Design and Synthesis of New and Significative Bifunctional Compounds Containing Two Pyrazolo[3,4-*b*]pyridine Nucleis through Multicomponent Reaction under Microwave Irradiation

Shujiang Tu,* Qian Wang, Yan Zhang, Jianing Xu, Jinpeng Zhang, Xiaotong Zhu, Feng Shi

Department of Chemistry, Xuzhou Normal University, Key Laboratory of Biotechnology on Medical Plant, Xuzhou; Jiangsu, 221009, P. R. China

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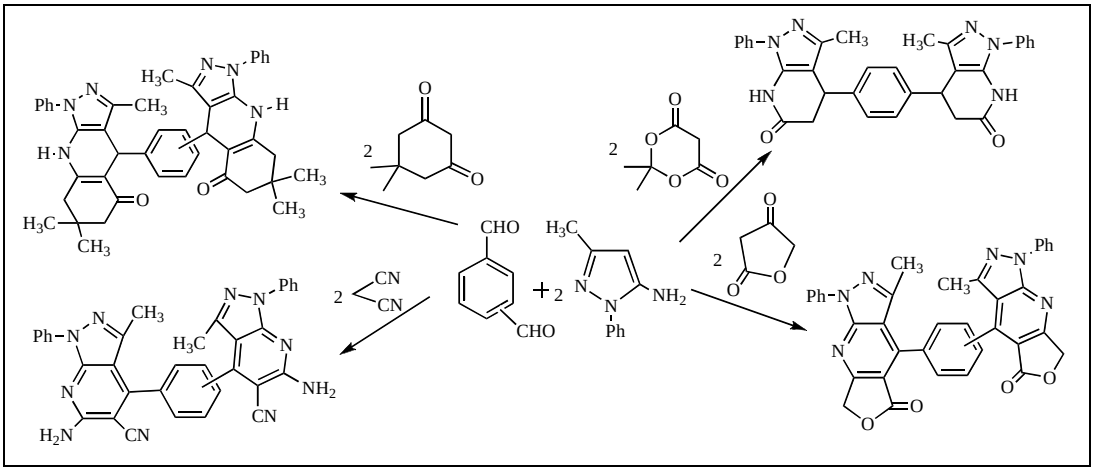

A series of new and significative bifunctional compounds containing two pyrazolo[3,4-*b*]pyridine moieties has been synthesized through a rapid one-pot three-component reaction of dialdehyde, 5-amino-3-methyl-1-phenylpyrazole and active methylene compounds in glycol under microwave irradiation without catalyst. The method has the advantages of good yield (85-98%), short route and reaction time (45-300s), wide reaction scope and easy work-up procedure.

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INTRODUCTION

The pyrazolo[3,4-*b*]pyridine system has many interesting biological and pharmacological properties, such as active antitubercular agents against gram positive and negative bacteria, in the treatment of a wide variety of stress-related illnesses [1-3]. Dihydropyrazolo[3,4-*b*]-pyridine has also shown vasodilating and anti-hypertension activities and produced prophylactic effect as calcium antagonist in strok-prone spontaneously hypertensive symptoms [4-5].

These important properties have aroused great interest in related researches of pyrazolo[3,4-*b*]pyridin ring system. However, so far attention has mainly been paid to the synthesis of monofunctional pyrazolo[3,4-*b*]pyridine derivatives [6] and the bifunctional ones are seldom investigated. It is well established that slight modification on pyrazolo[3,4-*b*]pyridine units may bring significant changes in pharmacological activities and may provide new classes of biological active compounds for bio-medical screening [7].

Multicomponent reactions (MCRs) by virtue of their convergence, productivity, ease of execution, energy savings and rapid assembly of molecular diversity have attracted considerable attention from the point of view of combinatorial chemistry [8]. MCRs leading to interesting heterocyclic scaffolds are not only atom economic and selective but also particularly useful for the creation of diverse chemical libraries of 'drug-like' molecules for biological screening. The efficiency of microwave irradiation (MWI) in promoting organic reaction and the success of its application in heterocyclic synthesis [9] triggered us to apply it to one-pot multicomponent reactions.

