Synthesis of benzimidazole thiazolinone derivatives under microwave irradiation

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Organic compounds containing the thiazolinone ring are of increasing interest due to their bactericidal, pesticidal, anticonvulsant, antiinflammatory, antithyroidal and antimicrobial activities. A rapid microwave-assisted synthesis thiazolinone derivatives is described. The 3-(1H-benzo[d]imidazol-2-yl)-2-substituted phenyl thiazolidin-4-one were identified by IR, ^{1}H NMR, elemental analyses. The target compounds were performed in a shorter reaction time compared to conventional heating methods.

Keywords: benzimidazole, thiazolinone, microwave irradiation

The derivatives of benzimidazole exhibit diverse biological properties, such as antiproliferative[1], antiparasitic[2], antiviral[3], antimicrobial activities.[4,5] Organic compounds containing the thiazolinone ring are of increasing interest due to their known biological activities that include bactericidal, pesticidal, anticonvulsant, antiinflammatory, antithyroidal and antimicrobial activities.[6,7]

Consequently, the synthesis of compounds containing both benzimidazole and thiazolinone groups has been intensely investigated.[8–10] However, these derivatives were synthesised by conventional heating, and the yields were not satisfactory.

We now report the synthesis of a series of new compounds containing benzimidazole and thiazolinone rings using microwave irradiation.[11,12]

Results and discussion

The 2-Aminobenzimidazole was prepared from o-phenylenediamine and cyanamide. The N-(substituted benzylidene)-1H-benzo[d]imidazol-2-amines (**3a–e**) were prepared by the reaction of 2-aminobenzimidazole and substituted benzaldehyde under microwave irradiation, and the 3-(1H-benzo[d] imidazol-2-yl)-2-substituted phenylthiazolidin-4-ones (**4a–e**) were then synthesised from N-(substituted benzylidene)-1H-benzo[d] imidazol-2-amine and thioglycollic acid in toluene under microwave irradiation as shown in Scheme 1. We synthesised and compared the derivatives both under microwave irradiation and by conventional heating method. The results are reported in Table 1.

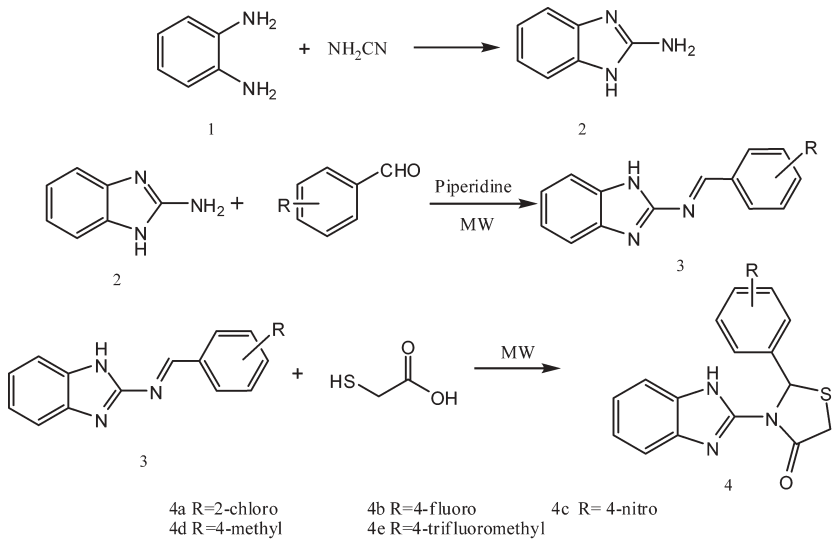
The 3-(1H-benzo[d]imidazol-2-yl)-2-substituted phenyl thiazolidin-4-one was synthesised with the previous conventional heating merthods over a long reaction time (12h). The yields were not satisfactory despite the long reaction time. We have developed a fast (30 min), convenient, and efficient method for the preparation of the derivatives under microwave irradiation. The ease of this method and workup, high yields, and very short reaction time make this procedure useful and attractive compared with the currently available methods.

Experimental

Melting points were recorded on an X-4 binocular microscope melting point apparatus. ^{1}H NMR spectra were recorded on an Avance Bruker-500 instrument and chemical shifts in ppm are reported with TMS as the internal standard. IR spectra in KBr were recorded by a Perkin-Elmer PE-683 IR spectrometer. Elemental analyses were performed on an Elementer Vario EL III elementary analysis instrument. MW experiments were carried out on a WF-4000M microwave fast reaction system (Shanghai Qiyao Analysis Instrument Co., Shanghai, China).

