

Synthesis of Heterocyclic 3-Aza-3-ene-1,5-diynes and Structural Characterization of their Thermolysis Products: Evidence for Unexpected Reactive Intermediates.

Asha K. Nadipuram, Wendi M. David, Dalip Kumar, Sean M. Kerwin*

Division of Medicinal Chemistry, College of Pharmacy, The University of Texas at Austin, Austin, TX 78681 USA

Supporting Information

General Information. All reactions were carried out under argon in oven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. THF was distilled from sodium/benzophenone immediately prior to use. CH₂Cl₂, DMF, and MeCN were distilled from CaH₂ immediately prior to use. Et₃N was distilled from CaH₂ and stored over KOH, and 1,4-cyclohexadiene was distilled immediately prior to use. Unless otherwise noted, organic extracts were dried with Na₂SO₄, filtered through a fritted glass funnel, and concentrated with a rotary evaporator (20 – 30 mm Hg). R_f values are reported for analytical thin layer chromatography (TLC) performed on EM Reagent 0.25 mm silica gel 60-F plates with UV light visualization. Flash chromatography was performed with EM Reagent silica gel (230–400 mesh) using the mobile phase indicated. Melting points (open capillary) are uncorrected. Unless otherwise noted, ¹H and ¹³C NMR spectra were determined in CDCl₃ on a spectrometer operating at 300 and 75 MHz, respectively and are reported in ppm using solvent as internal standard (7.24 ppm for ¹H and 77.0 ppm for ¹³C). All mass spectra were obtained by chemical ionization using methane as the ionizing gas.

1-(1,2-Dichloro-vinyl)benzimidazole (1). A solution of 1-*H*-benzimidazole (2.13 g, 18 mmol) in DMF (70 mL) in a 250 mL flask was heated at 60 °C until homogeneous, at which time NaH (20 mmol, 0.5 g) was added. The suspension was stirred with heating for 1.5 h until a clear brownish solution was obtained. The heating was discontinued and trichloroethylene (36 mmol, 3.25 mL) was added. A tannish precipitate formed immediately. The reaction mixture was stirred at room temperature overnight. Solvent was removed in vacuo and after dilution with EtOAc, MeOH and CH₂Cl₂, the solution was filtered to remove a white solid. The filtrate, upon concentration under reduced pressure and Kugelrohr distillation to remove traces of solvent yielded **3** as a yellowish oil (1.0 g, 35%). ¹H NMR δ 6.60 (s, 1H), 7.33–7.38 (m, 2H), 7.41–7.45 (m, 1H), 7.82–7.85 (m, 1H), 8.01 (s, 1H). ¹³C NMR δ 111.60, 115.81, 121.09, 123.96, 124.70, 125.04, 132.35, 142.13, 143.39; MS *m/e* 213, 215 (MH⁺).

1-Ethynylbenzimidazole (2). To 20 mL of THF cooled to –78 °C was added **1** (180 mg, 0.84 mmol). A solution of *n*-BuLi in hexanes (3.4 mmol, 2.81 mL) was added slowly, dropwise over a period of 10 min while keeping the temperature at –70 °C. The reaction mixture was stirred at this temperature for 1 h and then allowed to warm slightly for 5 min before the dropwise addition of 3 mL ice-cold aqueous NH₄Cl/MeOH (3:1). The mixture was stirred while warming to near room temperature and added into 100 mL EtOAc. The two layers were separated and the organic layer was washed with brine (1 × 20 mL) and dried (MgSO₄). The solvent was removed in vacuo and the residue purified by flash chromatography to yield 38 mg (32%) of **2** as a glassy white solid. ¹H NMR δ 3.29 (s, 1H), 7.33–7.44 (m, 2H), 7.57–7.61 (d, 1H, *J* = 8 Hz), 7.78–7.82 (d, 1H, *J* = 8 Hz), 8.09 (s, 1H). ¹³C NMR δ 62.09, 70.18, 110.86, 120.83, 124.10, 124.89, 134.32, 141.74, 143.56; HRMS: exact mass calcd for C₉H₇N₂ (MH⁺) 143.060923, found 143.061251.

2-Bromobenzimidazole (3). A suspension of 2-mercaptobenzimidazole (10.0 g, 66 mmol) in 100 mL HOAc and 48% aqueous HBr (10 mL, 89 mmol) was cooled in an ice bath and bromine (12 mL, 239 mmol) was added slowly dropwise. Within 5 min the mixture could no longer be

stirred and was transferred to a 1 L flask containing 200 mL of HOAc. The thick orange mixture was stirred for 4.5 h, diluted with 200 mL deionized water, and the product was precipitated by the addition of solid NaOH pellets until the pH reached 4. The resulting white precipitate was filtered, washed with water, and dried to afford **3** (8.8 g, 68%) whose ^1H NMR was identical to that reported previously.¹

2-Bromo-1-tert-butoxycarbonylbenzimidazole (4). To a solution of **3** (654 mg, 3.32 mmol) in 15 mL DMF and 15 mL MeCN was added Et_3N (0.555 mL, 3.98 mmol), and the mixture was stirred for 25 min. A solution of di-*tert*-butyl-dicarbonate in 5 mL DMF was added via canula to the reaction mixture, and the reaction was allowed to continue until no starting material remained by TLC. The solvent was removed under reduced pressure and the residue dissolved in EtOAc, washed with 1% HCl (1 \times 20 mL), NaHCO_3 (sat.) (1 \times 20 mL), and brine (1 \times 20 mL). The residue after drying and evaporation of solvent was purified by flash chromatography (15% EtOAc/hexanes) to afford **4** as a yellowish-white solid (692 mg, 67%): R_f 0.73 (30% EtOAc/hexanes); ^1H NMR δ 1.61 (s, 9), 7.15–7.19 (m, 2), 7.48–7.56 (m, 1), 7.72–7.78 (m, 1); ^{13}C NMR δ 27.74, 86.41, 114.42, 119.08, 124.17, 124.73, 126.57, 133.47, 142.37, 146.93; HRMS: exact mass calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2\text{Br}$ (MH^+) 297.023864, found 297.024002.

2-Phenylethynyl-1-tert-butoxycarbonylbenzimidazole (5a) To a 150 mL 3-necked flask containing Et_3N (5 mL) was added a solution of **4** (300 mg, 1.0 mmol) in Et_3N (5 mL). PPh_3 (53 mg, 0.2 mmol) was added and the flask was evacuated and purged with argon twice. Phenylacetylene (0.165 mL, 1.5 mmol) was added *via* syringe followed by CuI (29 mg, 0.15 mmol). A 5 mL pear-shaped flask containing $\text{Pd}(\text{OAc})_2$ (23 mg, 0.1 mmol) was connected to the 3-necked flask by a male-to-male joint. After flushing the system vigorously with argon, the Pd catalyst was dissolved into the solution and the reaction was stirred at room temperature for 20 h. The solution was then filtered through a plug of Celite, washed with 1:3 EtOAc/hexanes and concentrated under reduced pressure. The residue was dissolved in 80 mL EtOAc, washed with 1% HCl (1 \times 15 mL), water (1 \times 15 mL), and brine (1 \times 15 mL). The residue upon drying and evaporation of the solvent was purified by flash chromatography (10% EtOAc/hexanes) to afford **5a** as a tan solid (258 mg, 81%): R_f 0.51 (1:3 EtOAc/hexanes); ^1H NMR δ 1.68 (s, 9H), 7.33–7.39 (m, 5H), 7.60–7.64 (m, 2H), 7.70–7.74 (m, 2H), 7.95–7.99 (m, 2H); ^{13}C NMR δ 28.03, 80.62, 85.78, 94.83, 114.80, 120.12, 121.41, 124.69, 125.79, 128.40, 129.57, 132.06, 135.90 (2 C), 142.78, 147.69; HRMS: exact mass calcd for $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_2$ (MH^+) 319.144653, found 314.144579.

2-[(Triisopropylsilyl)-ethynyl]-1-tert-butoxycarbonylbenzimidazole (5b). To a 15 mL pear-shaped flask containing Et_3N (5 mL) was added a solution of **4** (315 mg, 1.06 mmol) in Et_3N (5 mL) and PPh_3 (53 mg, 0.2 mmol). The flask was evacuated and purged with argon twice. (Triisopropylsilyl)acetylene (0.357 mL, 1.59 mmol) was added *via* syringe followed by CuI (29 mg, 0.15 mmol). A 10 mL Kugelrohr bulb containing $\text{Pd}(\text{OAc})_2$ (23 mg, 0.1 mmol) was connected to the flask by a male-to-male joint. After flushing the system vigorously with argon, the Pd catalyst was added to the solution, and the reaction was stirred at room temperature, covered with foil, for 17 h. The solution was then filtered through a plug of Celite, washed with 1:3 EtOAc/hexanes and concentrated under reduced pressure. The residue was dissolved in 100 mL EtOAc, washed with 1% HCl (1 \times 20 mL), water (1 \times 20 mL), and brine (1 \times 20 mL). The residue upon drying and evaporation of solvent purified by flash chromatography (10% EtOAc/hexanes) to afford **5b** as a faint yellow oil (300 mg, 71%): R_f 0.71 (33% EtOAc/hexanes); ^1H NMR δ 1.12 (m, 21H), 1.61 (s, 9H), 7.25–7.38 (m, 2H), 7.69–7.75 (m, 1H), 7.82–7.88 (m, 1H); ^{13}C NMR δ 11.24, 18.53, 27.99, 85.65, 96.29, 100.18, 114.59, 120.31, 124.56, 125.75, 131.76, 135.69, 142.62, 147.45; MS m/e 399 (MH^+), 343, 299; HRMS: exact mass calcd for $\text{C}_{23}\text{H}_{35}\text{N}_2\text{O}_2\text{Si}$ (MH^+) 399.246782, found 399.246008.