In connection with our previous studies on the preparation of pyrazolo[3,4-*b*]pyridines [10], we here describe an efficient, simplified one-pot synthesis of bifunctional compounds containing two pyrazolo[3,4-*b*]-pyridine nuclei using dialdehyde **1** as a key starting material under microwave irradiation. These new compounds could be provided for biomedical screening.

A mixture of *p*-phenylenedialdehyde or *m*-phenylene-dialdehyde **1**, 5-amino-3-methyl-1-phenyl-pyrazole **2** and active methylene compounds **3** in 1:2:2 molar ratios was irradiated under microwave (250 W) using small amount of glycol as energy transfer reagent (Scheme 1 and 2). The reactions were completed in 45-300s.

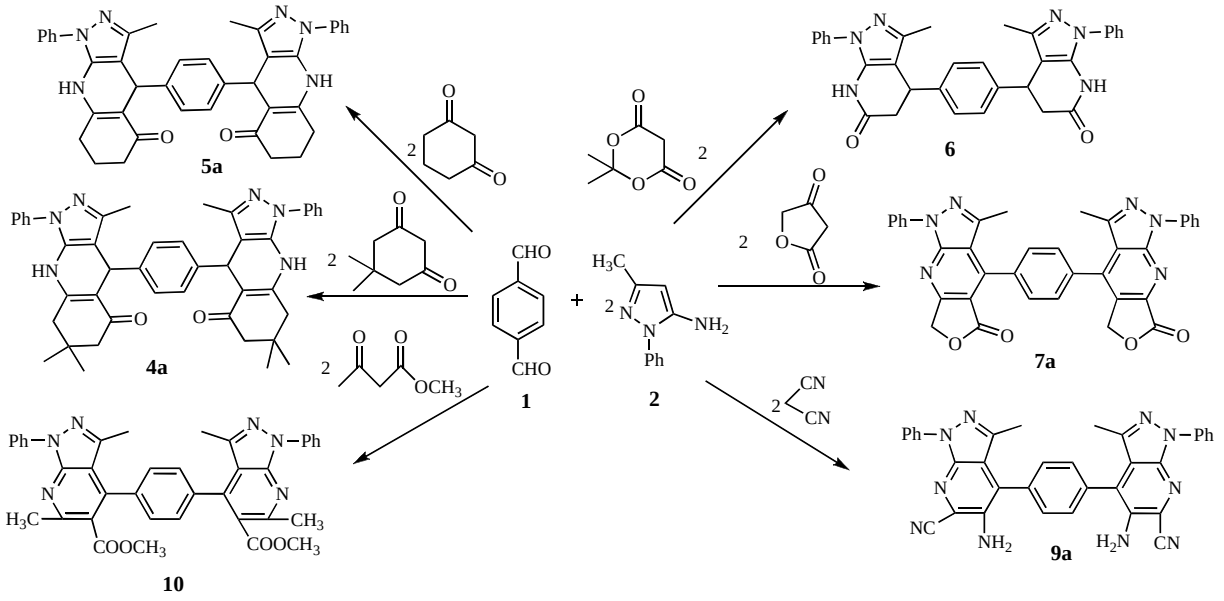
The reaction mixture was then cooled and poured into cold water and filtered. The solid was washed with a small amount of ethanol and ether. The crude products were purified by recrystallization from DMF to afford products with good yields (85–98%). All the reactions were followed by TLC and the experiments were replicated in order to ensure reproducibility. The main results for the synthesis of these compounds are listed in Table 1. All the products are conformed by their IR, ^{1}H NMR and elemental analysis.

RESULTS AND DISCUSSION

As shown in Table 1, we can see that these reactions have the advantage of short reaction time, good yields, convenient work up procedures and being environmentally friendly.

In summary, keeping in view the utility of MWI and the pharmacological importance of the above-mentioned heterocycles, we have synthesized a series of new and significant bifunctional compounds containing two pyrazolo[3,4-*b*]pyridine nuclei by MWI in order to provide a facile, rapid, efficient, and environmentally friendly method. These compounds may be proved to be of biological interest and provide new classes of biological active compounds for biomedical screening. This work is in progress in our laboratories.

