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Microwave-assisted synthesis of fused pyrazolo[3,4-*b*]pyrazines by the reaction of *ortho*-aminonitrosopyrazoles and cyclic β-diketones

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ABSTRACT

Novel fused pyrazolo[3,4-*b*]pyrazines **3** were prepared by assisted microwave cyclocondensation reaction of *ortho*-aminonitrosopyrazoles **1** and cyclic β-diketones **2** in dimethylformamide. This protocol provides a simple procedure for the synthesis of the title compounds with the advantages of easy work-up, mild reaction conditions and good yields.

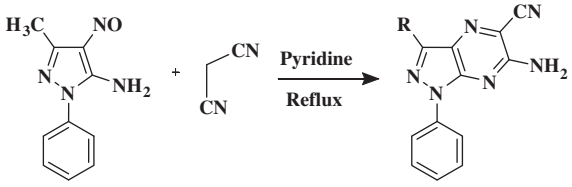
Pyrazolo[3,4-*b*]pyrazines are an interesting variety of heterocyclic compounds of great importance. It has been reported that some pyrazolopyrazine derivatives are used as bone metabolism improvers, anti-inflammatory, anti-aggregation of blood platelets and antitumoural agents.[1,2]

On the other hand, focused microwave irradiation (MWI) is emerging as a powerful tool to simplify and improve classic organic reactions, because it often leads to higher yields, cleaner and shorter reactions with precise control of its parameters.[3]

In general, aromatic nitroso derivatives react with compounds containing activated methylene groups. This procedure is known as the Ehrlich–Sachs reaction,[4] and has been used to prepare fused pyrazolo[3,4-*b*]pyrazines from malonodinitrile as shown in Scheme 1.[1a]

Acyclic and cyclic 1,3-dicarbonyl compounds constitute important synthetic precursors, which act either as nucleophilic or electrophilic species according to a large variety of synthetic transformations.[5]

Due to our interest in the development of synthetic strategies to obtain new functionalized heterocycles,[6] we have concentrated our recent efforts in the preparation of bioactive nitrogen-containing heterocycles. As mentioned previously, the pyrazolo[3,4-*b*]pyrazines present interesting properties, that have led us to focus this research on the development of derivatives of this system through the reaction of cyclic 1,3-dicarbonyl compounds with the title heterocyclic nitrosoamines.[5]



Scheme 1. Synthesis of pyrazolopyrazines.[1a]

As an extension of the Ehrlich–Sachs reaction, we are reporting here cyclocondensation reaction induced by focused microwave irradiation of *ortho*-aminonitrosopyrazoles **1** and cyclic β-diketones **2** to obtain the pyrazolo[3,4-*b*]pyrazine derivatives **3**.

In our initial study, various conditions, including solvents, temperature and microwave irradiation power, were tested, in order to find out the best conditions for the synthesis of **3a** from the nitrosoamine **1** (R = CH_3 and R′ = H) and dimedone **2a** as a model reaction. When pyridine was employed in the model reaction as a solvent at room temperature, no product was observed (Table 1, entry 1). This same reaction in pyridine using a reflux system afforded the product **3a** but after a long reaction time (10 h, entry 2). When the reaction was conducted in DMF under reflux, the desired product **3a** was obtained also in low yield (40%, entry 4). It should be noted that the desired product **3a** was obtained in high yield (85%, entry 5), when the reaction was conducted under microwave irradiation in DMF. Increasing the power or temperature in the microwave reactor did not improve the reaction efficiency, even

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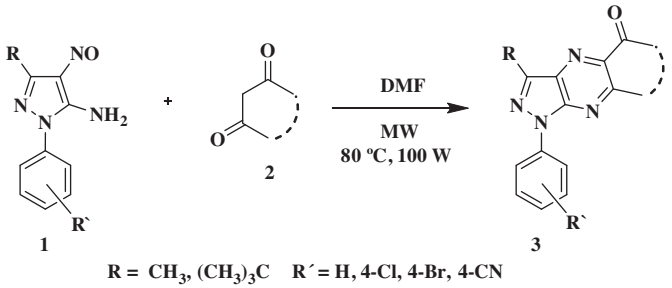
Table 1
A study of the reaction of 5-amino-3-methyl-4-nitroso-1-phenylpyrazole **1** with dimedone **2a**

