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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.

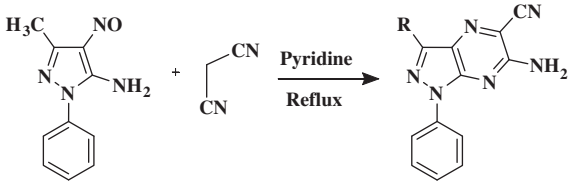
Pyrazolo[3,4-*b*]pyrazines are an interesting variety of heterocyclic compounds of great importance. It has been reported that some pyrazolopyrazine derivatives are used as bone metabolism improvers, anti-inflammatory, anti-aggregation of blood platelets and antitumoural agents.[1,2]

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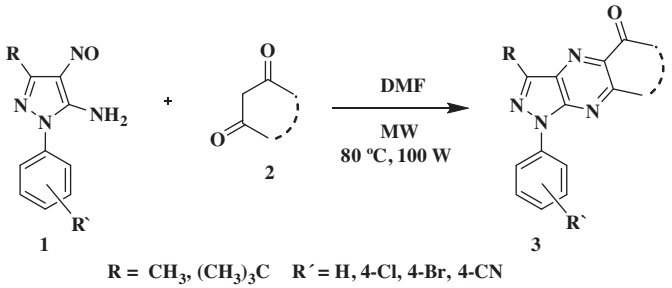
Table 1
A study of the reaction of 5-amino-3-methyl-4-nitroso-1-phenylpyrazole **1** with dimedone **2a**

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).

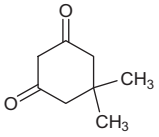
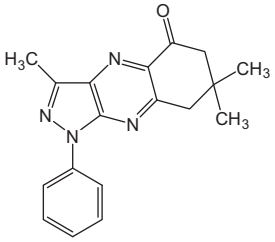
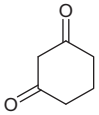
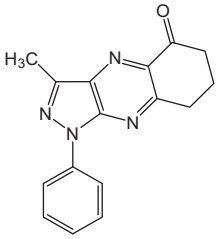
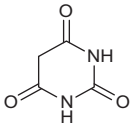
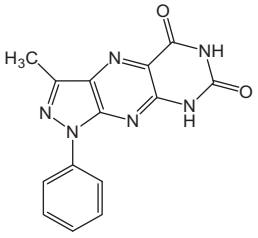
In a general experimental procedure (Table 1, entry 5), equimolar amounts of starting compounds **1** and **2** in dimethylformamide were exposed to MWI during 4–18 min. It was used as a focused microwave reactor (CEM Discover TM) at 80 °C, power 100 W, 10 psi with this procedure the compounds **3** 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