A Rapid and Convenient Synthesis of Derivatives of Imidazoles under Microwave Irradiation

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An efficient and a quick microwave-assisted synthesis of benzimidazoles and trisubstituted imidazoles was developed. Three benzimidazoles were obtained as a result of the condensation of 1,2-phenylenediamine with carboxylic acids and acetoacetic ester without catalyst. A series of trisubstituted imidazoles were synthesized by condensation of benzil, aromatic aldehyde and ammonium acetate in the presence of glacial acetic acid.

Keywords: Microwave-assisted; Imidazoles; Condensation; Ammonium acetate; Glacial acetic acid.

INTRODUCTION

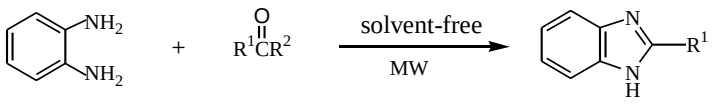
Microwave-assisted organic synthesis (MAOS) is an acknowledged quick alternative and green technology in synthetic organic chemistry.[1] Many organic reactions proceed much faster and with higher yields under microwave irradiation compared to conventional heating. Moreover, this technology provides easier work-up procedures.

Compounds with imidazole ring systems have many pharmaceutical activities and play important roles in biochemical processes.[2] Benzimidazoles and substituted imidazoles have been widely used in the medical field.[3] At the same time, some of them belong to highly stable fluorescent derivatives.[4,5] A number of methods are available for synthesis of these compounds. A traditional method for synthesis of benzimidazoles is the reaction between phenylenediamine and carboxylic acid under harsh dehydrating reaction conditions,[6] for example, in the presence of HCl, PPA (polyphosphoric acid), H_3BO_3 or *p*-toluenesulfonic acid. Some new methods reported under microwave irradiation require PPA as catalyst,[5,7] or Montmorillonite KSF or SiO_2 as a solid support.[8] Many methods for synthesizing substituted imidazoles have been reported. Traditional synthesis in refluxing HOAc or $HCON(Me)_2$ require a long reaction time of about 3 hours.[9] Two research groups have recently reported microwave-assisted synthesis of trisubstituted imidazoles on solid support.[10] But all these methods involve fussy treatment and a relatively long reaction time. Herein we report a simple and rapid synthesis of benzimidazoles (Scheme I) and trisubstituted imidazoles (Scheme II) with microwave assistance.

RESULTS AND DISCUSSION

At first, we synthesized three benzimidazoles based on the condensation of 1,2-phenylenediamine with carboxylic

Scheme I



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a: $R^1 = C_6H_5OCH_2–$, R^2 = OH　　b: $R^1 = 2,4\text{-}(Cl)_2C_6H_3OCH_2–$, R^2 = OH
c: $R^1 = –CH_3$, $R^2 = –CH_2COOEt$　　d: $R^1 = C_6H_5–$, R^2 = OH
e: $R^1 = \alpha\text{-}C_{10}H_7CH_2–$, R^2 = OH　　f : $R^1 = –CH_3$, R^2 = OEt

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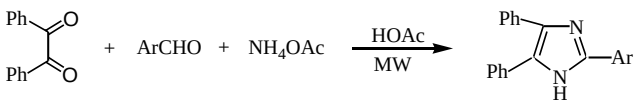
Scheme II



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acids and acetoacetic ester under solvent-free conditions using microwave irradiation without a catalyst. The yields are excellent (Table 1).

In our study, we failed to synthesize benzimidazoles when benzoic acid, α-Naphthylacetic acid and ethyl acetate were used as starting material. The attempts to use 2 equiv. of $ZnCl_2$, H_3BO_3, $FeCl_3 \cdot 6H_2O$ or *p*-toluenesulfonic acid as a catalyst were unsuccessful. To our surprise, 1,2-phenylenediamine would disappear but not the carboxylic acids (monitored by TLC) when we added *p*-toluenesulfonic acid in this reaction system. It was proposed that 1,2-phenylenediamine reacts with *p*-toluenesulfonic acid. In the meantime, we used the microwave with 495W as the optimal power. When lowering the power, the reaction time would be prolonged. On the contrary, the mixture would carbonize. In a word, we have developed a simple and efficient synthesis of substituted benzimidazole compounds under solvent-free and catalyst-free conditions.