Entry	Solvent	Conditions	Time (min)	Yield (%)
1	Pyridine	RT	60	—[a]
2	Pyridine	Reflux	600	35
3	AcOH	Reflux	60	—[a]
4	DMF	Reflux	480	40
5	DMF	MW (80 °C, 100 W)	9	85
6	DMF	MW (80 °C, 150 W)	8	70
7	DMF	MW (100 °C, 150 W)	8	70
8	DMF	MW (150 °C, 150 W)	6	60
9	DMF	MW (180 °C, 200 W)	5	45
10	DMF	MW (200 °C, 200 W)	5	40

[a] There was no reaction.



Scheme 2. Synthesis of fused pyrazolo[3,4-*b*]pyrazine derivates **3**.

in some cases complex reaction mixtures were obtained and difficult to purify (TLC control) (entries 9, 10).

In a general experimental procedure (Table 1, entry 5), equimolar amounts of starting compounds **1** and **2** in dimethylformamide were exposed to MWI during 4–18 min. It was used as a focused microwave reactor (CEM Discover TM) at 80 °C, power 100 W, 10 psi with this procedure the compounds **3** were isolated in a range of moderate to good yields, after purification by simple recrystallization from dimethylformamide or ethanol (Scheme 2, Table 1).[7] All the new compounds **3** present fluorescent properties. As shown in Table 2, this protocol can be applied not only to cyclohexanodione derivatives, but also to several cyclic 1,3-dicarbonyl compounds.

The structures of all new compounds were determined by analytical techniques: 1D and 2D NMR-spectroscopy, MS and elemental analysis. The analytical data are agreed with the proposed structures.

A possible mechanism for the described cyclocondensation reaction is outlined in Scheme 3. Presumably, the reaction starts with a nucleophilic addition of the activated methylene to the nitroso group of the pyrazole forming the intermediate imine **5**. This addition is favored due to the higher nucleophilicity that presents the activated methylene in contrast to the amino group of the pyrazole.[8] Subsequently, the intermediate **5** cyclizes via remaining NH_2 group with the terminal side chain carbonyl group (C=O) to form final pyrazolopyrazine **3**.

In summary, the described microwave-assisted synthesis is a simple and practical method for the preparation of novel pyrazolo[3,4-*b*]pyrazines with the advantages of easy work-up, mild reaction conditions and good yields. The biological and fluorescent