Preparation of **2***; general procedure*

A mixture of o-phenylenediamine **1** (0.01 mol) and hydrochloric acid was stirred and heated at 100 °C. Cyanamide (0.01 mol) was added dropwise into the reaction mixture. After the reaction was finished,



Scheme 1 The synthetic route of compounds **4a–e.**

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Table 1 Synthesis of compounds **4a–e**

Entry	R	Mode of activation	Time	Power/ temperature	Yield /%
4a	2-Chloro	MW	30 min	400 W	82%
4b	4-Fluoro	MW	30 min	400 W	79%
4c	4-Nitro	MW	30 min	400 W	85%
4d	4-Methyl	MW	30 min	400 W	82%
4e	4-Trifluoromethyl	MW	30 min	400 W	81%
4a	2-Chloro	CH	12h	110 °C	54%
4b	4-Fluoro	CH	12h	110 °C	51%
4c	4-Nitro	CH	12h	110 °C	60%
4d	4-Methyl	CH	12h	110 °C	56%
4e	4-Trifluoromethyl	CH	12h	110 °C	58%

MW, microware irradiation; CH, conventional heating.

50% NaOH (10 mL) was added. After cooling and filtering, crude compound **2** was obtained. The pure compound **2** was obtained by recrystallisation from ethanol.

Preparation of **3***; general procedure*

A mixture of compound **2** (0.01 mol), substituted benzaldehyde (0.015 mol) and a small amount of piperidine in toluene was stirred and irradiated in WF-4000M microwave fast reaction system under 400W for 12 min at 110 °C. After cooling and filtering, crude compound **3** was obtained. The pure compounds were obtained by recrystallisation from ethanol.

Preparation of **4***; general procedure*

A mixture of compound **3** (0.005 mol) and toluene (50 mL) was treated with thioglycollic acid (0.005 mol) dropwise and irradiated in an experimental MW instrument at 400W for 30 min (max. temp. 110 °C). After completion of the reaction, the remaining toluene was evaporated under reduced pressure. After cooling, the crude product precipitated. It was filtered, washed with ethanol, dried, and recrystallised from ethanol to afford the target compound.

N-(2-chlorobenzylidene)-1H-benzo[d]imidazol-2-amine (**3a**): Yield, 83%; m.p. 222–223 °C; ^{1}H NMR (DMSO-d6, 400 MHz) δ: 12.80 (s, 1H, $NH_{benzimidazole}$), 9.79 (s, 1H, H_{arom}), 7.20-8.28 (m, 8H, H_{ring}); IR(KBr)υ: 3056 (ArH), 1634 (C=N, ring), 1563 (C=N, imine), 1461 (C–N) cm^{-1}; Anal. Calcd for $C_{14}H_{10}ClN_3$: C, 65.76; H, 3.94; N, 16.43. Found: C, 65.02; H, 4.04; N, 16.17%.

N-(4-fluorobenzylidene)-1H-benzo[d]imidazol-2-amine (**3b**): Yield, 82%; m.p. 185–186 °C; ^{1}H NMR (DMSO-d6, 300 MHz) δ: 12.65 (s, 1H, $NH_{benzimidazole}$), 9.46 (s, 1H, H_{arom}), 7.07–8.17 (m, 7H, H_{ring}); IR (KBr)υ: 3065 (ArH), 1615 (C=N, ring), 1587 (C=N, imine), 1461 (C–N) cm^{-1}; Anal. Calcd for $C_{14}H_{10}FN_3$: C, 70.28; H, 4.21; N, 17.56. Found: C, 70.22; H, 4.25; N, 17.51%.

N-(4-nitrobenzylidene)-1H-benzo[d]imidazol-2-amine (**3c**): Yield, 90%; m.p. 285–286 °C; ^{1}H NMR (DMSO-d6, 400 MHz) δ: 12.85 (s, 1H, $NH_{benzimidazole}$), 9.60 (s, 1H, H_{arom}), 7.19–8.42 (m, 8H, H_{ring}); IR(KBr)υ: 3122 (ArH), 1613 (C=N, ring), 1590 (C=N, imine), 1425 (C–N) cm^{-1}; Anal. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 63.18; H, 3.25; N, 21.08%.

N-(4-methylbenzylidene)-1H-benzo[d]imidazol-2-amine (**3d**): Yield, 85%; m.p. 238–239 °C; ^{1}H NMR (DMSO-d6, 300 MHz) δ: 12.65 (s, 1H, $NH_{benzimidazole}$), 9.40 (s, 1H, H_{arom}), 7.07–7.97 (m, 8H, H_{ring}), 2.42 (s, 3H, CH_3); IR(KBr)υ: 3054 (ArH), 1666 (C=N, ring), 1566 (C=N, imine), 1440 (C–N) cm^{-1}; Anal. Calcd for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.51; H, 5.60; N, 17.82%.

N-(4-(trifluoromethyl)benzylidene)-1H-benzo[d]imidazol-2-amine (**3e**): Yield, 79%; m.p. 232–234 °C; ^{1}H NMR (DMSO-d6, 300MHz) δ: 12.80 (s, 1H, $NH_{benzimidazole}$), 9.56 (s, 1H, H_{arom}), 7.09–8.29 (m, 8H, H_{ring}); IR(KBr)υ: 3067 (ArH), 1611 (C=N, ring), 1576 (C=N, imine), 1429 (C–N) cm^{-1}; Anal. Calcd for $C_{15}H_{10}F_3N_3$: C, 62.28; H, 3.48; N, 14.53. Found: C, 62.33; H, 3.51; N, 14.60%.