Scheme 1



Scheme 2

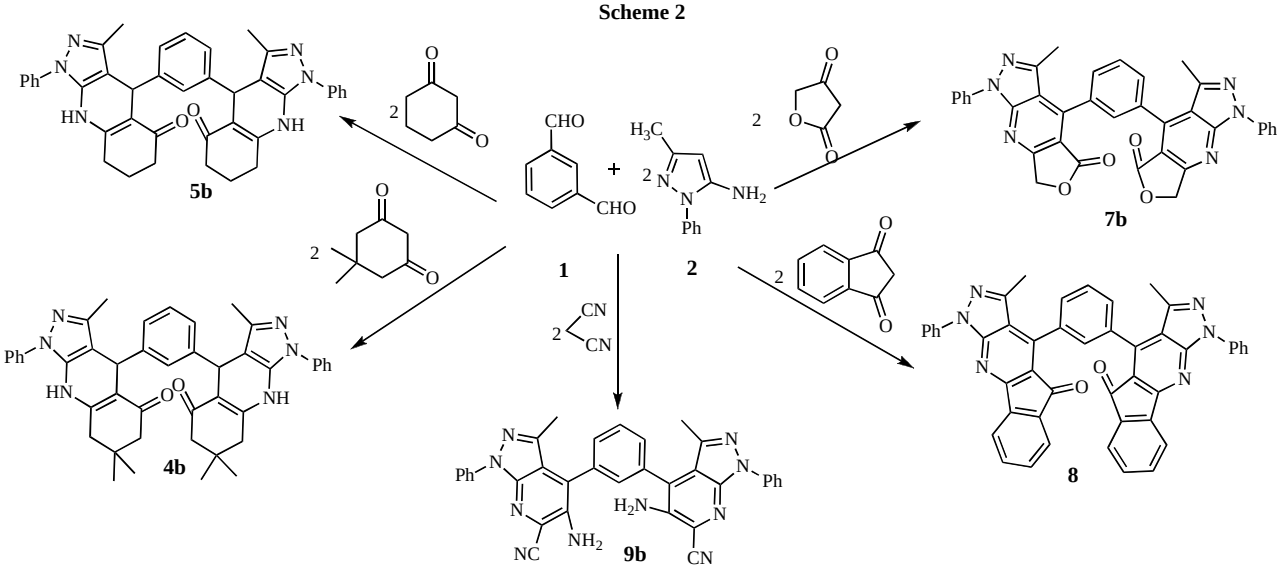
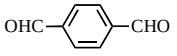
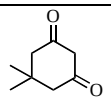
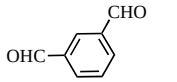
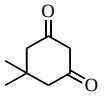
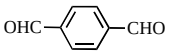
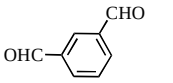
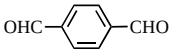
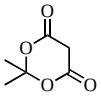
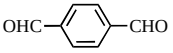
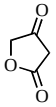
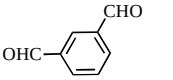
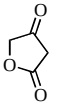
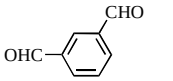
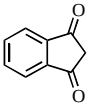
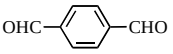
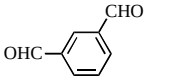
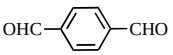
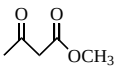


Table 1

Synthesis of **4**-**10** under microwave irradiation.

Entry	product	Starting material		Time (s)	Yield (%)	Mp(°C)
		1	**3**			
1	**4a**			60	97	>300
2	**4b**			60	98	>300
3	**5a**			60	96	>300
4	**5b**			60	97	>300
5	**6**			240	92	238-240
6	**7a**			45	98	>300
7	**7b**			45	98	>300
8	**8**			150	90	>300
9	**9a**			300	88	>300
10	**9b**			300	86	>300
11	**10**			300	85	240-242

EXPERIMENTAL

All reactions were performed in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Shimadzu spectrometer in KBr pellets and reported in cm^{-1}. ^1H NMR spectra were measured on a DPX 400 MHz spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. Elemental analysis was determined by using a Perkin-Elmer 240c elemental analysis instrument.

General procedure for the synthesis of 4-10. All reactions were performed in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Typically, in a 10-mL Emrys™ reaction vial, *p*-phenylenedialdehyde or *m*-phenylenedialdehyde **1** (1 mmol), 5-amino-3-methyl-1-phenylpyrazole 2 (2 mmol), active methylene compounds **3** (2 mmol) and glycol (0.25 mL) were mixed and then capped. The mixture was irradiated at 250 W and at 100 °C for a given time. The reaction mixture was cooled to room temperature and filtered to give the crude product, which was further washed with ether and ether, and then purified by recrystallization from DMF and ethanol to give pure products (**4-10**).