Table 2
New fused pyrazolo[3,4-*b*]pyrazines **3**

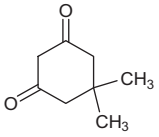
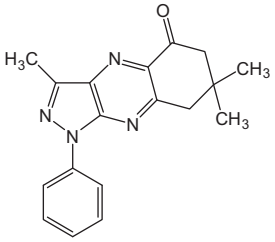
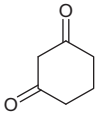
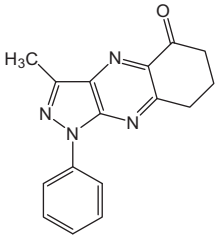
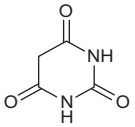
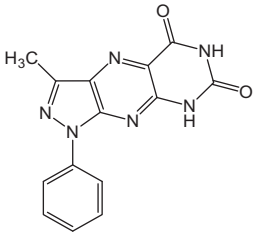
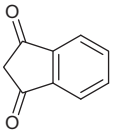
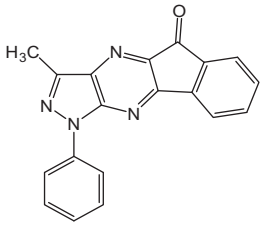
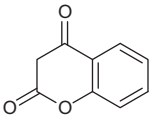
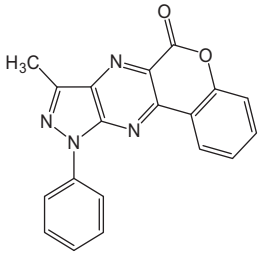
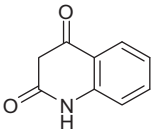
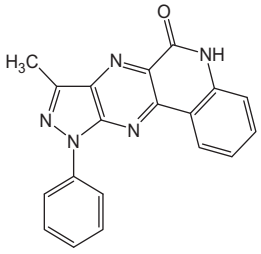
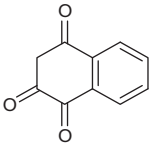
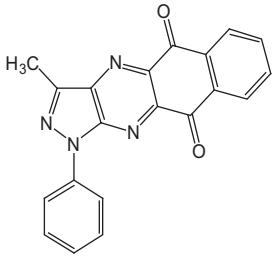
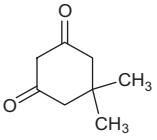
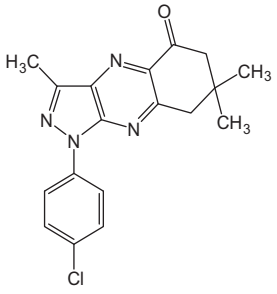
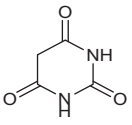
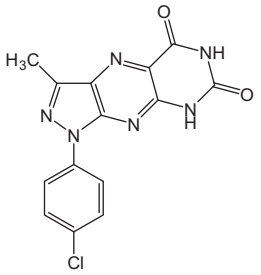
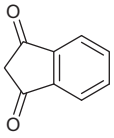
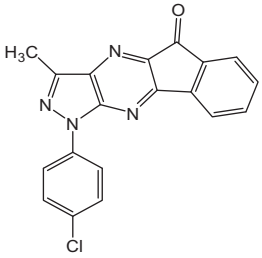
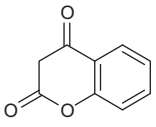
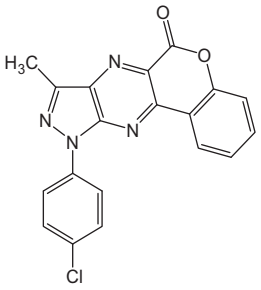
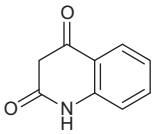
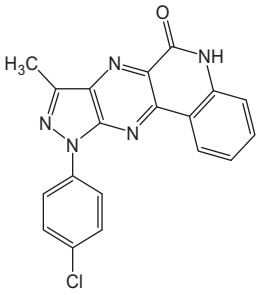
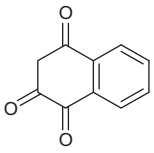
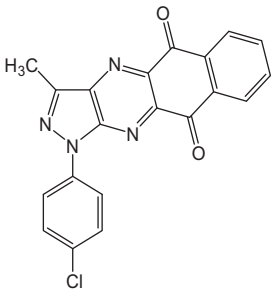
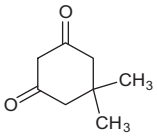
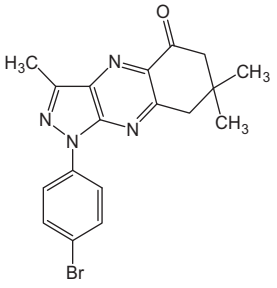
Entry	β-diketone	Product	Time (min)	Mp (°C)	Yield (%)
3a			8	188–190	85
3b			9	169–171	74
3c			10	>350	64

Table 2 (*continued*)

Entry	β-diketone	Product	Time (min)	Mp (°C)	Yield (%)
3d			4	228–230	65
3e			10	258–260	68
3f			6	>350	65
3g			8	257–259	63
3h			8	204–206	61
3i			8	>350	50

(*continued on next page*)

Table 2 (*continued*)

