

# Efficient and Practical Procedures for the Synthesis of Bis-benzimidazoles in Dry Media under Various Reaction Conditions

Kioumars Aghapoor, Farshid Mohsenzadeh, and Hossein Reza Darabi

Chemistry and Chemical Engineering Research Center of Iran, P. O. Box 14335-186, Tehran, Iran

Reprint requests to Dr. H. R. Darabi. E-mail: darabi@ccerci.ac.ir

Z. Naturforsch. **60b**, 901 – 903 (2005); received April 24, 2005

Some different approaches have been developed in order to determine the most efficient preparation of bis-benzimidazoles **1a–f** under solvent-free conditions. All of the selected methods are simple, avoiding heating with corrosive mineral acids. Heating of the reactants on a sand bath method appears to have higher efficiency.

**Key words:** Bis-benzimidazoles, Microwave Irradiation

## Introduction

Benzimidazole and its derivatives present interesting biological activities and have been used extensively in medicine and industry [1, 2]. The chemistry of bis-benzimidazoles has received attention because of the potential to act as a potent inhibitor of rhinoviruses [3] and as an effective chelating agent for metal ions [4].

A traditional approach to the synthesis of bis-benzimidazoles **1** is the condensation of two moles of ortho-phenylenediamines **2** and one mole of succinic acid in a mineral acid, *e.g.* polyphosphoric acid and hydrochloric acid as the solvent and catalyst. This method requires extended heating of reflux temperature and provides low product yields [5–7].

One other problem concerning this reaction is that the diamine often competes successfully for the proton of the acid catalyst, hence inhibiting nucleophilic addition to the carbonyl group. Therefore, the development of a better methodology is in high demand.

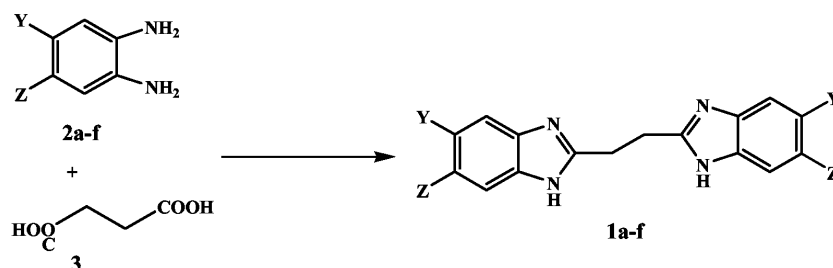
Herein we would like to report two general, novel approaches in the synthesis of bis-benzimidazoles **1** with a remarkable improved yield, ease work-up and avoiding the use of corrosive mineral acids.

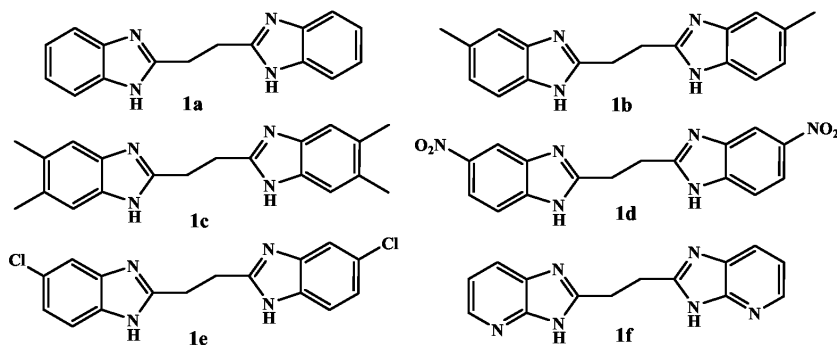
## Results and Discussion

### Microwave irradiation

Reactions promoted by microwave irradiation are advantageous in many ways because of short reaction time, cleaner reaction products and solvent free reaction conditions [8]. Although the use of microwave irradiation for dehydrating condensation reactions is well known in these days, the improved procedure for bis-benzimidazole, an interesting class of chelating ligands is worth reporting.

In continuation of our interest in the use of microwave heating in organic reactions [9–15], we would like to report the solvent-free synthesis of bis-benzimidazoles **1** under microwave irradiation. In a domestic microwave oven [16], a mixture of diamine **2a–f** (2 mmol) and succinic acid (1 mmol) was heated under 900 W power irradiation for 3 minutes. As shown in Table 1, in contrast with the classical approach, a significantly improved yield of products was observed. The reactions are also easier to work-up than reactions carried out in hot mineral acids. This simple, convenient and fast method makes this reaction more useful in synthesis.



Table 1. Yields of the solvent-free synthesis of bis-benzimidazoles **1a–f**.

