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Microwave enhanced solution synthesis of 1,4-benzodiazepin-5-ones

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Abstract—Some 2-methyl-1,4-benzodiazepin-5-ones have been synthesized by the application of microwave irradiation. Conventional heating and microwave irradiation of the reactions were compared. Synthesis by microwave irradiation gave the desired compounds in better yields than those obtained by conventional heating. The overall times for the syntheses were considerably reduced.

Heterocyclic compounds hold a special place among pharmaceutically important natural and synthetic materials. The remarkable ability of heterocyclic nuclei to serve both as biomimetics and active pharmacophores has largely been contributed to their unique value as traditional key elements of numerous drugs. Heterocyclic derivatives such as morphine alkaloids, β-lactam antibiotics, and benzodiazepines are just a few familiar examples from various pharmaceuticals featuring a heterocyclic component.[1]

The benzodiazepine nucleus is a well-studied traditional pharmacophoric scaffold that has emerged as a core structural unit of various sedative-hypnotic, muscle relaxant, anxiolytic, antistaminic, and anticonvulsant agents. Therefore diversely substituted benzodiazepine nuclei can serve as synthons for developing new drugs.

A number are 1,4-benzodiazepin-5-ones, e.g. the antibiotic Neothramicin, the antidepressant Flumazenil, and the antistaminic Clobenzepam.[2–6] The literature on this subject, although very copious, is mainly constituted by patents. This fact led us to carry out studies to improve the synthesis of this scaffold bearing in mind new synthetic methodologies.

The application of microwave energy to organic compounds for conducting synthetic reactions at highly accelerated rates is an emerging technique. In recent years, microwaves have become popular among synthetic organic chemists both to improve classical organic reactions,[7–13] shortening reaction times and/or improving yields, as well as to promote new reactions.

Moreover, often when carrying out a reaction in a microwave oven the use of a solvent can sometimes be avoided, which is important in order to make the synthesis more environmentally friendly ('green chemistry'). These observations led us to investigate the possibility of improving the methods used for the synthesis of the 1,4-benzodiazepin-5-one scaffold.

This paper describes a facile synthesis of 2-methyl-1,4-benzodiazepin-5-one,[14] based on an intramolecular azide cycloaddition, by application of microwave energy in the presence of solvents. Conventional heating (oil bath) and microwave irradiation of the reactions are compared.

The synthetic procedure, summarized in Scheme 1, was performed using a microwave oven (ETHOS 1600, Milestone) especially designed for organic synthesis. The experimental conditions used in our work were similar to those used by conventional heating, with the same concentration of starting material and volume of solvent. The parameters of power, time and temperature used for the irradiation were as reported in Tables 1 and 2.

Keywords: 2-methyl-1,4-benzodiazepin-5-ones; microwave irradiation in solution; medium ring heterocycles.

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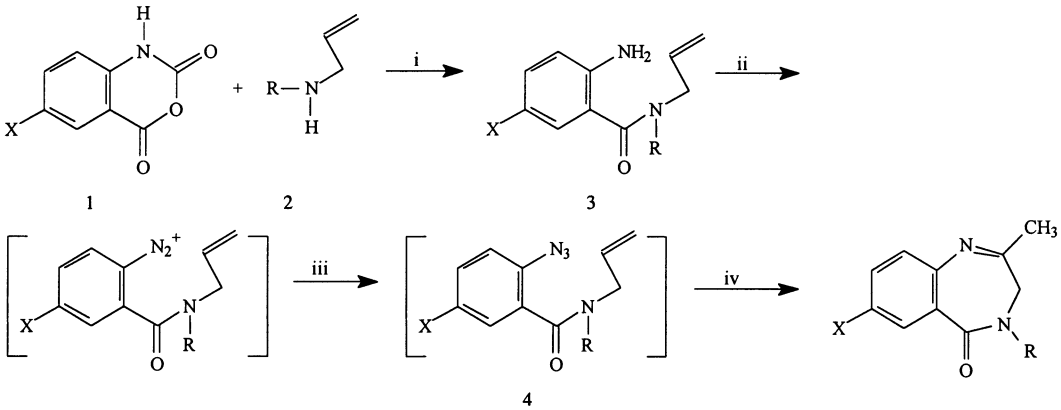
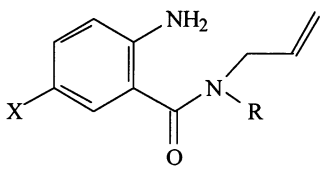


	X	R
a	H	Me
b	H	Allyl
c	Cl	Me
d	Cl	Allyl
e	Br	Me
f	Br	Allyl

Scheme 1. *Reagents*: (i) DMF, reflux 1 h, μv; (ii) 1N HCl, $NaNO_2$, AcOH, 30 min; (iii) NaN_3, Et_2O, 40 min; (iv) DMF, μv.

