



An efficient method for the synthesis of 1,5-benzodiazepine derivatives under microwave irradiation without solvent

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Abstract—2,3-Dihydro-1*H*-1,5-benzodiazepines have been synthesized in solvent-free conditions from *o*-phenylenediamines and ketones in the presence of a catalytic amount of acetic acid, under microwave irradiation. This method is a very easy, rapid and high yielding reaction for the synthesis of 1,5-benzodiazepine derivatives. © 2002 Elsevier Science Ltd. All rights reserved.

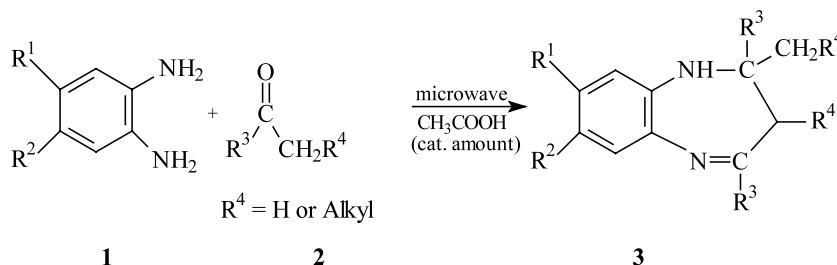
Benzodiazepines are very important compounds because of their pharmacological properties.^{1,2} Many members of the family are nowadays used as anticonvulsant, antianxiety and hypnotic agents. In addition, 1,5-benzodiazepines are used as starting materials for the preparation of fused ring compounds such as triazolo-,^{3–5} oxadiazolo-,⁵ oxazino-⁴ or furano-benzodiazepines.^{4,6}

Despite their importance from a pharmacological, industrial and synthetic point of view, comparatively few methods for their preparation are reported in the literature,^{7–10} a great number of which have appeared only very recently.^{11–15} These include condensation reactions of *o*-phenylenediamines with α,β -unsaturated carbonyl compounds,⁷ β -haloketones⁸ or ketones in the presence of BF_3 -etherate,⁹ NaBH_4 ,¹⁰ polyphosphoric acid,¹¹ SiO_2 ,¹¹ MgO and POCl_3 ,¹² $\text{Yb}(\text{OTf})_3$,¹³ and $\text{Al}_2\text{O}_3/\text{P}_2\text{O}_5$ under MW.¹⁴ Unfortunately, many of these processes suffer major or minor limitations, such as drastic reaction conditions, expensive reagents, low

yields, tedious work-up procedures and the occurrence of several side reactions. The application of microwave energy for conducting organic 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, shortening reaction times and/or improving yields, as well as to promote new reactions.¹⁶

Moreover, often when carrying out a reaction in a microwave oven, the use of a solvent can 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 1,5-benzodiazepine scaffold.

This paper describes a facile synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines by condensation of ketones with *o*-phenylenediamines (Scheme 1) by application of microwave irradiation without solvent. The syntheses



Scheme 1.

Keywords: benzodiazepines; *o*-phenylenediamines; microwave irradiation; green chemistry.

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Table 1. Synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines

