The Scope of Ru(II)-Catalyzed Synthesis of Pyridines from Alkynes and Nitriles

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I. General

Dry DMF (Fluka) was used as received. All other solvents and reagents were used as received, unless otherwise noted. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring, unless otherwise indicated.

II. Preparation of starting materials and catalysts

2,2-Diprop-2-ynyl malonic acid dimethyl ester (**2a**) was prepared following published procedures.¹ Catalysts $[\text{CpRu}(\text{CH}_3\text{CN})_3]\text{PF}_6$ and $[\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3]\text{PF}_6$ were also prepared following published procedures.^{2,3}

III. General procedures for the Ru-catalyzed [2+2+2] cycloadditions:

3-Cyanomethyl-5,7-dihydro-[2]pyridine-6,6-dicarboxylic acid dimethyl ester (4r). In a 25 mL round-bottomed flask was prepared, under argon, a solution of $[\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3]\text{PF}_6$ (25 mg, 10%) and Et_4NCl (8 mg, 10%) in DMF (3 mL). After stirring for 10 minutes at room temperature the two partners were successively added, the nitrile **3r** (66 mg, 1 mmol, 2eq.) and then, after 10 minutes, the diyne **2a** (104 mg, 0.5 mmol, 1 eq.). Stirring was continued for another 10 min and the reaction was quenched with saturated aqueous solution of NH_4Cl (10 mL) and extracted with ethyl ether (3 x 10 mL). The organic layers were collected, dried over anhydrous Na_2SO_4 and evaporated under vacuum. Column chromatography of the residue on silica gel using ethyl acetate/hexane (1:1) as eluents afforded pyridine **4r** in 84% yield. Similar results were obtained when using lower or higher concentration of starting materials.

Pyridine-2,3,6-tricarboxylic acid trimethyl ester (13ax). In a 25 mL round-bottomed flask was prepared, under argon, a solution of $[\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3]\text{PF}_6$ (25 mg, 5%) and Et_4NCl (8 mg, 5%) in DMF (3 mL). After stirring for 10 minutes at room temperature the two partners were successively added, the nitrile **3x** (85 mg, 0.08 mL, 1 mmol, 1 eq.) and then, after 10 minutes, the alkyne **11a** (84 mg, 0.09 mL, 1 mmol, 1 eq.). Stirring was continued for 12 h and the reaction was quenched with saturated aqueous solution of NH_4Cl (10 mL) and extracted with ethyl ether (3 x 10 mL). The organic layers were collected, dried over anhydrous Na_2SO_4 and evaporated under vacuum. Column chromatography of the residue on silica gel using ethyl acetate/hexane (4:6) as eluents afforded pyridine **13ax** in 82% yield.

3,6-Bis(trifluoromethyl)pyridine-2-carboxylic acid methyl ester (13bx): In a 25 mL round-bottomed flask was prepared, under argon, a solution of $[\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3]\text{PF}_6$ (25 mg, 5%) and Et_4NCl (8 mg, 5%) in DMF (3 mL). After stirring for 10 minutes at room temperature the two partners were successively added, the nitrile **3x** (85 mg, 0.08 mL, 1 mmol, 1 eq.) and then, after 10 minutes, excess alkyne **11b** was bubbled into the solution. Stirring was continued for 12 h and the reaction was quenched with saturated aqueous solution of NH_4Cl (10 mL) and extracted with ethyl ether (3 x 10 mL). The organic layers were collected, dried over anhydrous Na_2SO_4 and evaporated under vacuum to afford **13bx** in 20% yield.

3-Ethylsulfanyl-5,7-dihydro-[2]pyridine-6,6-dicarboxylic acid dimethyl ester (4e)

¹H-NMR (250 MHz, CDCl_3) δ (ppm): 8.23 (s, 1H), 7.01 (s, 1H), 3.72 (s, 6H), 3.52 (s, 2H), 3.49 (s, 2H), 3.10 (c, $J=7.3$ Hz, 2H), 1.32 (t, $J=7.3$ Hz, 3H). ¹³C-NMR, DEPT (63 MHz, CDCl_3) δ (ppm): 171.3 (2 x C), 157.4 (C), 149.9 (C), 144.8 (CH), 132.1 (C), 117.6 (CH), 60.1 (C), 53.1 (2 x CH_3), 39.9 (CH_2), 37.6 (CH_2), 24.6 (CH_2), 14.5 (CH_3). MS, m/z (% relative intensity) 296 ($\text{M}^+ + 1$, 100), 264 (23), 236 (22). HRMS: calcd. for $\text{C}_{14}\text{H}_{18}\text{NO}_4\text{S}$: 296.095655; found: 296.096117; calcd. for $\text{C}_{14}\text{H}_{17}\text{NO}_4\text{S}$: 295.087830; found: 295.088507.

