A novel facile one-pot synthesis of 3,1-benzoxazine derivatives

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The synthesis of 3,1-benzoxazine derivatives by the cyclocondensation of substituted *o*-aminobenzonitrile with aromatic aldehyde in the presence of anhydrous zinc chloride under classical heating and microwave irradiation is described. This is a novel efficient synthetic route of 3,1-benzoxazine cyclic compounds.

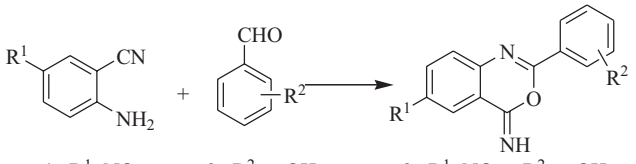
Keywords: 3,1-benzoxazine, aromatic aldehyde, intermediate, cyclocondensation

3,1-Benzoxazine derivatives have been proposed as herbicides, plant growth regulators and potent nonsteroidal progesterone receptor agonists.[1-3] In addition, this compounds can be used as the key intermediates in the synthesis of antimicrobial named carbapenems.[4,5] Among a series of benzoxazine compounds, little attentions have been paid for 3,1-benzoxazine compounds because there are only few methods for the synthesis of this kind of compounds, *e.g.* cyclocondensation of *o*-aminophenyl alcohol with ketone or aldehyde.[6-8] Herein, we report that the 3,1-benzoxazine derivatives were obtained by the tandem cyclocondensation of substituted *o*-aminobenzonitrile with aromatic aldehyde.

During our studies on the efficient synthesis of 3,1-benzoxazine derivatives, we have found that the oxazine ring formation occurs by refluxing the various commercially available aromatic aldehydes (**2a–c**) with substituted *o*-aminobenzonitrile (**1a–b**) in the presence of anhydrous zinc chloride as a catalyst (Scheme 1). Thus the 3,1-benzoxazine compound (**3a**) was obtained in 72% yield by heating a mixture of (**1a**) with an excess of salicylaldehyde (**2a**) in the presence of anhydrous zinc chloride. All products (**3a–f**) were precipitated from cooled reaction mixtures after the addition of water, and then were purified by recrystallisation from ethanol. The reaction proceeds without organic solvent. The optimised results are summarised in Table 1. The structures of products (3**a–f**) were characterised by ^{1}H NMR, ^{13}C NMR, IR, MS spectra and elemental analysis.

The formation of 3,1-benzoxazine derivatives could be explained by attack of the amino group onto the carbonyl carbon atom of the aromatic aldehyde to give intermediate **i** and subsequent cyclisation by attack of the oxygen atom onto the nitrile group (Scheme 2).

We then examined this reaction under microwave irradiation and found that process results in the rapid formation of 3,1-benzoxazine derivatives (**3a–f**). The reaction was performed in an Initiator microwave reactor manufactured by Biotage company. This microwave reactor introduces new single-mode applicator with the proven Dynamic Field Tuning feature. This feature offers faster heating of a broader range of reaction mixtures and makes the energy distribution more even. So, this method offers obvious improvements in reaction rates and yields. The optimised results are summarised in Table 1.



1a R^1=NO_2
1b R^1=H

2a R^2=*o*-OH
2b R^2=*p*-OCH_3
2c R^2=H

3a R^1=NO_2, R^2=*o*-OH
3b R^1=H, R^2=*o*-OH
3c R^1=NO_2, R^2=*p*-OCH_3
3d R^1=H, R^2=*p*-OCH_3
3e R^1=NO_2, R^2=H
3f R^1=H, R^2=H

Scheme 1

Table 1 Reaction of substituted o-aminobenzonitrile with aromatic aldehyde

		Conventional heating			Irradiation conditions	
Entry	Product	Time /h	Yield /%	Time /min	Temperature /°C	Yield /%
1	**3a**	1.5	72	10	180	80
2	**3b**	1.5	70	8	180	80
3	**3c**	1.0	73	8	170	82
4	**3d**	1.5	71	8	180	78
5	**3e**	1.0	74	10	180	85
6	**3f**	1.0	70	8	170	82

In conclusion, we have demonstrated that substituted *o*-aminobenzonitrile with aromatic aldehyde react in the presence of anhydrous zinc chloride under conventional thermal heating or microwave irradiation, providing a novel and convenient one-step procedure for the preparation of 3,1-benzoxazine derivatives. The especially features of this method are the high purity of products and simple work-up.

Experimental

Melting points were determinated using XT4 microscope melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer FT-IR spectrophotometer and were run as KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz on a Bruker 400 spectometer. Chemical shifts are reported in δ (ppm) relative to internal tetramethylsilane. Mass spectra were recorded on a ZAB-HS mass spectrometer using ESI ionisation. Elemental analyses were performed on an Elementar Vario EL.