1,4-Bis(4,4a,7,8,8a,9-hexahydro-3,7,7-trimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinolin-5(*6H*)-one-4-yl)benzene (4a). This compound was obtained according to above general procedure; ir (potassium bromide): 3234, 3047, 1683, 1624, 1600, 1531, 832 cm^{-1}; ^1H nmr (DMSO-d_6): δ□9.35 (s, 2H, 2NH), 7.52-7.06 (m, 14H, ArH), 4.95 (s, 2H, 2CH), 2.52-2.08 (m, 8H, $4CH_2$), 1.85 (s, 6H, $2CH_3$), 0.98 (s, 6H, $2CH_3$), 0.94 (s, 6H, $2CH_3$). Anal. Calcd for $C_{44}H_{44}N_6O_2$: C, 76.72; H, 6.44; N, 12.20; Found C, 76.85; H, 6.33; N, 12.15.

1,3-Bis(4,4a,7,8,8a,9-hexahydro-3,7,7-trimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinolin-5(6*H*)-one-4-yl)benzene (4b). This compound was obtained according to above general procedure; ir (potassium bromide): 3567, 3422, 1654, 1625, 1559, 1506, 768, 694 cm^{-1}; ^1H nmr (DMSO-d_6): δ 9.41 (s, 2H, 2NH), 7.58-6.91(m, 14H, ArH), 4.90 (s, 2H, 2CH), 2.54-1.93 (m, 8H, $4CH_2$), 1.82 (s, 6H, $2CH_3$), 0.97 (s, 6H, $2CH_3$), 0.87 (s, 6H, $2CH_3$). Anal. Calcd for $C_{44}H_{44}N_6O_2$: C, 76.72; H, 6.44; N, 12.20; Found C, 76.83; H, 6.36; N, 12.33.

1,4-Bis(4,4a,7,8,8a,9-hexahydro-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinolin-5(6*H*)-one-4-yl)benzene(5a). This compound was obtained according to above general procedure; ir (potassium bromide): 3443, 3222, 3147, 1615, 1528, 860 cm^{-1}; ^1H nmr (DMSO-d_6): δ 9.42 (s, 2H, 2NH), 7.53-7.06(m, 14H, ArH), 4.97 (s, 2H, 2CH), 2.66-1.81 (m, 12H, $6CH_2$), 1.85 (s, 6H, $2CH_3$). Anal. Calcd for $C_{40}H_{36}N_6O_2$: C, 75.93; H, 5.73; N, 13.28; Found C, 75.99; H, 5.70; N, 13.15.

1,3-Bis(4,4a,7,8,8a,9-hexahydro-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinolin-5(6*H*)-one-4-yl)benzene (5b). This compound was obtained according to above [general] procedure; ir (potassium bromide): 3433, 3228, 1620, 1532, 1501, 764, 694 cm^{-1}; ^1H nmr (DMSO-d_6): δ 9.53 (s, 2H, 2NH), 7.52-6.97(m, 14H, ArH), 4.99 (s, 2H, 2CH), 2.89-1.71 (m, 12H, $6CH_2$), 1.94 (s, 6H, $2CH_3$). Anal. Calcd for $C_{40}H_{36}N_6O_2$: C, 75.93; H, 5.73; N, 13.28; Found C, 76.01; H, 5.68; N, 13.16.

1,4-Bis(4,5-dihydro-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridin]-6(7*H*)-one-4-yl)benzene (6). This compound was obtained according to above general procedure; ir (potassium bromide): 3254, 1689, 1598, 1499, 832 cm^{-1}; ^1H nmr (DMSO-d_6): δ 10.52 (s, 2H, 2NH), 7.58-7.18(m, 14H, ArH), 4.23-4.20(m, 2H, 2CH), 3.04-2.63 (m, 4H, $2CH_2$), 1.89 (s, 6H, $2CH_3$). Anal. Calcd for $C_{32}H_{28}N_6O_2$: C, 72.71; H, 5.34; N, 15.90; Found C, 72.68; H, 5.27; N, 15.81.