2-Phenylethynylbenzimidazole (6a). A solution of **5a** (246 mg, 0.77 mmol) in 25 mL CH₂Cl₂ was cooled to -10 °C. TFA (10 mL) was added dropwise to the reaction mixture over a period of 40 min., at which time the solution was clear orange. The solution was stirred for 3 hours at -10 °C and overnight at 0 °C. After dilution with 30 mL CH₂Cl₂, the excess TFA was neutralized with bicarbonate (2 × 15 mL) and the organic layer was washed with water (2 × 15 mL), and brine (1 × 15 mL). The residue upon drying and evaporation of solvent was purified by flash chromatography (50% CH₂Cl₂/hexanes) to afford **6a** as a yellowish solid (129 mg, 77%): mp 183–185 °C; R_f 0.40 (2:3:0.1 EtOAc/hexanes/MeOH); ¹H NMR (CD₂Cl₂) δ 7.05–7.18 (m, 2H), 7.21–7.46 (m, 5H), 7.60–7.71 (m, 2H); ¹³C NMR (CD₂Cl₂) δ 75.88, 98.53, 114.92, 119.65, 125.83, 128.77, 130.91, 132.46, 133.65, 134.38; MS *m/e* 219 (MH⁺), 106; HRMS: exact mass calcd for C₁₅H₁₁N₂ (MH⁺) 219.092223, found 219.092042.

2-[(Triisopropylsilyl)-ethynyl]benzimidazole (6b). A solution of **5b** (301 mg, 0.75 mmol) in 5 mL CH₂Cl₂ was cooled to between -10 and 0 °C in a salt ice bath. TFA (10 mL) was added dropwise to the reaction over a period of 35 min and the resulting solution was stirred overnight at 0 °C. After dilution with 75 mL CH₂Cl₂, the excess TFA was neutralized with bicarbonate (20 mL) and the organic layer was washed with water (2 × 15 mL), and brine (1 × 20 mL). The residue upon drying and evaporation of solvent was purified by flash chromatography (25% EtOAc/hexanes) to afford **6b** as a clear light yellow oil (208 mg, 93%): R_f 0.71 (50% EtOAc/hexanes); ¹H NMR δ 1.00–1.03 (m, 21H), 7.36–7.40 (dd, 2H, *J* = 3, 3 Hz), 7.67–7.71 (dd, 2H, *J* = 3, 3 Hz); ¹³C NMR (CDCl₃) δ 13.96, 18.19, 89.10, 107.88, 114.41, 126.34, 131.33, 131.97; MS *m/e* 299 (MH⁺), 255; HRMS: exact mass calcd for C₁₈H₂₇N₂Si (MH⁺) 299.194352, found 299.193842.

1-(1,2-Dichloro-vinyl)-2-phenylethynylbenzimidazole (7a). To a solution of **6a** (129 mg, 0.59 mmol) in 5 mL of dry DMF was added NaH (20 mg, 0.65 mmol). The mixture was heated to 50 °C and stirred for 40 min, after which heating was discontinued and trichloroethylene (0.106 mL, 1.18 mmol) was added, resulting in an immediate cloudiness. The mixture was stirred at room temperature for 20 h, and the solvent removed in vacuo. The residue was diluted with 5 mL of MeOH and filtered to remove any particulate matter, rinsing with MeOH (10 mL) and 5:1 CH₂Cl₂/MeOH. Concentration of the organic filtrate under reduced pressure afforded 174 mg (94%) of **7** as a clear yellowish oil: ¹H NMR δ 6.83 (s, 1H), 7.33–7.40, (m, 1H), 7.59–7.62 (m, 2H), 7.77–7.81 (m, 1H); ¹³C NMR δ 77.84, 95.72, 110.53, 119.25, 120.63, 120.75, 124.23, 124.37, 125.19, 128.51, 129.54, 132.15, 132.58, 136.00, 142.86; MS *m/e* 317, 315, 313 (MH⁺); HRMS: exact mass calcd for C₁₇H₁₁N₂Cl₂ (MH⁺) 313.029929, found 313.029303.

1-(1,2-Dichloro-vinyl)-2-[(triisopropylsilyl)-ethynyl]benzimidazole (7b). KH (35%, 52 mg, 0.45 mmol) was weighed into a 25 mL flask in a glove bag and suspended in dry DMF (1 mL). A solution of **6b** (121 mg, 0.41 mmol) in dry DMF (3 mL) was added to the KH suspension. Immediately, a yellow flocculent precipitate formed and the solution gradually turned orange brown. The reaction mixture was stirred at room temperature for 20 min until evolution of H₂ ceased. Trichloroethylene (0.074 mL, 0.82 mmol) was added and the reaction mixture was stirred at room temperature for 20 h. Removal of solvent under reduced pressure followed by dilution with MeOH yielded some particulate matter that was filtered off and washed with MeOH and CH₂Cl₂. The filtrate upon concentration and purification by flash chromatography (5% EtOAc/hexanes) afforded **7b** as a clear oil (113 mg, 70%): ¹H NMR δ 1.07–1.20 (m, 21H), 6.77, (s, 1H), 7.30–7.38 (m, 3H), 7.75–7.78 (m, 1H); ¹³C NMR δ 11.06, 18.46, 93.80, 100.74, 110.29, 119.81, 120.73, 124.24, 124.45, 125.31, 132.41, 135.68, 142.56. MS *m/e* 397, 395, 393 (MH⁺), 391; HRMS: exact mass calcd for C₂₀H₂₇N₂SiCl₂ (MH⁺) 393.132058, found 393.131654.

1-Ethynyl-2-[(triisopropylsilyl)-ethynyl]benzimidazole (8b). To a solution of **7b** (76 mg, 0.193 mmol) in dry THF (5 mL) at -78°C was added *n*-BuLi (0.7 mL, 0.84 mmol) dropwise slowly with stirring. The reaction was allowed to warm to 0°C over 2 hours at which temperature 2.5 mL of a 3:1 $\text{NH}_4\text{Cl}:\text{MeOH}$ mixture was added and the reaction diluted with 60 mL of EtOAc. The organic layer was washed with water (1×20 mL), brine (1×20 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue purified by flash chromatography (20% EtOAc/hexanes) to afford 4.5 mg (7%) of **8b**: ^1H NMR δ 1.12–1.29 (m, 21H), 3.37 (s, 1H), 7.46–7.54 (m, 2H), 7.64–7.73 (m, 2H); HRMS: exact mass calcd for $\text{C}_{20}\text{H}_{27}\text{N}_2\text{Si}$ (MH^+) 323.194352, found 323.195141.

2-Iodo-1-phenylethynylimidazole (9). NaH (74 mg, 3.1 mmol) was added to an ice-cold solution of 2-iodoimidazole (300 mg, 1.55 mmol) in THF (3 mL) and the mixture was stirred for 20 min. The mixture was then transferred via canula to a solution of phenyl(phenylethynyl)iodinium tosylate² (1.47 g, 3.1 mmol) in dry CH_2Cl_2 (8 mL) at 0°C . The reaction mixture was allowed to warm to room temperature over 1.5 h. The solvent was evaporated and the residue extracted well with EtOAc (4×10 mL). The organic extracts were collected, and the solvent removed in vacuo. The residue was purified by flash chromatography (0–20% EtOAc/hexanes) to afford 135 mg (29%) of **9** as a light yellow oil: ^1H NMR δ 7.07 (d, 1H, $J = 1.5$ Hz), 7.32 (d, 1H, $J = 1.5$ Hz), 7.36–7.41 (m, 3H), 7.54–7.57 (m, 2H). ^{13}C NMR δ 74.39, 78.47, 94.09, 120.84, 125.42, 128.54, 129.16, 131.63, 132.40; HRMS: exact mass calcd for $\text{C}_{11}\text{H}_8\text{N}_2\text{I}$ (MH^+) 294.973225, found 294.974332.

1,2-Bis-(phenylethynyl)imidazole (10a). Phenylacetylene (0.093 mL, 0.847 mmol) was added to a solution of **9** (125 mg, 0.425 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (15 mg, 0.021 mmol) and CuI (8 mg, 0.042 mmol) in 4 mL of dry, degassed Et_3N . The reaction mixture was stirred for 20 h at room temperature. The solvent was removed in vacuo and the residue purified by flash chromatography (5–20% EtOAc/hexanes) to afford 50 mg (44%) of **10a** as a light yellow oil: ^1H NMR δ 7.11–7.12 (d, 1H, $J = 1.5$ Hz), 7.22–7.23 (d, 1H, $J = 1.5$ Hz), 7.33–7.39 (m, 6H), 7.52–7.59 (m, 4H); ^{13}C NMR (CD_2Cl_2) δ 73.75, 77.99, 78.14, 94.02, 121.54, 121.64, 122.93, 128.95, 128.97, 129.38, 129.93, 130.24, 131.84, 132.23, 135.60; HRMS: exact mass calcd for $\text{C}_{19}\text{H}_{13}\text{N}_2$ (MH^+) 269.107874, found 269.108112.