At the same time, we synthesized nine trisubstituted imidazoles by condensation of benzil, aromatic aldehyde and ammonium acetate in the presence of glacial acetic acid under microwave irradiation in good yields (Table 2).

Our investigation suggested that only 50% of benzil is transformed to corresponding imidazole along with formation of triphenyloxazole as by-product. If we use formic acid instead of glacial acetic acid, the yield can be improved somewhat. But it is still lower compared to using glacial acetic acid. Preliminary optimization of reaction conditions was done by using benzil, aldehydes, ammonium acetate, and acetic acid (1:1:8:20). Ammonium acetate and acetic acid play an important role in the reaction. If ammonium acetate and acetic acid are deficient, benzil can't transform completely.

Table 1. Solvent-free synthesis of benzimidazoles under microwave irradiation

Entry	Products	Time (min)	Yield (%)	m. p. (°C)	Ref.
a	1a	15	90	162-164	11a
b	1b	15	86	185-187	11b
c	1c	4	92	174-176	7
d	1d	30	0	-	-
e	1e	30	0	-	-
f	1f	30	0	-	-

From Table 2, it can be seen that when there is an electron-donating group on the aromatic aldehydes we can still obtain good yields by prolonging the reaction time. This method has obvious superiority for its short reaction time and easy work-up process. In conclusion, a facile and environmentally benign method for synthesis of trisubstituted imidazoles by a simple component condensation under microwave irradiation was developed.

EXPERIMENTAL SECTION

Melting points were determined with a Kolfer micro melting point apparatus and were uncorrected. IR spectra were recorded on a FTS-40 spectrophotometer in KBr. ^{1}H NMR were measured on a Bruker DPX-400M spectrometer using TMS as internal standard and DMSO as solvent. Elemental analyses were performed on PE-2400 CHN elemental analyzer. All the reactions were conducted in a household mi-

Table 2. Microwave-assisted synthesis of trisubstituted imidazoles

Entry	Ar	Microwave irradiation Time (min)	Yield (%)	m. p. (°C)	Ref.
a	C_6H_5	5	82	274-275	9b, 10b
b	*p*-$OMeC_6H_4$	5	90	233-235	10b, 12a
c	*p*-$CH_3C_6H_4$	5	94	234-236	12b
d	*p*-$(CH_3)_2NC_6H_4$	5	89	254-256	9b, 10b
e	*p*-$(C_2H_5)_2NC_6H_4$	5	88	223-224	12c
f	*m*-$O_2NC_6H_4$	3	90	300-301	10b, 12b
g	*p*-ClC_6H_4	3	86	261-262	12c
h	*p*-FC_6H_4	3	89	260-262	12b
i	*o*-BrC_6H_4	3	93	206-208	12d

crowave oven (Galanz Cambi-Grill 750W).

Typical procedure for preparation of benzimidazoles

1,2-Phenylenediamine (1 mmol) and phenoxy acetic acid (1 mmol) were mixed thoroughly in an agate mortar and then placed in a little glass bottle. The mixture was irradiated in the microwave oven with 495W for 15 minutes. After the reaction was completed (monitored by TLC), the crude products were recrystallized with 70% ethanol.

Typical procedure for the synthesis of trisubstituted imidazoles

Benzil (0.5 mmol), *p*-methylbenzaldehyde (0.5 mmol) ammonium acetate (4 mmol) and glacial acetic acid (0.6 g) were placed in a tube and mixed thoroughly. The mixture was irradiation in the microwave oven with 638W for 5 minutes. After the reaction was completed (monitored by TLC), the products were cooled to room temperature. A small amount of ethanol was dropped into the tube and then cool water was poured into the tube slowly. After 10 minutes, the resulting precipitate was filtrated, dried and then recrystallized from 95% ethanol.

