A New Synthesis of Novel 1-Aryl-3-heteroaryl-1*H*-pyrazolo[3,4-*b*]quinoxalines *via* a Key Intermediate

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The chlorination of the α-hydrazonoester **4** with phosphoryl chloride/pyridine gave 3-[α-(*o*-chlorophenylhydrazono)methoxycarbonylmethyl]-2-chloroquinoxaline **5**, whose cyclization with 1,8-diazabicyclo[5,4,0]-7-undecene afforded 3-methoxycarbonyl-1-(*o*-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **6**. The reaction of **6** with hydrazine hydrate provided 3-hydrazinocarbonyl-1-(*o*-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **7**, whose reactions with methyl and allyl isothiocyanates furnished 3-(2,3-dihydro-4-methyl-3-thioxo-4*H*-1,2,4-triazol-5-yl)-1-(*o*-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **2** and 3-(4-allyl-2,3-dihydro-3-thioxo-4*H*-1,2,4-triazol-5-yl)-1-(*o*-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **8**, respectively. Moreover, the reactions of **7** with triethyl orthoformate and orthoacetate gave 1-(*o*-chlorophenyl)-3-(1,3,4-oxadiazol-5-yl)-1*H*-pyrazolo-[3,4-*b*]quinoxaline **9a** and 1-(*o*-chlorophenyl)-3-(2-methyl-1,3,4-oxadiazol-5-yl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **9b**, respectively.

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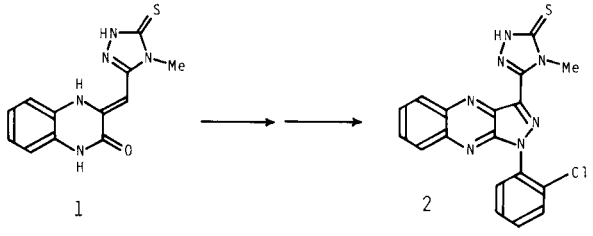
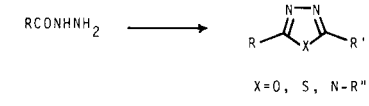
In a previous paper [1], we reported the synthesis of 3-(2,3-dihydro-4-methyl-3-thioxo-4*H*-1,2,4-triazol-5-yl)-1-(*o*-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **2** from the 3-triazolylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline **1** (Scheme 1). However, the starting material **1** was not



SCHEME 1

suitable for the synthesis of 1-aryl-1*H*-pyrazolo[3,4-*b*]quinoxalines possessing the various heteroaryl groups at the C_3-position. Since acyl hydrazides have been well known to be converted into various azoles [2-4] (Scheme 2), the synthesis of 3-hydrazinocarbonyl-1-(*o*-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **7** would offer an access to the various 1-aryl-3-heteroaryl-1*H*-pyrazolo[3,4-*b*]quinoxalines **2, 8** and **9a,b**. This paper describes a new synthesis of the 1-aryl-3-heteroaryl-1*H*-pyrazolo[3,4-*b*]quinoxalines **2, 8** and **9a,b** *via* the key intermediate **7**, using the α-hydrazonoester **4** as a starting material, which has been previously synthesized by us from the ester **3** [5].

The chlorination of **4** with phosphoryl chloride/pyridine gave 3-[α-(*o*-chlorophenylhydrazono)methoxycarbonylmethyl]-2-chloroquinoxaline **5**, whose cyclization with 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) afforded 3-methoxycarbonyl-1-(*o*-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **6**. The reaction of **6** with hydrazine hydrate provided **7**, whose reactions with methyl and allyl isothiocyanates in the presence of DBU furnished **2** and 3-(4-allyl-2,3-dihydro-3-thioxo-4*H*-1,2,4-triazol-5-yl)-1-(*o*-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **8**, respectively. Furthermore, the reactions of **7** with triethyl orthoformate and orthoacetate in the presence of DBU gave 1-(*o*-chlorophenyl)-3-(1,3,4-oxadiazol-5-yl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **9a**