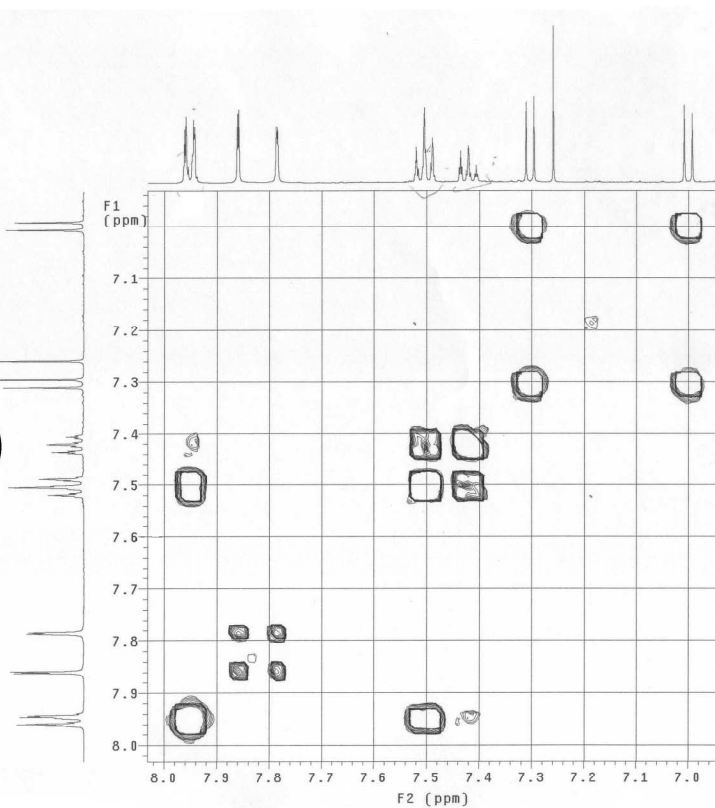
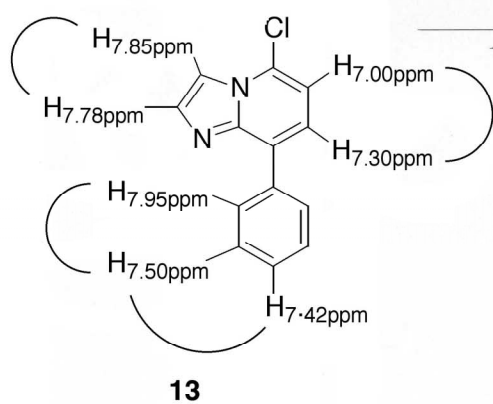
1-Phenylethynyl-2-[(triisopropylsilyl)-ethynyl]imidazole (10b). (Triisopropylsilyl)-acetylene (0.38 mL, 1.7 mmol) was added to a solution of **9** (50 mg, 0.17 mmol), $\text{Pd}(\text{PPh}_3)_4$ (9.8 mg, 0.0085 mmol) and CuI (3.3 mg, 0.017 mmol) in 2.5 mL of dry, degassed Et_3N . The reaction mixture was stirred for 4 h at room temperature and filtered. The solvent was removed in vacuo and the residue purified by flash chromatography (5–20% EtOAc/hexanes) to afford 40 mg (67%) of **10b** as a light yellow oil: ^1H NMR δ 1.10–1.02 (m, 21H), 7.04 (d, 1H, $J = 1.5$ Hz), 7.16 (d, 1H, $J = 1.5$ Hz), 7.32–7.38 (m, 3H), 7.48–7.52 (m, 2H); ^{13}C NMR (CDCl_3) δ 11.08, 18.53, 73.03, 93.90, 121.07, 122.34, 127.77, 127.80, 128.37, 129.00, 129.06, 129.47, 131.87; HRMS: exact mass calcd for $\text{C}_{22}\text{H}_{29}\text{N}_2\text{Si}$ (MH^+) 349.210003, found 349.210084.

2-Ethynyl-1-phenylethynyl-1H-imidazole (10c). To a solution of **10b** (33 mg, 0.095 mmol) in THF (0.5 mL) at -78°C was added a solution of tetrabutyl ammonium fluoride (26.1 mg, 0.1 mmol) in dry THF (0.1 mL). The solution was stirred at this temperature for 10 min and poured into ice. The aqueous layer was extracted well with CH_2Cl_2 (4×15 mL) and the residue upon drying and evaporation of solvent was purified by flash chromatography (10–30% EtOAc/hexanes) to afford 14 mg (77%) of **10c** as a white solid: mp $107\text{--}108^{\circ}\text{C}$ (dec); ^1H NMR δ 3.40 (s, 1H), 7.75 (d, 1H, $J = 1.5$ Hz), 7.195 (d, 1H, $J = 1.5$ Hz), 7.36–7.39 (m, 3H), 7.51–7.54 (m, 2H). ^{13}C NMR δ 72.25, 73.71, 77.30, 82.54, 121.18, 122.87, 128.78, 129.40, 129.95, 132.02, 134.49; HRMS: exact mass calcd for $\text{C}_{13}\text{H}_9\text{N}_2$ (MH^+) 193.076573, found 193.076197.

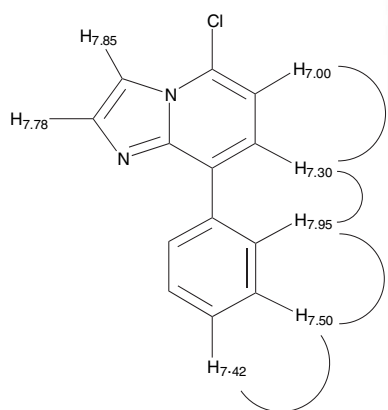
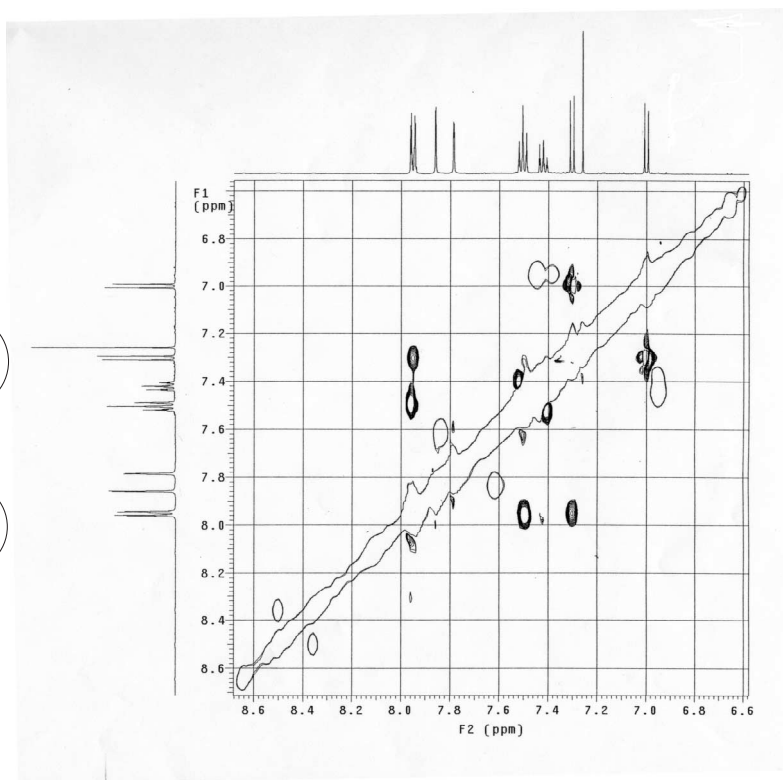
Thermolysis of 10c in 1,4-cyclohexadiene. A solution of **10c** (20 mg, 0.105 mmol) in 1,4-cyclohexadiene (5 mL) was heated in a sealed vacuum pyrolysis tube which was purged with argon at 100 °C for 2.5 days, after which the solvent was evaporated and the residue subjected to flash chromatography (10–30% EtOAc/hexanes) to afford 1 mg (4%) of **12b** as a white solid, 8 mg (28%) of **12a** as a light yellow solid and 6 mg (30%) of **11** as a red oil. **11**: ^1H NMR δ 3.63 (d, 2H J = 2.4 Hz), 7.22 (t, 1H, J = 2.4 Hz), 7.26–7.41 (m, 1H), 7.45–7.50 (m, 2H), 8.01–8.04 (m, 2H), 8.34 (d, 1H, J = 2.8 Hz), 8.48 (d, 1H, J = 3.2 Hz); ^{13}C NMR δ 37.67, 127.40, 128.54, 128.70, 133.35, 134.51, 139.35, 141.64, 142.73, 156.33, 159.91; HRMS: exact mass calcd for $\text{C}_{13}\text{H}_{11}\text{N}_2$ (MH^+) 195.092223, found 195.092584. **12a**: mp 128 °C; ^1H NMR δ 2.42–2.47 (m, 2H), 2.72–2.76 (m, 4H), 5.83 (s, 2H), 7.32–7.36 (m, 2H), 7.43–7.47 (m, 2H), 8.02–8.04 (m, 2H), 8.204 (d, 1H, J = 2.8 Hz), 8.43 (d, 1H, J = 2.8 Hz); ^{13}C NMR δ 22.97, 28.06, 40.45, 123.97, 126.68, 127.47, 128.13, 133.58, 134.84, 137.82, 140.15, 140.19, 154.31, 161.62; HRMS: exact mass calcd for $\text{C}_{19}\text{H}_{17}\text{N}_2$ (MH^+) 273.139174, found 273.138264. **12b**: ^1H NMR δ 2.32–2.37 (m, 2H), 2.54–2.65 (m, 4H), 5.89 (s, 2H), 6.81 (s, 1H), 7.31–7.35 (m, 1H), 7.42–7.46 (m, 2H), 7.98–8.01 (m, 2H), 8.24 (d, 1H, J = 2.8 Hz), 8.37 (d, 1H, J = 2.8 Hz); HRMS calculated for $\text{C}_{19}\text{H}_{17}\text{N}_2$ (MH^+) 273.139174, found 273.139283.

