

A New Method for the Synthesis of Novel 1-Aryl-3-heteroaryl-1*H*-pyrazolo[3,4-*b*]quinoxalines

Yoshihisa Kurasawa,* Muneto Muramatsu, Kaoru Yamazaki, Setsuko Tajima,
Yoshihisa Okamoto and Atsushi Takada

School of Pharmaceutical Sciences, Kitasato University, 9-1, Shirokane 5-chome, Minato-ku,
Tokyo 108, Japan

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The reaction of 3-(2,3-dihydro-4-methyl-3-thioxo-4*H*-1,2,4-triazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline **4** with *o*-chlorobenzediazonium chloride gave 3-[α -(*o*-chlorophenylhydrazono)-2,3-dihydro-4-methyl-3-thioxo-4*H*-1,2,4-triazol-5-ylmethyl]-2-oxo-1,2-dihydroquinoxaline **6**, whose refluxing in phosphoryl chloride/pyridine afforded 1-(*o*-chlorophenyl)-3-(2,3-dihydro-4-methyl-3-thioxo-4*H*-1,2,4-triazol-5-yl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **7**. The reactions of **6** and **7** with nitrous acid resulted in sulfur extrusion to provide 1-(*o*-chlorophenyl)-3-(4-methyl-4*H*-1,2,4-triazol-5-yl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **8** and 3-[α -(*o*-chlorophenylhydrazono)-4-methyl-4*H*-1,2,4-triazol-5-ylmethyl]-2-oxo-1,2-dihydroquinoxaline **9**, respectively.

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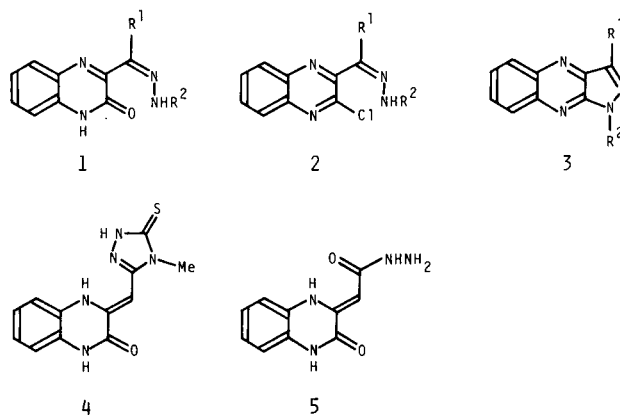
Various 1*H*-pyrazolo[3,4-*b*]quinoxalines **3** (flavazoles) have been synthesized so far by the direct dehydrative cyclization of the hydrazones **1** in a diluted base or acetic acid under reflux (Method 1) [1-4] or the dehydrochlorination of the chlorinated hydrazones **2** (Method 2) [5,6], but there have been few compounds possessing the heteroaryl substituents at the C₃-position (R¹) of **3** (Chart). In order to provide the heteroaryl substituent at the C₃-position of **3**, 3-(2,3-dihydro-4-methyl-3-thioxo-4*H*-1,2,4-triazol-5-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline **4** was employed as a starting material, which was previously synthesized by us from the hydrazide **5** [7]. That is, a convenient diazotization [6,8] of **4** into the hydrazone **6** and the subsequent cyclization of **6** would afford the requisite 1-aryl-3-heteroaryl-1*H*-pyrazolo[3,4-*b*]quinoxaline **7**. This paper describes a new method for the synthesis of novel 1-aryl-3-heteroaryl-1*H*-pyrazolo[3,4-*b*]quinoxalines **7** and **8**.

The reaction of **4** with *o*-chlorobenzediazonium chloride gave 3-[α -(*o*-chlorophenylhydrazono)-2,3-dihydro-4-methyl-3-thioxo-4*H*-1,2,4-triazol-5-ylmethyl]-2-oxo-1,2-dihydroquinoxaline **6**, whose one-step cyclization was found to be accomplished by refluxing in phosphoryl chloride/pyridine, furnishing 1-(*o*-chlorophenyl)-3-(2,3-dihydro-4-methyl-3-thioxo-4*H*-1,2,4-triazol-5-yl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **7**. The above method 1 was not effective for the one-step cyclization of **6**. The reaction of **7** with nitrous acid resulted in sulfur extrusion [7] to provide 1-(*o*-chlorophenyl)-3-(4-methyl-4*H*-1,2,4-triazol-5-yl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **8**. A similar sulfur extrusion took place in the reaction of **6** with nitrous acid, giving 3-[α -(*o*-chlorophenylhydrazono)-4-methyl-4*H*-1,2,4-triazol-5-ylmethyl]-2-oxo-1,2-dihydroquinoxaline **9**.

