# A Facile Synthesis of 1-Aryl-3-heteroaryl-1*H*-pyrazolo[3,4-*b*]quinoxalines and Related Compounds with Antifungal Activity [1]



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The novel 1*H*-pyrazolo[3,4-*b*]quinoxalines (flavazoles) **9-15** were synthesized from 3-methoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline **6** *via* a convenient hydrazone synthesis, and these flavazoles were clarified to have the antifungal activity.

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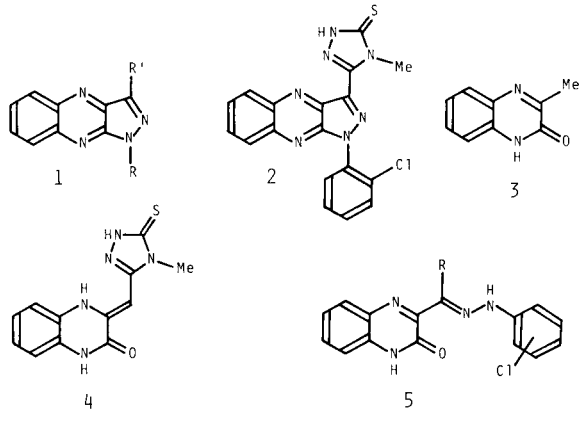
There have been reported the syntheses of the 1*H*-pyrazolo[3,4-*b*]quinoxalines (flavazoles) **1** possessing the various substituents at the $N_1$- and $C_3$-positions (R and R') (Chart) [2-6], wherein 1-aryl-3-heteroaryl-1*H*-pyrazolo[3,4-*b*]quinoxalines such as 3-(2,3-dihydro-4-methyl-3-thioxo-4*H*-1,2,4-triazol-5-yl)-1-(*o*-chlorophenyl)-1*H*-pyrazolo[3,4*b*]-quinoxaline **2** have seldom appeared so far in literatures. In previous papers [7-9], we synthesized the flavazoles **1** (R = aryl, R' = H) and **2** from the quinoxalines **3** and **4**, respectively, *via* a facile preparation of the hydrazones **5** utilizing aryl diazonium salts. However, the starting material **4** was not suitable for the synthesis of the 1-aryl-1*H*-pyrazolo[3,4-*b*]quinoxalines having the various heteroaryl-groups at the $C_3$-position. Since acyl hydrazides have been well known to be converted into various azoles [10-12] (Scheme 1), the synthesis of 3-hydrazinocarbonyl-1-(*o*-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **10** (Scheme 2) would provide an access to the various 1-aryl-3-heteroaryl-1*H*-pyrazolo[3,4-*b*]quinoxalines **2**, **11**, **12a,b**. Accordingly, the ester **6** was employed as a starting material in the present investigation, since the ester **6** could be converted into the α-hydrazonoester **7** [13], which would lead to the production of the hydrazide **10**. This paper describes a convenient synthesis of 1-aryl-3-heteroaryl-1*H*-pyrazolo-[3,4-*b*]quinoxalines **2**, **11**, **12a,b** from the starting material **6** *via* the key intermediate **10**. In addition, the above flavazoles were clarified to possess the antifungal activity by our screening test, and hence the hydrazide **10** was converted into the novel flavazoles **13-15**, which were also submitted to the screening test.



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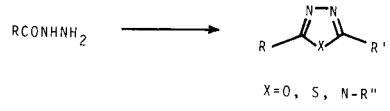
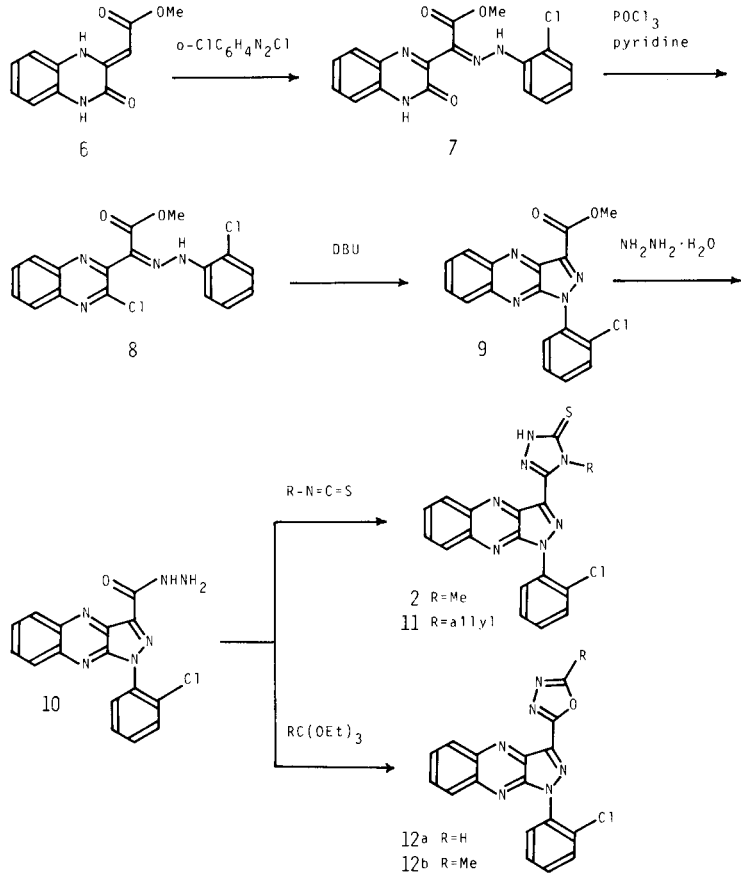


