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A facile synthesis of oxazolo[3,2-*a*][1,10]phenanthrolines via a new multicomponent reaction

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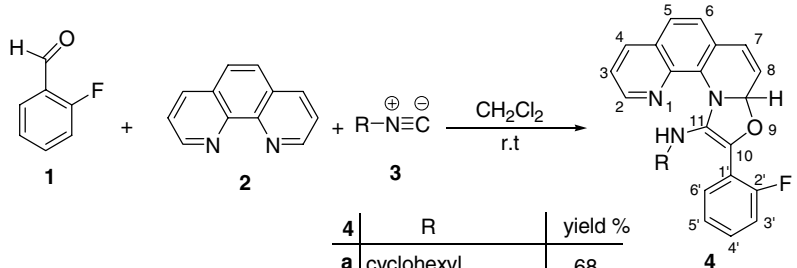
Abstract—The synthesis of *N*-cyclohexyl-10-(2-fluorophenyl)-8a*H*-oxazolo[3,2-*a*][1,10]phenanthroline and *N*-(2,6-dimethylphenyl)-10-(2-fluorophenyl)-8a*H*-oxazolo[3,2-*a*][1,10]phenanthroline by reaction of 2-fluorobenzaldehyde, phenanthroline and cyclohexyl or 2,6-dimethylphenyl isocyanide is reported.

The discovery of novel synthetic routes towards oxazole derivatives is an area of continued interest for organic chemists. Oxazoles are key building blocks of natural products, pharmaceuticals and synthetic intermediates.[1] They are most commonly obtained by the Hantzsch reaction[2] or by cyclodehydration of β-ketoamides.[3] Amino-oxazole-containing structures possess biological activity and therapeutic potential.[4] As a part of our current studies[5] on the development of new routes to heterocyclic systems, we report an efficient one-pot synthetic route to 8a*H*-oxazolo[3,2-*a*][1,10]phenanthrolin-1-amines using isocyanides and phenanthroline in the presence of 2-fluorobenzaldehyde.

We observed that the multicomponent reaction of aldehyde **1** phenanthroline **2** and isocyanides **3** afforded *N*-cyclohexyl-10-(2-fluorophenyl)-8a*H*-oxazolo[3,2-*a*]-[1,10]phenanthrolin-1-amine (**4a**) or *N*-(2,6-dimethylphenyl)-10-(2-fluorophenyl)-8a*H*-oxazolo[3,2-*a*][1,10]-phenanthrolin-1-amine (**4b**), respectively, (Scheme 1).

The structure of compound **4a** was determined on the basis of its elemental analyses, mass spectrum, ^{1}H and ^{13}C NMR and IR spectroscopic data. The ^{1}H NMR spectrum of **4a** exhibited distinct signals arising from cyclohexyl, NC*H*, NC*H*O ($\delta = 1.18$–1.96, 3.81, 7.16) ppm protons, respectively. The NH proton resonance



4	R	yield %
a	cyclohexyl	68
b	2,6-dimethylphenyl	72

Scheme 1.

Keywords: Cycloaddition reaction; Oxazolo[3,2-*a*][1,10]phenanthroline derivatives; Phenanthroline; 2-Fluorobenzaldehyde; Isocyanides.
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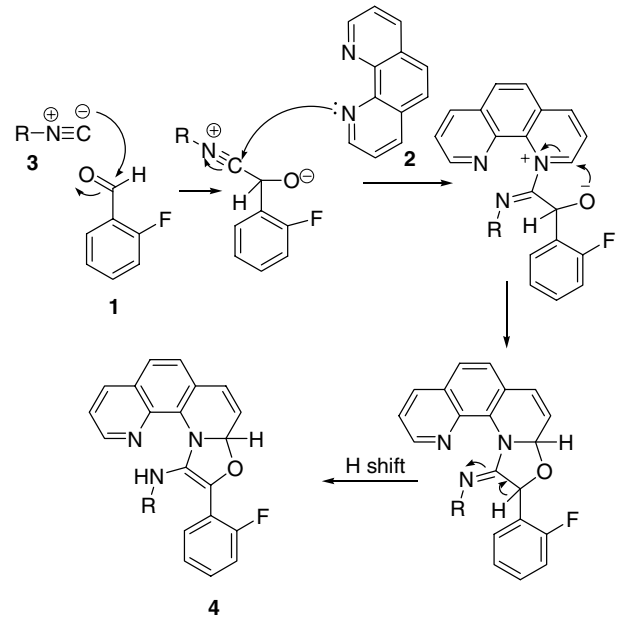

