Copper-Catalyzed Cyanation of Heterocycle C-H Bonds with Ethyl (ethoxymethylene)cyanoacetate as a Cyanating Agent and its Mechanism

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1. General information

All compounds are characterized by $^1$H NMR, $^{13}$C NMR and MS. Analytical thin-layer chromatography is performed on glass plates precoated with silica gel impregnated with a fluorescent indicator (254 nm), and the plates are visualized by exposure to ultraviolet light. $^1$H NMR and $^{13}$C NMR spectra are recorded on an AVANCE 500 Bruker spectrometer operating at 500 MHz and 125 MHz in CDCl$_3$, respectively, and chemical shifts are reported in ppm. GC analyses are performed on an Agilent 7890A instrument (Column: Agilent 19091J-413:30 m × 320 µm × 0.25 µm, H, FID detection). GC-MS data was recorded on a 5975C Mass Selective Detector, coupled with a 7890A Gas Chromatograph (Agilent Technologies).

2. General procedure

**General procedure for the synthesis of cyanating product:** To a mixture of benzothiazoles (0.5 mmol) 1a, Cu(OAc)$_2$ (1.0 equiv.), DTBP (3.5 equiv.) and solvent (DMF =2.0 ml) in a reaction tube was then added additive KI (0.1 equiv.). The reaction mixture was stirred at 135°C for 24h in air. The reaction mixture was extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the desired products 3.
3. Characterization data

**benzo[d]thiazole-2-carbonitrile (3a):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give 3a as white solid (57.6mg, 72%). $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 8.28 – 8.22 (m, 1H), 8.04 – 7.96 (m, 1H), 7.66 (pd, $J$ = 7.2, 1.5 Hz, 2H). $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 151.3, 135.6, 134.4, 127.7, 127.0, 124.4, 120.8, 112.0. GC-MS (EI) $m/z$: 160.

**6-chlorobenzo[d]thiazole-2-carbonitrile (3b):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give 3b as white solid (55.3mg, 57%). $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 8.24 (d, $J$ = 1.9 Hz, 1H), 7.93 (d, $J$ = 8.7 Hz, 1H), 7.63 (dd, $J$ = 8.7, 2.0 Hz, 1H). $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 152.1, 137.3, 133.5, 131.5, 128.4, 124.0, 121.6, 111.6. GC-MS (EI) $m/z$: 194.

**6-bromobenzo[d]thiazole-2-carbonitrile (3c):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give 3c as white solid (63.1mg, 53%). $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 8.16 (d, $J$ = 1.8 Hz, 1H), 8.10 (d, $J$ = 8.8 Hz, 1H), 7.78 (dd, $J$ = 8.8, 1.9 Hz, 1H). $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 150.1, 135.8, 130.8, 126.0, 125.3, 123.4, 122.1, 111.6. GC-MS (EI) $m/z$: 238.

**5-methoxybenzo[d]thiazole-2-carbonitrile (3d):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give 3d as white solid (64.6mg, 68%). $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.82 (d, $J$ = 9.0 Hz, 1H), 7.63 (d, $J$ = 2.4 Hz, 1H), 7.28 (dd, $J$ = 9.0, 2.5 Hz, 1H), 3.93 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 159.3, 152.9, 126.5, 120.9, 119.1, 113.1, 112.1, 105.2, 54.8. GC-MS (EI) $m/z$: 190.

