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Original article

Cp_2ZrCl_2-catalyzed synthesis of 2-aminovinyl benzimidazoles under microwave conditions

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ABSTRACT

A microwave-assisted general method for the synthesis of 2-aminovinyl benzimidazoles has been developed. Treatment of the 1,2-phenylenediamines and *N*-arylated/*N*,*N*-dialkylated 3-aminoacroleins with bis(cyclopentadienyl)zirconium(IV) dichloride (Cp_2ZrCl_2) as the catalyst under microwave irradiation for 3–5 min followed by in situ MnO_2 oxidation afforded thirteen 2-aminovinyl benzimidazoles in good yields.

1. Introduction

1,2-Disubstituted benzimidazoles have been recognized as valuable scaffolds in the development of novel pharmaceutical agents and functional materials [1]. In modern drug discovery, a myriad of benzimidazole-based compounds have been synthesized and displayed a variety of pharmacological effects, such as anti-infective, anti-inflammatory, anti-tumor, and anti-diabetic activities [2].

In our previous research on the synthesis of AKT inhibitor IV (ChemBridge 5233705), the unique 2-aminovinyl benzimidazole core structure posed a huge challenge to the existing synthetic methods for benzimidazoles [3]. The conventional condensation of 1,2-phenylenediamines with an *N*-arylated 3-aminoacrolein (**1**) in refluxing ethanol followed by *in situ* oxidation only afforded the products in low yields (<20%) [1,4]. Our attempt to promote the reaction by adding oxidants (*e.g.*, potassium peroxymonosulfate [5], I_2 [6], MnO_2 [7], and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) [8]), acidic catalysts (*e.g.*, $BF_3{\cdot}Et_2O$ [9] and polyphosphoric acid (PPA) [10]), or reducing agents (*e.g.*, $SnCl_2$ [11]) according to precedent reports failed to generate the desired product. Interestingly, in our search for potential metal catalyst [12], we found that $ZrOCl_2{\cdot}8H_2O$ and $ZrCl_4$ exhibited a dramatic catalytic effect on the reactions of 1,2-phenylenediamines with **1** and improved the yields to 50%–70% [3]. However, the understanding of this metal-catalyzed condensation/cyclization reaction is still very limited and the extension of this approach to *N*,*N*-dialkylated 3-aminoacroleins has never been explored. We report herein a microwave-assisted method for the synthesis of a diversity of 2-aminovinyl benzimidazoles with bis(cyclopentadienyl)zirconium(IV) dichloride (Cp_2ZrCl_2) as a more effective catalyst.

2. Experimental

1,2-Phenylenediamines (**7**–**12**) were prepared according to the reported procedures [3]. All NMR spectra were obtained with a 400 MHz instrument with chemical shifts reported in parts per million (ppm, δ) and referenced to $CDCl_3$ or DMSO-d_6. IR spectra were recorded on a FT-IR spectrometer. High-resolution mass spectra were obtained with a TOFQ mass spectrometer and reported as *m*/*z*. Microwave reactions were performed on an Anton Paar Monowave 300 instrument with 30 mL reaction vials. The characterization data of known compounds (**1**–**3**, **5**, and **13**–**18**) and ^1H NMR and ^{13}C NMR spectra of new compounds (**4**, **6**, and **19**–**25**) were included in the Supporting information.

2.1. General procedure for the synthesis of 3-aminoacroleins (*1*–*6*)

To a solution of amine (10 mmol) and propargyl alcohol (20 mmol) in toluene (20 mL) was slowly added activated MnO_2

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(200 mmol) at 0 °C. The reaction was stirred for 2 h and then warmed up to 22 °C. After 24 h, MnO_2 was filtered off and washed with ethyl acetate (10 mL). The combined filtrate was concentrated *in vacuo*. Flash column chromatography on silica gel afforded the product.

(E)-3-N-Cyclohexyl-N-ethylaminoacrolein (**4**): Yellow solid; mp 58–60 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94–1.26 (m, 6H), 1.26–1.40 (m, 2H), 1.50–1.61 (m, 1H), 1.74 (d, 4H, J = 10.6 Hz), 2.90–3.19 (m, 3H), 5.06 (dd, 1H, J_1 = 8.7 Hz, J_2 = 12.5 Hz), 6.98 (d, 1H, J = 12.8 Hz), 8.92 (d, 1H, J = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.3, 25.0, 25.5, 32.3, 42.1, 65.1, 100.9, 156.7, 189.1; IR (neat, cm^{-1}): ν_{max} 2927, 2848, 1595, 1442, 1350, 1161, 893, 795; HRMS (ESI+): m/z calcd. for $C_{11}H_{19}NO$ $[M+H]^+$: 182.1467; found: 182.1458.

