[Chem. Pharm. Bull.]
32(4)1604—1607(1984)

Transformation of Pyrazolo[3,4-*c*][1,5]benzothiazepines into Quinolines

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(Received July 29, 1983)

Pyrazolo[3,4-*c*][1,5]benzothiazepines (**4**, **5**) were transformed into quinolines (**6**, **7**) in refluxing xylene in the presence of sodium hydride. The reaction of **6** with *N,N*-dimethylformamide dimethylacetal gave 1-methyl-4-oxo-3-phenyl-1,2,3,4-tetrahydropyrimido[5,4-*b*]-quinoline (**10**). The photochemical reaction of 4-anilino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (**12**) in xylene under a 100 W high pressure Hg-lamp gave 1,2-dihydro-1-methyl-3-oxo-2-phenyl-3*H*-pyrazolo[4,3-*b*]quinoline (**3**).

Keywords—pyrazolo[3,4-*c*][1,5]benzothiazepine; pyrazolone; pyrazole; quinoline; desulfurization; pyrazolo[4,3-*b*]quinoline; photochemical reaction

Previously we obtained 1,2-dihydro-4-hydroxy-1-methyl-2-phenyl-3*H*-benz[*f*]indazol-3-one (**1**)¹⁾ by thermal desulfurization of 1-methyl-2-phenyl-1,2,3,10-tetrahydro-4*H*-benzo[6,7]thiepine[3,4-*c*]pyrazole-3,4-dione (**2**).²⁾ In connection with that work, we have studied the desulfurization of 1-methyl-3-oxo-2-phenyl-1,2,3,10-tetrahydro-4*H*-pyrazolo[3,4-*c*][1,5]benzothiazepine (**4**) in order to obtain 1,2-dihydro-1-methyl-3-oxo-2-phenyl-3*H*-pyrazolo[4,3-*b*]quinoline (**3**). We report here a ring transformation reaction of pyrazolo[3,4-*c*][1,5]benzothiazepines into quinolines.

Chart 1

Our previous results¹⁾ suggested that thermal desulfurization of **4** might give **3**. Thus, a xylene solution of **4** was heated at 170–180 °C in an autoclave. However, it was found that the desulfurized product obtained here was 3-methylamino-2-quinolinecarboxanilide (**6**) (5.7% yield) instead of the expected compound (**3**). The yield of this desulfurized material (**6**) increased to 46% when **4** was refluxed in xylene in the presence of a base such as sodium hydride. The structural assignment of **6** was carried out in the following way. The mass spectrum [*m/z*: 277 (*M*⁺)] and elemental analysis established the formula C₁₇H₁₅N₃O. The infrared (IR) spectrum showed absorptions at 3400 cm⁻¹ (NH) and 1660 cm⁻¹ (amidocarbonyl). Acetylation of **6** with acetic anhydride or acetyl chloride gave the mono *N*-acetyl derivative (**8**), whose IR spectrum showed an absorption due to the remaining secondary amine at 3280 cm⁻¹. On the other hand, methylation of **6** with methyl iodide in the presence of sodium hydride gave 3-dimethylamino-*N*-methyl-2-quinolinecarboxanilide (**9**), whose IR

spectrum did not show a secondary amino group. The nuclear magnetic resonance (NMR) spectrum indicated that two methyl groups had been introduced. The reaction of **6** with *N,N*-dimethylformamide dimethylacetal gave 1-methyl-4-oxo-3-phenyl-1,2,3,4-tetrahydropyrimido[5,4-*b*]quinoline (**10**) (10%) and 3-(*N*-methylformamido)-2-quinolinecarboxanilide (**11**) (18%). The NMR spectrum of **10** revealed an N-CH₂-N function (δ 3.15 ppm) and the mass spectrum [m/z = 289 (M^+)] established the assigned structure.

