Aza-Michael addition of acrylonitrile with 2-aryloxymethylbenzimidazole derivatives under microwave irradiation

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A simple, rapid, and highly efficient method has been developed for the aza-Michael addition of acrylonitrile to 2-aryl-oxymethylbenzimidazole derivatives in the presence of anhydrous potassium carbonate under microwave irradiation. A series novel of 1-cyanoethyl-2-aryloxymethylbenzimidazole derivatives have been prepared and characterised by ^{1}H NMR, ^{13}C NMR, IR spectra and elemental analysis.

Keywords: Aza-Michael reaction, cyanoethylation, benzimidazoles, microwave irradiation

Benzimidazoles derivatives have been examined as antibacterial,[1] anticancer,[2,3] and antiulcer agents.[4,5] Organonitriles are useful intermediates in the construction of C–N bonds and in the preparation of β amino carbonyl or nitrile compounds by the aza-Michael addition. However, reports on the cyanoethylation of substituted benzimidazole derivatives with α, β-unsaturated nitriles are rare.

The aza-Michael addition is an important carbon–nitrogen bond-forming reaction which has been explored in organic synthesis. There are some reports on the base-catalysed aza-Michael addition of heterocyclic compounds[6–7], but they have some disadvantages due to the long reaction time (several days), vigorous reaction conditions and tedious workup.

In recent years, microwave technology has become a well-established procedure in organic synthesis which can increase the purity of the products, enhance the chemical yield, and shorten the reaction time.[8,9] In continuation of our earlier work on the synthesis and study of the biological activity of benzimidazole derivatives,[10,11] we synthesised a series of new compounds containing the 2-aryloxymethylbenzimidazole and acrylonitrile groups using microwave irradiation. The reactions are shown in the Scheme 1.

Results and discussion

In order to select the best reaction condition for synthesis **4a–j**, we carried out a series of experiments as following: firstly, we examined as a model reaction the preparation of compound **4a** using different catalysts. The results are shown in Table 1. We found that the yields of **4a** were 84% in the presence of anhydrous potassium carbonate. This was the most efficient catalyst for this reaction.

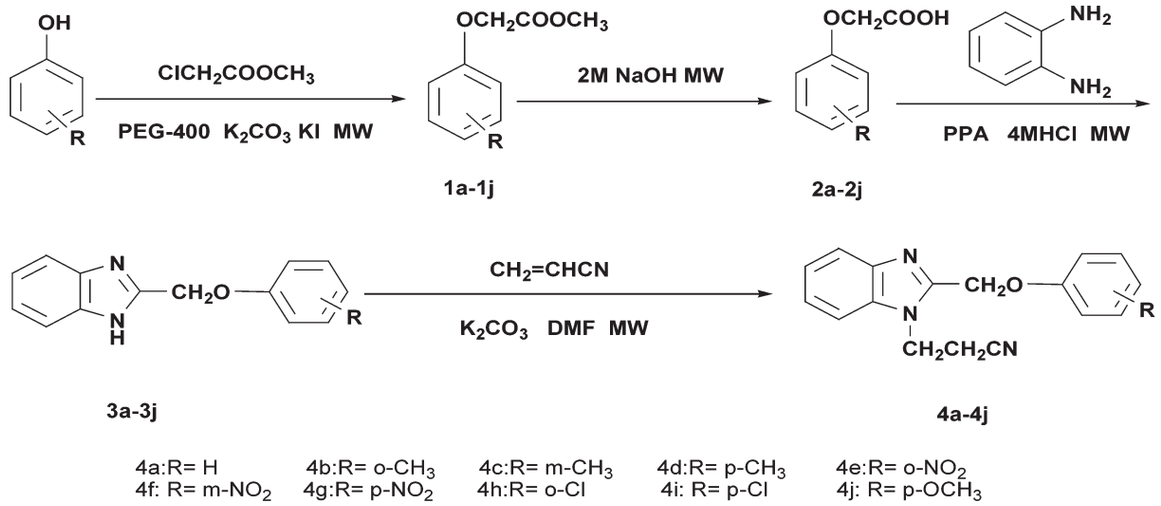
Secondly, organic solvents strongly affected the aza-Michael addition. In order to improve the activity of K_2CO_3, some conventional organic solvents were screened in Table 2. The yields of **4a** were more than 80% in highly polar aprotic solvents. DMF was the appropriate solvent for this reaction.