(E)-3-(4-Methylpiperazin-1-yl)acrylaldehyde (**6**): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88–1.99 (m, 3H), 2.00–2.21 (m, 4H), 2.74–3.28 (m, 4H), 4.76–4.89 (m, 1H), 6.64–6.78 (m, 1H), 8.65–8.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.4, 45.3, 53.5, 100.4, 158.4, 188.6; IR (neat, cm^{-1}): ν_{max} 2944, 1597, 1435, 1317, 1173, 767; HRMS (ESI+): m/z calcd. for $C_8H_{14}N_2O$ $[M+H]^+$: 155.1106; found: 155.1112.

2.2. General procedure for the synthesis of 2-aminovinyl benzimidazoles (**13–25**)

To a solution of 1,2-phenylenediamine (0.1 mmol) and 3-aminoacrolein (0.12–0.15 mmol) in ethanol (15 mL) was added Cp_2ZrCl_2 (0.05 mmol). The solution was subjected to microwave heating at 80 °C for 3–5 min. Then, MnO_2 (0.5 mmol) was added, and the reaction was stirred for 5 min. MnO_2 was filtered off and washed with ethanol (5 mL). The combined filtrate was concentrated *in vacuo*. Flash column chromatography on silica gel afforded the product.

[(E)-2-(5-Benzothiazole-2-yl-1-phenyl-1H-benzoimidazole-2-yl)ethenyl]isopropylphenylamine (**19**): Yellow solid; mp 172–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (d, 6H, J = 6.7 Hz), 3. 84–3. 98 (m, 1H), 4.84 (d, 1H, J = 13.3 Hz), 7.08 (d, 1H, J = 8.4 Hz), 7.13 (d, 2H, J = 7.8 Hz), 7.21 (dd, 1H, J_1 = J_2 = 7.2 Hz), 7.27–7.52 (m, 9H), 7.86 (d, 1H, J = 7.9 Hz), 7.93 (d, 1H, J = 8.4 Hz), 8.00–8.10 (m, 2H), 8.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 54.7, 84.2, 109.3, 117.0, 120.5, 121.5, 122.9, 124.6, 126.1, 126.9, 127.3, 128.0, 128.1, 128.5, 129.3, 129.7, 135.1, 135.9, 138.7, 142.5, 144.1, 145.0, 154.5, 156.6, 169.6; IR (neat, cm^{-1}): ν_{max} 3651, 1619, 1586, 1502, 1460, 1412, 1071, 869, 754; HRMS (ESI+): m/z calcd. for $C_{31}H_{26}N_4S$ $[M+H]^+$: 487.1878; found: 487.1869.

[(E)-2-(5-Benzothiazole-2-yl-1-phenyl-1H-benzoimidazole-2-yl)ethenyl]methylbenzylamine (**20**): Yellow solid; mp 72–74 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.72 (s, 3H), 4.36 (s, 2H), 4.84 (d, 1H, J = 13.0 Hz), 7.08 (d, 1H, J = 8.4 Hz), 7.20 (d, 2H, J = 7.2 Hz), 7.27–7.36 (m, 4H), 7.38–7.51 (m, 4H), 7.52–7. 63 (m, 2H), 7.87 (d, 1H, J = 7.9 Hz), 7.94 (d, 1H, J = 8.2 Hz), 8.05 (d, 2H, J = 10.6 Hz), 8.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.7, 59.5, 81.7, 109.3, 116.9, 120.5, 121.5, 122.9, 124.7, 126.1, 127.5, 127.6, 127.8, 128.2, 128.7, 128.8, 129.9, 135.2, 136.1, 136.9, 139.9, 144.1, 147.7, 154.5, 156.7, 169.7; IR (neat, cm^{-1}): 3674, 1626, 1595, 1497, 1466, 1276, 1052, 895, 755; HRMS (ESI+): m/z calcd. for $C_{34}H_{24}N_4S$ $[M+H]^+$: 473.1722; found: 473.1716.