2-Phenoxy-methyl-benzimidazole (1a)

White needles; IR (KBr) ν (cm^{-1}): 3094, 3058, 1600, 1590, 1496, 1445; ^{1}H NMR (DMSO) δ: 12.61 (s, 1H, NH), 7.56-6.95 (m, 9H, C_6H_4, C_6H_5), 5.33 (s, 2H, CH_2); Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 75.00; H, 5.36; N, 12.50. Found: C, 74.89; H, 5.33; N, 12.41.

2-(*p*-Methylphenyl)-4,5-diphenylimidazole (2c)

White needles; IR (KBr) ν (cm^{-1}): 3062, 3032, 1602, 1506, 1494, 1450; ^{1}H NMR (DMSO) δ: 12.55 (s, 1H, NH), 7.98 (d, 2H, *J* = 8 Hz, C_6H_4), 7.54-7.37 (m, 10H, $2C_6H_5$), 7.29 (d, 2H, *J* = 8 Hz, C_6H_4), 2.36 (s, 3H, CH_3); Anal. Calcd. for $C_{22}H_{18}N_2$: C, 85.16; H, 5.81; N, 9.03. Found: C, 85.03; H, 5.78; N, 9.11.

2-(*p*-Diethylaminophenyl)-4,5-diphenylimidazole (2e)

Pale yellow needles; IR (KBr) ν (cm^{-1}): 3067, 3031, 1617, 1500, 1409; ^{1}H NMR (DMSO) δ: 12.21 (s, 1H, NH), 7.88 (d, 2H, *J* = 9.2 Hz, C_6H_4), 7.53-7.28 (m, 10H, $2C_6H_5$), 6.74 (d, 2H, *J* = 9.2 Hz, C_6H_4), 3.40 (q, 4H, *J* = 7.2 Hz, $2CH_2$), 1.14 (t, 6H, *J* = 7.2 Hz, $2CH_3$); Anal. Calcd. for $C_{25}H_{25}N_3$: C, 81.74; H, 6.81; N, 11.44. Found: C, 81.65; H, 6.77; N, 11.32.

2-(*p*-Chlorophenyl)-4,5-diphenylimidazole (2g)

White needles; IR (KBr) ν (cm^{-1}): 3060, 3029, 1604, 1486, 1448; ^{1}H NMR (DMSO) δ: 12.74 (s, 1H, NH), 8.11 (d, 2H, *J* = 8.4 Hz, C_6H_4), 7.55 (d, 2H, *J* = 8.4 Hz, C_6H_4), 7.48-7.37 (m, 10H, $2C_6H_5$); Anal. Calcd. for $C_{21}H_{15}ClN_2$: C, 76.25; H, 4.54; N, 8.47. Found: C, 76.18; H, 4.43; N, 8.43.

2-(*p*-Fluorophenyl)-4,5-diphenylimidazole (2h)

White needles; IR (KBr) ν (cm^{-1}): 3067, 3033, 1609, 1494, 1454; ^{1}H NMR (DMSO) δ: 12.65 (s, 1H, NH), 8.13 (d, 2H, *J* = 8.8 Hz, C_6H_4), 7.53-7.34 (m, 10H, $2C_6H_5$), 7.31 (d, 2H, *J* = 8.8 Hz, C_6H_4); Anal. Calcd. for $C_{21}H_{15}FN_2$: C, 80.25; H, 4.78; N, 8.92. Found: C, 80.13; H, 4.72; N, 8.87.

2-(*o*-Bromophenyl)-4,5-diphenylimidazole (2i)

White needles; IR (KBr) ν (cm^{-1}): 3065, 3029, 1602, 1503, 1479, 1446; ^{1}H NMR (DMSO) δ: 12.58 (s, 1H, NH), 7.80-7.24 (m, 14H, $2C_6H_5$, C_6H_4); Anal. Calcd. for $C_{21}H_{15}BrN_2$: C, 67.20; H, 4.00; N, 7.47. Found: C, 67.15; H, 3.94; N, 7.39.

