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MICROWAVE-ASSISTED SYNTHESIS OF ARYL AND HETEROARYL DERIVATIVES OF BENZIMIDAZOLE

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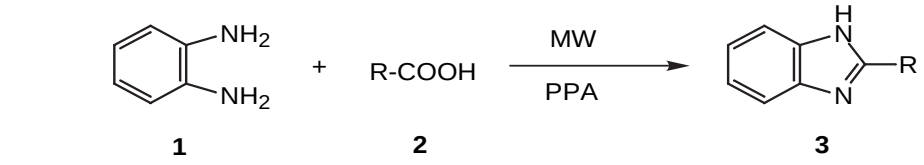
Abstract - A series of benzimidazoles containing aryl and heteroaryl substituents were efficiently and quickly synthesized by condensation of 1,2-phenylenediamine with carboxylic acids in the presence of polyphosphoric acid under microwave irradiation.

Microwave-assisted organic synthesis is a quickly growing area in synthetic organic chemistry.[1-3] The signature of microwave-enhanced chemistry is that the rates of reactions involving polar components are usually very fast. Reactions that require hours or days of conventional heating may often be accomplished in minutes by microwave heating. Benzimidazole and some substituted compounds have been widely investigated in medical industrial fields.[4] At the same time, some of them belong to highly stable fluorescent derivatives[5,6] as well as metal coordinate ligands.[7] A number of methods are available for the synthesis of benzimidazoles.[8-10] Traditional method is the reaction between phenylenediamine and carboxylic acid under harsh dehydrating reaction conditions.[11] In continuation of our studies on high-throughput synthesis under microwave irradiation,[12] we decided to explore the synthesis of benzimidazole compounds for fluorescence emitters. Although microwave-assisted synthesis of benzimidazole from 1,2-phenylenediamine and acetoacetic ester or aldehydes has been reported,[13] the reactions were promoted with mineral supports such as Montmorillonite KSF or SiO_2 which prevented facile isolation of the products. Microwave-assisted reaction using readily available reagents would be desirable to enhance synthetic throughput for benzimdazoles. Herein we report rapid synthesis of benzimidazoles by condensation of 1,2-phenylenediamine with carboxylic acids in the presence of polyphosphoric acid (PPA) using microwave irradiation.

A limitation with the majority of benzimidazole syntheses is that *N*-substitution is generally non-regioselective and a mixture of isomers is often obtained. Purification and characterization of the two

regioisomers can also be problematic. With these difficulties in mind, we choose unsubstituted 1,2-phenylenediamine as precursors. PPA seems to be suitable acid for the procedure, it behaves as a strong catalyst as well as a good dehydrating agent. The attempts to use $ZnCl_2$ or *p*-toluenesulfonic acid in place of PPA were unsuccessful. Preliminary optimization of reaction conditions was done using the 1:1 (equiv.) mixture of **1** (10 mmol) and **2a** (10 mmol). Comparison of different amount of PPA showed that 10 g of PPA was the most suitable amount for the synthesis of **3a**, and therefore it was used in all subsequent experiments. The excess of PPA probably played a role of solvents, despite other solvents were not added to the reaction mixtures. The every reaction temperature was measured by fiber thermometer and regulated to be kept in the range 200-270 °C. To circumvent the problem of the localized heating of the mixture, we conducted the reaction with intermittent heating and mixing at a moderate power level to provide better yields. After the first irradiation for one minute, the reaction mixture was then take out, mixed again for 20 seconds and then heated at the same power level for an additional 30 seconds. This step was repeated until the starting materials were disappeared using TLC analysis.



1 **2** **3**

R =

a : **b :** **c :** **d :** **e :** **f :** **g :** **h :** **i :**

The results are summarized in **Table 1**. All the reactions were completed within several minutes. The reactivities with **2a-c**, **2f** and **2i** under microwave irradiation were high to afford the corresponding products (**3)** in good yields. The desired products (**3d**, **3e**, **3g** and **3h)** can be provided in moderate yields. For comparison, conventional heating was applied for the preparation of benzimidazoles (**3a**, **3c**, **3f and 3i**). The conventional heating method gave the corresponding products (**3a**, **3c**, **3f** and **3I)** in comparable yields, but longer reaction time from 4 to 16 h and presence of twice amount of PPA (20 g) were needed to complete the reactions (**Table 1)**.

Table 1. Reaction of 1,2-phenylenediamine with carboxylic acids

Carboxylic acid	Product	Microwave heating		Conventional heating			Ref.
		Irradiation time (min)	Yield (%)	Reaction temp. (°C)	Reaction time (h)	Yield (%)	
2a	**3a**	3	96	170	4	95	14a
2b	**3b**	4	85				11
2c	**3c**	2.5	85	170	12	61	14b
2d	**3d**	2	48				14c
2e	**3e**	2	61				14d
2f	**3f**	3	78	170	4	60	14e
2g	**3g**	2.5	73				
2h	**3h**	6.5	59				14f
2i	**3i**	4	97	200	16	91	6

All of the benzimidazole derivatives prepared revealed blue emissions under balck light irradiation in methanol solutions. The fluorescence spectra of the compounds were centered around the range from 370 to 430 nm. The fluorescence intensity of compound (**3i**) has been recently reported to be very strong.[6] We have found that the compound (**3h)** also has comparable strong fluorescence intensity at around 397 nm.

