

HETEROCYCLES, Vol. 78, No. 4, 2009, pp. 905 - 909. © The Japan Institute of Heterocyclic Chemistry
Received, 29th October, 2008, Accepted, 18th December, 2008, Published online, 19th December, 2008
DOI: 10.3987/COM-08-11588

SILICA GEL CATALYZED SYNTHESIS OF QUINOXALINE 1,4-DIOXIDES UNDER SOLVENT-FREE CONDITIONS USING MICROWAVE IRRADIATION

Yusuke Sumiyoshi, Hiroaki Saito, Shinichi Miyairi, and Tohru Takabatake*

College of Pharmacy, Nihon University, 7-7-1 Narashinodai,
Funabashi-shi, Chiba 274-8555, Japan
takabatake.toru@nihon-u.ac.jp

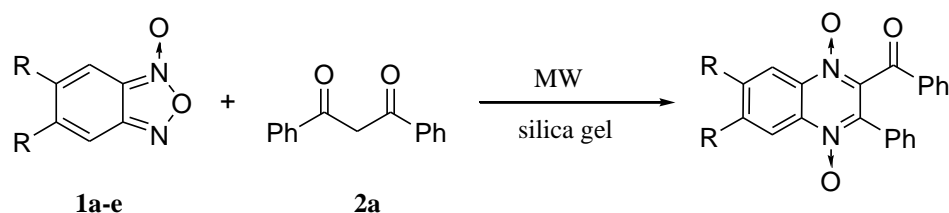
Abstract – We report on the simple and quick synthesis of quinoxaline 1,4-dioxides in solvent-free conditions under microwave irradiation. Heating of various benzofuroxans and β -ketoesters or 1,3-diketones adsorbed on silica gel in a microwave oven for two minutes affords diverse biologically attractive quinoxaline 1,4-dioxides in high to excellent yields. Silica gel functions not only as support using microwave but also as catalyst and dehydration reagent.

Benzofuroxan (benzofurazan *N*-oxide) 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, and the antibacterial activity of quinoxaline 1,4-dioxides has been reported.^{2a-d} 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} The toxicity of benzofurazans in *Escherichia coli* has been reported to be caused by an increase in intracellular flux of superoxide on aerobic incubation.^{5a} The superoxide production was confirmed using the cytochrome *c* reduction method and ESR spectra.^{5b} 4,7-Dimethylbenzofurazan was transformed by $^1\text{O}_2$ into 4,7-dimethylbenzofurazan 4,7-endoperoxide, in excellent yields.⁶

Microwave-assisted organic synthesis is a new and rapidly developing area in synthetic organic chemistry because it is an environmentally benign reaction.⁷ In order to overcome a serious risk of fire or explosion

due to sparking, several solvent-free procedures were developed.⁸ Herein, we report not only increased in the chemical yield, but also dramatic acceleration of the reaction rate in solvent-free conditions under microwave irradiation using silica gel as support. We investigated the scope of this process with respect to the substituents on the benzene ring of benzofuroxans (Table 1).⁹ Both the short reaction time and high yield were maintained with either electron-withdrawing (-F, -Cl) or electron-donating (-CH₃, -OCH₃) groups on the 5, 6-positions of benzofuroxans. The benzofuroxans that having electron-withdrawing groups at position 5 and 6 (**1a**, **b**) gave the purpose products around 90% yield using only 1.1 equivalents of diketone **2** (Entries 1, 2).