SCHEME 2

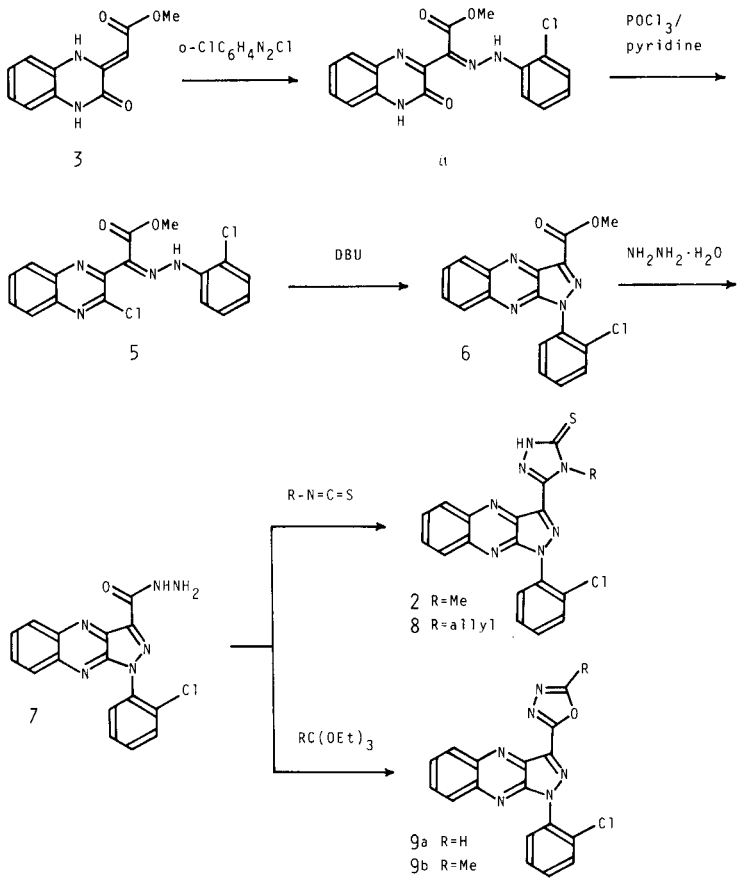
and 1-(*o*-chlorophenyl)-3-(2-methyl-1,3,4-oxadiazol-5-yl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **9b**, respectively.

General Procedure.

3-[α-(*o*-Chlorophenylhydrazono)methoxycarbonylmethyl]-2-chloroquinoxaline **5**.

A solution of **4** (20 g) in phosphoryl chloride (200 ml) and pyridine (5 ml) was refluxed in an oil bath for 3 hours. The solution was evaporated *in vacuo* gave yellow crystals **5**, which were triturated with dioxane. The mixture was poured onto crushed ice to precipitate yellow crystals **5**, which were collected by suction filtration (20.91 g, 99%). Recrystallization from ethanol afforded yellow needles, mp 164-165°; ms: m/z 374 (M^+), 376 ($M^+ + 2$); ir: ν cm^{-1} 1680; pmr (deuteriodimethylsulfoxide): δ 12.88 (s, 1H, NH), 8.40-7.00 (m, 8H, aromatic), 3.84 (s, 3H, Me).

Anal. Calcd. for $C_{17}H_{11}ClN_4O_2$: C, 54.42; H, 3.22; Cl, 18.90; N, 14.93. Found: C, 54.59; H, 3.18; Cl, 19.12; N, 14.99.



SCHEME 3

3-Methoxycarbonyl-1-(*o*-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]-quinoxaline **6**.

A solution of **5** (20 g, 0.0533 mole) and DBU (8.10 g, 0.0533 mole) in *N,N*-dimethylformamide (200 ml) and dioxane (200 ml) was refluxed in an oil bath for 2 hours. The solvent was evaporated *in vacuo* to a small volume, and then addition of water precipitated yellow crystals **6**, which were collected by suction filtration (17.45 g, 97%). Recrystallization from *N,N*-dimethylformamide/ethanol gave yellow needles, mp 228-229°; ms: m/z 338 (M^+), 340 ($M^+ + 2$); ir: ν cm^{-1} 1720; pmr (deuteriodimethylsulfoxide): δ 8.57-7.60 (m, 8H, aromatic), 4.07 (s, 3H, Me).

Anal. Calcd. for $C_{17}H_{11}ClN_4O_2$: C, 60.27; H, 3.26; Cl, 10.47; N, 16.53. Found: C, 60.30; H, 3.32; Cl, 10.73; N, 16.40.

3-Hydrazinocarbonyl-1-(*o*-chlorophenyl)-1*H*-pyrazolo-[3,4-*b*]quinoxaline **7**.

A suspension of **6** (10 g, 0.0295 mole) and hydrazine hydrate (7.38 g, 0.148 mole) in ethanol (300 ml) was refluxed on a boiling water bath for 3 hours to precipitate yellow needles **7**, which were collected by suction filtration (8.40 g). Evaporation of the filtrate *in vacuo* gave additional yellow needles **7** (1.45 g). Total yield, 9.85 g (99%). Recrystallization from *N,N*-dimethylformamide/ethanol afforded yellow needles, mp 232-233°, ms: m/z 338 (M^+), 340 ($M^+ + 2$); ir: ν cm^{-1} 3320, 3260, 1680; pmr (deuteriodimethylsulfoxide): δ 8.57-7.20 (m, 8H, aromatic), 4.00 (br, $NHNH_2$ and water).