3-Chloromethyl-5,7-dihydro-[2]pyridine-6,6-dicarboxylic acid dimethyl ester (4i)

¹H-NMR (250 MHz, CDCl₃) δ (ppm): 8.35 (s, 1H), 7.29 (s, 1H), 4.58 (s, 2H), 3.70 (s, 6H), 3.57 (s, 2H), 3.56 (s, 2H). ¹³C-NMR, DEPT (63 MHz, CDCl₃) δ (ppm): 171.1 (2 x C), 154.9 (C), 150.7 (C), 144.9 (CH), 135.6 (C), 118.7 (CH), 60.0 (C), 53.1 (2 x CH₃), 46.6 (CH₂), 40.1 (CH₂), 37.9 (CH₂). MS, m/z (% relative intensity) 286 (M⁺ + 3, 24), 284 (M⁺ + 1, 98), 248 (100). HRMS: calcd. for C₁₃H₁₅NO₄³⁷Cl: 286.066011; found: 286.066188; calcd. for C₁₃H₁₅NO₄³⁵Cl: 284.068961; found: 284.068930; calcd. for C₁₃H₁₄NO₄³⁵Cl: 283.061136; found: 283.061284.

3-Cyanomethyl-5,7-dihydro-[2]pyridine-6,6-dicarboxylic acid dimethyl ester (4r)

¹H-NMR (250 MHz, CDCl₃) δ (ppm): 8.31 (s, 1H), 7.22 (s, 1H), 3.82 (s, 2H), 3.68 (s, 6H), 3.53 (s, 2H), 3.52 (s, 2H). ¹³C-NMR, DEPT (63 MHz, CDCl₃) δ (ppm): 170.9 (2 x C), 151.1 (C), 148.6 (C), 145.2 (CH), 135.5 (C), 118.1 (CH), 117.0 (C), 59.8 (C), 53.0 (2 x CH₃), 39.9 (CH₂), 37.6 (CH₂), 26.0 (CH₂). MS, m/z (% relative intensity) 275 (M⁺ + 1, 100), 243 (13), 215 (11). HRMS: calcd. for C₁₄H₁₅N₂O₄: 275.103182; found: 275.102322; calcd. for C₁₄H₁₄N₂O₄: 274.095357; found: 274.095857.

3-(Cyanodimethylmethyl)-5,7-dihydro-[2]pyridine-6,6-dicarboxylic acid dimethyl ester (4r')

¹H-NMR (250 MHz, CDCl₃) δ (ppm): 8.41 (s, 1H), 7.40 (s, 1H), 3.70 (s, 6H), 3.55 (s, 4H), 1.67 (s, 6H). ¹³C-NMR, DEPT (63 MHz, CDCl₃) δ (ppm): 171.1 (2 x C), 157.9 (C), 150.8 (C), 144.9 (C), 135.1 (C), 124.2 (C), 115.6 (CH), 59.9 (C), 53.0 (2 x CH₃), 40.1 (CH₂), 39.2 (C), 37.8 (CH₂), 27.7 (2 x CH₃). MS, m/z (% relative intensity) 303 (M⁺ + 1, 100), 276 (76), 243 (42). HRMS: calcd. for C₁₆H₁₉N₂O₄: 303.134482; found: 303.133521.