Finally, to investigate the effect of microwave irradiation on this reaction, we compared it with the classical method.[7] It required 8 hours to prepare **4a** by the classic method, while only 3 minutes of microwave activation was required for the synthesis of **4a**. Obviously, the latter method considerably reduced the reaction time. This method was used in the preparation of other products. The results are listed in Table 3.

In conclusion, we have developed a facile, clean, efficient procedure for the preparation of a series of novel 1-cyanoethyl-2-aryloxymethylbenzimidazole derivatives in the presence of anhydrous potassium carbonate under microwave irradiation. In comparison with other conditions for the reaction, this methodology has led to a great improvement in shortening the reaction time, affording high yields and simplifying the work-up.

Experimental

Melting points were determined on the X-4 micro melting point apparatus and are uncorrected. IR spectra were recorded using KBr disc on TFS-3000 spectrophotometer and ^{1}H NMR spectra on a



Scheme 1

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Table 1 Yields of **4a** in different catalysts in DMF

Entry	Solvents	Yields of **4a** / %
1	K_2CO_3	84
2	Na_2CO_3	77
3	Na OH	52
4	KOH	61
5	Na_3PO_4	68

Table 2 Yields of **4a** in different solvents using K_2CO_3

Entry	Solvents	Yields of **4a** / %
1	DMF (10 mL)	84
2	DMSO (10 mL)	81
3	Acetone (10 mL)	78
4	Ethyl acetate (10 mL)	60
5	Ethanol (10 mL)	48
6	H_2O (10 mL)	15

Table 3 Reaction times, melting points and yields of the products **4a–j** in DMF

Entry	R	Time[a] / min		M.p. / °C	Yield[c] / %
		230W	400W		
4a	R= H	1	2	148–149	84
4b	R=*o*-CH_3	1	2.5	141–143	89
4c	R=*m*-CH_3	1	2.5	128–129	82
4d	R=*p*-CH_3	1	2.5	138–139	89
4e	R=*o*-NO_2	1.5[b]	0.3[b]	181–183	81
4f	R=*m*-NO_2	1.5[b]	0.3[b]	149–151	80
4g	R=*p*-NO_2	1.5[b]	0.3[b]	195–196	87
4h	R=*o*-Cl	1.5	2	187–189	91
4i	R=*p*-Cl	1.5	2	118–119	93
4j	R=*p*-OCH_3	1	3	149–150	85

[a] Reactions were carried out with pulse of 30s (1min cooling time).
[b] Reactions were carried out with pulse of 20s (1min cooling time).
[c] Isolated yield from three runs.

Varian Mercury plus-400 MHz instrument using TMS as the internal reference. Elemental analyses were determined on PE-2400 CHN instrument. The reactions were monitored by TLC. For the microwave irradiation experiments described below, a conventional microwave oven was equipped with a condenser-Allihn type (Whirlpool Micro V-100 having maximum output of 850 W).

All the compounds 3a–j had been reported previously[11] by ^{1}H NMR, ^{13}C NMR, IR spectra and elemental analysis.

Aza-Michael reaction of acrylonitrile with **4a***; general procedure*

It should be noted that the conventional domestic microwave oven was modified by equipping it with a condenser-Allihn type in order to improve the reproducibility.

To a 50 mL round bottom flask was successively added **3a** (5 mmol), anhydrous potassium carbonate (5 mmol), DMF (10 mL) and acrylonitrile (5 mmol) and thoroughly mixed properly. The flask was placed into a microwave oven, and the mixture was irradiated at 230 W and 400 W for the appropriate time. (The progress of the reaction was monitored by TLC). After irradiation, ice-cold water (10 mL) was added, and the product obtained was filtered, washed with H_2O (15 mL) three times, and dried. The product was crystallised from DMF–EtOH–H_2O.