Product	MW <sup>a</sup> (%)	MW + Silica gel (%)	Sand bath <sup>b</sup> (%)	Reflux (%) [ref.]
<b>1a</b>	60	81	90	28 [6]
<b>1b</b>	63	83	91	30 [7]
<b>1c</b>	64	88	93	33 [7]
<b>1d</b>	57	78	75	31 [7]
<b>1e</b>	50	72	71	35 [7]
<b>1f</b>	68	85	89	–

<sup>a</sup> MW = Microwave; <sup>b</sup> the temperature of the thermal synthesis was held at 130 °C except for **1d** (195 °C).

#### Using a solid support under microwave irradiation

The initial laboratory-scale feasibility of microwave promoted solvent-free procedures has now been illustrated for a wide variety of useful chemical reactions on mineral supports [17]. The general procedure involves simple mixing of neat reactants with the catalyst, their absorption on mineral or “doped supports”, and exposing the reaction mixture to irradiation in a commercial microwave oven [18]. As shown in Table 2, several solvent-free experiments with various solid supports under microwave irradiation were studied. The effects of these solid supports in the improvement of reaction are obvious in all cases, with silica gel showing the highest efficiency on the yield of products.

Silica gels are essentially used as supports due to their high surface and large pore volumes. They can be also used to catalyze reactions that are catalyzed with acid [19]. Our rationale behind this exercise was that silica gels are weakly acidic supports due to the presence of silanol groups on their surfaces.

As shown in Table 1, a remarkable improved yield of products **1a–f** was observed when the solvent-free reaction mixture was irradiated on silica gel in a microwave oven. The yields are remarkably improved and products were easily purified. Products **1a–f** were identified by the melting point, <sup>1</sup>H NMR and mass

Table 2. The effect of solid supports on the yield of **1a**.

Solid support	Acidic Al <sub>2</sub> O <sub>3</sub>	Montmorillonite K10	HY-Zeolite	Silica gel
Yield (%)	77	68	68	83

spectra. Although all products, except **1f**, are known, we have found only their melting points and elemental analysis data.

#### Solvent-free reaction with sand bath heating

As shown in Table 1, in contrast to classical reactions, a solvent-free treatment of starting materials **2** and **3** in the absence of inorganic acids under sand bath heating condition gave highly improved yields. In order to arrange the reaction temperature, we considered two parameters; one parameter is the melting point of the starting materials. When one of these materials starts to melt, the other becomes soluble in it. Therefore, in each case we considered the melting point of the lower melting compound. The second parameter is a sufficient temperature for removal of the formed water in order to shift the reaction equilibrium. Therefore, a range of reaction temperatures between 130 and 195 °C was applied. In this range, a homogeneous melt of the reactants was observed. The yields of products **1a–f** varied from 71 to 93%. While the classical reaction in presence of acids as solvents and catalyst gave poor yields of products and required a rather harsh work-up, we solved these problems with a highly improved yield and a simple work-up.

#### Conclusion

In some different approaches, we have developed sufficient methods with the new viewpoints for the synthesis of bis-benzimidazoles **1a–f**. All methods are characterized by simple set-up, high yields, simple work-up and environmental advantages.

## Experimental Section

**General procedure.** It is essential to work in an open vessel to enable the water formed to escape from the reaction mixture.

**Synthesis of **1** by microwave irradiation on silica gel:** In a domestic microwave oven [16], a mixture of diamine **2** (2 mmol) and succinic acid **3** (1 mmol) on silica gel (1 g, 200–300 mesh) was heated under 900 W power irradiation for 3 minutes. The dark mixture was treated with hot water to dissolve the remaining amount of starting materials. The solid was filtered and washed with aqueous ethanol. Recrystallization from 70% ethanol afforded a pure white product. TLC and  $^1\text{H}$  NMR analysis showed that coloured products were nearly pure. The colour could be removed with activated carbon. Products **1a–f** were identified by the melting point,  $^1\text{H}$  NMR and mass spectra.

**Synthesis of **1** under sand bath heating:** A mixture of diamine **2a–f** (2.2 mmol) and succinic acid **3** (1 mmol) in a flask was heated for 30 minutes on a sand bath. The mixture was washed with warm water to remove the excess of diamine. The solid was filtered and recrystallization from 70% ethanol to afford a pure product. TLC and  $^1\text{H}$  NMR analysis

showed that coloured products were nearly pure. The colour could be removed with activated carbon.

**1a:** M.p. 325 °C. –  $^1\text{H}$  NMR (250 MHz,  $\text{CD}_3\text{COOD}$ ):  $\delta$  = 4.05 (s, 4H), 7.40–7.80 (m, 4H), 8.20 (d, 4H). – MS (EI, 70 eV):  $m/z$  (%) = 262 ( $\text{M}^+$ , 90), 145 (45), 131 (22).