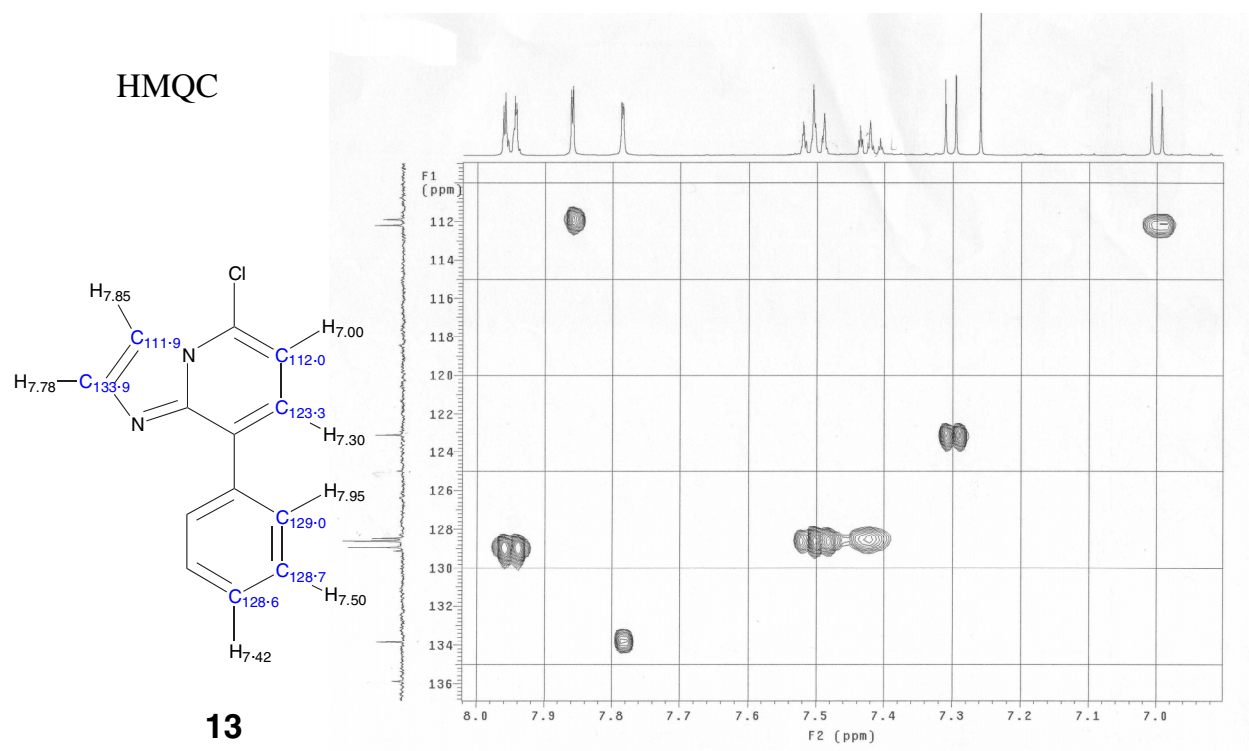
Thermolysis of 10c in Chlorobenzene. A solution of **10c** (14 mg, 0.073 mmoles) in dry chlorobenzene containing 20 eq. 1,4-cyclohexadiene (138 μL) was heated in a sealed tube purged with argon at 100 °C for 24 h. The solvent was evaporated and the residue purified by flash chromatography (10–30% EtOAc/hexanes) to afford 4.5 mg (27%) of **13**: ^1H NMR δ 7.00 (d, 1H, J = 7.6 Hz), 7.30 (d, 1H, J = 8 Hz), 7.40–7.44 (m, 1H), 7.48–7.52 (m, 2H), 7.78 (d, 1H, J = 1.2 Hz), 7.85 (d, 1H, J = 1.2 Hz), 7.93–7.96 (m, 2H); ^{13}C NMR δ 112.11, 112.42, 123.27, 125.10, 128.58, 128.71, 129.01, 129.18, 133.90, 135.89, 144.83; HRMS: exact mass calcd for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{Cl}$ (MH^+) 229.053251, found 229.052959.

COSY

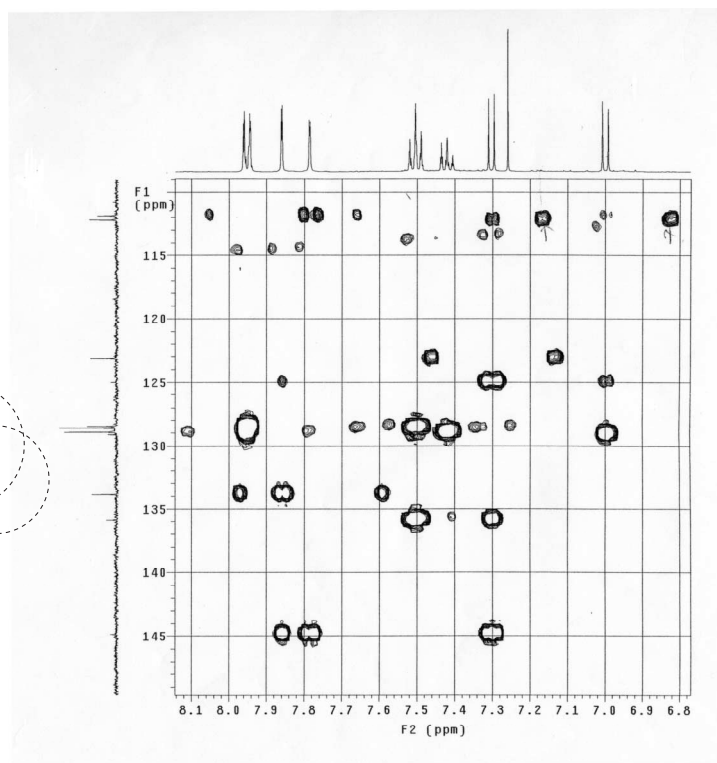
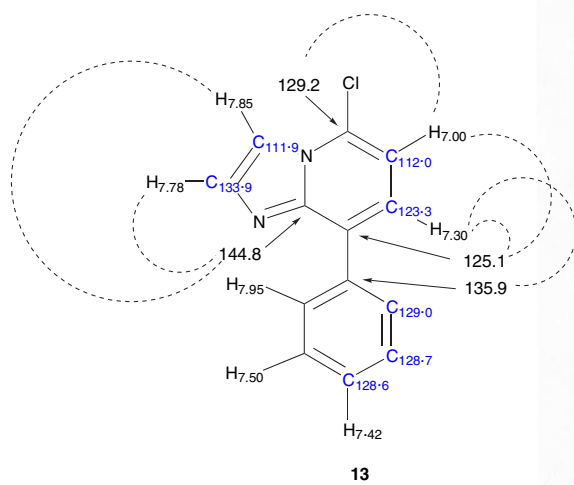


NOESY

**13**



HMBC



X-ray Experimental for 12a: Crystals grew as pale yellow prisms by slow crystallization from EtOAc-hexanes. The data crystal was cut from a large cluster of crystals and had approximate dimensions; 0.35x0.26x0.20mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoK α radiation ($\lambda = 0.71073\text{\AA}$). A total of 499 frames of data were collected using ω -scans with a scan range of 1° and a counting time of 33 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table S1. Data reduction were performed using DENZO-SMN.³ The structure was solved by direct methods using SIR92⁴ and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.⁵ The hydrogen atoms were observed in a ΔF map and refined with isotropic displacement parameters. There are two crystallographically unique molecules in the asymmetric unit. The molecules have only minor conformational differences (Figure S3). The function, $\sum w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0369*P)^2 + (0.1973*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.0939, with $R(F)$ equal to 0.0408 and a goodness of fit, S , = 1.06. Definitions used for calculating $R(F)$, $R_w(F^2)$ and the goodness of fit, S , are given below.⁶ The data were corrected for secondary extinction effects. The correction takes the form: $F_{\text{corr}} = kF_c/[1 + (3.3(2)\times 10^{-5}) * F_c^2 \lambda^3/(\sin 2\theta)]^{0.25}$ where k is the overall scale factor. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).⁷ All figures were generated using SHELXTL/PC.⁸ Tables of positional and thermal parameters, bond lengths and angles, torsion angles, figures and lists of observed and calculated structure factors are located in tables S1 through S7.