Scheme 2.

at ($\delta = 6.71$) disappeared after addition of D_2O to the $CDCl_3$solution of **4a**. The ^{13}C NMR spectrum of **4a** showed 24 distinct resonances in agreement with the proposed structure. The IR spectrum showed an NH absorption at 3475 cm^{-1}. The mass spectrum of **4a** displayed a molecular ion peak at the appropriate *m*/*z* value. The ^1H and ^{13}C NMR data for compounds **4a** and **4b** are given in the experimental section.[6]

A proposed mechanism is shown in Scheme 2 in agreement with the predicted structure.

In summary, we have developed an efficient synthetic method for the preparation of oxazolo[3,2-*a*][1,10]phenanthrolines. The present reaction is performed under neutral conditions and starting materials and reagent can be reacted without any prior activation.

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6. *General procedure* (*exemplified by* **4a**): To a magnetically stirred solution of 1,10-phenanthroline (0.198 g, 1 mmol) and 2-fluorobenzaldehyde (0.149 g, 1.2 mmol) in 10 mL of CH_2Cl_2 was added dropwise a mixture of cyclohexyl isocyanide (0.131 g, 1.2 mmol) in 4 mL of CH_2Cl_2 at −5 °C over 10 min and the reaction stirred for 5 days at room temperature. Filtration of the resulting solid product and washing with cold diethyl ether (2 × 5 mL) gave the desired product. Compound (**4a**): Pale white powder, yield: 0.28 g (68%), mp 91.5–93.5 °C, IR (KBr) (ν_{max}, cm^{-1}): 3475 (N–H), 1679 (C=N), 1094 (C–F). ^1H NMR (300.1 MHz, $CDCl_3$): δ_H 1.18–1.96 (10H, m, 5 CH_2 of cyclohexyl), 3.81 (1H, m, N–CH), 6.71 (1H, d, $J = 6.0$ Hz, NH), 7.02 (1H, d, $J = 9.1$ Hz, C-5–H), 7.08 (1H, d, $J = 9.1$ Hz, C-6–H), 7.11 (1H, dd, $J_1 = 8.0$, $J_2 = 2.5$ Hz, C-7–H), 7.13 (1H, dd, $J_1 = 8.0$, $J_2 = 2.0$ Hz, C-8–H), 7.16 (1H, dt, $J_1 = 7.6$, $J_2 = 2.5$, $J_3 = 2.0$ Hz, C-8a–H), 7.27 (1H, m, C-3′–H), 7.47 (1H, m, C-5′–H), 7.50 (1H, m, C-4′–H), 7.56 (1H, dd, $J_1 = 7.5$, $J_2 = 4.5$ Hz, C-3–H), 7.89 (1H, dd, $J_1 = 7.5$, $J_2 = 1.3$ Hz, C-6′–H), 8.16 (1H, dd, $J = 7.5$, $J_2 = 1.8$ Hz, C-4–H), 9.13 (1H, dd, $J_1 = 4.5$, $J_2 = 1.8$ Hz, C-2–H). ^{13}C NMR ($CDCl_3$): δ_C 24.57, 24.61, 25.47, 32.72, 32.77 and 48.12 (6CH_2 of cyclohexyl), 71.39 (N–*C*H–O), 115.9 (d, $^2J_{CF} = 21.2$ Hz, C-3′), 116.91 (C-3), 117.21 (C-5), 117.65 (d, $^3J_{CF} = 10.0$ Hz, C-10), 123.17 (C-6a), 123.44 (d, $^2J_{CF} = 13.7$ Hz, C-1′), 124.37 (d, $^4J_{CF} = 3.4$ Hz, C-5′), 124.53 (C-6), 126.58 (C-8), 128.69 (C-4a), 130.29 (C-7), 130.89 (d, $^3J_{CF} = 8.5$ Hz, C-6′), 132.76 (C-4), 135.34 (d, $^3J_{CF} = 9.3$ Hz, C-4′), 136.36 (C-4b), 159.17 (C-6b), 161.90 (d, $^1J_{CF} = 257.8$ Hz, C-2′), 162.48 (C-2), 162.60 (d, $^4J_{CF} = 3.5$ Hz, C-11). MS (*m*/*z*, %): 413 (M^+, 3), 374 (43), 332 (2), 303 (63), 248 (47), 182 (68), 181 (100), 180 (68), 123 (80), 83 (11). Anal. Calcd for $C_{26}H_{24}FN_3O$ (413): C, 75.54; H, 5.81; N, 10.17. Found: C, 76.05; H, 5.95; N, 10.25. Compound (**4b**): White crystals, yield: 0.31 g (72%), mp 101.5–103.5 °C, IR (KBr) (ν_{max}, cm^{-1}) : 3435 (N–H), 1685 (C=N), 1091 (C–F). ^1H NMR (300.1 MHz, $CDCl_3$): δ_H 2.24 (6H, s, Ar*Me*$_2$), 6.71 (1H, br s, NH), 7.06 (2H, d, $J = 4.8$ Hz, C-3″,5″–H), 7.09 (1H, dd, $J_1 = 8.7$, $J_2 = 3.3$ Hz, C-7–H), 7.11 (1H, t, $J = 4.8$ Hz, C-4″–H), 7.13 (1H, d, $J = 7.6$ Hz, C-5–H), 7.16 (1H, dd, $J_1 = 8.7$, $J_2 = 2.1$ Hz, C-8–H), 7.19 (1H, dt, $J_1 = 7.7$, $J_2 = 3.3$, $J_3 = 2.1$ Hz, C-8a–H), 7.27 (1H, d, $J = 7.6$ Hz, C-6–H), 7.28 (1H, dd, $J_1 = 5.4$, $J_2 = 2.2$ Hz, C-3′–H), 7.38 (1H, m, C-5′–H), 7.59 (1H, m, C-4′–H), 7.67 (1H, dd, $J_1 = 7.6$, $J_2 = 2.8$ Hz, C-6′–H), 7.74