**1b:** M.p. 266 °C. –  $^1\text{H}$  NMR (250 MHz,  $\text{CD}_3\text{COOD}$ ):  $\delta$  = 2.60 (s, 6H), 4.15 (s, 4H), 7.35 (d, 2H), 7.42 (d, 2H), 8.20 (s, 2H). – MS (EI, 70 eV):  $m/z$  (%) = 290 ( $\text{M}^+$ , 100), 159 (50), 145 (40).

**1c:** M.p. 245 °C. –  $^1\text{H}$  NMR (250 MHz,  $\text{CD}_3\text{COOD}$ ):  $\delta$  = 2.35 (s, 12H), 3.97 (s, 4H), 7.47 (s, 4H). – MS (EI, 70 eV):  $m/z$  (%) = 318 ( $\text{M}^+$ , 100), 159 (70).

**1d:** M.p. 290 °C. –  $^1\text{H}$  NMR (250 MHz,  $\text{CD}_3\text{COOD}$ ):  $\delta$  = 3.60 (s, 4H), 7.75 (d, 2H), 8.15 (d, 2H), 8.50 (s, 2H). – MS (EI, 70 eV):  $m/z$  (%) = 352 ( $\text{M}^+$ , 80), 165 (30).

**1e:** M.p. 280 °C. –  $^1\text{H}$  NMR (250 MHz,  $\text{CD}_3\text{COOD}$ ):  $\delta$  = 3.55 (s, 4H), 7.60 (d, 2H), 8.07 (d, 2H), 8.43 (s, 2H). – MS (EI, 70 eV):  $m/z$  (%) = 331 ( $\text{M}^+$ , 76), 167 (30).

**1f:** M.p. 270 °C. –  $^1\text{H}$  NMR (250 MHz,  $\text{CD}_3\text{COOD}$ ):  $\delta$  = 3.75 (s, 4H), 7.40–7.46 (dd, 2H), 8.22–8.27 (dd, 2H), 8.43–8.46 (d, 2H). – MS (EI, 70 eV):  $m/z$  (%) = 264 ( $\text{M}^+$ , 100), 132 (30).

- [1] P. N. Preston, *Chem. Rev.* **74**, 310 (1974).
- [2] D. G. O'Sullivan, D. Pentic, A. K. Willis, *J. Med. Chem.* **15**, 103 (1972).
- [3] W. R. Roderick, C. W. Nordeew, *J. Med. Chem.* **15**, 655 (1972).
- [4] M. S. Haddad, D. N. Hendrickson, G. D. Stucky, *Inorg. Chem.* **17**, 2622 (1978).
- [5] M. A. Phillips, *J. Chem. Soc.* 2393 (1928).
- [6] R. L. Shriner, R. W. Upson, *J. Am. Chem. Soc.* **63**, 2277 (1941).
- [7] L. L. Wang, M. M. Joullie, *J. Am. Chem. Soc.* **79**, 5706 (1957).
- [8] K. V. Gothelf, K. A. Jorgensen, *Chem. Rev.* **98**, 863 (1998).
- [9] M. Nooshabadi, K. Aghapoor, H. R. Darabi, M. M. Mojtahedi, *Tetrahedron Lett.* **40**, 7549 (1999).
- [10] H. R. Darabi, K. Aghapoor, K. Tabar-Heydar, *Phosphorus, Sulfur and Silicon* **177**, 1189 (2002).
- [11] K. Aghapoor, H. R. Darabi, M. Nooshabadi, K. Tabar-Heydar, *Phosphorus, Sulfur and Silicon* **177**, 1183 (2002).
- [12] K. Aghapoor, H. R. Darabi, K. Tabar-heydar, L. Nakhshab, *Sulfur Lett.* **25**, 259 (2002).
- [13] H. R. Darabi, K. Aghapoor, L. Nakhshab, *Z. Naturforsch.* **59b**, 601 (2004).
- [14] H. R. Darabi, K. Aghapoor, M. Tajbakhsh, *Tetrahedron Lett.* **45**, 4167 (2004).
- [15] H. R. Darabi, K. Aghapoor, K. Tabar-heydar, *Monatsh. Chem.* **135**, 79 (2004).
- [16] The reactions were carried out in a domestic microwave oven (National, model NN-6755) at a power 900 W.
- [17] A. Gutiérrez, A. Loupy, G. Bram, E. Ruiz-Hitzky, *Tetrahedron Lett.* **30**, 945 (1989); R. S. Varma, *Tetrahedron* **58**, 1235 (2002).
- [18] A. Loupy, *Microwaves in Organic Synthesis*, Wiley-VCH, New York (2002).
- [19] V. J. Patil, U. Mävers, *Tetrahedron Lett.* **37**, 1281 (1996).