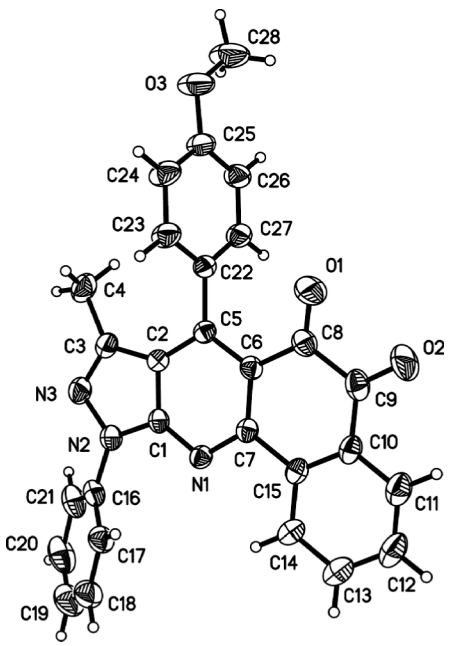


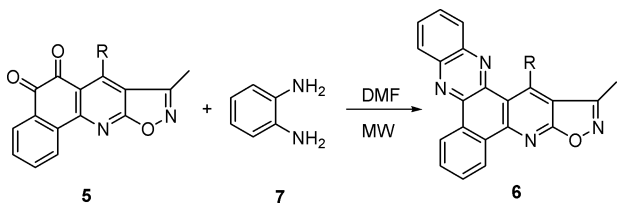
Fig. 1 The ORTEP drawing of product **4h**.

To study the applicational scope of this reaction, benzoquinolines **5** were further employed to react with benzene-1,2-diamine under microwave irradiation. After several solvents were

Table 3 Synthesis of compounds **6** under MW Irradiation

Entry	6	*R*	Time (min)	Yield (%)
1	**6a**	4-Fluorophenyl (**5a**)	8	94
2	**6b**	4-Chlorophenyl (**5b**)	10	96
3	**6c**	4-Bromophenyl (**5c**)	8	91
4	**6d**	4-Nitrophenyl (**5d**)	10	97
5	**6e**	3-Nitrophenyl (**5e**)	10	96
6	**6f**	4-Methylphenyl (**5g**)	10	92
7	**6g**	Benzo[*d*][1,3]dioxol-5-yl (**5i**)	12	91
8	**6h**	4-Me_2N-phenyl (**5j**)	12	89

screened, DMF was found to be the most suitable solvent for this condensation to afford quinoxaline-fused benzo[*h*]isoxazolo[5,4-*b*]quinolines **6** in excellent yields (89–97%) (Scheme 2, Table 3). This conversion can be finished within 8–12 min in this solvent at 120 °C. It should be mentioned that the resulting isoxazole-containing multiheterocycles would be endowed with many significant pharmacological properties, such as hypoglycemic, analgesic, anti-inflammatory, antibacterial, anti-HIV, and anti-cancer activity.[14] In addition, they showed agrochemical properties including herbicidal and soil fungicidal activity for the use of pesticides and insecticides.[15]



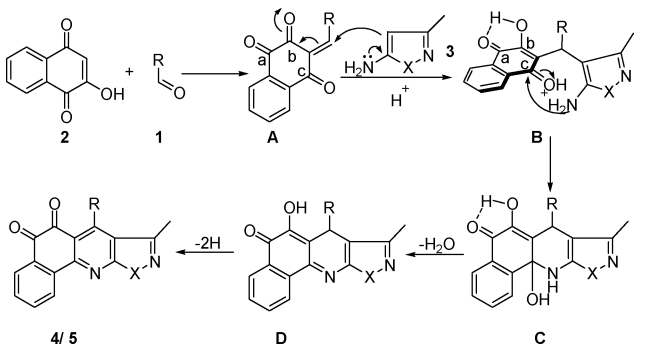
5 7 6

Scheme 2

Similar to our previous multicomponent domino processes,[7] the present reaction also showed *the following attractive characteristics*: (1) fast reaction rates which enable the reaction to be completed within 10–24 min, which can save energy and manpower for future industrial production; (2) the environmentally friendly process in which water is nearly a sole byproduct; (3) the convenient work-up which only needs simple filtration since the products directly precipitate out after the reaction is finished;[16–17] (4) high regioselectivity in which the reactions generated benzoquinolines with *ortho*-diketone unit that serve as important building blocks.

Proposed reaction mechanism

On the basis of all the above results, a possible mechanism has been proposed for the formations of benzoquinolines derivatives as shown in Scheme 3. The formation of **4** involves a ring closure cascade process that consists of initial condensation, intermolecular Michael addition (**A** to **B**), intramolecular nucleophilic cyclization (**B** to **C**) and dehydration (**C** to **D**) (Scheme 3). The intermediate **B** favors formation of intramolecular hydrogen bond between carbonyl group (position a) and *ortho*-hydroxyl group (position b), in which enolization of hydroxyl group was further enhanced. During this process, the carbonyl group (position c) would be easily attracted by the amino group (-NH_2) to give intermediate **C** which is then converted into the final product *via* dehydration and dehydrogenation steps.



2 1 A B 4/ 5 D C

Scheme 3

Conclusion

In summary, a new multicomponent domino reaction have been established to afford benzo[*h*]pyrazolo[3,4-*b*]quinolines and benzo[*h*]isoxazolo[5,4-*b*]quinolines that serve as versatile building. The reactions showed high regioselectivity and a broad scopes of substrates which can employ a wide range of common commercial starting materials. A new mechanism has been proposed to explain the reaction process and regioselectivity. The resulting benzoquinoline products have been successfully converted into quinoxaline-fused benzo[*h*]isoxazolo[5,4-*b*]quinolines by reacting with benzene-1,2-diamine under microwave irradiation.