(1H, dd, $J_1 = 4.4$, $J_2 = 8.1$ Hz, C-3–H), 8.34 (1H, dd, $J_1 = 8.1$, $J_2 = 1.4$ Hz, C-4–H), 9.13 (1H, dd, $J_1 = 4.4$, $J_2 = 1.4$ Hz, C-2–H). ^{13}C NMR ($CDCl_3$): δ_C 18.28 (2C, s, Ar*Me*$_2$), 71.73 (N–*C*H–O), 115.9 (d, $^2J_{CF} = 21.2$ Hz, C-3′), 116.98 (C-3), 117.28 (C-5), 117.49 (d, $^3J_{CF} = 9.8$ Hz, C-10), 123.04 (d, $^2J_{CF} = 11.5$ Hz, C-1′), 123.48 (C-6a), 124.50 (d, $^4J_{CF} = 3.6$ Hz, C-5′), 126.58 (C-8), 126.69 (C-6), 128.26 (C-4a), 128.83 (C-3″,5″), 130.32 (C-7), 131.11 (d, $^3J_{CF} = 8.4$ Hz, C-6′), 132.78 (C-4″), 132.81 (C-4), 135.45 (C-2″,6″), 135.50 (d, $^3J_{CF} = 9.3$ Hz, C-4′), 136.98 (C-4b), 149.91 (C-6b), 159.03 (C-1″), 162.03 (d, $^1J_{CF} = 258.4$ Hz, C-2′), 162.33 (C-2), 162.82 (d, $^4J_{CF} = 3.6$ Hz, C-11). MS (*m*/*z*, %): 435 (M^+, 1), 395 (2), 248 (6), 181 (15), 180 (100), 153 (18), 76 (39). Anal. Calcd for $C_{28}H_{22}FN_3O$ (435): C, 77.24; H, 5.06; N, 9.66. Found: C, 77.87; H, 5.18; N, 9.52.