Table 1. Results using the microwave method (MW) of several benzofuroxans



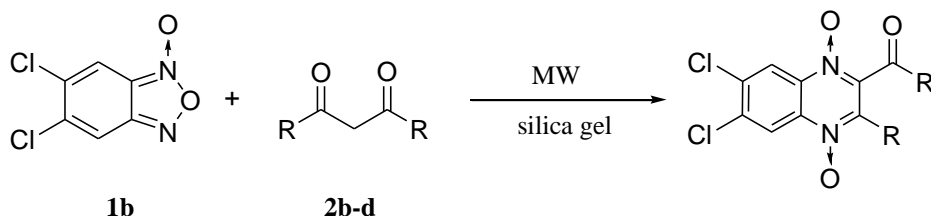
Entry	Substrate		Time (min)	Yield (%)
		R		
1	1a	F	2	90
2	1b	Cl	2	89
3	1c	Me	2	77 ^a
4	1d	OMe	3	62
5	1e	H	2	65 ^b

^a The yield was increased to 92% if 3 equivalents of diketone **2a** were used.

^b The yield was increased to 79% if 3 equivalents of diketone **2a** were used.

Next we explored the effects of the diketones. We used 5,6-dichlorobenzofuroxan as a substrate for the reaction. The dramatic acceleration of the reaction rate was achieved without affecting the chemical yields (Table 2). The method is also applicable to aliphatic diketone **2d** (Entry 3).

Table 2. Effects of the diketone derivatives on chemical yield using the microwave method

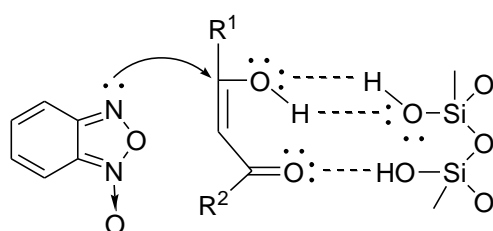


Entry	Diketone ^a		Time (min)	Yield(%)
		R		
1	2b	4-ClC ₆ H ₄	1.5	86
2	2c	4-MeOC ₆ H ₄	1.5	81
3	2d	Me	2	90

^a 1.1 equivalents of diketone **2b-d** were used

It was suggested that one of the reasons for the acceleration under microwave irradiation could be due to specific microwave effects.^{7b} The effects act stronger to more polar molecules in the course of the reaction.


Reaction of various β -ketoesters and 1,3-diketones **2d-g** with compound **1e** was examined (Table 3). Compound **2e** failed to react with compound **1e** and unreacted **2e** was almost completely recovered. The enol form of carbonyl compounds was previously shown to be necessary for the formation of quinoxalines, whose yields depended on the enol content in compound **2d-g**.¹⁰ Silica gel may serve to enhance the stability of the enol form of carbonyl compounds (Scheme 1).



Scheme 1

And, effect of dehydration activity of silica gel was examined. For example, Synthesis of **2g** in the presence of H₂O yield is 13 %. Dryness of silica gel shown to be necessary for the formation of quinoxalines, whose yields decreased with an increase of H₂O adsorbed on silica gel. The dehydration capacity of silica gel must significantly determine the possibility of synthesis of quinoxaline 1,4-dioxides.

Table 3. Effect of enol content of carbonyl compounds on the condensations with benzofuroxan

Entry	Substrate		Enol Content of 2d-g (%) (in Ethanol) ¹⁰	Time (min)	Yield (%) ^a	
	R ¹	R ²				
1	2e	OMe	OMe	0	4	0
2	2f	Me	OMe	12.6	2	15
3					4	32
4	2d	Me	Me	84	2	56
5					4	85
6	2g	Me		94	2	83

^a Compound **1e** was used at 0.25 mM and silica gel at 4 g.

In conclusion, we have developed a new procedure for the preparation of quinoxaline 1,4-dioxides under microwave irradiation. Silica gel functions not only as support using microwave but also as catalyst and

dehydration reagent. This method offers several advantages including an easier experimental procedure than previously described methods, shorter reaction times and excellent yields.

ACKNOWLEDGEMENTS

This research was supported by A Grant from “Academic Frontier” Project for Private Universities: matching fund subsidy from MEXT (Ministry of Education, Culture, Sports, Science and Technology) 2002-2006.

