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MOLECULAR SIEVES CATALYZED SYNTHESIS OF PHENAZINE 5,10-DIOXIDES UNDER SOLVENT-FREE CONDITIONS USING MICROWAVE IRRADIATION

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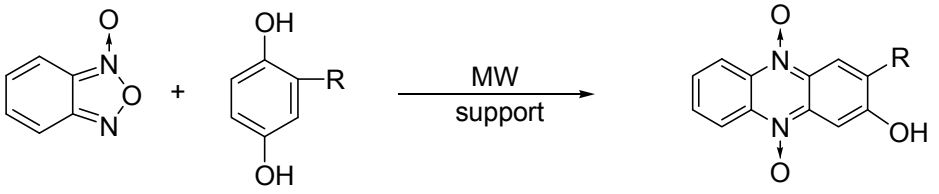
Abstract – We report on the simple and quick synthesis of phenazine 5,10-dioxides in solvent-free conditions under microwave irradiation. Heating of benzofuroxan and dihydroxybenzene derivatives adsorbed on molecular sieves in a microwave oven for 30 seconds affords diverse biologically attractive phenazine 5,10-dioxides derivatives. Molecular sieves functions not only as support using microwave but also as catalyst and dehydration reagent. Synthesis of phenazine 5,10-dioxides seems to proceed on molecular sieves, not in molecular sieves.

Benzofuroxan (benzofurazan N-oxide) **1** has been shown to have numerous pharmacological and industrial applications.[1a-d] As a part of benzofurazan chemistry, reactions of various benzofuroxans with active methylene compounds catalyzed by silica gel or molecular sieves yield the corresponding quinoxaline 1,4-dioxides, the antibacterial activity of quinoxaline 1,4-dioxides, and synthesis of quinoxaline 1,4-dioxides in solvent-free conditions under microwave irradiation has been reported.[2a-e] Pyrido[2,3-*b*]pyrazine 1,4-dioxides have been obtained from a reaction of pyrido[2,3-*c*]furoxan with active methylene compounds catalyzed by treatment with silica gel, alumina, or molecular sieves and the antibacterial activity of pyrido[2,3-*b*]pyrazine 1,4-dioxides has been reported.[3a-b] Reactions of benzofuroxan with various phenolic compounds catalyzed by silica gel, alumina, or molecular sieves provide the corresponding phenazine 5,10-dioxide derivatives and the antibacterial activity of phenazine 5,10-dioxide derivatives has been reported.[4a-b]

Microwave-assisted organic synthesis is a new and rapidly developing area in synthetic organic chemistry because it is an environmentally benign reaction.[5] In order to overcome a serious risk of fire or explosion due to sparking, several solvent-free procedures were developed.[6] Herein, we report on the simple and quick synthesis of phenazine 5,10-dioxides in solvent-free conditions under microwave irradiation.

Reactions of various dihydroxybenzenes with compound **1** using various supports were examined. Table 1 shows the results of the reactions using microwave.

Table 1. Results using the microwave method (MW) of benzofuroxan with several dihydroxy benzene

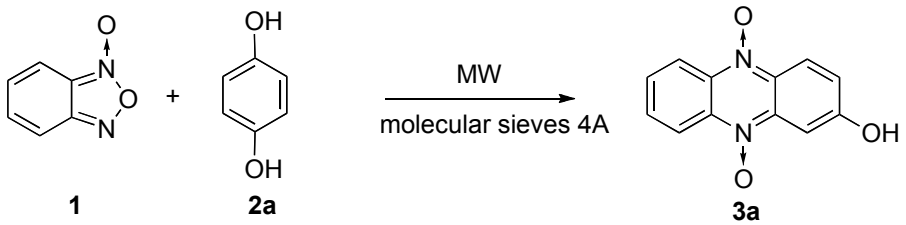


1 **2a-c** **3a-c**

Entry	Substrate	R	Time (sec.)	Support	Yield (%)
1	**2a**	H	30	molecular sieves 4A	72 (**3a**)
2	**2b**	Me	30	molecular sieves 4A	70 (**3b**)
3	**2c**	OMe	30	molecular sieves 4A	73 (**3c**)
4	**2a**	H	30	molecular sieves 13X	38 (**3a**)
5	**2a**	H	60	silica gel	8 (**3a**)
6	**2a**	H	60	aluminum oxide basic	45 (**3a**)

And, effect of dehydration activity of molecular sieves was examined (Table 2). For example, Synthesis of **3a** in the presence of H_2O yield is 21 %. Dryness of molecular sieves shown to be necessary for the formation of phenazine 5,10-dioxide derivatives, whose yields decreased with an increase of H_2O adsorbed on molecular sieves. The dehydration capacity of molecular sieves must significantly determine the possibility of synthesis of phenazine 5,10-dioxide derivatives. As shown in Table 1 entry 5, the low dehydration activity is one of reasons for the poor yield using silica gel as support.

