A Facile Synthesis of Novel 1-Aryl-1*H*-pyrazolo[3,4-*b*]quinoxalines

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The reactions of 3-methyl-2-oxo-1,2-dihydroquinoxaline **3** with chlorophenyl diazonium salts afforded the hydrazones **4a-c**, whose chlorinations with phosphoryl chloride gave the dichlorides **5a-c**. Refluxing of the dichlorides **5a-c** and base in *N,N*-dimethylformamide provided the 1-aryl-1*H*-pyrazolo[3,4-*b*]quinoxalines **6a-c**.

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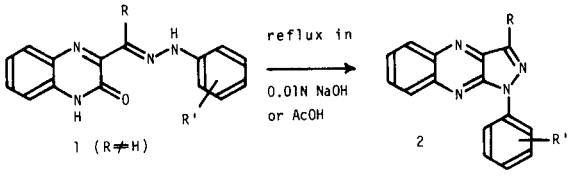
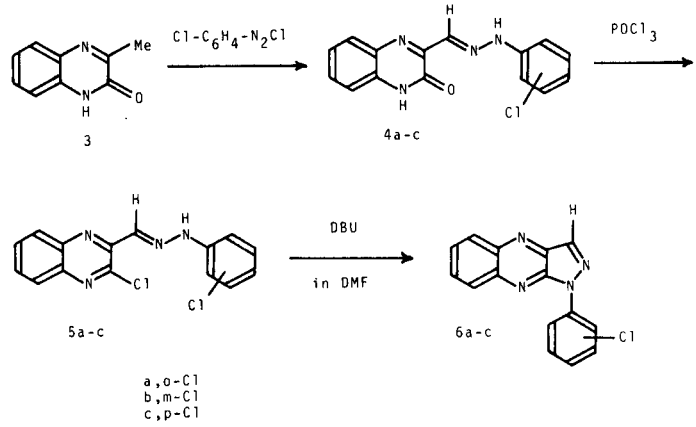
1,3-Disubstituted pyrazolo[3,4-*b*]quinoxalines **2** have been synthesized by dehydrative cyclizations of 3-acyl-2-oxo-1,2-dihydroquinoxaline arylhydrazones **1** [1-4], wherein the presence of substituents (R) at the hydrazone carbon facilitates the dehydrative cyclizations [1] (Scheme 1).



SCHEME 1

For example, refluxing of **1** in 0.01 *N* sodium hydroxide solution or in acetic acid easily resulted in the above cyclizations to afford **2**. However, when there is no substituent at the hydrazone carbon of **1** (namely, R = H), the dehydrative cyclizations do not take place under the above reaction conditions. In fact, starting materials were recovered in the attempted cyclizations of 3-formyl-2-oxo-1,2-dihydroquinoxaline chlorophenylhydrazones **4a-c** (**a** = *o*-Cl, **b** = *m*-Cl, **c** = *p*-Cl), previously prepared from the reactions of 3-methyl-2-oxo-1,2-dihydroquinoxaline **3** with chlorophenyl diazonium salts in 81-98% yields [5] (Scheme 2). Accordingly, the other effective method had to be devised for the production of the 3-unsubstituted 1-aryl-1*H*-pyrazolo[3,4-*b*]quinoxalines **6a-c** from **4a-c**. This paper describes the facile synthesis of the novel 1-aryl-1*H*-pyrazolo[3,4-*b*]-quinoxalines **6a-c** from **3**.

The diazotizations of **3** conveniently provided the chlorophenylhydrazones **4a-c** [6], whose chlorinations with phosphoryl chloride gave the dichlorides **5a-c** in 85-90% yields. Refluxing of the dichlorides **5a-c** in diazabicyclo-[5,4,0]-7-undecene (DBU) and *N,N*-dimethylformamide resulted in the cyclization to afford the 1-aryl-1*H*-pyrazolo-[3,4-*b*]quinoxalines **6a-c** in 79-83% yields. Thus, 1-aryl-1*H*-pyrazolo[3,4-*b*]quinoxalines **6a-c** were synthesized with facility from 3-methyl-2-oxo-1,2-dihydroquinoxaline **3** by three steps in good yields (Scheme 2). The pmr spectra of **6a-c** exhibited the C_3-H proton signals at δ 9.10 (**6a**), 9.07 (**6b**) and 9.07 (**6c**) ppm. The other spectral and analytical data supported the structures of **6a-c**.



SCHEME 2

EXPERIMENTAL

General Procedure.

All melting points are uncorrected. Infrared (ir) spectra were recorded from potassium bromide discs on a JASCO IRA-1 spectrophotometer. Proton magnetic resonance (pmr) spectra were measured with an EM-390 spectrometer at 90 MHz using tetramethylsilane as an internal reference. Chemical shifts are given in the δ scale, relative to the internal reference. Mass spectra (ms) were determined with a JMS-01S spectrometer (JEOL).