**5-chlorobenzo[d]thiazole-2-carbonitrile (3e):** The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give 3e as white solid (66.0mg, 68%). $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 8.23 (d, $J$ = 1.8 Hz, 1H), 7.92 (d, $J$ = 8.7 Hz, 1H), 7.62 (dd, $J$ = 8.7, 1.9 Hz, 1H). $^{13}$C NMR (126 MHz,
5-bromobenzo[d]thiazole-2-carbonitrile (3f): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give 3f as white solid (66.6mg, 56%). $^1$H NMR (500 MHz, Chloroform-$d$) δ 8.15 (d, $J = 1.8$ Hz, 1H), 8.08 (d, $J = 8.8$ Hz, 1H), 7.76 (dd, $J = 8.8$, 1.8 Hz, 1H). $^{13}$C NMR (126 MHz, Chloroform-$d$) δ 150.1, 135.9, 135.8, 130.8, 125.3, 123.4, 122.1, 111.6. GC-MS (EI) $m/z$: 238.

benzo[d]oxazole-2-carbonitrile (3g): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give 3g as white solid (28.1mg, 39%). $^1$H NMR (500 MHz, Chloroform-$d$) δ 7.91 (d, $J = 8.1$ Hz, 1H), 7.68 (d, $J = 8.3$ Hz, 1H), 7.62 (t, $J = 7.8$ Hz, 1H), 7.54 (t, $J = 7.7$ Hz, 1H). $^{13}$C NMR (126 MHz, Chloroform-$d$) δ 149.5, 136.3, 128.1, 125.6, 110.6. GC-MS (EI) $m/z$: 144.

1H-indole-3-carbonitrile (4a): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give 4a as white solid (44.7mg, 63%). $^1$H NMR (500 MHz, Chloroform-$d$) δ 8.79 (s, 1H), 7.84 (d, $J = 7.8$ Hz, 1H), 7.79 (d, $J = 3.0$ Hz, 1H), 7.53 (d, $J = 7.7$ Hz, 1H), 7.43 – 7.34 (m, 2H). 13C NMR (126 MHz, Chloroform-$d$) δ 133.9, 130.8, 126.0, 123.4, 121.5, 118.8, 114.8, 111.0, 86.7. GC-MS (EI) $m/z$: 142.

1-methyl-1H-indole-3-carbonitrile (4b): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give 4b as white solid (53.0mg, 68%). $^1$H NMR (500 MHz, Chloroform-$d$) δ 7.80 (d, $J = 8.0$ Hz, 1H), 7.58 (d, $J = 1.6$ Hz, 1H), 7.47 – 7.32 (m, 3H), 3.89 (d, $J = 1.6$ Hz, 3H). $^{13}$C NMR (126 MHz, Chloroform-$d$) δ 135.0, 134.6, 126.8, 122.9, 121.2, 118.8, 115.0, 109.4, 84.5, 32.7. GC-MS (EI) $m/z$: 156.
2-methyl-1H-indole-3-carbonitrile (4c): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give 4c as white solid (47.6mg, 61%). $^1$H NMR (500 MHz, Chloroform-\(d\)) $\delta$ 8.42 (s, 1H), 7.69 – 7.63 (m, 1H), 7.39 – 7.33 (m, 1H), 7.25 (dd, $J$ = 5.8, 2.5 Hz, 2H), 2.64 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-\(d\)) $\delta$ 143.4, 133.6, 126.7, 122.5, 121.1, 118.1, 115.2, 110.2, 85.1, 12.1. GC-MS (EI) m/z: 156.

6-methoxy-1H-indole-3-carbonitrile (4d): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give 4d as white solid (49.9mg, 58%). $^1$H NMR (500 MHz, Chloroform-\(d\)) $\delta$ 8.64 (s, 1H), 7.73 (d, $J$ = 3.1 Hz, 1H), 7.40 (d, $J$ = 8.9 Hz, 1H), 7.24 (d, $J$ = 2.4 Hz, 1H), 7.03 (dd, $J$ = 8.9, 2.4 Hz, 1H), 3.94 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-\(d\)) $\delta$ 155.1, 130.7, 128.6, 126.9, 115.0, 114.3, 111.9, 99.7, 86.5, 54.8. GC-MS (EI) m/z: 172.