Experimental

General

Microwave irradiation was carried out with microwave oven Emrys Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and were uncorrected. ^{1}H NMR (^{13}C NMR) spectra were measured on a Bruker DPX 400 (100) MHz spectrometer in DMSO-d_6 (or $CDCl_3$)with chemical shift (δ) given in ppm relative to TMS as internal standard. The exact mass measurements were obtained by high resolution mass instrument (GCT-TOF instrument). X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Semens P4 diffractometer.

General procedure for the synthesis of compounds 4a, 5a, and 6a

Preparation of compounds 4a or 5a, Microwave heating: 4-fluorobenzaldehyde **1a** (1.0 mmol) was introduced in a 10-mL Emrys reaction vial, and 2-hydroxy-1,4-naphthoquinone **2** (1.0 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **3a** or (3-methyl-isoxazol-5-amine **3b**) (1.1 mmol) and HOAc (1.5 mL) were then successively added. Subsequently, the reaction vial was capped and then stirred for 20 s. The mixture was irradiated (initial power 100 W and maximum power 200 W) at 120 °C until TLC (petroleum ether/acetone, 4 : 1 v/v) revealed that conversion of the starting material **1a** was complete (10 min or 12 min). The reaction mixture was then cooled to room temperature and diluted with cold water (40 mL). The solid product was collected by Büchner filtration and was purified by flash column chromatography (silica gel, mixtures of petroleum ether/ethyl acetate, 5 : 1 v/v) to afford the desired pure products **4a** (or **5a**) as a red solid.

Preparation of compounds 6a: In a 10-mL Emrys™ reaction vial, quinoxaline-fused benzo[*h*]isoxazolo[5,4-*b*]quinolines **5a** and benzene-1,2-diamine (**7**, 1.1 mmol) and DMF (2.5 mL) were mixed and capped, and then stirred for 20 s. The mixture was irradiated for a given time at 120 °C under microwave irradiation (initial power 100 W and maximum power 250 W). When the reaction was completed (monitored by TLC). The reaction mixture was then cooled to room temperature and diluted with cold water (40 mL). The solid product was collected by Büchner filtration and was purified by recrystallization from 95% EtOH to afford the desired pure products **6a** as a pale yellow solid.

7-(4-Fluorophenyl)-8-methyl-10-phenyl-*5H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,6(*10H*)-dione (4a)

Red solid, mp: >300 °C

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.76 (d, J = 8.0 Hz, 1H, ArH), 8.30 (d, J = 7.6 Hz, 2H, ArH), 8.05 (d, J = 7.2 Hz, 1H, ArH), 7.95 (t, J = 7.6 Hz, 1H, ArH), 7.72 (d, J = 7.6 Hz, 1H, ArH), 7.67 (t, J = 8.0 Hz, 2H, ArH), 7.46–7.36 (m, 5H, ArH), 1.89 (s, 3H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 179.19, 153.28, 145.50, 138.23, 136.57, 135.62, 132.50, 131.94, 131.42, 129.64, 129.57, 129.45, 128.15, 128.13, 127.12, 126.56, 126.48, 120.79, 116.25, 115.12, 114.90, 14.23.

IR (KBr, ν, cm^{-1}): 3073, 1680, 1559, 1509, 1419, 1382, 1286, 1217, 1159, 1087, 947, 840, 773, 693, 647.

HRMS (ESI) m/z: calc. for $C_{27}H_{16}FN_3O_2Na$: 456.1119, found: 456.1119.

7-(4-Fluorophenyl)-8-methylbenzo[*h*]isoxazolo[5,4-*b*]quinoline-5,6-dione (5a)

Red solid, mp: 262–264 °C

^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.72 (d, J = 8.0 Hz, 1H, ArH), 8.06 (d, J = 7.6 Hz, 1H, ArH), 7.93 (t, J = 7.2 Hz, 1H, ArH), 7.74 (t, J = 7.6 Hz, 1H, ArH), 7.48–7.44 (m, 2H, ArH), 7.18 (t, J = 9.2 Hz, 2H, ArH), 1.89 (s, 3H, CH_3).

IR (KBr, ν, cm^{-1}): 3069, 1692, 1672, 1573, 1510, 1442, 1341, 1219, 1162, 1076, 936, 842, 774, 611.

^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 178.44, 178.11, 169.04, 163.45, 161.01, 157.21, 155.32, 151.12, 135.56, 132.18, 131.99, 129.78, 129.70, 128.27, 126.83, 123.32, 115.17, 114.96, 113.33, 11.98.

HRMS (ESI) m/z: calc. for $C_{21}H_{11}FN_2O_3Na$: 381.0646, found: 381.0640.

Hexacyclic quinoxaline-fused benzo[*h*]pyrazolo[3,4-*b*] quinolines (6a)

Pale yellow solid, mp: > 300 °C

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.30–9.25 (m, 2H, ArH), 8.22 (d, J = 7.6 Hz, 1H, ArH), 7.85–7.77 (m, 3H, ArH), 7.71–7.67 (m, 1H, ArH), 7.39–7.28 (m, 5H, ArH), 2.04 (s, 3H, CH_3);

IR (KBr, ν, cm^{-1}): 1590, 1569, 1509, 1419, 1383, 1322, 1221, 1126, 998, 810.

HRMS (ESI): m/z calcd for $C_{27}H_{16}FN_4O$: 431.1303, found: 431.1301.

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