Table S1. Crystal data and structure refinement for **12a**.

Empirical formula	C ₁₉ H ₁₆ N ₂	
Formula weight	272.34	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.6360(1) Å	$\alpha = 92.812(1)^\circ$.
	b = 10.1513(1) Å	$\beta = 91.680(1)^\circ$.
	c = 14.2933(2) Å	$\gamma = 92.388(1)^\circ$.
Volume	1394.56(3) Å ³	
Z	4	
Density (calculated)	1.297 Mg/m ³	
Absorption coefficient	0.077 mm ⁻¹	
F(000)	576	
Crystal size	0.35 x 0.26 x 0.20 mm	
Theta range for data collection	2.98 to 27.50°	
Index ranges	-9 ≤ h ≤ 12, -13 ≤ k ≤ 13, -18 ≤ l ≤ 17	
Reflections collected	10003	
Independent reflections	6315 [R(int) = 0.0198]	
Completeness to theta = 27.50°	98.3 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	6315 / 0 / 508	
Goodness-of-fit on F ²	1.056	
Final R indices [I > 2σ(I)]	R1 = 0.0408, wR2 = 0.0839	
R indices (all data)	R1 = 0.0680, wR2 = 0.0939	
Extinction coefficient	3.3(2) × 10 ⁻⁵	
Largest diff. peak and hole	0.220 and -0.193 e.Å ⁻³	

Table S2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for 1. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N1	7211(1)	3043(1)	4368(1)	29(1)
C2	7061(2)	1718(1)	4265(1)	32(1)
C3	5996(2)	1066(1)	3739(1)	32(1)
N4	4987(1)	1693(1)	3287(1)	30(1)
C5	5132(1)	2998(1)	3388(1)	25(1)
C6	4214(1)	3977(1)	3013(1)	25(1)
C7	4882(1)	5254(1)	3347(1)	25(1)
C8	6055(1)	5098(1)	3868(1)	23(1)
C9	6231(1)	3673(1)	3912(1)	24(1)
C10	3413(1)	3710(1)	2074(1)	28(1)
C11	3266(2)	4797(1)	1403(1)	33(1)
C12	2409(1)	5905(1)	1750(1)	33(1)
C13	1726(1)	5914(1)	2539(1)	34(1)
C14	1704(2)	4828(1)	3207(1)	32(1)
C15	2629(1)	3709(1)	2951(1)	28(1)
C16	7009(1)	6147(1)	4293(1)	24(1)
C17	8436(1)	5969(1)	4374(1)	26(1)
C18	9339(2)	6973(1)	4745(1)	30(1)
C19	8826(2)	8164(1)	5057(1)	31(1)
C20	7411(2)	8350(1)	4994(1)	30(1)
C21	6509(1)	7356(1)	4612(1)	26(1)
N1'	2445(1)	52(1)	1373(1)	31(1)
C2'	2420(2)	-504(1)	2210(1)	33(1)
C3'	1402(2)	-302(1)	2849(1)	32(1)
N4'	324(1)	474(1)	2701(1)	30(1)
C5'	341(1)	1023(1)	1879(1)	25(1)
C6'	-668(1)	1910(1)	1498(1)	26(1)
C7'	-131(1)	2224(1)	578(1)	27(1)
C8'	1061(1)	1598(1)	401(1)	25(1)
C9'	1382(1)	826(1)	1217(1)	25(1)
C10'	-1404(1)	2875(1)	2161(1)	28(1)

C11'	-1656(2)	4257(1)	1870(1)	30(1)
C12'	-2733(1)	4328(1)	1101(1)	32(1)
C13'	-3463(2)	3298(1)	711(1)	33(1)
C14'	-3323(2)	1901(1)	975(1)	32(1)
C15'	-2214(1)	1717(1)	1718(1)	28(1)
C16'	1901(1)	1702(1)	-440(1)	25(1)
C17'	3321(1)	1509(1)	-402(1)	30(1)
C18'	4113(2)	1636(1)	-1190(1)	35(1)
C19'	3492(2)	1960(1)	-2028(1)	34(1)
C20'	2079(2)	2142(1)	-2082(1)	34(1)
C21'	1288(2)	2015(1)	-1296(1)	30(1)

Table S3. Bond lengths [\AA] and angles [$^\circ$] for **12a**.

N1-C9	1.3347(16)	C18-C19	1.3838(19)
N1-C2	1.3470(17)	C18-H18	0.988(14)
C2-C3	1.3804(19)	C19-C20	1.385(2)
C2-H2	0.985(14)	C19-H19	0.976(14)
C3-N4	1.3507(17)	C20-C21	1.3843(19)
C3-H3	0.989(14)	C20-H20	0.988(14)
N4-C5	1.3271(16)	C21-H21	1.001(14)
C5-C9	1.4126(17)	N1'-C9'	1.3372(15)
C5-C6	1.4674(17)	N1'-C2'	1.3478(17)
C6-C7	1.4745(17)	C2'-C3'	1.375(2)
C6-C10	1.5357(17)	C2'-H2'	0.992(14)
C6-C15	1.5393(18)	C3'-N4'	1.3485(17)
C7-C8	1.3544(17)	C3'-H3'	0.986(14)
C7-H7	0.982(12)	N4'-C5'	1.3251(16)
C8-C9	1.4673(17)	C5'-C9'	1.4120(18)
C8-C16	1.4735(17)	C5'-C6'	1.4634(17)
C10-C15	1.4833(19)	C6'-C7'	1.4717(18)
C10-C11	1.5056(19)	C6'-C15'	1.5379(18)
C10-H10	0.995(13)	C6'-C10'	1.5384(17)
C11-C12	1.496(2)	C7'-C8'	1.3595(18)
C11-H11A	0.992(16)	C7'-H7'	0.999(13)
C11-H11B	1.013(15)	C8'-C9'	1.4687(17)
C12-C13	1.322(2)	C8'-C16'	1.4741(18)
C12-H12	1.008(15)	C10'-C15'	1.4875(18)
C13-C14	1.494(2)	C10'-C11'	1.5101(19)
C13-H13	0.990(14)	C10'-H10'	0.985(14)
C14-C15	1.5101(19)	C11'-C12'	1.4954(19)
C14-H14A	0.998(14)	C11'-H11D	1.016(14)
C14-H14B	0.979(16)	C11'-H11C	0.988(15)
C15-H5	0.976(14)	C12'-C13'	1.3252(19)
C16-C17	1.3956(18)	C12'-H12'	1.010(14)
C16-C21	1.3983(17)	C13'-C14'	1.496(2)
C17-C18	1.3876(18)	C13'-H13'	0.997(15)
C17-H17	0.969(13)	C14'-C15'	1.5090(19)

C14'-H14C	1.031(17)	C18'-C19'	1.382(2)
C14'-H14D	0.989(15)	C18'-H18'	0.998(16)
C15'-H15'	0.998(13)	C19'-C20'	1.382(2)
C16'-C17'	1.3906(18)	C19'-H19'	0.980(15)
C16'-C21'	1.3992(18)	C20'-C21'	1.3851(19)
C17'-C18'	1.3877(19)	C20'-H20'	0.984(15)
C17'-H17'	0.984(15)	C21'-H21'	0.995(15)
C9-N1-C2	113.63(11)	C11-C10-C6	120.19(11)
N1-C2-C3	123.57(13)	C15-C10-H10	115.2(8)
N1-C2-H2	116.4(8)	C11-C10-H10	116.9(7)
C3-C2-H2	120.1(8)	C6-C10-H10	110.4(7)
N4-C3-C2	123.27(12)	C12-C11-C10	114.48(12)
N4-C3-H3	116.8(8)	C12-C11-H11A	109.4(8)
C2-C3-H3	119.9(8)	C10-C11-H11A	109.1(8)
C5-N4-C3	113.31(11)	C12-C11-H11B	108.9(8)
N4-C5-C9	123.70(11)	C10-C11-H11B	108.3(8)
N4-C5-C6	127.74(11)	H11A-C11-H11B	106.4(12)
C9-C5-C6	108.55(10)	C13-C12-C11	124.40(13)
C5-C6-C7	103.82(10)	C13-C12-H12	119.9(8)
C5-C6-C10	121.16(10)	C11-C12-H12	115.6(8)
C7-C6-C10	125.41(11)	C12-C13-C14	124.94(13)
C5-C6-C15	120.67(11)	C12-C13-H13	120.3(9)
C7-C6-C15	123.52(11)	C14-C13-H13	114.7(9)
C10-C6-C15	57.68(8)	C13-C14-C15	114.41(12)
C8-C7-C6	111.97(11)	C13-C14-H14A	110.2(8)
C8-C7-H7	125.5(7)	C15-C14-H14A	109.8(8)
C6-C7-H7	122.5(7)	C13-C14-H14B	107.3(9)
C7-C8-C9	107.12(11)	C15-C14-H14B	108.9(9)
C7-C8-C16	127.16(11)	H14A-C14-H14B	105.8(12)
C9-C8-C16	125.70(11)	C10-C15-C14	120.55(12)
N1-C9-C5	122.50(11)	C10-C15-C6	61.04(8)
N1-C9-C8	128.95(11)	C14-C15-C6	118.39(11)
C5-C9-C8	108.53(10)	C10-C15-H5	116.6(8)
C15-C10-C11	120.85(12)	C14-C15-H5	115.7(8)
C15-C10-C6	61.28(8)	C6-C15-H5	113.1(8)