Entry	β-diketone	Product	Time (min)	Mp (°C)	Yield (%)
3j			6	274–276	49
3k			10	304–306	65
3l			14	>350	46
3m			12	251–253	52
3n			6	193–195	61

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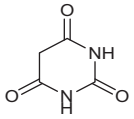
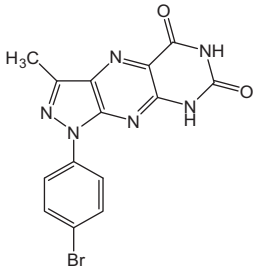
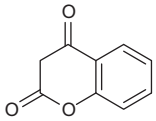
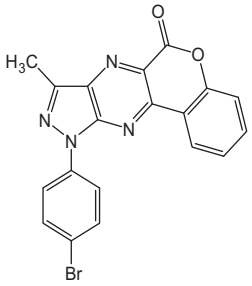
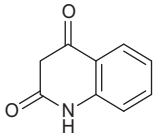
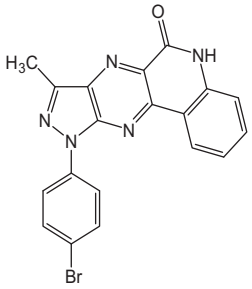
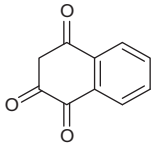
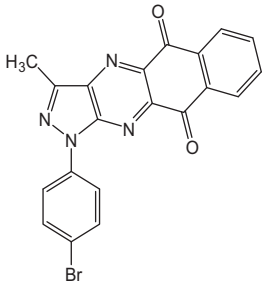
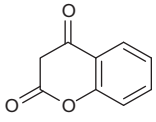
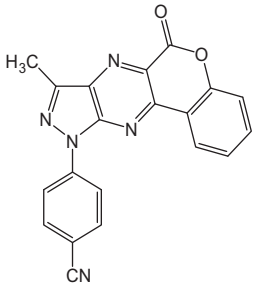
3o			16	293–295	43
3p			8	315–316	55
3q			14	>350	51
3r			12	268–270	45
3s			8	323–325	42

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Table 2 (*continued*)