The conversion of 1-methyl-2-phenyl-6-trifluoromethyl-1,2,3,10-tetrahydro-4*H*-pyrazolo[3,4-*c*][1,5]benzothiazepin-3-one (**5**)³⁾ into 3-methylamino-7-trifluoromethyl-2-quinolinecarboxanilide (**7**) was carried out in the same manner as the synthesis of **6** from **4**. The above experiments implied that cleavage of the N-N bond of the pyrazolone ring occurred in the course of the desulfurization of **4**. An alternative synthesis of **3** was accomplished

Chart 2

Chart 3

by the photochemical reaction (100 W high pressure Hg-lamp 10 h) of 4-anilino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (**12**)⁴⁾ in xylene in 73% yield.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The ultraviolet (UV) spectra were recorded on a Hitachi EPS-3T recording spectrophotometer ESP-3T, and the IR spectra were measured with a Nihon Bunko model IR-S. The NMR spectra were measured with a Japan Electron

Optics Laboratory Co. JNM-MH-100 spectrometer using tetramethylsilane as internal standard. Mass spectra were measured with a Hitachi M-52 mass spectrometer.

3-Methylamino-2-quinolinecarboxanilide (6)—A mixture of **4** (620 mg), xylene (60 ml), and sodium hydride (50% mineral oil dispersion, 200 mg) was refluxed for 5 h. The reaction mixture was poured into water and extracted with benzene. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was distilled off and the residue was recrystallized from ether to give yellow needles of mp 138–139 °C. Yield 256 mg (46%). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3400 (NH), 1660 (CON). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 263 (5.25), 319 (3.86). NMR (CDCl_3) δ : 2.95 (3H, s, N-Me), 7.00–7.90 (10H, m, aromatic protons), 8.10 (1H, br s, Me-NH-), 10.42 (1H, br s, Ph-NH-CO-). MS m/z : 277 (M^+). Anal. Calcd for $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.55; H, 5.25; N, 15.05.

3-Methylamino-7-trifluoromethyl-2-quinolinecarboxanilide (7)—A mixture of **5** (750 mg), xylene (60 ml) and sodium hydride (50% mineral oil dispersion, 200 mg) was treated in the same manner as described for the synthesis of **6**. Yellow needles, mp 172–173 °C. Yield 275 mg (40%). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3340 (NH), 1665 (CON<). NMR (CDCl_3) δ : 2.98 (3H, s, N-Me), 7.15–8.20 (9H, m, aromatic protons), 8.50 (1H, br s, MeNH-), 10.35 (1H, br s, -CONHPh). Anal. Calcd for $\text{C}_{18}\text{H}_{14}\text{F}_3\text{N}_3\text{O}$: C, 62.61; H, 4.09; N, 12.17. Found: C, 62.90; H, 4.33; N, 12.41.

3-(N-Acetyl-N-methyl)amino-2-quinolinecarboxanilide (8)—(i) Compound **6** (300 mg) was dissolved in 10 ml of acetic anhydride, and the solution was refluxed for 1 h. Excess acetic anhydride was distilled off. The residue was washed with ether to obtain a crystalline powder. Recrystallization from ethanol gave colorless prisms of mp 201–203 °C. Yield 305 mg (88%). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3280 (NH), 1660 (C=O). NMR (CDCl_3) δ : 1.85 (3H, s, -COCH₃), 3.37 (3H, s, N-Me), 7.10–8.30 (10H, m, aromatic protons), 10.20 (1H, br s, -CONHPh). Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_2$: C, 71.45; H, 5.37; N, 13.16. Found: C, 71.69; H, 5.51; N, 13.28. (ii) Compound **6** (300 mg) was dissolved in 10 ml of acetyl chloride and the solution was refluxed for 1 h. Excess acetyl chloride was distilled off. The residue was added to saturated sodium bicarbonate solution and extracted with chloroform. The chloroform extract was washed with water and dried over anhydrous sodium sulfate. Evaporation of chloroform gave colorless prisms of mp 201–203 °C. Yield 312 mg (90%).