Table 1. Conventional heating versus microwave irradiation for intermediates 2-amino-5-X-*N*-alkyl-*N*-(2-propenyl)benzamide (**3a–f**)[a]

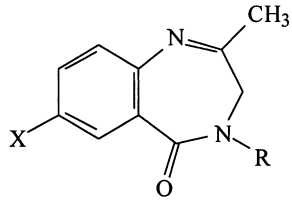


Compd.	R	X	Conventional heating[b]			Microwave irradiation			
			Yield[c] (%)	Time (min)	Temp. (°C)	Yield[c] (%)	Time (min)	Power (W)	Temp. (°C)
3a	Me	H	65	180	Reflux	91	5	150	80
							50	250	110
							5	300	110
3b	Allyl	H	20	180	Reflux	50	5	150	80
							50	250	120
							5	300	110
3c	Me	Cl	69	180	Reflux	97	5	150	80
							50	250	110
							5	300	110
3d	Allyl	Cl	60	180	Reflux	85	5	150	80
							50	250	120
							5	300	110
3e	Me	Br	65	180	Reflux	92	5	150	80
							50	250	120
							5	300	110
3f	Allyl	Br	45	180	Reflux	60	5	150	80
							50	250	120
							5	300	110

[a] All the reactions were performed three times and the reaction time and yields given are the average values.
[b] Oil bath.
[c] With respect to the starting amount of anhydride.

The general procedure is as follows: the 5-X-isatoic anhydride (**1**) (2.0 mmol) was dissolved in DMF (10 ml) and was introduced into the reaction vessel followed by the allylamine (**2**) (4.5 mmol). The desired parameters (microwave power, temperature and time) were set as reported in Table 1. After irradiation, the solution was

Table 2. Conventional heating versus microwave irradiation for final compounds (**5a–f**)[a]



Compd.	R	X	Conventional heating[b]			Microwave irradiation			
			Yield[c] (%)	Time (min)	Temp. (°C)	Yield[c] (%)	Time (min)	Power (W)	Temp. (°C)
5a	Me	H	40	60	Reflux	69	5	150	80
							50	250	110
							5	300	110
5b	Allyl	H	45	60	Reflux	61	5	150	80
							50	250	120
							5	300	110
5c	Me	Cl	38	60	Reflux	55	5	150	80
							50	250	110
							5	300	110
5d	Allyl	Cl	34	60	Reflux	58	5	150	80
							50	250	120
							5	300	110
5e	Me	Br	30	60	Reflux	60	5	150	80
							50	250	120
							5	300	110
5f	Allyl	Br	27	60	Reflux	60	5	150	80
							50	250	120
							5	300	110

[a] All the reactions were performed three times and the reaction time and yields given are the average values.
[b] Oil bath.
[c] With respect to the starting amount of amine.

treated as follows. The pH of the solution was adjusted to pH 9 with 5% NaOH and extracted with Et_2O. The organic layer was dried and evaporated under reduced pressure to give compounds **3a–f**.

The results obtained with the various reagents are summarized in Table 1.

In the second step, intermediates **3a–f** (6.3 mmol) were subjected to diazotization ($NaNO_2$ 12.6 mmol/1N HCl 30 ml and CH_3COOH 65 ml at 0°C) and subsequent nucleophilic substitution by sodium azide (37.8 mmol). Since the species (**4**) so-formed were rather unstable, we preferred to use them as crude materials without full characterization. The intermediates (**4**) were cyclized either by refluxing in DMF or by subjecting to a second exposure to microwave irradiation. After evaporation of the solvent, the crude products were purified by chromatography on silica gel (diethyl ether/EtOH, 9.5:0.5 v/v). The final compounds (**5a–f**) listed in Scheme 1 were characterized by ^1H NMR spectroscopy and the data were in agreement with the assigned structures.[14]

The results obtained with the various reagents are summarized in the Table 2.

Transposition of two steps of the synthesis of 2-methyl-1,4-benzodiazepin-5-ones to microwave irradiation of solutions gave the desired compounds **5a–f** in better yields and cleaner reactions to those obtained by conventional heating. The overall times for the syntheses were considerably reduced.

In conclusion, we have described a rapid synthesis of the 2-methyl-1,4-benzodiazepin-5-ones using a microwave oven and provided further example of the utility of microwave irradiation in organic synthesis in the presence of solvents.

References

1. Roth, H. J.; Kleemann, A. *Pharmaceutical Chemistry*; Vol. 1: Drug Synthesis. Wiley: New York, 1988.
2. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 1, Chapter 1/06.
3. *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 7, Chapter 5/18.
4. Mohiuddin, G.; Reddy, P. S.; Ahmed, K.; Ratnam, C. V. *Heterocycles* **1986**, *24*, 3489.
5. Frostl, W.; Maitre, L. *Pharmacopsych*. **1989**, *22*, 54.
6. Walser, A.; Fryer, R. I. *Bicyclic Diazepines*; Wiley: New York, 1991; Chapter VII.
7. Varma, R. S. *Green Chem*. **1999**, 43–55.

8. Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Francoise, P.; Mathe, D. *Synthesis* **1998**, 1213–1234.
9. Bose, A. K.; Banik, B. K.; Lavlinskaia, N.; Jayaraman, M.; Manhas, M. S. *Chemtech* **1997**, *27*, 18–24.
10. Galema, S. A. *Chem. Soc. Rev.* **1997**, *26*, 233–238.
11. Majetich, G.; Hicks, R. *Radiat. Phys. Chem.* **1995**, *45*, 567–579.
12. Caddick, S. *Tetrahedron* **1995**, *51*, 10403–10432.
13. Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665–1692.
14. Brogini, G.; Zecchi, G.; Molteni, G. *Gazz. Chim. Ital.* **1997**, *127*, 809–810.