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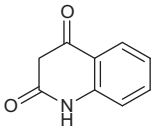
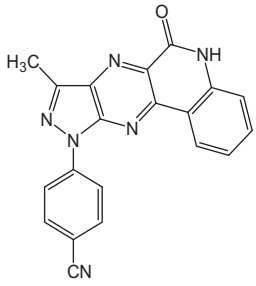
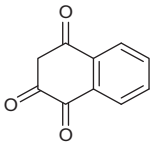
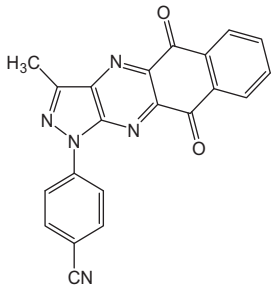
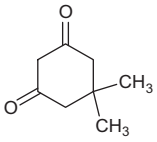
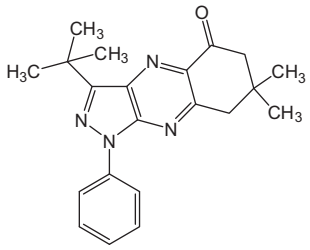
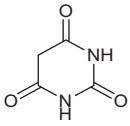
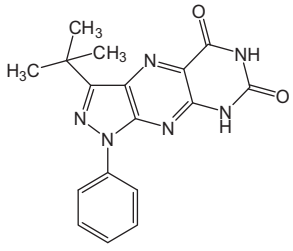
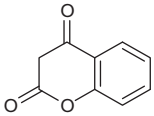
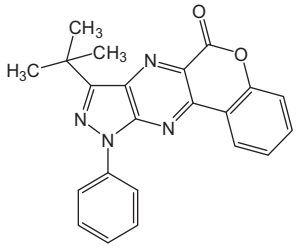
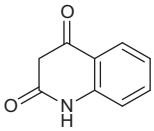
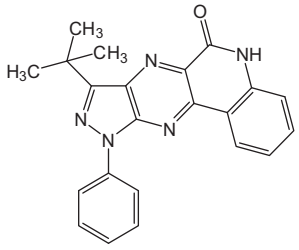
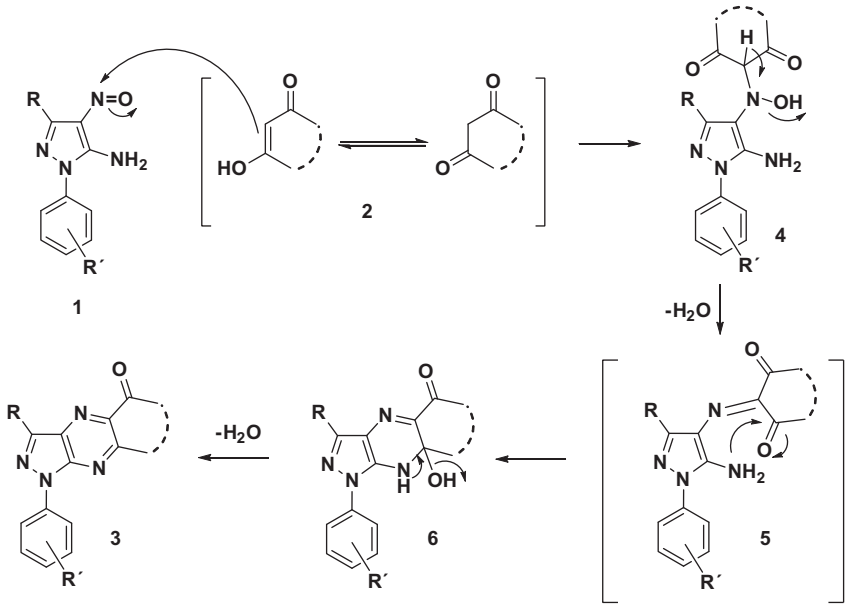
3t			10	>350	40
3u			8	298–300	48
3v			13	166–168	51
3w			18	>350	50
3x			15	264–265	51
3y			14	>350	41



Scheme 3. Possible mechanism for the formation of fused pyrazolopyrazines **3**.

properties of the new compounds obtained in this research are under investigation.

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7. *General procedure for the preparation of fused pyrazolo[3,4-b]pyrazines* **3**: Microwave experiment was carried out using a focused microwave reactor (CEM Discover TM). A mixture of equimolar amounts of *ortho*-aminonitrosopyrazole **1** (1 mmol) and β-diketone **2** (1 mmol) in dimethylformamide (1 mL) was exposed to microwave radiation from 4 to 18 min at 80 °C and 100 W of power. Then, the reaction mixture was allowed to cool to room temperature, and the resulting solid products were collected by filtration, washed with ethanol, dried in air and recrystallized from dimethylformamide. Data for *3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinoxalin-5(6H)-one* **3a**: Yellow solid, yield 85%, 188–190 °C. ^{1}H NMR (400 MHz $CDCl_3$) δ: 1.20 (s, 6H, CH_3-7), 2.81 (s, 2H, CH_2-8), 2.82 (s, 3H, CH_3-3), 3.30 (s, 2H, CH_2-6), 7.35 (t, 1H, H_p), 7.55 (t, 2H, H_m), 8.29 (d, 2H, H_o). ^{13}C NMR (100 MHz $CDCl_3$) δ: 11.8 (CH_3-3), 28.3 (CH_3-7), 32.8 (C-7), 47.2 (CH_2-8), 53.2 (CH_2-6), 120.4 (C*o*), 126.4 (C*p*), 129.3 (C*m*), 135.4 (C-3a), 138.6 (C_i), 139.2 (C-4a), 143.1 (C-9a), 146.3 (C-3), 157.3 (C-8a), 195.9 (C-5). EI EM: *m*/*z*: 306 (M^+, 100). Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29; Found: C, 70.79; H, 5.98; N, 18.16.
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