1-cyanoethyl-2-aryloxymethylbenzimidazole (**4a**): Yellow crystals; yield; 84%; m.p. 148–149 °C ; IR (K Br) *v*: 2246 (C≡N), 1594 (C=N, C=C) cm^{-1}.^{1}H NMR (DMSO-d_6, 400 MHz) δ3.11 (2H, t, J = 6.4Hz, CH_2C≡N), 4.69 (2H, t, J = 6.8Hz, NCH_2), 5.47 (2H, s, CH_2O), 6.98–7.77 (9H, m, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.18, 39.50, 62.44, 110.85, 114.80, 118.59,119.48, 121.41, 122.23, 123.05, 129.60, 134.97, 141.83, 149.36, 157.64; Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63, H, 5.45; N, 15.15. Found: C, 73.62; H, 5.47; N, 15.16%.

1-Cyanoethyl-2-o-methyl-aryloxymethylbenzimidazole (**4b**): Yellow crystals; yield; 89%; m.p. 141–143 °C; IR（KBr）ν: 2249 (C≡N), 1599 (C=N,C=C) cm^{-1}.^{1}H NMR (DMSO-d_6, 400 MHz) δ2.19 (3H, s, CH_3), 3.10 (2H, t, J = 6.8Hz, CH_2C≡N), 4.73 (2H, t, J = 6.8Hz, NCH_2), 5.48 (2H, s, CH_2O),6.89–7.78 (8H, m, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.25, 39.50,62.64, 109.31, 110.89, 111.91, 118.57, 119.54, 121.09, 122.26, 123.08, 125.85, 127.03,130.70, 134.98, 141.90, 149.45, 155.83; Anal. Calcd for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.21; H, 5.61; N, 14.40%.

1-Cyanoethyl-2-m-methyl-aryloxymethylbenzimidazole (**4c**): Yellowish crystals; yield; 82%; m.p. 128–129 °C; IR（KBr）ν: 2247 (C≡N), 1612 (C=N, C=C) cm^{-1}.^{1}H NMR (DMSO-d_6, 400 MHz) δ2.29 (3H, s, CH_3), 3.10 (2H, t, J = 6.8Hz, CH_2C≡N), 4.65 (2H, t, J = 6.8Hz, NCH_2), 5.44 (2H, s, CH_2O),6.81–7.77 (8H, m, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.21, 21.12, 39.50,62.43, 110.86, 111.74, 115.46, 118.63, 119.50, 122.18, 122.23, 123.05, 129.35, 134.39,139.17, 141.85, 149.42, 157.68; Anal. Calcd for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.21; H, 5.87; N, 14.41%.

1-Cyanoethyl-2-p-methyl-aryloxymethylbenzimidazole (**4d**): Yellowish solids; yield; 89%; m.p. 138–139 °C; IR（KBr）ν: 2249 (C≡N), 1613 (C=N, C=C) cm^{-1}.^{1}H NMR (DMSO-d_6, 400 MHz) δ2.23 (3H, s, CH_3), 3.10 (2H, t, J = 6.4Hz, CH_2C≡N), 4.67 (2H, t, J = 6.8Hz, NCH_2), 5.42 (2H, s, CH_2O),7.02–7.76 (8H, m, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.16, 20.07, 62.58,110.82, 114.67, 118.58, 119.46, 122.20, 123.02, 129.91, 130.20, 134.97, 141.83,149.47, 155.54; Anal. Calcd for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.22; H, 5.90; N, 14.40%.

1-Cyanoethyl-2-o-nitryl-aryloxymethylbenzimidazole (**4e**): Yellowish crystals; yield; 81%; m.p. 181–183 °C; IR（KBr）ν: 2253 (C≡N), 1608 (C=N, C=C) cm^{-1}.^{1}H NMR (DMSO-d_6, 400 MHz) δ3.11 (2H, t, J = 6.8Hz, CH_2C≡N), 4.75 (2H, t, J = 6.8Hz, NCH_2), 5.70 (2H, s, CH_2O), 7.17–7.95 (8H, m, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.07, 63.54, 111.05, 115.63, 118.54,119.63, 121.42, 122.41, 123.33, 125.21, 134.56, 135.01, 139.49, 141.78, 148.18,150.35; Anal. Calcd for$C_{17}H_{14}N_4O_3$: C, 63.35; H, 4.38; N, 17.38. Found: C, 63.38; H, 4.36; N, 17.41%.