[(E)-2-(5-Benzothiazole-2-yl-1-phenyl-1H-benzoimidazole-2-yl)ethenyl]ethylcyclohexylamine (**21**): Yellow solid; mp 132–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98–1.16 (m, 3H), 1.18–1.36 (m, 3H), 1.37–1.52 (m, 2H), 1.58–1.70 (m, 1H), 1.82 (d, 4H, J = 10.8 Hz), 3.03–3.31 (m, 3H), 4.74 (d, 1H, J = 13.1 Hz), 7.05 (d, 1H, J = 8.3 Hz), 7.31 (dd, 1H, J_1 = J_2 = 7.6 Hz), 7.39–7.50 (m, 4H), 7.56 (dd, 2H, J_1 = J_2 = 7.6 Hz), 7.84 (d, 1H, J = 3.4 Hz), 7.87 (s, 1H), 7.90 (d, 1H, J = 8.4 Hz), 8.03 (d, 1H, J = 8.2 Hz), 8.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.3, 25.4, 26.0, 32.4, 41.2, 64.1, 79.8, 109.0, 116.5, 120.1, 121.5, 122.8, 124.6, 126.0, 127.6, 128.0, 128.5, 129.8, 135.1, 136.3, 138.9, 144.3, 144.7, 154.5, 157.6, 169.8; IR (neat, cm^{-1}): 3674, 1622, 1497, 1460, 1395, 1275, 1218, 1067, 809, 754; HRMS (ESI+): m/z calcd. for $C_{30}H_{30}N_4S$ $[M+H]^+$: 479.2191; found: 479.2184.

4-[(E)-2-(5-Benzothiazol-2-yl-1-phenyl-1H-benzoimidazol-2-yl)ethenyl]morpholine (**22**): Yellow solid; mp 172–174 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.12–3.24 (m, 4H), 3.71 (t, 4H, J = 4.6 Hz), 4.95 (d, 1H, J = 13.3 Hz), 7.10 (d, 1H, J = 8.4 Hz), 7.34 (dd, 1H, J_1 = J_2 = 7.7 Hz), 7.39–7.49 (m, 3H), 7.52 (dd, 1H, J_1 = J_2 = 7.2 Hz), 7.60 (dd, 2H, J_1 = J_2 = 7.2 Hz), 7.73 (d, 1H, J = 13.3 Hz), 7.88 (d, 1H, J = 7.9 Hz), 7.95 (d, 1H, J = 8.3 Hz), 8.05 (d, 1H, J = 8.0 Hz), 8.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.6, 66.3, 83.3, 109.5, 117.2, 120.9, 121.6, 123.0, 124.8, 126.2, 127.7, 128.5, 128.9, 130.1, 135.3, 136.0, 138.9, 144.0, 147.0, 154.6, 156.1, 169.5; IR (neat, cm^{-1}): 3674, 1624, 1498, 1443, 1392, 1081, 890, 759; HRMS (ESI+): m/z calcd. for $C_{26}H_{22}N_4OS$ $[M+H]^+$: 439.1514; found: 439.1506.

4-Methyl-[(E)-2-(5-benzothiazol-2-yl-1-phenyl-1H-benzoimidazol-2-yl)ethenyl]piperazine (**23**): Yellow solid; mp 180–182 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 2.40 (t, 4H, J = 4.7 Hz), 3.19 (t, 4H, J = 4.6 Hz), 4.89 (d, 1H, J = 13.2 Hz), 7.07 (d, 1H, J = 8.4 Hz), 7.33 (dd, 1H, J_1 = J_2 = 7.7 Hz), 7.37–7.47 (m, 3H), 7.50 (dd, 1H, J_1 = J_2 = 7.2 Hz), 7.58 (dd, 2H, J_1 = J_2 = 7.4 Hz), 7.74 (d, 1H, J = 13.2 Hz), 7.87 (d, 1H, J = 7.9 Hz), 7.93 (d, 1H, J = 8.4 Hz), 8.03 (d, 1H, J = 8.1 Hz), 8.24 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.3, 48.3, 54.4, 82.3, 109.4, 117.0, 120.6, 121.5, 122.9, 124.7, 126.1, 127.6, 128.2, 128.8, 130.0, 135.2, 136.0, 138.8, 144.0, 146.8, 154.5, 156.5, 169.6; IR (neat, cm^{-1}): 3680, 1623, 1495, 1408, 1380, 1240, 1056, 899, 751; HRMS (ESI+): m/z calcd. for $C_{27}H_{25}N_5S$ $[M+H]^+$: 452.1831; found: 452.1841.