REFERENCES AND NOTES

- (a) A. J. Boulton and P. B. Ghosh, *Adv. Heterocyclic Chem.*, 1969, **10**, 1; (b) A. Gasco and A. J. Boulton, *Adv. Heterocyclic Chem.*, 1981, **29**, 251; (c) P. B. Ghosh, B. Ternai, and M. W. Whitehouse, *Med. Res. Rev.*, 1981, **1**, 159; (d) A. R. Katritzky and M. F. Gordeev, *Heterocycles*, 1993, **35**, 483.
- (a) M. Hasegawa and T. Takabatake, *Synthesis*, 1985, 938; (b) T. Takabatake and M. Hasegawa, *J. Heterocycl. Chem.*, 1987, **24**, 529; (c) T. Takabatake, Y. Hasegawa, and M. Hasegawa, *J. Heterocycl. Chem.*, 1993, **30**, 1477; (d) T. Takabatake, Y. Takabatake, T. Miyazawa, and M. Hasegawa, *Yakugaku Zasshi*, 1996, **116**, 491.
- (a) T. Takabatake, T. Miyazawa, and M. Hasegawa, *Heterocycles*, 1997, **45**, 107; (b) T. Miyazawa, T. Takabatake, and M. Hasegawa, *Yakugaku Zasshi*, 1997, **117**, 126.
- (a) T. Takabatake, T. Miyazawa, M. Kojo, and M. Hasegawa, *Heterocycles*, 2000, **53**, 2151; (b) T. Takabatake, T. Miyazawa, A. Takei, and M. Hasegawa, *Medicine and Biology*, 2001, **142**, 5.
- (a) T. Takabatake, M. Hasegawa, T. Nagano, and M. Hirobe, *Chem. Pharm. Bull.*, 1990, **38**, 128; (b) T. Takabatake, M. Hasegawa, T. Nagano, and M. Hirobe, *J. Biol. Chem.*, 1992, **267**, 4613.
- T. Takabatake, T. Miyazawa, M. Hasegawa, and C. S. Foote, *Tetrahedron Lett.*, 2001, **42**, 987.
- (a) S. Caddick, *Tetrahedron*, 1995, **51**, 10403; (b) L. Perreux and A. Loupy, *Tetrahedron*, 2001, **57**, 9199; (c) P. Lidström, J. Tierney, B. Wathey, and J. Westman, *Tetrahedron*, 2001, **57**, 9225; (d) A. K. Bose, M. S. Manhas, S. N. Ganguly, A. H. Sharma, and B. K. Banik, *Synthesis*, 2002, 1578.
- (a) A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault, and D. Mathé, *Synthesis*, 1998, 1213; (b) S. Paul, P. Nanda, R. Gupta, and A. Loupy, *Tetrahedron Lett.*, 2002, **43**, 4261; (c) S. Kotha, K. Mandal, A. C. Deb, and S. Banerjee, *Tetrahedron Lett.*, 2004, **45**, 9603.
- All experiments were carried out by using a RE-T13 domestic oven manufactured by SHARP Inc. Silica gel (Wakogel® C-200, Wako Pure Chemical Industries, Ltd) was dried by heating at 110 °C for 1 h. A typical experimental procedure for synthesizing quinoxaline 1,4-dioxide is as follows (Table 1): In a round bottom flask, silica gel (6 g) was impregnated with a solution of benzofuroxan **1e** (27 mg, 0.2 mmol) and dibenzoylmethane **2a** (49.5 mg, 0.22mmol) in CH₂Cl₂ (8 mL). The

solvent was evaporated on a rotatory evaporator followed by standing under microwave irradiation (700 W) for 1 min without stirring. For stirring, the reaction mixture was stirred by hand and standing at room temperature for 30 sec. It was re-irradiated in a microwave oven for 1 min. The crude solid was extracted with EtOAc (50 mL) and evaporated in vacuo, which was purified by column chromatography (silica gel, 30:1 CH₂Cl₂ /MeOH) to provide quinoxaline 1,4-dioxide **3e** in 65 % yield.

10. K. H. Meyer, *Ber.*, 1912, **45**, 2843.