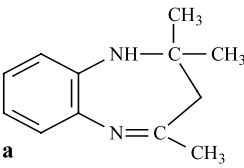
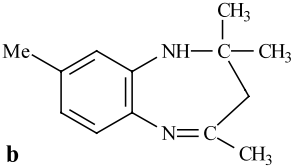
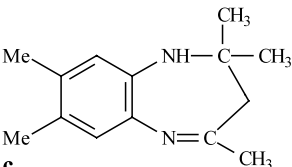
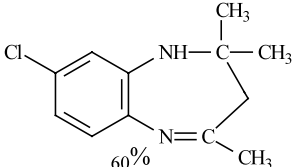
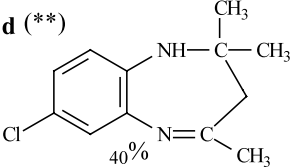
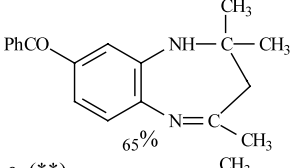
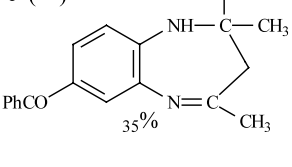
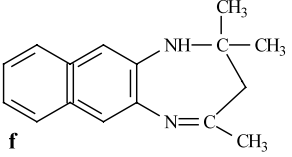
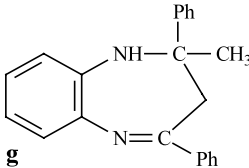
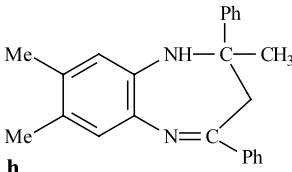
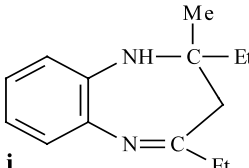
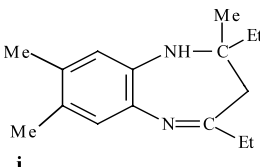
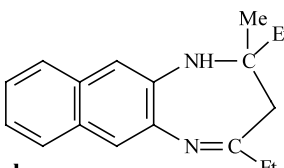
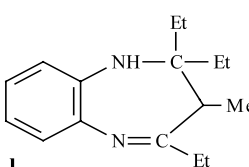
Reactants	Product 3	Yield (%)*	Irrad. time (min)	Power (W)	Ref.
1,2-Phenylenediamine	Acetone  a	97	2	80	11
4-Methyl-1,2-phenylenediamine	Acetone  b	97	4	240	17
4,5-Dimethyl-1,2-phenylenediamine	Acetone  c	96	2	80	17
4-Chloro-1,2-phenylenediamine	Acetone  d (**) 	93	2	560	New
4-Benzoyl-1,2-phenylenediamine	Acetone  e (**) 	95	7	400	New
2,3-Naphthalenediamine	Acetone  f	97	2	80	New

Table 1. (Continued)

Reactants	Product 3	Yield (%)*	Irrad. time (min)	Power (W)	Ref.
1,2-Phenylenediamine	Acetophenone 	98	2	80	11
4,5-Dimethyl-1,2-phenylenediamine	Acetophenone 	99	2	80	New
1,2-Phenylenediamine	2-Butanone 	98	2	80	13
4,5-Dimethyl-1,2-phenylenediamine	2-Butanone 	99	7	560	New
2,3-Naphthalenediamine	2-Butanone 	98	2	560	New
1,2-Phenylenediamine	3-Pentanone 	90	2	560	13

* Yields of pure isolated products characterized by IR, MS, ^1H and ^{13}C NMR spectra.¹⁸

** Inseparable regioisomers.

were carried out simply by mixing the *o*-phenylenediamine (1 mmol) with the ketone (2.1 mmol) in the presence of a catalytic amount of acetic acid and irradiating in a domestic microwave oven, whereupon the benzodiazepine derivatives were obtained in almost quantitative yield.

The desired parameters (microwave power, time) were set as reported in Table 1. The crude products were

purified either by recrystallization from *n*-hexane or by preparative thick layer chromatography using ethyl acetate and cyclohexane (1:6) as eluant.

In conclusion, we have described a rapid and efficient (90–99%) synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines using a microwave oven and provided a further example of the utility of microwave irradiation in environmentally friendly (absence of solvent) organic synthesis.

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18. Selected data for compound **3h** are given: mp 114–116°C; IR (cm⁻¹) 3280 (NH), 1610 (C=N); ¹H NMR (CDCl₃, 300 MHz) δ 7.59–7.54 (m, 4H), 7.29–7.14 (m, 6H), 7.12 (s, 1H), 6.61 (s, 1H), 3.40 (br s, 1H), 3.10 (d, 12.7 Hz, 1H), 2.94 (d, 12.7 Hz, 1H), 2.23 (s, 6H), 1.71 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz), δ 166.64, 147.73, 139.73, 137.62, 135.75, 134.71, 129.57, 129.42, 129.36, 128.15, 127.85, 126.88, 126.83, 125.35, 122.24, 73.05, 43.15, 29.72, 19.29, 18.72.