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Fast preparation of benzofuroxans by microwave-assisted pyrolysis of *o*-nitrophenyl azides

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Microwave-assisted pyrolysis of *o*-nitrophenyl azides gives benzofuroxans in good yields in short reaction times.

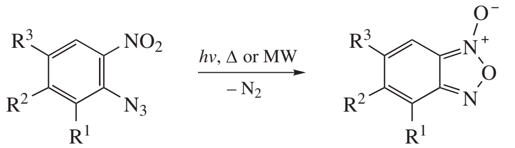
Benzofuroxans (benzo-2,1,3-oxadiazole *N*-oxides) are important heterocyclic compounds with diverse biological activity.[1] They have gained interest as cardiovascular agents since they generate nitric oxide which plays an important role as a biological messenger.[2] They have been extensively investigated as calcium channel modulators,[3] herbicides[1] and energetic materials.[4]

In organic synthesis, benzofuroxans have been used for the preparation of many pharmaceutical compounds like benzimidazole-3-oxides.[5] They react very easily with carbonyl compounds in basic media to give quinoxaline-1,4-dioxides.[5] Benzofuroxans bearing electron-withdrawing substituents (fluoro, chloro or nitro) are highly reactive and they have been applied in the synthesis of a variety of heterocyclic compounds.[5]

Several methods to prepare benzofuroxans have been reported.[6,7] *o*-Nitroaryl azides are the suitable precursors for heterocyclization synthesis of benzofuroxans (Scheme 1) by photolysis or pyrolysis.[8–10]

Fluid phase photolysis of *o*-nitrophenyl azides produces benzofuroxans only in moderate yields (30–35%), while photolysis in the crystalline state affords the corresponding heterocyclic compounds in quantitative yields.[10] However, this latter method provides good yields only in cases of crystalline substrates having a high melting point above 50 °C because the reaction proceeds under topotactic control due to the proximity of reacting groups NO_2 and N_3 in the crystal.[11]

Thermal cyclization of *o*-nitrophenyl azides is most widely used in the preparation of benzofuroxans.[10] It has been proposed that an *ortho*-nitro substituent participates in a pericyclic process with little nitrene character.[12] The computational studies support these assertions.[13] To induce this reaction, an aryl azide is usually refluxed for several hours at high temperature (100–160 °C) in toluene, xylene, DMSO or acetic acid. The principal drawback of this method is the long reaction time.[10]



1a–i **2a–i**

Scheme 1

The application of microwave irradiation (MW) as a non-conventional energy source for reactions has become a very popular and useful technique in organic chemistry.[14] In general, the use of MW energy leads to enhanced conversion rates, higher yields, easier work up and cleaner reactions demonstrating the real advantages of this methodology. In this paper, we report the preparation of benzofuroxans by microwave-assisted pyrolysis of *o*-nitrophenyl azides **1a–i** (Scheme 1). This procedure represents a fast methodology to prepare benzofuroxans.

At first, we performed the pyrolysis under conventional conditions and refluxed the corresponding *o*-nitrophenyl azides **1a–i** at 110 °C in acetic acid for 6 to 10 h (Table 1). Under these conditions, we obtained the corresponding benzofuroxans **2b–i** in reasonable yields. However, benzofuroxan **2a** was obtained in moderate yield (50%). In this case, TLC analysis of the reaction mixture indicated the presence of several by-products.

Table 1 Preparation of benzofuroxans **2a–i** from *o*-nitrophenyl azides **1a–i**.

Product	R^1	R^2	R^3	Traditional pyrolysis[a]		Microwave pyrolysis[b]		Mp/°C
				Time/h	Yield (%)	Time/min	Yield (%)	
2a	H	H	H	6	50	10	65	68–71[15]
2b	Me	H	H	6	85	15	80	84–86[16]
2c	H	Me	H	6	81	15	80	96–97[16]
2d	H	H	Me	6	82	15	80	96–97[16]
2e	H	H	OMe	6	65	10	60	116–117[16]
2f	H	H	Cl	6	67	10	65	47–48[16]
2g	H	Cl	Cl	6	91	10	90	130–131[17]
2h	NO_2	H	H	10	65	15	60	141–143[17]
2i	H	H	NO_2	6	75	10	70	71–72[18]

[a] A solution of *o*-nitrophenyl azide (150 mg) in acetic acid (20 ml) was refluxed. [b] A solution of *o*-nitrophenyl azide (150 mg) in DMSO (5 ml) and H_2O (1 ml) was irradiated in a microwave reactor (Discover CEM) at 120 °C (100 W). The reaction mixture was poured into ice-water. Each product was recrystallized from ethanol and characterized by UV-VIS, IR, Raman spectroscopy and mass spectrometry.

In order to choose an appropriate solvent, pyrolysis of *o*-nitrophenyl azide **1b** was investigated under microwave irradiation (100 W) at 120 °C for 20 min using AcOH, DMF/H_2O and DMSO/H_2O as solvents. The crude product mixtures were analyzed by TLC, which indicated that the reaction proceeded only in DMSO/H_2O. The microwave-assisted pyrolysis of *o*-nitrophenyl azides **1a–i** provided the corresponding crystalline benzofuroxans **2a–i** in reasonable yields (Table 1).

The starting *o*-nitrophenyl azides were prepared following the procedure previously reported by us.[10] An amount of each azide **1a–i** in DMSO/H_2O was irradiated (100 W) in a microwave reactor at 120 °C for several minutes. The microwave method accelerated the synthesis of benzofuroxans **2a–i** and also gave purer crystalline products. The isolated yields of products were comparable with those obtained by conventional refluxing (see Table 1). Substrates bearing electron-withdrawing and electron-donating substituents showed good reactivity.

In conclusion, microwave-assisted pyrolysis of *o*-nitrophenyl azides in DMSO/H_2O represents a versatile, fast and cleaner technique to prepare benzofuroxans.

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