General Procedure.

Synthesis of the Hydrazone 6.

A solution of sodium nitrite (8.28 g, 0.12 mole) in water



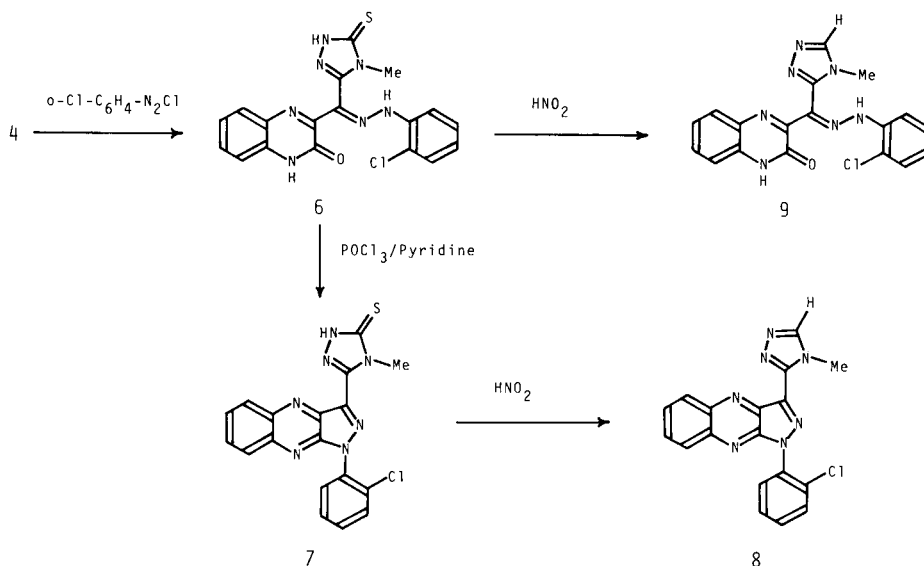
CHART

(100 ml) was added to a suspension of *o*-chloroaniline hydrochloride (18.1 g, 0.11 mole) in 10% hydrochloric acid (200 ml) with stirring in an ice-water bath to give a clear solution, which was successively added to a suspension of **4** (25.0 g, 0.092 mole) in acetic acid (300 ml) and water (100 ml) with stirring in an ice-water bath to afford a yellow suspension. The suspension was heated on a boiling water bath for 2 hours with an initial stirring to provide orange crystals **6** (36.73 g, 97%). Recrystallization from *N,N*-dimethylformamide/ethanol gave orange needles, mp 314-315°; ms: *m/z* 411 (M⁺), 413 (M⁺+2); ir: ν cm⁻¹ 1663; pmr (deuteriodimethylsulfoxide): δ 14.47 (s, 1H, NH), 13.72 (s, 1H, NH), 12.72 (s, 1H, NH), 8.00-6.80 (m, 8H, aromatic), 3.49 (s, 3H, Me).

Anal. Calcd. for C₁₈H₁₄ClN₃OS: C, 52.49; H, 3.42; Cl, 8.51; N, 23.80; S, 7.78. Found: C, 52.22; H, 3.45; Cl, 8.62; N, 23.90; S, 7.65.

Synthesis of the 1-Aryl-3-heteroaryl-1*H*-pyrazolo[3,4-*b*]quinoxaline 7.

