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Abstract: A high-yielding one-pot procedure for the generation of 2-substituted benzimidazoles first from esters using a microwave procedure is described.

Keywords: Benzimidazole formations, microwave, preparation

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 than with conventional heating. Moreover, this technology provides easier workup procedures.

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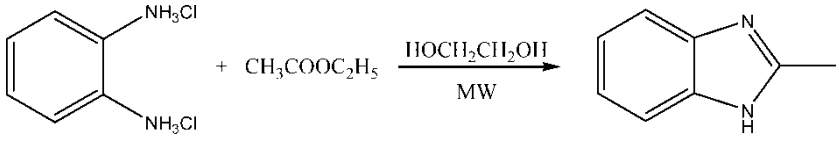


Scheme 1.

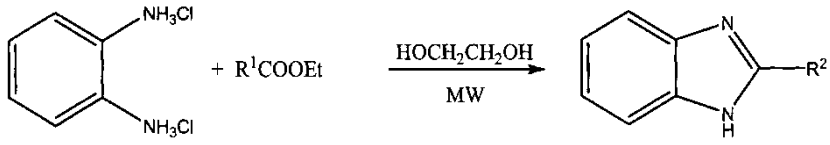
Compounds with imidazole ring systems have many pharmaceutical activities and play important roles in biochemical processes.[2] Benzimidazoles and substituted imidazoles have been widely used in the medical field.[3] At the same time, some of them belong to highly stable fluorescent derivatives.[4,5] 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 solid support.[8] Many methods for synthesizing substituted imidazoles have been reported. Traditional synthesis in refluxing HOAc or DMF require a long reaction time of about 3 h.[9] Two research groups have recently reported microwave-assisted synthesis of benzimidazoles on solid support,[10] but all these methods involve fussy treatment and a relatively long reaction time. Until now, microwave-assisted synthesis of benzimidazoles from esters has not been reported. Herein we report a simple and rapid synthesis of benzimidazoles from esters with microwave assistance.

RESULTS AND DISCUSSION

At first, we wanted to synthesize N,N′-diacetyl-1,2-phenylenediamine based on the reaction of 1,2-phenylenediamine with ethyl acetate in ethyldiol

Table 1. Microwave-assisted synthesis of substituted benzimidazoles

Entry	R^1	R^2	T (min)	Yield (%)	Mp (°C)
a	$ClCH_2$	$ClCH_2$	1.5	95	165–166
b	CH_3	CH_3	1.5	>99	174–176
c	$HOCH_2$	$HOCH_2$	1.5	97	177–179
d	Et	Et	1.5	>99	173–174
e	H	H	1.5	94	171–172
f	n-C_5H_{10}	n-C_5H_{10}	1.5	94	162–163
g	CH_2CO_2Et	2-Benzimidazoleyl	1.5	92	>300



Scheme 2.

Table 2. Analytical data for the compounds **a**–**g**

Compound	^{1}H NMR	MS(FAB)	IR	Mp (°C)
a	7.56 (t, 2H, $J = 3.2$ Hz, $J = 5.7$ Hz), 7.21 (t, 2H, $J = 3.1$ Hz, $J = 5.9$ Hz), 4.89 (s, 2H)	166:(M^+)	3059, 3004, 2941, 2850, 1623, 1488, 1441, 741, 700	165–166
b	12.17 (s, 1H), 7.43 (s, 2H), 7.09 (t, 2H, $J = 3.0$ Hz, $J = 5.7$ Hz), 2.47 (s, 3H)	132:(M^+)	3061, 2992, 2918, 1624, 1555, 1449, 1418, 1386, 736	174–176
c	12.06 (s, 1H), 7.27 (d, 2H, $J = 60.6$ Hz), 6.90 (s, 2H), 5.59 (s, 1H), 4.72 (s, 1H), 1.29 (d, 3H, $J = 3.1$ Hz)	162:(M^+)	3176, 3142, 3054, 2823, 2706, 1623, 1591, 1535, 1486, 1455, 1434, 747	177–179
d	9.80 (s, 1H), 7.58 (s,2H), 7.25 (s, 2H), 3.03 (d, 2H, $J = 7.1$ Hz), 1.47 (m, 3H)	146:(M^+)	3053, 2974, 2915, 2762, 1545, 1410, 1382, 745	173–174
e	12.46 (s, 1H), 8.21 (s, 1H), 7.59 (t, 2H, $J = 23.9$ Hz, $J = 26.9$ Hz), 7.12 (m, 2H)	118:(M^+)	3115, 3063, 2941, 2860, 2795, 1587, 1458, 1409, 748	171–172
f	7.55 (m, 2H), 7.22 (t, 2H, $J = 2.9$ Hz, $J = 5.5$ Hz), 2.95 (t, 2H, $J = 7.6$ Hz), 1.86 (td, 1H, $J = 7.5$ Hz, J = 14.9 Hz), 1.31 (m, 1H), 0.82 (m, 3H)	188:(M^+)	3051, 2952, 2928, 2865, 2734, 1624, 1538, 1420, 748	162–163
g	12.42 (m, 2H), 7.50(s, 4H), 7.14(s, 4H)	256:(M^+)	3062, 2846, 2739, 1624, 1591, 1545, 1486, 1433, 743	>300

using microwave irradiation. However, we got 2-ethyl-benzimidazole quantitatively instead (Scheme 1).

Based on this reaction, we synthesized several substituted benzimidazoles, and the results are given in Table 1 and Scheme 2. Our investigation suggested that the substituted benzimidazoles are very easily obtained in yields of more than 90% when irradiating 1,2-phenylenediamine with esters in the microwave oven with 165 W for only about 90 s. When lowering the power, the reaction time would be prolonged. However, the yields would be lower. When the power is greater than 500 W, the mixture would carbonize. In a word, we have developed a simple and efficient synthesis of substituted benzimidazole compounds from esters.

EXPERIMENTAL

Melting points were determined with a Kolfer micromelting-pointing apparatus and were uncorrected. IR spectra were recorded on a FTS-40 spectrophotometer in KBr. ^{1}H NMR were measured on a Bruker DPX-600M spectrometer. Chemical shifts are referred to TMS on the δ scale. MS were performed on ZAB-HS spectrometer.

Typical Procedure for Preparation of Substituted Benzimidazoles

1,2-Phenylenediamine dihydrochloride (1 mmol) was added to the ester (1 mmol) solution of 10 ml of $HOCH_2CH_2OH$, and the solution was irradiated in the microwave oven at 165 W for 1.5 min. After cooling, the reaction mixture was diluted with 100 ml of water and neutralized with aq Na_2CO_3 (PH = 7.0–8.0). The solid was filtered and crystallized from 90% EtOH to give the titled compound.

All the analytical data for the compounds **a**–**g** are given in Table 2.

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