1-Cyanoethyl-2-m-nitryl-aryloxymethylbenzimidazole (**4f**): Yellowish solids; yield; 80%; m.p. 149–151 °C; IR（KBr）ν: 2249 (C≡N), 1616 (C=N, C=C) cm^{-1}.^{1}H NMR (DMSO-d_6, 400 MHz) δ3.13 (2H, t, J = 6.8Hz, CH_2C≡N), 4.71 (2H, t, J = 6.8Hz, NCH_2), 5.64 (2H, s, CH_2O), 7.25 – 8.02 (8H, m, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.24, 62.98, 109.48, 110.96, 116.29,116.40,118.63, 119.57, 122.26, 123.20, 130.74, 134.94, 141.86, 148.65, 148.70, 158.23; Anal. Calcd for $C_{17}H_{14}N_4O_3$: C, 63.35; H, 4.38; N, 17.38. Found: C, 63.34; H, 4.42; N, 17.36%.

1-Cyanoethyl-2-p-nitryl-aryloxymethylbenzimidazole (**4g**): Yellow crystals; yield; 87%; m.p. 195–196 °C; IR（KBr）ν: 2248 (C≡N), 1592 (C=N, C=C) cm^{-1}.^{1}H NMR (DMSO-d_6, 400 MHz) δ3.18 (2H, t, J = 6.8Hz, CH_2C≡N), 4.70 (2H, t, J = 6.4Hz, NCH_2), 5.67 (2H, s, CH_2O), 7.20 – 8.30 (8H, m, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.23, 63.08, 110.98, 115.42, 115.53,118.61, 119.59, 122.38, 123.24, 125.85, 125.91, 134.94, 141.44, 141.86, 148.47,162.89; Anal. Calcd for$C_{17}H_{14}N_4O_3$: C, 63.35; H, 4.38; N, 17.38. Found: C, 63.36; H, 4.37; N, 17.37%.

1-Cyanoethyl-2-o-chloro-aryloxymethylbenzimidazole (**4h**): Yellow crystals; yield; 91%; m.p. 187–189 °C; IR（KBr）ν: 2249 (C≡N), 1616 (C=N, C=C) cm^{-1}.^{1}H NMR (DMSO-d_6, 400 MHz) δ3.15 (2H, t, J = 6.8Hz, CH_2C≡N), 4.76 (2H, t, J = 6.8Hz, NCH_2), 5.59 (2H, s, CH_2O), 7.01–7.80 (8H, m, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.28, 63.28, 110.95, 114.51, 118.53,119.58, 121.30, 122.34, 122.41, 123.22, 128.38, 130.10, 135.04, 141.78, 148.67,152.91; Anal. Calcd for$C_{17}H_{14}ClN_3O$: C, 65.49; H, 4.53; N, 13.48. Found: C, 65.47; H, 4.55; N, 13.46%.

1-Cyanoethyl-2-p-chloro-aryloxymethylbenzimidazole (**4i**): White solids; yield; 93%; m.p. 118–119 °C; IR（KBr）ν: 2249 (C≡N), 1595 (C= N, C= C) cm^{-1}.^{1}H NMR (DMSO-d_6, 400 MHz) δ3.12 (2H, t, J = 6.4Hz, CH_2C≡N), 4.69 (2H, t, J = 6.8Hz, NCH_2), 5.50 (2H, s, CH_2O), 7.18–7.82 (8H, m, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.22, 62.77, 110.89, 116.66, 118.61,119.53, 122.29, 123.12, 125.20, 129.34, 134.96, 141.84, 149.06, 156.53; Anal. Calcd for: $C_{17}H_{14}ClN_3O$: C, 65.49; H, 4.53; N, 13.48. Found: C, 65.51; H, 4.51; N, 13.50%.

1-cyanoethyl-2-p-methoxyl-aryloxymethylbenzimidazole (**4j**): White solids; yield; 93%; m.p. 118–119 °C; IR（KBr）ν：2248 (C≡N), 1591 (C=N, C=C) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ3.10 (2H, t, *J* = 6.8Hz, $CH_2C{\equiv}N$), 3.70 (3H, s, OCH_3), 4.68 (2H, t, *J* = 6.8Hz, NCH_2), 5.40 (2H, s, CH_2O),6.89–7.77 (8H, m, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.18, 55.37, 63.09,110.84, 114.67, 115.85, 118.63, 119.47, 122.21, 123.03, 134.97, 141.82, 149.55,151.60, 153.60; Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.14; H, 5.61; N, 13.66%.

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