A solution of the hydrazone **6** (20 g) in phosphoryl



chloride (200 ml) and pyridine (20 ml) was refluxed in an oil bath for 3 hours. The solution was evaporated *in vacuo* to leave an oily residue, which was dissolved in dioxane. The solution was poured onto crushed ice to give yellow crystals, which were collected by suction filtration. (These yellow crystals were confirmed to include no open-chained 3-chloro compound when checked by mass spectroscopy). A solution of the above whole yellow crystals and 1,8-diazabicyclo[5,4,0]-7-undecene (6.4 g) in *N,N*-dimethylformamide (400 ml) was refluxed in an oil bath for 3 hours. Evaporation of the solvent *in vacuo* followed by trituration with water furnished yellow crystals 7, which were collected by suction filtration (17.94 g, 94%). Recrystallization from *N,N*-dimethylformamide/ethanol gave orange needles, mp 344-345°; ms: m/z 393 (M^+), 395 ($\text{M}^+ + 2$); ir: ν cm^{-1} 1570, 1510, 1490, 1475, 1460; pmr (deuteriodimethylsulfoxide): δ 14.37 (brs, 1H, NH), 8.67-7.60 (m, 8H, aromatic), 3.91 (s, 3H, Me).

Anal. Calcd. for $\text{C}_{18}\text{H}_{12}\text{ClN}_7\text{S}$: C, 54.89; H, 3.06; Cl, 9.00; N, 24.89; S, 8.14. Found: C, 54.92; H, 3.15; Cl, 9.30; N, 25.09; S, 8.12.

Synthesis of the 1-Aryl-3-heteroaryl-1H-pyrazolo[3,4-*b*]quinoxaline 8.

A solution of sodium nitrite (3.51 g, 0.0509 mole) in water (20 ml) was added to a suspension of 7 (5 g, 0.0127 mole) in acetic acid (300 ml) with stirring in an ice-water bath. The whole mixture was heated on a boiling water bath for 2 hours to give a clear solution. The solvent was evaporated *in vacuo* to afford yellow crystals, which were trituated with hot water, and the residual yellow crystals 8 were collected by suction filtration (4.49 g, 98%). Recrystallization from *N,N*-dimethylformamide/ethanol afforded yellow needles, mp 319-320°; ms: m/z 361 (M^+), 363 ($\text{M}^+ + 2$); ir: ν cm^{-1} 3080, 1585, 1560, 1515, 1490, 1470; pmr (trifluoroacetic acid): δ 9.81 (s, 1H, $\text{C}_3\text{-H}$), 9.00-7.57 (m, 8H, aromatic), 4.63 (s, 3H, Me).

Anal. Calcd. for $\text{C}_{18}\text{H}_{12}\text{ClN}_7$: C, 59.76; H, 3.34; Cl, 9.80; N, 27.10. Found: C, 59.65; H, 3.21; Cl, 9.71; N, 27.31.

Synthesis of the Hydrazone 9.

A solution of sodium nitrite (10.07 g, 0.146 mole) in water (50 ml) was added to a suspension of the hydrazone 6 (20 g, 0.0486 mole) in acetic acid (500 ml) and water (50 ml) with stirring in an ice-water bath. The whole mixture was heated on a boiling water bath for 3 hours. After the yellow crystals which precipitated were filtered off, the solvent was evaporated *in vacuo* to provide crystals, which were trituated with hot water, and residual yellow crystals 9 were collected by suction filtration (14.85 g, 81%). Recrystallization from *N,N*-dimethylformamide/ethanol gave yellow needles as 1:1 complex of 9 and *N,N*-dimethylformamide, mp 316-317°; ms: m/z 379 (M^+), 381 ($\text{M}^+ + 2$); ir: ν cm^{-1} 1680, 1645, 1610; pmr (trifluoroacetic acid): δ 9.28 (s, 1H, $\text{C}_3\text{-H}$), 8.67-7.13 (m, 9H, aromatic and CH of HCONMe_2), 4.16 (s, 3H, $\text{N}_4\text{-Me}$), 3.38 (s, 3H, Me of HCONMe_2), 3.27 (s, 3H, Me of HCONMe_2).

Anal. Calcd. for $\text{C}_{21}\text{H}_{21}\text{ClN}_8\text{O}_2$: C, 55.69; H, 4.67; Cl, 7.83; N, 24.74. Found: C, 55.57; H, 4.39; Cl, 7.92; N, 24.58.

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