4-[(E)-2-Phenyl-1H-benzoimidazole-2-yl)ethenyl]morpholine (**24**): Yellow solid; mp 64–66 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.11 (t, 4H, J = 4.8 Hz), 3.68 (t, 4H, J = 4.8 Hz), 4.97 (d, 1H, J = 13.4 Hz), 7.00–7.09 (m, 2H), 7.19 (dd, 1H, J_1 = J_2 = 7.6 Hz), 7.39 (d, 2H, J = 7.2 Hz), 7.48 (dd, 1H, J_1 = J_2 = 7.3 Hz), 7.56 (dd, 2H, J_1 = J_2 = 7.2 Hz), 7.63 (d, 1H, J = 7.6 Hz), 7.66 (d, 1H, J = 13.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.5, 66.3, 84.0, 109.2, 117.5, 121.0, 122.4, 127.7, 128.5, 129.8, 136.4, 136.6, 143.6, 146.3, 154.3; IR (neat, cm^{-1}): 3406, 1624, 1585, 1459, 1381, 1254, 1027, 956, 767; HRMS (ESI+): m/z calcd. for $C_{19}H_{19}N_3S$ $[M+H]^+$: 306.1528; found: 306.1519.

{(E)-2-[5-Benzothiazole-2-yl-1-(4-methoxyphenyl)-1H-benzoimidazole-2-yl]ethenyl}methylbenzylamine (**25**): Yellow solid; mp 76–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.71 (s, 3H), 3.88 (s, 3H), 4.36 (s, 2H), 4.80 (d, 1H, J = 13.0 Hz), 7.04 (d, 3H, J = 8.3 Hz), 7.20 (d, 2H, J = 7.6 Hz), 7.27–7.36 (m, 6H), 7.45 (dd, 1H, J_1 = J_2 = 7.3 Hz), 7.87 (d, 1H, J = 7.9 Hz), 7.94 (d, 1H, J = 8.3 Hz), 8.02 (d, 1H, J = 8.0 Hz), 8.04–8.06 (m, 1H), 8.25 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.8, 36.6, 55.7, 59.5, 81.8, 109.2, 115.1, 116.8, 120.4, 121.5, 122.9, 124.6, 126.1, 127.5, 127.8, 128.0, 128.6, 128.8, 135.2, 136.9, 139.3, 144.1, 147.5, 154.5, 157.1, 159.6, 169.8; IR (neat, cm^{-1}): 3046, 1631, 1514, 1467, 1278, 1027, 839, 760; HRMS (ESI+): m/z calcd. for $C_{31}H_{26}N_4OS$ $[M+H]^+$: 503.1827; found: 503.1819.

3. Results and discussion

To explore the scope of the reaction, a series of *N*-arylated and *N*,*N*-dialkylated 3-aminoacroleins **1**–**6** were synthesized *via* a modified procedure described in Scheme 1 [13]. Treatment of 1.0 equiv. of propargyl alcohol with 0.5 equiv. of amino compounds in the presence of 10 equiv. of activated MnO_2 afforded **1**–**6** in 53%–75% yields. Compared to the δ_H values of the aldehyde protons of benzaldehyde (10.02), *n*-hexyl aldehyde (9.66), and cinnamaldehyde (9.74), the δ_H value of 3-(*N*-phenyl-*N*-methyl)aminoacrolein (**1**) was much smaller (9.27), indicating that the electropositivity of the carbonyl group was remarkably lowered due to the conjugation of electron-donating aniline moiety. This result explained why the conventional condensation methods for regular aldehyde

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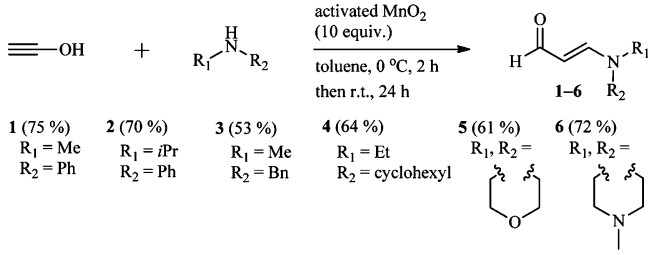


Scheme 1. A general method for the synthesis of *N*-arylated and *N*,*N*-dialkylated 3-aminoacroleins **1**–**6**.