3-(2-Cyanovinyl)-5,7-dihydro-[2]pyridine-6,6-dicarboxylic acid dimethyl ester (4s)

¹H-NMR (250 MHz, CDCl₃) δ (ppm): 8.43 (s, 1H), 7.32 (d, J=16.1 Hz, 1H), 7.17 (s, 1H), 6.48 (d, J=16.1 Hz, 1H), 3.74 (s, 6H), 3.62 (s, 2H), 3.58 (s, 2H). ¹³C-NMR, DEPT (63 MHz, CDCl₃) δ (ppm): 171 (2 x C), 150.6 (C), 149.9 (C), 148.7 (CH), 146.0 (CH), 138.1 (C), 120.1 (CH), 118.0 (C), 100.1 (CH), 59.9 (C), 53.2 (2 x CH₃), 40.0 (CH₂), 38.2 (CH₂). MS, m/z (% relative intensity) 287 (M⁺ + 1, 100). HRMS: calcd. for C₁₅H₁₅N₂O₄: 287.103182; found: 287.103357; calcd. for C₁₅H₁₄N₂O₄: 286.095357; found: 286.094273.

3-(2-Cyanophenyl)-5,7-dihydro-[2]pyridine-6,6-dicarboxylic acid dimethyl ester (4t)

¹H-NMR (250 MHz, CDCl₃) δ (ppm): 8.58 (s, 1H), 7.76 (d, J=7.6 Hz, 2H), 7.64 (t, J=7.6 Hz, 1H), 7.59 (s, 1H), 7.46 (t, J=7.6 Hz, 1H), 3.76 (s, 6H), 3.68 (s, 4H). ¹³C-NMR, DEPT (63 MHz, CDCl₃) δ (ppm): 171.2 (2 x C), 153.8 (C), 150.5 (C), 145.4 (CH), 143.4 (C), 136.0 (C), 134.0 (CH), 133.4 (CH), 133.0 (CH), 132.6 (CH), 118.9 (CH), 110.8 (C), 59.9 (C), 53.1 (2 x CH₃), 40.2 (CH₂), 38.0 (CH₂). MS, m/z (% relative intensity) 337 (M⁺ + 1, 100). HRMS: calcd. for C₁₉H₁₇N₂O₄: 337.118832; found: 337.118282.

3-(4-Cyanophenyl)-5,7-dihydro-[2]pyridine-6,6-dicarboxylic acid dimethyl ester (4u)

¹H-NMR (250 MHz, CDCl₃) δ (ppm): 8.53 (s, 1H), 8.03 (d, J=8.4 Hz, 2H), 7.70 (d, J=8.4 Hz, 2H), 7.60 (s, 1H), 3.76 (s, 6H), 3.66 (s, 2H), 3.85 (s, 2H). ¹³C-NMR, DEPT (63 MHz, CDCl₃) δ (ppm): 171.2 (2 x C), 153.9 (C), 150.8 (C), 145.6 (CH), 143.4 (C), 136.0 (C), 132.4 (2 x CH), 127.3 (2 x CH), 118.7 (C), 116.8 (CH), 112.0 (C), 60.0 (C), 53.2 (2 x CH₃), 40.2 (CH₂), 38.0 (CH₂). MS, m/z (% relative intensity) 337 (M⁺ + 1, 100). HRMS: calcd. for C₁₉H₁₇N₂O₄: 337.118832; found: 337.117530.

3-(6-Cyanopyridin-2-yl)-5,7-dihydro-[2]pyridine-6,6-dicarboxylic acid dimethyl ester (4v)

¹H-NMR (250 MHz, CDCl₃) δ (ppm): 8.56 (d, J= 8.3 Hz, 1H), 8.45 (s, 1H), 8.26 (s, 1H), 7.9 (t, J= 8.3 Hz, 1H), 7.65 (d, J= 8.3 Hz, 1H), 3.73 (s, 3H), 3.65 (s, 4H). ¹³C-NMR, DEPT (63 MHz, CDCl₃) δ (ppm): 171.2 (2 x C), 157.5 (C), 152.7 (C), 150.9 (C), 144.8 (CH), 137.7 (CH), 137.5 (C), 132.9

(C), 127.9 (CH), 124.2 (CH), 117.4 (CH), 117.3 (C), 60.0 (C), 53.15 (2 x CH₃), 40.2 (CH₂), 38.12 (CH₂). MS, m/z (% relative intensity) 338 (M⁺ + 1, 100), 306 (6), 278 (6). HRMS: calcd. for C₁₈H₁₆N₃O₄: 338.114081; found: 338.115307.