Preparation of the Dichlorides **5a-c**.

A solution of **4a** (20 g) in phosphoryl chloride (300 ml) was refluxed in an oil bath for 9 hours. Phosphoryl chloride was evaporated *in vacuo* to precipitate yellow needles **5a**, to which 1,4-dioxane (300 ml) was added. The mixture was poured onto crushed ice to precipitate the yellow needles **5a**, which were collected by suction filtration (19.76 g, 90%). Recrystallization from *N,N*-dimethylformamide/ethanol gave orange needles, mp 182-183°; ms: m/z 316 (M^+), 318 ($M^+ + 2$); ir: ν cm^{-1} 3060, 3020, 1602, 1590, 1550, 1510; pmr (trifluoroacetic acid): 8.52 (s, 1H, hydrazone CH), 8.40-7.80 (m, 8H, aromatic). The NH proton signal was unobservable.

Anal. Calcd. for $C_{15}H_{10}Cl_2N_4$: C, 56.80; H, 3.18; Cl, 22.36; N, 17.66. Found: C, 56.83; H, 2.97; Cl, 22.13; N, 17.90.

Compounds **5b,c** were obtained by a similar manner to the above [**5b** (85%), **5c** (86%)].

Compounds **5b** and **5c** had mp 163-164° and 211-212°, respectively; ms: m/z 316 (M^+), 318 ($M^+ + 2$), (**5b,c**); ir: ν cm^{-1} 3060, 3030, 1600, 1560, 1510 (**5b**), 3060, 3040, 1600, 1555, 1515, 1510 (**5c**); pmr (trifluoroacetic acid): 8.47-7.27 (m, hydrazone CH and aromatic) (**5b**), 8.40-7.00 (m, hydrazone CH and aromatic) (**5c**). The NH proton signals of **5b,c** were unobservable.

Anal. Calcd. for $C_{15}H_{10}Cl_2N_4$: C, 56.80; H, 3.18; Cl, 22.36; N. 17.66. Found: C, 56.72; H, 3.09; Cl, 22.18; N, 17.42 (**5b**); C, 56.93; H, 3.31; Cl, 22.54; N, 17.91 (**5c**).

Preparation of the 1-Aryl-1*H*-pyrazolo[3,4-*b*]quinoxalines **6a-c**.

A solution of **5a** (2 g, 0.0063 mole) and DBU (0.96 g, 0.0076 mole) in *N,N*-dimethylformamide (100 ml) was refluxed in an oil bath for 3 hours. Removal of the solvent by evaporation *in vacuo* left an oily residue, which was triturated with water to give yellow crystals **6a** (1.46 g, 83%). Recrystallization from ethanol afforded yellow needles, mp 108-109°; ms: m/z 280 (M^+), 282 ($M^+ + 2$); ir: ν cm^{-1} 3080, 3055, 1585, 1575, 1565, 1490, 1470; pmr (deuteriodimethyl sulfoxide): 9.10 (s, 1H, C_3-H), 8.47-7.57 (m, 8H, aromatic).

Anal. Calcd. for $C_{15}H_9ClN_4$: C, 64.18; H, 3.23; Cl, 12.63; N, 19.96. Found: C, 63.95; H, 3.50; Cl, 12.77; N, 19.74.

Compounds **6b,c** were obtained by a similar manner to the above [**6b** (81%), **6c** (79%)].

Compounds **6b** and **6c** had mp 151-152° and 199-200°, respectively; ms: m/z 280 (M^+), 282 ($M^+ + 2$) (**6b,c**); ir: ν cm^{-1} 3120, 3080, 1600, 1590, 1570, 1560, 1540, 1520 (**6b**), 3110, 3060, 1600, 1580, 1570, 1560, 1540, 1500 (**6c**); pmr (trifluoroacetic acid): 9.07 (s, 1H, C_3-H), 8.80-7.50 (m, 8H, aromatic) (**6b**), 9.07 (s, 1H, C_3-H), 8.80-7.50 (m, 8H, aromatic) (**6c**).

Anal. Calcd. for $C_{15}H_9ClN_4$: C, 64.18; H, 3.23; Cl, 12.63; N, 19.96. Found: C, 64.08; H, 3.30; Cl, 12.33; N, 19.72 (**6b**); C, 63.90; H, 3.16; Cl, 12.38; N, 19.97 (**6c**).

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[6] 3-Formyl-2-oxo-1,2-dihydroquinoxaline arylhydrazones have been synthesized by the condensation of 3-formyl-2-oxo-1,2-dihydroquinoxaline with arylhydrazines. However, our method can synthesize the above arylhydrazones from 3-methyl-2-oxo-1,2-dihydroquinoxaline and substituted anilines by means of a facile diazotization.