In conclusion, we have developed the simple and rapid synthesis of substituted benzimidazole compounds that occurs under solvent-free condition using readily available inexpensive reagents and a microwave oven.

EXPERIMENTAL

^{1}H-NMR spectra were measured on a JEOL JNM-GSX270 spectrometer with tetramethylsilane as an internal standard. IR spectra were recorded on a JASCO FT/IR-300E spectrophotometer. Melting points were not corrected. MS spectra were carried out with a Perkin Elmer ELAN 600. All the reagents were commercially available and used without further purification.

General procedure for preparation by microwave irradiation

1,2-Phenylenediamine (1.08 g, 10.0 mmol), carboxylic acid (10.0 or 20.0 mmol) and polyphosphoric acid (10 g) were introduced in a breaker (50 mL) and properly mixed with the help of a glass rod. The so-obtained mixture was irradiated in a household microwave oven (Crystal AM-533WA-960W) with 200

W (2.45 GHz) at 210-270 °C for appropriate minutes. After irradiation, the mixture was poured onto cold water and then slowly neutralized with a solution of concentrated ammonium hydroxide to pH 8. The precipitate was collected by filtration, washed with water, dried and recrystallized. Several products were separated by silica gel column chromatography using ethyl acetate and methanol.

2-(*p*-Octylphenyl)-1*H*-benzimidazole (3g). Recrystallized from methanol; mp 152-153°C.; ^{1}H-NMR (DMSO-d_6) δ: 8.09 (d, 2H, J = 8.1 Hz), 7.56 (m, 2H), 7.36 (d, 2H, J = 8.1 Hz), 7.18 (m, 2H), 2.61 (t, 2H, J = 7.6 Hz), 1.58 (m, 2H), 1.25 (m, 10H), 0.86 (t, 3H, J = 6.8 Hz); IR (KBr) 3038, 1495, 1477 cm^{-1}. MS m/z (rel intensity): 307 ($M+1^+$, 100), 306 (M^+, 15).

REFERENCES

1. 'Microwave-Enhanced Chemistry: Fundamentals, Sample Preparation, and Application,' ed. by H. M. (Skip) Kingston and S. J. Haswell, American Chemical Society, Washington, DC 1997.
2. 'Microwaves in Organic Synthesis,' ed. by A. Loupy, Wiley-VCH, Weinheim, 2002.
3. P. Lidstrom, J. Tierney, B. Wathey, and J. Westman, *Tetrahedron*, 2001, **57**, 9225.
4. M. Ana, C. Ana, G. Carmen, and P. Concepcion, *Med. Res. Rev.*, 2001, **21**, 227; R. J. Sundberg and R. B. Martin, *Chem. Rev*., 1974, **74**, 471.
5. S. Santra, G. Krishnamoorthy, and S. K. Dogra, *Chem. Phys. Lett*., 1999, **311**, 55.
6. H. Ishida and S. Oishi, Jpn. Patent 2002-237781, 2002; H. Ishida, K. Horie, and S. Oishi, Submitted.
7. B. Sujoy, B. Pradip, and N. Kamalaksha, *Polyhedron*, 2002, **21**, 2481; E. Bouwmann, W. L. Driessen, and J. Reedijk, *Coord. Chem. Rev*., 1990, **104**, 143; S. W. Lai, M. C. W. Chan, S. M. Peng, and C. M. Che, *Angew. Chem. Int. Ed*., 1999, **38**, 669.
8. Z. Wu, P. Rea, and G. Wickam, *Tetrahedron Lett*., 2000, **41**, 9871 and references cited therein.
9. R. J. Perry and B. D. Wilson, *J. Org. Chem*., 1993, **58**, 7016.
10. D. Anastasion, E. M. Campi, H. Chaouk, and W. R. Jackson, *Tetrahedron*, 1992, **48**, 7476.
11. D. W. Hein, R. J. Alheim, and J. J. Leavitt, *J. Am. Chem. Soc*., 1957, **79**, 427.
12. H. Koshima and K. Kutsunai, *Heterocycles*, 2002, **57**, 1299; H. Koshima, M. Hamada, M. Tani, S. Iwasaki, and F. Sato, *Heterocycles*, 2002, **57**, 2145.
13. K. Bougrin and M. Soufaoui, *Tetrahedron Lett*., 1995, **36**, 3683; A. Ben-Alloum, S. Bakkas, and M. Soufaoui, *Tetrahedron Lett*., 1998, **39**, 4481.
14. a) M. Ichikawa, S. Nabeya, K. Muraoka, and T. Hisano, *Chem. Pharm. Bull*., 1979, **27**, 1255; b) P.M. Dzadzic, M. V. Piletic, and B. Bastic, *Glas. Hem. Drus. Beograd.*, 1972, **37**, 257 (*Chem. Abstr.*, 1973, **79**, 53215m); c) H. C. Francis, *J. Heterocycl. Chem*., 1968, **5**, 223; d) E. Alcalde, I. Dinares, L. Perez-Garcia, and T. Roca, *Synthesis*, 1992,395; e) R. Aries, Fr. Demande, 2,104,717, 1972 (*Chem. Abstr.*, 1973, **78**, 39352b); f) J. J. Kane and R. T. Conley, *J. Heterocycl. Chem.*, 1970, **7**, 943.