General procedure under conventional heating: The substituted *o*-aminobenzonitrile (6.0 mmol), aromatic aldehyde (12.0 ml) and zinc chloride (6.0 mmol) were taken in a dry three-neck flask at room temperature, and the reaction mixture was refluxed for a given time (see Table 1). The cooled reaction mixture was quenched with water (10 ml) and the precipitate was separated by filtration. The filtration residue was dispersed into water and titrated to pH 12–13 by 20% sodium hydroxide. After filtration, the rude product was recrystallised from ethanol to give the corresponding products.

General procedure under microwave irradiation: A 20 ml Initiator Microwave reaction vessel with a stir bar was charged with substituted *o*-aminobenzonitrile (6.0 mmol), aromatic aldehyde (12.0 ml) and zinc chloride (6 mmol). The reaction mixture pre-stirred 2 min and then irradiated at 180°C for a given time (see Table 1). After completion of the reaction, the cooled reaction mixture was quenched with water (10 ml) and the precipitate was separated by filtration. The filtration residue was dispersed into water and titrated to pH 12–13 by 20% sodium hydroxide. After filtration, the crude product was recrystallised from ethanol to give the corresponding products.

3a: Yellow powder, m.p. 213–215°C. IR (KBr), ν_{max} cm^{-1}: 3435, 3092, 1675, 1614, 1564, 1505, 1347, 1224, 748. ^{1}H NMR (DMSO): δ ppm 13.02 (s, 2H, ArOH and = NH), 8.82 (d, 1H, *J* = 2.6 Hz, ArH), 8.57 (dd, 1H, *J* = 2.6, 2.6 Hz, ArH), 8.23 (d, 1H, *J* = 8.0 Hz, ArH),

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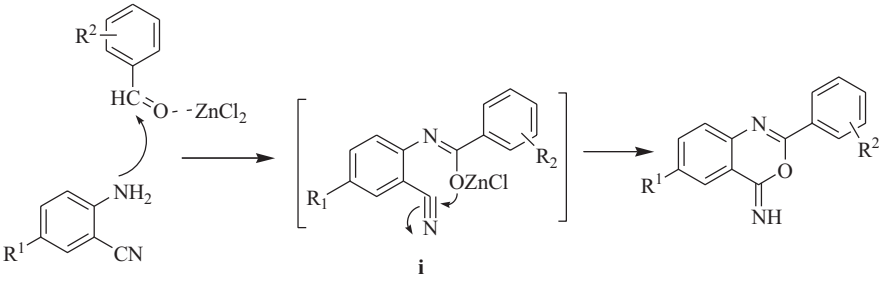

Scheme 2

7.97 (d, 1H, *J* = 8.0 Hz, ArH), 7.50 (t, 1H, *J* = 6.8, 6.8 Hz, ArH), 7.02 (m, 2H, *J* = 8.0, 8.0 Hz, ArH). ^{13}C NMR (DMSO): δ ppm 117.94, 117.94, 119.08, 119.08, 120.78, 122.05, 122.05, 128.58, 128.58, 128.66, 128.66, 134.43, 144.67, 160.01. ESIMS (*m/z*): 282.1 (M-H$^+$). Calcd. for $C_{14}H_9N_3O_4$: C, 59.37; H, 3.20; N, 14.84. Found C, 59.07; H, 3.30; N, 14.41.

3b: Yellow powder, m.p. 258–260°C. IR (KBr), ν_{max} cm^{-1}: 3427, 3102, 1671, 1607, 1563, 1512, 1332, 1252. ^{1}H NMR (DMSO): δ ppm 13.79 (s, 1H, = NH), 12.49 (s, 1H, ArOH), 8.23 (dd, 1H, *J* = 1.4, 1.4 Hz, ArH), 8.15 (dd, 1H, *J* = 1.2, 1.2 Hz, ArH), 7.85 (m, 1H, *J* = 1.5, 1.5 Hz, ArH), 7.75 (d, 1H, *J* = 8.0 Hz, ArH), 7.54 (m, 1H, *J* = 0.8, 0.8, 8.0 Hz, ArH), 7.45 (m, 1H, *J* = 1.4, 1.4 Hz, ArH), 6.98 (m, 2H, *J* = 0.7, 0.7, 0.8, 0.8 Hz, ArH). ^{13}C NMR (DMSO): δ ppm 113.70, 117.87, 118.78, 120.69, 126.02, 126.91, 127.68, 133.69, 134.92, 146.04, 153.76, 160.07, 160.07, 161.42. ESIMS (*m/z*): 237.1 (M-H$^+$). Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found C, 70.52; H, 4.34; N, 11.44.