3-Dimethylamino-N-methyl-2-quinolinecarboxanilide (9)—Compound **6** (0.5 g) was dissolved in refluxing xylene (60 ml). Sodium hydride (50% mineral oil dispersion, 200 mg) was added. Refluxing and stirring were continued for 3 h. After cooling of the mixture, methyl iodide (2 ml) was added and stirring was continued for 2 h under cooling with ice. The reaction mixture was poured into water and extracted with benzene. The benzene-extract was washed with water, and dried over anhydrous sodium sulfate. Benzene was distilled off and the residue was purified by column chromatography on silica gel to give colorless prisms of mp 120–122 °C. Yield 230 mg (42%). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1645 (CON<). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 263 (4.86), 356 (3.54). NMR (CDCl_3) δ : 2.65 (6H, s, -N^{Me}₂), 3.55 (3H, s, CONMe), 6.90–7.55 (10H, m, aromatic protons). MS m/z : 305 (M^+). Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}$: C, 74.73; H, 6.27; N, 13.76. Found: C, 74.66; H, 6.09; N, 13.51.

1-Methyl-4-oxo-3-phenyl-1,2,3,4-tetrahydropyrimido[5,4-*b*]quinoline (10)—A mixture of **6** (0.3 g) and dimethylformamide dimethylacetal (5 g) was refluxed on a mantle heater for 3 h. On cooling of the mixture, crystals appeared and were recrystallized from ethanol to give yellow prisms of mp 192–193 °C. Yield 197 mg (63%). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1675 (C=O). MS m/z : 289 (M^+). NMR (CDCl_3) δ : 3.15 (2H, s, N-CH₂-N), 3.20 (3H, s, N-CH₃), 7.40–8.30 (10H, m, aromatic protons). Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}$: C, 74.72; H, 5.23; N, 14.53. Found: C, 74.98; H, 5.41; N, 14.66.

3-(N-Methyl)formamido-2-quinolinecarboxanilide (11)—(i) A mixture of **6** (0.3 g) and dimethylformamide dimethylacetal (5 g) was refluxed on a mantle heater for 3 h. On cooling of the mixture, crystals appeared and were recrystallized from ethanol to obtain compound **10**. The mother liquor was concentrated to obtain crystals, which were recrystallized from ethanol, mp 185–187 °C. Yield 60 mg (18%). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3300 (NH), 1675 (C=O). MS m/z : 305 (M^+). Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_2$: C, 70.80; H, 4.95; N, 13.76. Found: C, 70.69; H, 5.01; N, 13.46. (ii) A mixture of **6** (300 mg) and 5 ml of 99% formic acid was refluxed for 1 h. The mixture was poured into water and extracted with chloroform. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was recrystallized from ethanol to give colorless prisms of mp 185–187 °C, yield 290 mg (88%).

This compound was identical with the compound prepared by method (i) in terms of the IR spectra and the mixed melting point.

1,2-Dihydro-1-methyl-2-phenyl-3-oxo-3H-pyrazolo[4,3-*b*]quinoline (3)—A solution of **12** (1 g) in 50 ml of xylene was irradiated with a 100 W Hg-lamp for 10 h. The solvent was distilled off and the residue was purified by column chromatography on silica gel. The chloroform eluate provided crystals, yield 150 mg (15%). Recrystallization from ethanol gave colorless needles of mp 253–254 °C. MS m/z : 275 (M^+). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 322 (4.15), 329 (4.15), 336 (4.27). NMR (CDCl_3): 3.59 (3H, s, N-Me), 7.40–8.00 (10H, m, aromatic protons). Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}$: C, 74.16; H, 4.76; N, 15.26. Found: C, 74.36; H, 4.91; N, 15.37.

Acknowledgement The authors are indebted to the members of the Laboratory of Instrumental Analysis of this Faculty for elemental analyses and NMR spectral measurements.

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