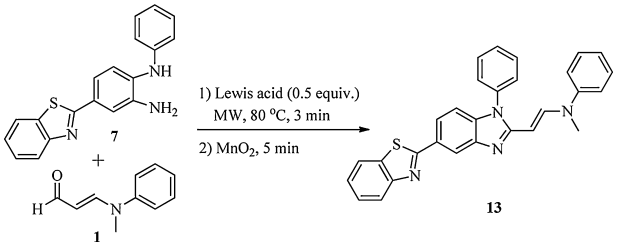
substrates were not applicable on **1**. The aldehyde proton peaks of *N*,*N*-dialkyl 3-aminoacroleins **3–6** moved toward higher magnetic field (8.92–8.74), suggesting that *N*,*N*-dialkylated 3-aminoacroleins might be less reactive toward nucleophiles because of the higher electron-donating capability of the dialkylamino moiety.

Compared to thermal heating, microwave irradiation has showed positive effects on both reaction time and yield in precedent synthesis of benzimidazoles [7,14]. In our research, we explored the possibility to improve the synthetic efficacy of 2-aminovinyl benzimidazoles under microwave conditions. In the preliminary experiments, the ethanol solution of **1** (1.2 equiv.) and 4-benzothiazol-2-yl-N^1-phenylbenzene-1,2-diamine (**7**, 1.0 equiv.) with different Lewis acids (0.5 equiv.) was irradiated with microwave at 80 °C for 3 min. To the reaction solution was then added activated MnO_2 (5.0 equiv.) to generate the 2-aminovinyl benzimidazole **13**. The experimental results listed in Table 1 (entries 1–16) showed that most tested Lewis acids resulted in no reaction or only gave **13** in poor yields. In contrast, all of the zirconium(IV) salts exhibited comparable catalytic effect on the formation of **13**. Compared to the previously reported $ZrCl_4$ and $ZrOCl_2{\cdot}8H_2O$, Cp_2ZrCl_2-catalyzed reaction afforded **13** in even higher yield (78%). The solvent effect on this reaction was also investigated. The data in Table 1 (entries 16–22) showed that the catalytic effect of Cp_2ZrCl_2 was specific in ethanol and not simply related the dielectric constants and polarity of the solvents, suggesting that Zr(IV) salts might go through a solvolysis process and ethanol was possibly involved in reactive metal complex that promoted the condensation of **1** and **7**. It was also confirmed that a minimum of 0.5 equiv. of Cp_2ZrCl_2 was required for complete consumption of **7**.

As shown in Scheme 2, the reactions of a variety of 1,2-phenylenediamines **7**–**12** and *N*-arylated 3-aminoacroleins **1** and **2** with Cp_2ZrCl_2 as the catalyst under microwave conditions followed by MnO_2 oxidation yielded the corresponding 2-aminovinyl benzimidazoles **14**–**19** in 70%–76% yields. In contrast, when *N*,*N*-dialkylated 3-aminoacroleins **3**–**6** were applied, a higher equivalent of 3-aminoacroleins (1.5 equiv.) and longer microwave irradiation time (5 min) were required to afford **20**–**25** in good yields (68%–76%). These results were in agreement with our speculation that *N*,*N*-dialkylated 3-aminoacroleins were less reactive than their *N*-arylated counterparts. Moreover, control experiments based on thermal heating were also performed. The reaction of **7** and *N*-arylated 3-aminoacrolein **1** in refluxing ethanol needed 30 min for the first step, whereas that of **7** and *N*,*N*-dialkylated 3-aminoacrolein **5** required 2 h. Compared to thermal heating, microwave irradiation also improved the yields of **13** (72% for thermal heating and 78% for MW) and **22** (60% for thermal heating and 70% for MW).

TLC monitoring of the first step reaction of **1** and **7** showed that the major product spot was an orange-colored polar band, which was unstable to isolate. After MnO_2 oxidation, it was completely converted to the less polar spot of **13**. Due to the fact that benzimidazoline intermediate is typically less polar than the corresponding benzimidazole, we proposed that the condensation of **1** and **7** favored the formation of imine instead of the cyclized

Table 1
Effects of Lewis acid and solvent on the synthesis of 2-aminovinyl benzimidazole **13**.