C17-C16-C21	118.31(11)	C8'-C7'-H7'	126.8(8)
C17-C16-C8	121.01(11)	C6'-C7'-H7'	121.6(8)
C21-C16-C8	120.67(11)	C7'-C8'-C9'	107.25(11)
C18-C17-C16	120.97(12)	C7'-C8'-C16'	126.54(12)
C18-C17-H17	119.6(8)	C9'-C8'-C16'	126.19(11)
C16-C17-H17	119.5(8)	N1'-C9'-C5'	122.08(11)
C19-C18-C17	119.94(13)	N1'-C9'-C8'	129.59(12)
C19-C18-H18	121.1(8)	C5'-C9'-C8'	108.34(11)
C17-C18-H18	118.9(8)	C15'-C10'-C11'	121.01(12)
C18-C19-C20	119.80(13)	C15'-C10'-C6'	61.07(8)
C18-C19-H19	120.2(8)	C11'-C10'-C6'	119.88(11)
C20-C19-H19	119.9(8)	C15'-C10'-H10'	115.3(8)
C21-C20-C19	120.38(12)	C11'-C10'-H10'	116.9(8)
C21-C20-H20	118.9(8)	C6'-C10'-H10'	110.6(8)
C19-C20-H20	120.6(8)	C12'-C11'-C10'	114.28(12)
C20-C21-C16	120.58(12)	C12'-C11'-H11D	107.9(8)
C20-C21-H21	120.9(7)	C10'-C11'-H11D	108.6(8)
C16-C21-H21	118.5(7)	C12'-C11'-H11C	109.1(8)
C9'-N1'-C2'	113.70(11)	C10'-C11'-H11C	110.0(8)
N1'-C2'-C3'	123.70(12)	H11D-C11'-H11C	106.7(11)
N1'-C2'-H2'	117.3(8)	C13'-C12'-C11'	124.75(13)
C3'-C2'-H2'	119.0(8)	C13'-C12'-H12'	119.2(8)
N4'-C3'-C2'	123.20(13)	C11'-C12'-H12'	116.0(8)
N4'-C3'-H3'	116.9(8)	C12'-C13'-C14'	124.86(13)
C2'-C3'-H3'	119.8(8)	C12'-C13'-H13'	120.1(8)
C5'-N4'-C3'	113.42(11)	C14'-C13'-H13'	115.0(8)
N4'-C5'-C9'	123.90(11)	C13'-C14'-C15'	114.45(12)
N4'-C5'-C6'	127.46(11)	C13'-C14'-H14C	108.6(8)
C9'-C5'-C6'	108.64(11)	C15'-C14'-H14C	105.9(8)
C5'-C6'-C7'	104.22(10)	C13'-C14'-H14D	111.1(8)
C5'-C6'-C15'	119.69(11)	C15'-C14'-H14D	109.7(8)
C7'-C6'-C15'	125.13(11)	H14C-C14'-H14D	106.7(12)
C5'-C6'-C10'	119.95(11)	C10'-C15'-C14'	120.56(12)
C7'-C6'-C10'	125.22(11)	C10'-C15'-C6'	61.10(8)
C15'-C6'-C10'	57.83(8)	C14'-C15'-C6'	120.44(12)
C8'-C7'-C6'	111.55(11)	C10'-C15'-H15'	116.9(7)

C14'-C15'-H15'	115.6(7)	C17'-C18'-H18'	119.2(9)
C6'-C15'-H15'	110.9(7)	C20'-C19'-C18'	120.01(13)
C17'-C16'-C21'	118.34(12)	C20'-C19'-H19'	119.5(8)
C17'-C16'-C8'	121.02(11)	C18'-C19'-H19'	120.5(8)
C21'-C16'-C8'	120.64(12)	C19'-C20'-C21'	119.99(13)
C18'-C17'-C16'	120.82(13)	C19'-C20'-H20'	120.3(9)
C18'-C17'-H17'	120.8(9)	C21'-C20'-H20'	119.7(9)
C16'-C17'-H17'	118.3(9)	C20'-C21'-C16'	120.79(13)
C19'-C18'-C17'	120.04(14)	C20'-C21'-H21'	120.1(8)
C19'-C18'-H18'	120.8(9)	C16'-C21'-H21'	119.1(8)

Table S4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **12a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N1	25(1)	28(1)	34(1)	6(1)	-1(1)	3(1)
C2	32(1)	28(1)	37(1)	7(1)	-1(1)	5(1)
C3	35(1)	24(1)	37(1)	3(1)	2(1)	3(1)
N4	32(1)	25(1)	32(1)	1(1)	2(1)	1(1)
C5	25(1)	25(1)	24(1)	2(1)	4(1)	-1(1)
C6	23(1)	25(1)	27(1)	2(1)	-2(1)	0(1)
C7	24(1)	24(1)	28(1)	2(1)	1(1)	1(1)
C8	22(1)	25(1)	23(1)	1(1)	3(1)	1(1)
C9	22(1)	28(1)	23(1)	3(1)	3(1)	2(1)
C10	28(1)	29(1)	27(1)	-1(1)	-5(1)	-1(1)
C11	36(1)	37(1)	27(1)	4(1)	-2(1)	4(1)
C12	30(1)	35(1)	34(1)	8(1)	-5(1)	2(1)
C13	28(1)	37(1)	37(1)	3(1)	-3(1)	7(1)
C14	22(1)	42(1)	33(1)	5(1)	0(1)	2(1)
C15	23(1)	29(1)	30(1)	4(1)	-4(1)	-5(1)
C16	25(1)	26(1)	20(1)	4(1)	0(1)	-1(1)
C17	26(1)	27(1)	26(1)	2(1)	0(1)	1(1)
C18	26(1)	34(1)	29(1)	4(1)	-2(1)	-2(1)
C19	34(1)	31(1)	28(1)	1(1)	-3(1)	-9(1)
C20	36(1)	26(1)	28(1)	1(1)	1(1)	1(1)
C21	26(1)	28(1)	25(1)	4(1)	0(1)	1(1)
N1'	30(1)	31(1)	31(1)	0(1)	-2(1)	5(1)
C2'	35(1)	33(1)	32(1)	1(1)	-5(1)	7(1)
C3'	39(1)	29(1)	27(1)	2(1)	-4(1)	2(1)
N4'	33(1)	29(1)	26(1)	0(1)	-1(1)	-1(1)
C5'	27(1)	24(1)	24(1)	-2(1)	-1(1)	-2(1)
C6'	24(1)	29(1)	26(1)	0(1)	3(1)	2(1)
C7'	27(1)	27(1)	26(1)	0(1)	0(1)	2(1)
C8'	25(1)	25(1)	24(1)	-3(1)	-1(1)	-1(1)
C9'	25(1)	23(1)	25(1)	-3(1)	-3(1)	-1(1)
C10'	27(1)	33(1)	25(1)	-1(1)	3(1)	3(1)

C11'	31(1)	29(1)	31(1)	-3(1)	3(1)	1(1)
C12'	33(1)	32(1)	32(1)	2(1)	4(1)	6(1)
C13'	29(1)	38(1)	33(1)	-1(1)	-1(1)	6(1)
C14'	26(1)	34(1)	37(1)	-2(1)	0(1)	1(1)
C15'	25(1)	28(1)	30(1)	0(1)	4(1)	1(1)
C16'	27(1)	23(1)	26(1)	-3(1)	1(1)	-1(1)
C17'	27(1)	36(1)	28(1)	-1(1)	1(1)	0(1)
C18'	29(1)	39(1)	37(1)	-4(1)	6(1)	-1(1)
C19'	40(1)	31(1)	29(1)	-2(1)	10(1)	-4(1)
C20'	43(1)	31(1)	27(1)	3(1)	1(1)	1(1)
C21'	31(1)	29(1)	30(1)	0(1)	1(1)	1(1)

Table S5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$) for **12a**.