6-Cyano-1,3,4,5-tetrahydroindene-2,2-dicarboxylic acid dimethyl ester (5)

¹H-NMR (250 MHz, CDCl₃) δ (ppm): 6.60 (s, 1H), 3.74 (s, 6H), 3.09 (s, 4H), 2.46 (t, J= 9.8 Hz, 2H), 2.29 (t, J= 9.8 Hz, 2H). ¹³C-NMR, DEPT (63 MHz, CDCl₃) δ (ppm): 170.9 (2 x C), 139.7 (C), 135.6 (CH), 128.5 (C), 105.6 (C), 57.1 (C), 52.1 (2 x CH₃), 42.5 (CH₂), 39.6 (CH₂), 23.4 (CH₂), 21.7 (CH₂). MS, m/z (% relative intensity) 262 (M⁺ + 1, 100), 202 (17).

Pyridine-2,3,6-tricarboxylic acid trimethyl ester (13ax)

¹H-NMR (250 MHz, CDCl₃) δ (ppm): 8.28 (d, J= 8.1 Hz, 1H), 8.22 (d, J= 8.1 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.89 (s, 3H). ¹³C-NMR, DEPT (63 MHz, CDCl₃) δ (ppm): 165.7 (C), 164.8 (C), 164.1 (C), 150.8 (C), 149.5 (C), 138.9 (CH), 128.6 (C), 125.9 (C), 53.2 (3 x CH₃). MS, m/z (% relative intensity) 254 (M⁺ + 1, 100), 222 (26). HRMS: calcd. for C₁₁H₁₂NO₆: 254.066462; found: 254.065702.

6-(Toluene-4-sulfonyl)pyridine-2,5-dicarboxylic acid dimethyl ester (13ay)

¹H-NMR (250 MHz, CDCl₃) δ (ppm): 8.20 (d, J= 7.5 Hz, 1H), 8.03 (d, J= 7.5 Hz, 1H), 7.96 (d, J= 8.3 Hz, 2H), 7.31 (d, J= 8.3 Hz, 2H), 4.00 (s, 3H), 3.90 (s, 3H), 2.36 (s, 3H). ¹³C-NMR, DEPT (63 MHz, CDCl₃) δ (ppm): 165.7 (C), 163.3 (C), 155.6 (C), 148.6 (C), 145.2 (C), 138.5 (CH), 135.1 (C), 131.3 (C), 129.5 (CH), 129.4 (CH), 127.0 (CH), 53.5 (CH₃), 53.0 (CH₃), 21.5 (CH₃). MS, m/z (% relative intensity) 350 (M⁺ + 1, 100), 318 (11), 196 (16), 125 (43). HRMS: calcd. for C₁₆H₁₆NO₆S: 350.069834; found: 350.070702.

6-Trichloromethylpyridine-2,5-dicarboxylic acid dimethyl ester (13az)

¹H-NMR (250 MHz, CDCl₃) δ (ppm): 8.21 (d, J= 7.9 Hz, 1H), 8.05 (d, J= 7.9 Hz, 1H), 3.99 (s, 3H), 3.94 (s, 3H). ¹³C-NMR, DEPT (63 MHz, CDCl₃) δ (ppm): 166.7 (C), 163.9 (C), 153.9 (C), 147.0 (C), 139.9 (CH), 129.7 (C), 125.7 (CH), 77.1 (C), 53.2 (2 x CH₃). MS, m/z (% relative intensity) 316 (M⁺ + 5, 17), 314 (M⁺ + 3, 52), 312 (M⁺ + 1, 57), 278 (85), 276 (100), 253 (33), 242 (33), 221 (73), 173 (42). HRMS: calcd. for C₁₀H₉Cl₃NO₄: 311.959716; found: 311.959867.

3,6-Bistrifluoromethylpyridine-2-carboxylic acid methyl ester (13bx)

¹H-NMR (250 MHz, CDCl₃) δ (ppm): 8.23 (d, J= 8.3 Hz, 1H), 7.89 (d, J= 8.3 Hz, 1H), 3.98 (s, 3H).

IV. References

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V. Spectra

4e

4e

4i

4r

4r'

4r'

4s

4s

4t

4u

4v

5

13ax

13ay

13ay

13az

13az

13bx