1,4-Bis(3-methyl-1-phenyl-1,7-dihydro-5*H*-furo[3,4-*b*]pyrazolo[4,3-*e*]pyridine-5-one-4-yl) benzene (7a). This compound was obtained according to above general procedure; ir (potassium bromide): 1769, 1715, 1573, 1509, 818 cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.19 (d, 4H, *J*=8.0Hz, ArH), 7.63-7.39(m, 10H, ArH), 5.49 (s, 4H, $2CH_2$), 2.08(s, 6H, $2CH_3$). Anal. Calcd for $C_{36}H_{24}N_6O_4$: C, 71.51; H, 4.00; N, 13.90; Found: C, 71.44; H, 3.92; N, 13.81.

1,3-Bis(3-methyl-1-phenyl-1,7-dihydro-5*H*-furo[3,4-*b*]pyrazolo[4,3-*e*]pyridine-5-one-4-yl) benzene (7b). This compound was obtained according to above general procedure; ir (potassium bromide): 1770, 1717, 1578, 1507, 791, 760, 690 cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.20 (d, 4H, *J*=8.0 Hz, ArH), 7.81-7.39(m, 10H, ArH), 5.51 (s, 4H, $2CH_2$), 2.21(s, 6H, $2CH_3$). Anal. Calcd for $C_{36}H_{24}N_6O_4$: C, 71.51; H, 4.00; N, 13.90; Found C, 71.49; H, 3.89; N, 13.80.

1,3-Bis(3-methyl-1-phenyl-1,7-dihydro-5*H*-indeno[1,2-*b*]pyridin[3,4-*b*]pyrazolo-5-one-4-yl)benzene (8). This compound was obtained according to above general procedure; ir (potassium bromide): 1711, 1677, 1597, 1566, 1503, 764, 705 cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.31-7.43(m, 22H, ArH), 2.24(s, 6H, $2CH_3$). Anal. Calcd for $C_{46}H_{28}N_6O_2$: C, 79.30; H, 4.05; N, 12.06; Found C, 79.39; H, 3.96; N, 11.99.

1,4-Bis(6-amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-carbonitrile-4-yl) benzene (9a). This compound was obtained according to above general procedure; ir (potassium bromide): 3480, 3338, 2212,1621, 1580, 1514, 1469, 839 cm^{-1}. ^1H nmr (DMSO-d_6): δ 8.22 (d, 4H, *J*=8.0 Hz, ArH), 7.79 (d, 4H, *J*=8.0 Hz, ArH), 7.60-7.52 (m, 4H, ArH), 7.33-7.30 (m, 2H, ArH), 7.35 (s, 4H, $2NH_2$), 1.97(s, 6H, $2CH_3$). Anal. Calcd for $C_{34}H_{24}N_{10}$: C, 71.31; H, 4.22; N, 24.46; Found C, 71.42; H, 4.17; N, 24.48.

1,3-Bis(6-amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-carbonitrile-4-yl) benzene (9b). This compound was obtained according to above general procedure; ir (potassium bromide): 3461, 3358, 2215, 1580, 1498, 785, 693 cm^{-1}; ^1H nmr (DMSO-d6): δ 8.19 (d, 4H, *J*=7.6 Hz, ArH), 7.83-7.50(m, 8H, ArH), 7.31-7.29 (m, 2H, ArH), 7.33 (s, 4H, $2NH_2$), 1.96(s, 6H, $2CH_3$). Anal. Calcd for $C_{34}H_{24}N_{10}$: C, 71.31; H, 4.22; N, 24.46; Found C, 71.40; H, 4.18; N, 24.37.

1,4-Bis(methyl-3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridin-5-carboxylate-4-yl) benzene (10). This compound was obtained according to above general procedure; ir (potassium bromide): 1727, 1595, 1575, 1506, 836 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.34-8.29 (m, 14H, ArH), 3.60(s, 6H, $2CH_3$), 2.71 (s, 6H, $2CH_3$), 2.10(s, 6H, $2CH_3$). Anal. Calcd for $C_{38}H_{32}N_6O_4$: C, 71.68; H, 5.07; N, 13.20; Found C, 71.76; H, 5.00; N, 13.11.

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