	x	y	z	U(eq)
H2	7758(15)	1213(13)	4594(9)	34(4)
H3	5951(14)	90(14)	3677(10)	37(4)
H7	4505(13)	6103(12)	3192(9)	24(3)
H10	3612(13)	2821(13)	1798(9)	28(3)
H11A	4204(16)	5153(14)	1253(10)	40(4)
H11B	2832(15)	4401(14)	793(11)	40(4)
H12	2329(15)	6659(14)	1320(10)	40(4)
H13	1160(15)	6671(14)	2720(10)	41(4)
H14A	1950(14)	5189(13)	3855(10)	33(4)
H14B	743(17)	4480(14)	3225(10)	46(4)
H5	2339(14)	2847(13)	3171(9)	30(4)
H17	8798(13)	5127(13)	4174(9)	25(3)
H18	10340(16)	6805(13)	4811(10)	37(4)
H19	9451(15)	8853(14)	5353(10)	34(4)
H20	7023(14)	9169(14)	5257(10)	35(4)
H21	5485(15)	7482(13)	4562(9)	31(4)
H2'	3189(15)	-1082(13)	2367(10)	35(4)
H3'	1438(14)	-744(13)	3448(10)	33(4)
H7'	-600(14)	2852(13)	170(9)	32(4)
H10'	-1091(14)	2781(13)	2815(10)	30(4)
H11D	-1973(14)	4798(13)	2435(10)	35(4)
H11C	-778(16)	4685(14)	1677(10)	36(4)
H12'	-2908(15)	5239(14)	882(10)	38(4)
H13'	-4175(16)	3426(14)	207(10)	39(4)
H14C	-4246(17)	1574(15)	1250(11)	49(4)
H14D	-3168(15)	1316(14)	418(11)	41(4)
H15'	-2370(13)	942(13)	2111(9)	28(3)
H17'	3740(15)	1225(13)	188(11)	38(4)
H18'	5127(17)	1475(14)	-1146(11)	47(4)
H19'	4038(15)	2022(14)	-2592(11)	40(4)

H20'	1631(15)	2370(14)	-2677(11)	41(4)
H21'	268(16)	2134(13)	-1336(10)	37(4)

Table S6. Torsion angles [°] for **12a**.

C9-N1-C2-C3	-0.08(19)	C11-C12-C13-C14	0.1(2)
N1-C2-C3-N4	-1.0(2)	C12-C13-C14-C15	4.2(2)
C2-C3-N4-C5	0.87(19)	C11-C10-C15-C14	-2.19(19)
C3-N4-C5-C9	0.26(18)	C6-C10-C15-C14	107.73(13)
C3-N4-C5-C6	-178.50(12)	C11-C10-C15-C6	-109.92(14)
N4-C5-C6-C7	179.86(12)	C13-C14-C15-C10	-2.98(18)
C9-C5-C6-C7	0.95(13)	C13-C14-C15-C6	68.35(16)
N4-C5-C6-C10	-32.4(2)	C5-C6-C15-C10	-109.67(13)
C9-C5-C6-C10	148.73(12)	C7-C6-C15-C10	113.79(14)
N4-C5-C6-C15	36.06(19)	C5-C6-C15-C14	139.16(12)
C9-C5-C6-C15	-142.85(11)	C7-C6-C15-C14	2.62(18)
C5-C6-C7-C8	-0.47(14)	C10-C6-C15-C14	-111.17(14)
C10-C6-C7-C8	-146.42(12)	C7-C8-C16-C17	-146.03(13)
C15-C6-C7-C8	142.00(12)	C9-C8-C16-C17	32.10(18)
C6-C7-C8-C9	-0.19(14)	C7-C8-C16-C21	32.86(19)
C6-C7-C8-C16	178.23(11)	C9-C8-C16-C21	-149.00(12)
C2-N1-C9-C5	1.20(18)	C21-C16-C17-C18	-1.13(18)
C2-N1-C9-C8	179.59(12)	C8-C16-C17-C18	177.79(12)
N4-C5-C9-N1	-1.39(19)	C16-C17-C18-C19	1.10(19)
C6-C5-C9-N1	177.58(11)	C17-C18-C19-C20	-0.2(2)
N4-C5-C9-C8	179.93(12)	C18-C19-C20-C21	-0.6(2)
C6-C5-C9-C8	-1.10(14)	C19-C20-C21-C16	0.61(19)
C7-C8-C9-N1	-177.77(12)	C17-C16-C21-C20	0.28(18)
C16-C8-C9-N1	3.8(2)	C8-C16-C21-C20	-178.65(11)
C7-C8-C9-C5	0.80(14)	C9'-N1'-C2'-C3'	0.05(19)
C16-C8-C9-C5	-177.64(11)	N1'-C2'-C3'-N4'	0.0(2)
C5-C6-C10-C15	108.84(13)	C2'-C3'-N4'-C5'	0.07(18)
C7-C6-C10-C15	-110.61(14)	C3'-N4'-C5'-C9'	-0.25(18)
C5-C6-C10-C11	-140.20(13)	C3'-N4'-C5'-C6'	179.89(12)
C7-C6-C10-C11	0.4(2)	N4'-C5'-C6'-C7'	179.29(12)
C15-C6-C10-C11	110.96(14)	C9'-C5'-C6'-C7'	-0.59(13)
C15-C10-C11-C12	6.20(19)	N4'-C5'-C6'-C15'	-34.84(18)
C6-C10-C11-C12	-66.35(17)	C9'-C5'-C6'-C15'	145.28(11)
C10-C11-C12-C13	-5.4(2)	N4'-C5'-C6'-C10'	32.91(19)

C9'-C5'-C6'-C10'	-146.98(11)	C7'-C8'-C16'-C17'	152.55(13)
C5'-C6'-C7'-C8'	0.54(14)	C9'-C8'-C16'-C17'	-25.55(19)
C15'-C6'-C7'-C8'	-142.89(12)	C7'-C8'-C16'-C21'	-26.54(19)
C10'-C6'-C7'-C8'	144.58(12)	C9'-C8'-C16'-C21'	155.35(12)
C6'-C7'-C8'-C9'	-0.27(14)	C21'-C16'-C17'-C18'	0.51(19)
C6'-C7'-C8'-C16'	-178.67(11)	C8'-C16'-C17'-C18'	-178.61(12)
C2'-N1'-C9'-C5'	-0.23(17)	C16'-C17'-C18'-C19'	0.2(2)
C2'-N1'-C9'-C8'	179.50(12)	C17'-C18'-C19'-C20'	-0.8(2)
N4'-C5'-C9'-N1'	0.35(19)	C18'-C19'-C20'-C21'	0.8(2)
C6'-C5'-C9'-N1'	-179.76(11)	C19'-C20'-C21'-C16'	-0.1(2)
N4'-C5'-C9'-C8'	-179.43(11)	C17'-C16'-C21'-C20'	-0.54(19)
C6'-C5'-C9'-C8'	0.46(14)	C8'-C16'-C21'-C20'	178.58(12)
C7'-C8'-C9'-N1'	-179.88(12)		
C16'-C8'-C9'-N1'	-1.5(2)		
C7'-C8'-C9'-C5'	-0.12(14)		
C16'-C8'-C9'-C5'	178.28(11)		
C5'-C6'-C10'-C15'	-108.24(13)		
C7'-C6'-C10'-C15'	112.83(14)		
C5'-C6'-C10'-C11'	140.59(13)		
C7'-C6'-C10'-C11'	1.66(19)		
C15'-C6'-C10'-C11'	-111.18(14)		
C15'-C10'-C11'-C12'	-1.67(18)		
C6'-C10'-C11'-C12'	70.53(16)		
C10'-C11'-C12'-C13'	2.3(2)		
C11'-C12'-C13'-C14'	-0.3(2)		
C12'-C13'-C14'-C15'	-2.4(2)		
C11'-C10'-C15'-C14'	-0.87(19)		
C6'-C10'-C15'-C14'	-110.25(14)		
C11'-C10'-C15'-C6'	109.38(14)		
C13'-C14'-C15'-C10'	2.81(19)		
C13'-C14'-C15'-C6'	-69.49(16)		
C5'-C6'-C15'-C10'	108.68(13)		
C7'-C6'-C15'-C10'	-112.99(14)		
C5'-C6'-C15'-C14'	-140.88(12)		
C7'-C6'-C15'-C14'	-2.55(19)		
C10'-C6'-C15'-C14'	110.44(14)		

Figure S1. View of molecule 1 of **12a** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