3-(1H-benzo[d]imidazol-2-yl)-2-(2-chlorophenyl)thiazolidin-4-one (**4a**): Yield, 82%; m.p. 219–220 °C; ^{1}H NMR (DMSO-d6, 300 MHz) δ: 4.04, 4.13 (d, 2H, CH_2), 6.83 (s, 1H, CH), 7.05–7.55 (m, 8H, H_{ring}), 12.47 (s, 1H, $NH_{benzimidazole}$); IR(KBr)υ: 3063, 2918, 1684, 1536, 1470, 1111 cm^{-1}; Anal. Calcd for $C_{16}H_{12}ClN_3OS$: C, 58.27; H, 3.67; N, 12.74. Found: C, 58.18; H, 3.46; N, 12.51%.

3-(1H-benzo[d]imidazol-2-yl)-2-(4-fluorophenyl)thiazolidin-4-one (**4b**): Yield, 79%; m.p. 191–192 °C; ^{1}H NMR (DMSO-d6, 500MHz) δ: 3.96, 4.23 (d, 2H, CH_2), 6.77 (s, 1H, CH), 7.07–7.52 (m, 8H, H_{ring}), 12.41 (s, 1H, $NH_{benzimidazole}$); IR(KBr)υ: 3063, 2914, 1705, 1535, 1485, 1222 cm^{-1}; Anal. Calcd for $C_{16}H_{12}FN_3OS$: C, 61.33; H, 3.86; N, 13.41. Found: C, 62.08; H, 3.46; N, 13.01%.

3-(1H-benzo[d]imidazol-2-yl)-2-(4-nitrophenyl)thiazolidin-4-one (**4c**): Yield, 85%; m.p. 225–226 °C; ^{1}H NMR (DMSO-d6, 300MHz) δ: 4.01, 4.23 (d, 2H, CH_2), 6.90 (s, 1H, CH), 7.09–8.19 (m, 8H, H_{ring}), 12.41 (s, 1H, $NH_{benzimidazole}$); IR(KBr)υ: 3077, 2927, 1710, 1604, 1534, 1486 cm^{-1}; Anal. Calcd for $C_{16}H_{12}N_4O_3S$: C, 56.46; H, 3.55; N, 16.46. Found: C, 56.28; H, 3.46; N, 16.01%.

3-(1H-benzo[d]imidazol-2-yl)-2-p-tolylthiazolidin-4-one (**4d**): Yield, 82%; m.p. 255–256 °C; ^{1}H NMR (DMSO-d6, 300MHz) δ: 2.31 (t, 3H, CH_3), 3.91, 4.14 (d, 2H, CH_2), 6.73 (s, 1H, CH), 7.08–7.45 (m, 8H, H_{ring}), 12.25 (s, 1H, $NH_{benzimidazole}$); IR(KBr)υ: 3051, 2919, 1703, 1536, 1484 cm^{-1}; Anal. Calcd for $C_{17}H_{15}N_3OS$: C, 66.00; H, 4.89; N, 13.58. Found: C, 66.08; H, 4.56; N, 13.41%.

3-(1H-benzo[d]imidazol-2-yl)-2-(4-(trifluoromethyl)phenyl)thiazolidin-4-one (**4e**): (81%): m.p. 247–248 °C; ^{1}H NMR (DMSO-d6, 300MHz) δ: 3.97, 4.22 (d, 2H, CH_2), 6.87 (s, 1H, CH), 7.07–7.71 (m, 8H, H_{ring}), 12.44 (s, 1H, $NH_{benzimidazole}$); IR(KBr)υ: 3054, 2910, 1709, 1537, 1488, 1226 cm^{-1}; Anal. Calcd for $C_{17}H_{12}F_3N_3OS$: C, 56.19; H, 3.33; N, 11.56. found: C, 56.28; H, 3.39; N, 11.51%.

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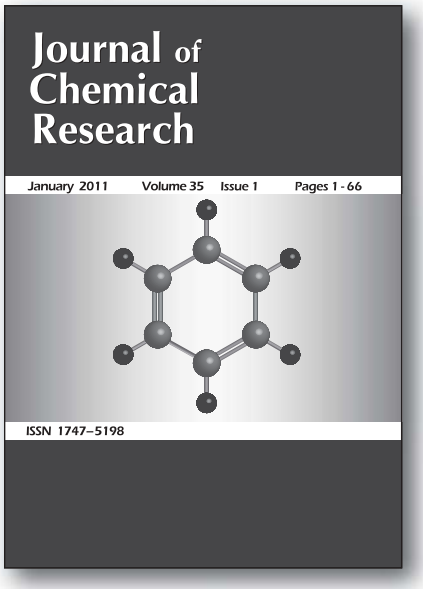

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