Anal. Calcd. for $C_{16}H_{11}ClN_6O$: C, 56.73; H, 3.27; Cl, 10.47; N, 24.81. Found: C, 56.96; H, 3.22; Cl, 10.59; N, 24.78.

3-(2,3-Dihydro-4-methyl-3-thioxo-4*H*-1,2,4-triazol-5-yl)-1-(*o*-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **2**.

A suspension of **7** (2 g, 5.92 mmoles) and methyl isothiocyanate (0.519 g, 7.10 mmoles) in 1-butanol (50 ml) was refluxed in an oil bath for 10 minutes, and then DBU (0.5 ml) was added to the mixture. The whole mixture was refluxed for additional 50 minutes to precipitate orange crystals **2**, which were collected by suction filtration (1.28 g). Acetic acid (10 ml) was added to the filtrate, and the

whole solution was evaporated *in vacuo* to give additional crystals **2**, which were triturated with ethanol/water and then collected by suction filtration (0.87 g). Total yield, 2.15 g (92%). Recrystallization from *N,N*-dimethylformamide/ethanol afforded orange needles, whose ir spectrum and melting point were identical with those of an authentic sample [1].

3-(4-Allyl-2,3-dihydro-3-thioxo-4*H*-1,2,4-triazol-5-yl)-1-(*o*-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **8**.

A suspension of **7** (2 g, 5.92 mmoles) and allyl isothiocyanate (0.704 g, 7.10 mmoles) in 1-butanol (50 ml) was refluxed in an oil bath for 10 minutes, and then DBU (0.5 ml) was added to the mixture. The whole mixture was refluxed for additional 50 minutes to give a clear solution. After addition of acetic acid (10 ml) to the solution, the solvent was evaporated *in vacuo* to provide orange crystals **8**, which were triturated with ethanol/water and then collected by suction filtration (2.19 g, 88%). Recrystallization from *N,N*-dimethylformamide/ethanol gave orange needles, mp 261-262°, ms: m/z 419 (M^+), 421 ($M^+ + 2$); ir: ν cm^{-1} 1640, 1570, 1500, 1490; pmr (deuteriodimethylsulfoxide): δ 14.47 (s, 1H, NH), 8.53-7.57 (m, 8H, aromatic), 5.90 (m, 1H, $-CH_2-CH=CH_2$), 5.27-4.83 (m, 4H, $-CH_2-CH=CH_2$).

Anal. Calcd. for $C_{20}H_{14}ClN_7S$: C, 57.21; H, 3.36; Cl, 8.44; N, 23.35. Found: C, 57.33; H, 3.18; Cl, 8.29; N, 23.41.

1-(*o*-Chlorophenyl)-3-(1,3,4-oxadiazol-5-yl)-1*H*-pyrazolo-[3,4-*b*]quinoxalines **9a,b**.

A suspension of **7** (2 g) and the appropriate triethyl orthoester (20 ml) in 1-butanol (50 ml) was refluxed in an oil bath for 10 minutes, and then DBU (0.5 ml) was added to the mixture. The whole mixture was refluxed for additional 50 minutes to give a clear solution. After addition of acetic acid (10 ml) into the solution, the solvent was evaporated *in vacuo* to afford yellow crystals **9a,b**, which were triturated with ethanol/water and then collected by suction filtration [**9a** (1.84 g, 89%), **9b** (1.94 g, 93%)]. Recrystallization from *N,N*-dimethylformamide/ethanol provided yellow needles **9a,b**.

Compound **9a** had mp 269-270°; ms: m/z 348 (M^+), 350 ($M^+ + 2$); ir: ν cm^{-1} 3080, 1601, 1582, 1570, 1540; pmr (deuteriodimethylsulfoxide): δ 9.65 (s, 1H, $C_{2'}$-H), 8.67-7.20 (m, 8H, aromatic).

Anal. Calcd. for $C_{17}H_9ClN_7O$: C, 58.55; H, 2.60; Cl, 10.16; N, 24.10. Found: C, 58.43; H, 2.81; Cl, 10.22; N, 24.33.

Compound **9b** had mp 256-257°; ms: m/z 362 (M^+), 364 ($M^+ + 2$); ir: ν cm^{-1} 1601, 1584, 1570, 1540; pmr (deuteriodimethylsulfoxide):δ 8.60-7.57 (m, 8H, aromatic), 2.72 (s, 3H, Me).

Anal. Calcd. for $C_{18}H_{11}ClN_6O$: C, 59.60; H, 3.06; Cl, 9.77; N, 23.17. Found: C, 59.55; H, 3.18; Cl, 9.87; N, 23.29.

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