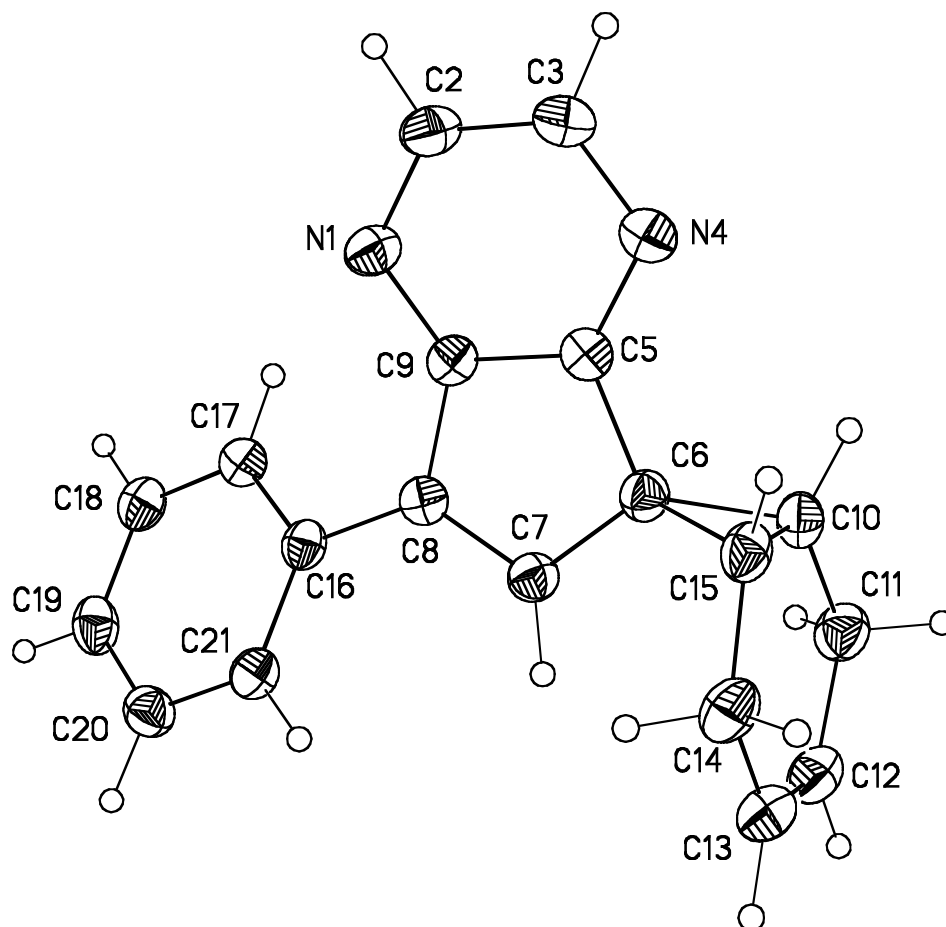


Figure S2. View of molecule 2 of **12a** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

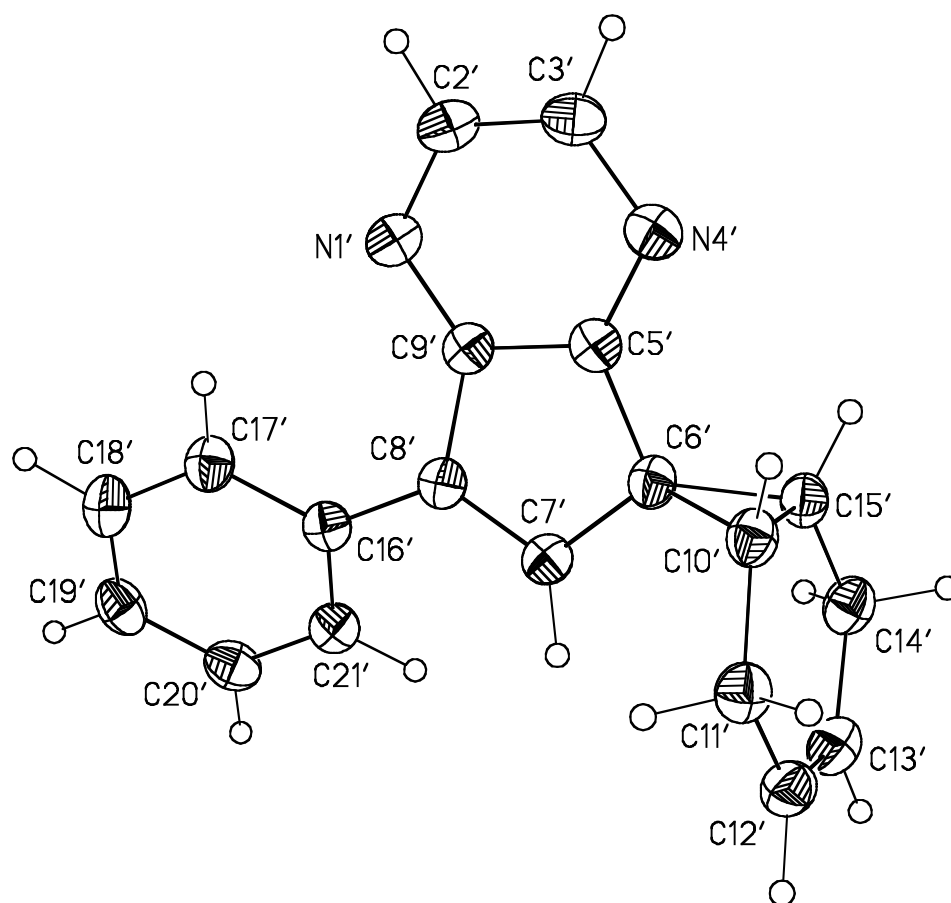
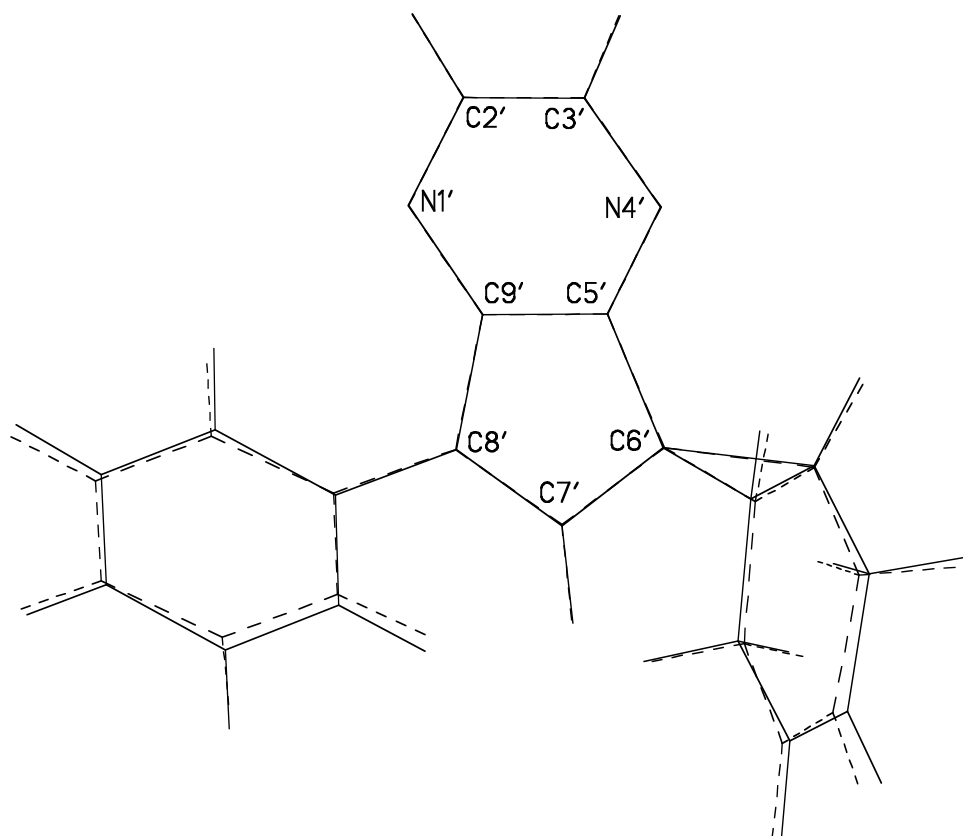


Figure S3. Fit by least-squares of selected atoms of molecule 1 (dashed lines) onto the equivalent atoms of molecule 2 (solid lines). The atoms of molecule 2 that were used in the fit are labeled.



References

-
1. Ellingboe, J. W.; Spinelli, W.; Winkley, M. W.; Nguyen, T. T.; Parsons, R. W.; Moubarak, I. F.; Kitzen, J. M.; Von Engen, D.; Bagli, J. F. *J. Med. Chem.* **1992**, *35*, 705–716.
 2. Koser, G. F.; Rebrovic, L.; Wettach, R. H. *J. Org. Chem.* **1981**, *46*, 4324–4326.
 3. DENZO-SMN. (1997). Z. Otwinowski and W. Minor, *Methods in Enzymology*, **276**: Macromolecular Crystallography, part A, 307 – 326, C. W. Carter, Jr. and R. M. Sweets, Editors, Academic Press.
 4. SIR92. (1993). A program for crystal structure solution. Altomare, A., Cascarano, G., Giacovazzo, C. & Guagliardi, A. *J. Appl. Cryst.* *26*, 343–350.
 5. Sheldrick, G. M. (1994). SHELXL97. Program for the Refinement of Crystal Structures. University of Gottingen, Germany.
 6. $R_w(F^2) = \{ \sum w(|F_o|^2 - |F_c|^2)^2 / \sum w(|F_o|^4) \}^{1/2}$ where w is the weight given each reflection. $R(F) = \sum (|F_o| - |F_c|) / \sum |F_o|$ for reflections with $F_o > 4(\sigma(F_o))$. $S = [\sum w(|F_o|^2 - |F_c|^2)^2 / (n - p)]^{1/2}$, where n is the number of reflections and p is the number of refined parameters.
 7. International Tables for X-ray Crystallography (1992). Vol. C, Tables 4.2.6.8 and 6.1.1.4, A. J. C. Wilson, editor, Boston: Kluwer Academic Press.
 8. Sheldrick, G. M. (1994). SHELXTL/PC (Version 5.03). Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin, USA.