Table 2. Effect of adding H_2O

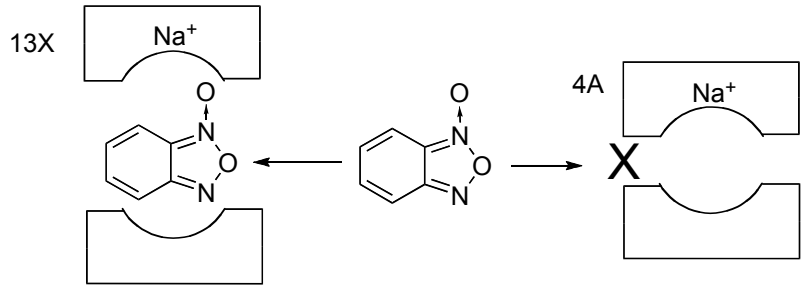


1 **2a** **3a**

Entry	Condition	Time (sec.)	Yield (%)
1	-	30	72
2	adding H_2O	30	21

In comparison with 2 kinds of molecular sieves, Table 1 showed the results of the reactions using molecular sieves 4A as a support to give a better yield than those using molecular sieves 13X. Extraction results of benzofuroxan were shown in Table 3. After benzofuroxan and dihydroxybenzene were adsorbed by the molecular sieves 4A or 13X, the adsorbed benzofuroxan was washed with CH_2Cl_2 to remove extra benzofuroxan from external surface of molecular sieves. Then, the molecular sieves were collected by filtration. After dissolving the entire molecular sieves framework in H_2SO_4, the benzofuroxan, which was adsorbed in the internal surface of molecular sieves, were able to be extracted with CH_2Cl_2. In comparison with the amount of extracted benzofuroxan before dissolving the molecular sieves in acid, benzofuroxan was obtained in perfect recovery in the case of molecular sieves 4A. The results of the reactions using molecular sieves 4A to give better yields of phenazine than those using molecular sieves 13X, is due to the difference in pore size. The benzofuroxan adsorbed in the internal surface of molecular sieves 13X cannot react with dihydroxybenzenes. Synthesis of phenazines seems to proceed on molecular sieves, not in molecular sieves.

Table 3. Comparison with molecular sieves 4A and 13X



	Molecular sieves 13X	Molecular sieves 4A
on molecular sieves (benzofuroxan %)	79	100
in molecular sieves (benzofuroxan %)	20	0

After washed three times with CH_2Cl_2

In conclusion, we have developed a new procedure for the preparation of phenazine 5,10-dioxides under microwave irradiation. Molecular sieves functions not only as support using microwave but also as catalyst and dehydration reagent. Synthesis of phenazine 5,10-dioxides seems to proceed on molecular sieves, not in molecular sieves. This method offers several advantages including an easier experimental procedure than previously described methods, shorter reaction times.

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7. All experiments were carried out by using a RE-T13 domestic oven manufactured by SHARP Inc. Molecular sieves (powder, Union Showa) were dried by heating at 250 ^{o}C for 2 h. In the case of adding H_2O (Table 2, Entry 2), dried molecular sieves (4 g) were put into 9:1 MeOH / H_2O (10 mL) and stand overnight, and thereafter filtrated. The resulting molecular sieves were washed with MeOH and CH_2Cl_2, and dried using air carefully at room temperature.

   A typical experimental procedure for synthesizing phenazine 5,10-dioxides is as follows (Table 1): In a round bottom flask, dried molecular sieves 4A (4 g) was impregnated with a solution of benzofuroxan **1** (68 mg, 0.5 mmol) and dihydroxybenzene **2a** (60.5 mg, 0.55 mmol) in MeOH (10 mL). The solvent was evaporated on a rotatory evaporator followed by standing under microwave irradiation (700 W) for 30 seconds without stirring. Then, It was purified by column chromatography (silica gel, 20:1 CH_2Cl_2 / MeOH) to provide phenazine 5,10-dioxides in 72 % yield.