3c: Yellow powder, m.p. >300°C. IR (KBr), ν_{max} cm^{-1}: 3439, 3098, 1681, 1603, 1560, 1513, 1474, 1344, 1260. ^{1}H NMR (DMSO): δ ppm 12.83 (s, 1H, = NH), 8.80 (d, 1H, *J* = 2.4 Hz, ArH), 8.53 (dd, 1H, *J* = 2.4, 8.0 Hz, ArH), 8.25 (d, 2H, *J* = 8.0 Hz, ArH), 7.86 (d, 1H, *J* = 8.0 Hz, ArH), 7.12 (d, 2H, *J* = 8.0 Hz, ArH), 3.85 (s, 1H, CH_3). ^{13}C NMR (DMSO): δ ppm 55.6, 114.2, 114.2, 114.2, 120.6, 122.1, 124.0, 128.5, 130.2, 130.2, 130.2, 144.3, 155.2, 161.7, 162.7. ESIMS (*m/z*): 298.1 (M + H$^+$). Calcd. for $C_{15}H_{11}N_3O_4$: C, 60.61; H, 3.73; N, 14.14. Found C, 60.80; H, 4.01; N, 14.51.

3d: White powder, m.p. >300°C. IR (KBr), ν_{max} cm^{-1}: 3436, 3036, 1672, 1611, 1587, 1506, 1472, 1222. ^{1}H NMR (DMSO): δ ppm 12.55 (s, 1H, = NH), 8.15 (t, 1H, *J* = 8.0 Hz, ArH), 7.82 (m, 2H, *J* = 1.2, 1.2 Hz, ArH), 7.75 (dd, 2H, *J* = 1.5, 1.5 Hz, ArH), 7.52 (m, 1H, ArH), 7.47 (t, 1H, *J* = 8.0 Hz, ArH), 7.16 (m, 1H, *J* = 2.4, 2.4 Hz, ArH), 3.87 (s, 3H, OCH_3). ^{13}C NMR (DMSO): δ ppm 55.37, 112.51, 117.58, 120.10, 121.01, 125.83, 126.61, 127.53, 129.72, 134.00, 134.59, 148.65, 152.01, 159.33, 162.20. EIMS (*m/z*): 251.5 (M-H$^+$). Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.79; N, 11.10. Found C, 71.57; H, 4.97; N, 10.66.

3e: Yellow powder, m.p. 308–310°C. IR (KBr), ν_{max} cm^{-1}: 3169, 3078, 1670, 1619, 1601, 1562, 1477,1344, 1286. ^{1}H NMR (DMSO): δ ppm 13.02 (s, 1H, = NH), 8.85 (d, 1H, *J* = 2.4 Hz, ArH), 8.58 (dd, 1H, *J* = 2.4, 9.0 Hz, ArH), 8.24 (d, 2H, *J* = 7.2 Hz, ArH), 7.93 (d, 1H, *J* = 9.0 Hz, ArH), 7.67 (t, 1H, *J* = 7.2 Hz, ArH), 7.61(t, 2H, *J* = 7.2, 7.2 Hz, ArH). ^{13}C NMR (DMSO): δ ppm 121.44, 122.49, 128.69, 128.93, 129.16, 129.23, 129.23, 129.52, 132.57, 132.69, 145.09, 153.38, 156.25, 162.20. ESIMS (*m/z*): 268.1 (M + H$^+$). Calcd. for $C_{14}H_9N_3O_3$: C, 62.87; H, 3.39; N, 15.72. Found C, 62.38; H, 3.37; N, 15.25.

3f: White powder, m.p. 240–242°C. IR (KBr), ν_{max} cm^{-1}: 3137, 3062, 1668, 1603, 1558, 1482, 1453, 1346, 1297. ^{1}H NMR (DMSO): δ ppm 12.57 (s, 1H, = NH), 8.20 (t, 3H, *J* = 8.0, 9.2 Hz, ArH), 7.87 (t, 1H, *J* = 7.2, 8.0 Hz, ArH), 7.77 (d, 1H, *J* = 8.0 Hz, ArH), 7.60 (m, 4H, *J* = 8.0, 9.2 Hz, ArH). ^{13}C NMR (DMSO): δ ppm 120.97, 125.83, 126.58, 127.50, 127.74, 127.74, 128.59, 128.59, 131.37, 132.69, 134.60, 148.72, 152.28, 162.21. ESIMS (*m/z*): 223.1 (M + H$^+$). Calcd. for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found C, 75.58; H, 4.54; N, 12.17.

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