Entry	Lewis acid	Solvent	Isolated yield (%)
1	None	EtOH	n.r.
2	$ZnCl_2$	EtOH	n.r.
3	$CuCl_2$	EtOH	n.r.
4	$MgCl_2$	EtOH	n.r.
5	$NiCl_2$	EtOH	n.r.
6	$InCl_3$	EtOH	n.r.
7	$CeCl_3$	EtOH	5
8	$AlCl_3$	EtOH	13
9	$FeCl_3$	EtOH	28
10	$TiCl_4$	EtOH	15
11	$Et_2O{\cdot}BF_3$	EtOH	18
12	$ZrO(NO_3)_2$	EtOH	54
13	$Zr(NO_3)_4$	EtOH	62
14	$ZrOCl_2{\cdot}8H_2O$	EtOH	67
15	$ZrCl_4$	EtOH	72
16	Cp_2ZrCl_2	EtOH	78
17	Cp_2ZrCl_2	CH_2Cl_2	n.r.
18	Cp_2ZrCl_2	THF	n.r.
19	Cp_2ZrCl_2	CH_3CN	n.r.
20	Cp_2ZrCl_2	Toluene	n.r.
21	Cp_2ZrCl_2	DMF	n.r.
22	Cp_2ZrCl_2	DMSO	n.r.

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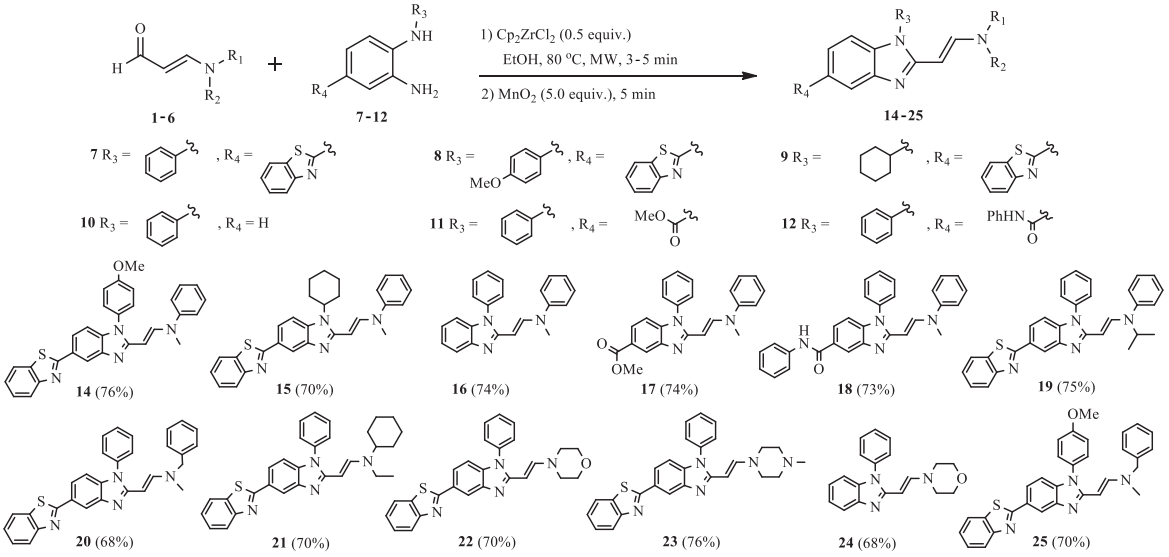

Scheme 2. Microwave-assisted synthesis of 2-aminovinyl benzimidazoles **14**–**25** with Cp_2ZrCl_2 as the catalyst.

benzimidazoline intermediate in the presence of Cp_2ZrCl_2. Only after oxidant was added to transform the benzimidazoline intermediate to **13**, the cyclization reaction was driven to completion.

4. Conclusion

In summary, we developed a general method for the synthesis of a variety of 2-aminovinyl benzimidazole compounds. Our experimental results showed that Cp_2ZrCl_2 exhibited the best catalytic effect on the condensation of 1,2-phenylenediamine and 3-aminoacrolein substrates under microwave conditions. This novel synthetic method provides facile and efficient access to diverse 2-aminovinyl benzimidazoles and will facilitate the investigation of their applications in pharmaceutical and material sciences.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2014.11.014.

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