ACKNOWLEDGEMENT

We are grateful to the Chinese Acadamy of Science and Technology (KGCX 2-SW-602-5).

Received September 23, 2004.

REFERENCES

1. (a) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. (b) André, L.; Alain, P.; Jack, H. *Synthesis* **1998**, *9*, 1213. (c) Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J. L.; Petit, A. *Tetrahedron* **1999**, *55*, 10851. (d) Varma, R. S. *Green Chem.* **1999**, *1*, 43. (e) Ramesh, C.; Mahender, G.; Ravindranath, N.; Biswanath Das. *Green Chem.* **2003**, *5*, 68. (f) Sun, T.; Jing, L.; Wang, Y. L. *J. Chin. Chem. Soc.* **2003**, *50*, 425. (g) Li, J. P.; Luo, Q. F.; Wang, Y. L. *J. Chin. Chem. Soc.* **2001**, *48*, 73.
2. (a) Lombardino, J. G.; Wiseman, E. H. *J. Med. Chem.* **1974**, *17*, 1182. (b) Sundberg, R. J.; Martin, R. B. *Chem. Rev.* **1974**, *74*, 471.
3. (a) Ucucu, U.; Karaburun, N. G.; Isikdag, I. *Farmaco* **2001**, *56*, 285. (b) Tebbe, M. J.; Jensen, C. B.; Spitzer, W. A.; Franklin, R. B. *Antiviral Res.* **1999**, *42*, 25.
4. Upadhyay, R. K.; Srivastava, S. D. *Indian J. Pharm Sci.* **1995**, *57*, 12.
5. Yu, H.-T.; Kawanishi, H.; Koshima, H. *Heterocycles* **2003**, *60*, 1457.
6. Hein, D. W.; Alheim, R. J.; Leavitt, J. J. *J. Am. Chem. Soc.*

1957, *79*, 427.

7. Lu, J.; Ge, H.-G.; Bai, Y.-J. *Chin. J. Org. Chem*. **2002**, *22*, 782.
8. (a) Villemin, D.; Hammad, M.; Martin, B. *Synth. Commun.* **1996**, *26*, 2895. (b) Bougrin, K.; Soufaoui, M. *Tetrahedron Lett.* **1995**, *36*, 3683. (c) Ben-Alloum, A.; Bakkas, S.; Soufaoui, M. *Tetrahedron Lett.* **1998**, *39*, 4481.
9. (a) Schneiders, P.; Heinze, J.; Baumgartel, H. *Chem. Ber.* **1973**, *106*, 2415. (b) Hellmut, B.; Rudolf, G.; Dieter, H. *Chem. Ber.* **1959**, *92*, 338.
10. (a) Usyatinsky, A. Y.; Khmelnitsky, Y. L. *Tetrahedron Lett.* **2000**, *41*, 5031. (b) Xu, Y.; Wan, L.-F.; Salehi, H.; Deng, W.; Guo, Q.-X. *Heterocycles* **2004**, *63*, 1613.
11. (a) Tan, R.-H.; Ding, L.-C.; Wei, X.-J. *Chin. J. Med. Chem.* **2001**, *11*, 259. (b) *Standard Infrared Grating Spectra*; Srotler Research Laboratories, Inc., 1980.
12. (a) Yang, W.-H.; Xiao, G.-M.; Kong, X.-X. *Hua Xue Shi Jie* **2002**, *42*, 653. (b) Philbrook, G. E.; Maxwell, M. A.; Taylor, R. E.; Totter, J. R. *Photochem. Photobiol*. **1965**, *4*, 1175. (c) Wilhelm, N.; Martha, T. K.; Hans, B. *Pat Ger.* 1,106,599, **1961**: *Chem. Abstr.* **1962**, *56,* 3065f. (d) Lawrence, A. C. *Fr.* 1,351,818, **1964**: *Chem. Abstr.* **1964**, *60*, 15883c.