6-chloro-1H-indole-3-carbonitrile (4e): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give 4e as white solid (44.9mg, 51%). $^1$H NMR (500 MHz, Chloroform-\(d\)) $\delta$ 8.74 (s, 1H), 7.81 – 7.71 (m, 2H), 7.53 (d, $J$ = 1.7 Hz, 1H), 7.34 (dd, $J$ = 8.6, 1.8 Hz, 1H). $^{13}$C NMR (126 MHz, Chloroform-\(d\)) $\delta$ 134.2, 131.3, 129.6, 115.1, 114.7, 119.7, 114.1, 113.4, 111.1, 87.3. GC-MS (EI) m/z: 176.

picolinonitrile (5a): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give 5a as white solid (36.9mg, 71%). $^1$H NMR (500 MHz, Chloroform-\(d\)) $\delta$ 8.69 (d, $J$ = 4.6 Hz, 1H), 7.90 – 7.84 (m, 1H), 7.70 (d, $J$ = 7.8 Hz, 1H), 7.57 – 7.52 (m, 1H). $^{13}$C NMR (126 MHz, Chloroform-\(d\)) $\delta$ 150.1, 136.3, 132.8, 127.6, 126.2, 116.3. GC-MS (EI) m/z: 104.

3-fluoropicolinonitrile (5b): The crude product was purified by column
chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give 5b as white solid (42.1mg, 69%). $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 8.56 (dd, $J$ = 4.1, 1.8 Hz, 1H), 7.73 – 7.49 (m, 2H). $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 161.4, 159.2, 146.1, 127.8, 123.7, 122.0, 112.0. GC-MS (EI) m/z: 122.

3-chloropicolinonitrile (5c): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give 5c as white solid (46.2mg, 67%). $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 8.62 (dd, $J$ = 4.7, 1.4 Hz, 1H), 7.89 (dd, $J$ = 8.3, 1.4 Hz, 1H), 7.52 (dd, $J$ = 8.4, 4.6 Hz, 1H). $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 147.8, 136.6, 135.0, 132.3, 126.6, 113.7. GC-MS (EI) m/z: 138.

3-bromopicolinonitrile (5d): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give 5d as white solid (57.3mg, 63%). $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 8.66 (dd, $J$ = 4.6, 1.4 Hz, 1H), 8.04 (dd, $J$ = 8.3, 1.4 Hz, 1H), 7.43 (dd, $J$ = 8.3, 4.6 Hz, 1H). $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 148.1, 139.7, 134.3, 126.7, 123.6, 114.7. GC-MS (EI) m/z: 182.

6-methylpicolinonitrile (5e): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give 5e as white solid (36.6mg, 62%). $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 7.73 (t, $J$ = 7.8 Hz, 1H), 7.53 (d, $J$ = 7.6 Hz, 1H), 7.40 (d, $J$ = 7.9 Hz, 1H), 2.62 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 159.7, 136.1, 132.2, 125.9, 124.7, 116.4, 23.4. GC-MS (EI) m/z: 118.

6-methylpicolinonitrile (5f): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give 5f as white solid (40.1mg, 68%). $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 8.55 (d, $J$ = 5.0 Hz, 1H), 7.52 (s, 1H), 7.33 (d, $J$ = 5.0 Hz, 1H), 2.43 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 149.8, 147.8, 132.8, 128.4, 126.9, 116.4, 19.9. GC-MS (EI) m/z: 118.
quinoline-2-carbonitrile (5g): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give 5g as white solid (51.6mg, 67%). $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 8.32 (d, $J$ = 8.4 Hz, 1H), 8.19 (d, $J$ = 8.2 Hz, 1H), 7.91 (d, $J$ = 8.2 Hz, 1H), 7.86 (ddd, $J$ = 8.5, 6.9, 1.5 Hz, 1H), 7.75 – 7.69 (m, 2H). $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 147.3, 136.5, 132.7, 130.3, 129.1, 128.5, 127.7, 126.8, 122.4, 116.6. GC-MS (EI) $m/z$: 154.
4. NMR spectra