SCHEME 1

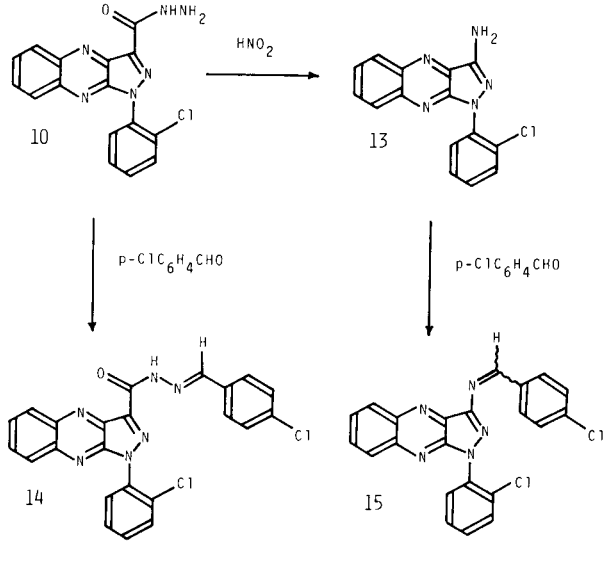
The chlorination **7** with phosphoryl chloride/pyridine gave 3-[α-(*o*-chlorophenylhydrazono)methoxycarbonylmethyl]-2-chloroquinoxaline **8**, whose cyclization with 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) afforded 3-methoxycarbonyl-1-(*o*-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **9**. The reaction of **9** with hydrazine hydrate provided **10**, whose reactions with methyl and allyl isothiocyanate 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 **11**, respectively. Furthermore, the reactions of **10** with triethyl orthoformate and orthoacetate in the presence of DBU provided 1-(*o*-chlorophenyl)-3-(1,3,4-oxadiazol-5-yl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **12a** and 3-(2-methyl-1,3,4-oxadiazol-5-yl)-1-(*o*-chlorophenyl)-1*H*-pyrazolo-[3,4-*b*]quinoxaline **12b**, respectively.

On the other hand, the reaction of **10** with nitrous acid resulted in the Curtius rearrangement to give 3-amino-1-(*o*-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **13** (Scheme 3). The reactions of **10** and **13** with *p*-chlorobenzaldehyde afforded 1-(*o*-chlorophenyl)-3-(*p*-chlorophenylmethylenehydrazinocarbonyl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **14** and 1-(*o*-chlorophenyl)-3-(*p*-chlorophenylmethyleneamino)-1*H*-pyrazolo[3,4-*b*]quinoxaline **15**, respectively.

The above flavazoles **9-15** and the dichloride **8** were found to possess the antifungal activity against *Pathium*




SCHEME 2




SCHEME 3

*debaryanum*, *Pyriclaria oryzae* and *Rhizoctonia solani*, as shown in Table. In general, compounds **9-15** were comparably potent against *Pathium debaryanum* and less potent against *Rhizoctonia solani*. In addition, compound **11** was the most potent among all the above flavazoles against the above three fungi.

## EXPERIMENTAL

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

3-[$\alpha$-(*o*-Chlorophenylhydrazono)methoxycarbonylmethyl]-2-chloroquinoxaline **8**.

A solution of **7** (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 **8**, which were triturated with dioxane. The

Table

Antifungal Activity of Compounds **8-15**

| Compound | Concentration (ppm) | Activity [a] P.d | P.o. | R.s. [b] |
|---|---|---|---|---|
| **8** | 100 | 58 | 42 | 10 |
| | 50 | 32 | 34 | 5 |
| | 10 | 4 | 6 | 9 |
| **9** | 100 | 76 | 26 | 10 |
| | 50 | 46 | 17 | 8 |
| | 10 | 25 | 3 | 6 |
| **10** | 100 | 80 | 47 | 47 |
| | 50 | 65 | 42 | 43 |
| | 10 | 17 | 16 | 7 |
| **11** | 100 | 89 | 56 | 69 |
| | 50 | 60 | 55 | 48 |
| | 10 | 5 | 40 | 45 |
| **12a** | 100 | 80 | 48 | 29 |
| | 50 | 24 | 40 | 12 |
| | 10 | 14 | 18 | 8 |
| **12b** | 100 | 73 | 53 | 50 |
| | 50 | 62 | 55 | 34 |
| | 10 | 11 | 23 | 4 |
| **13** | 100 | 43 | 45 | 62 |
| | 50 | 22 | 32 | 46 |
| | 10 | 1 | 13 | 40 |
| **14** | 100 | 48 | 22 | 36 |
| | 50 | 20 | 4 | 38 |
| | 10 | 0 | 0 | 1 |
| **15** | 100 | 61 | 11 | 26 |
| | 50 | 37 | 17 | 16 |
| | 10 | 8 | 9 | 17 |

[a] Growth inhibition (%). [b] P.d.: *Pythium debaryanum*, P.o.: *Pyriclaria oryzae*, R.s.: *Rhizoctonia solani*.

mixture was poured onto crushed ice to precipitate yellow crystals **8**, 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: $\nu$ $cm^{-1}$ 1680; pmr (deuteriodimethylsulfoxide): 12:88 (s, 1H, NH), 8.40-7.00 (m, 8H, aromatic), 3.84 (s, 3H, Me).

*Anal.* Calcd. for $C_{17}H_{12}Cl_2N_4O_2$: C, 54.42; H, 3.22; Cl, 18.90; N, 14.93. Found: C, 54.49; H, 3.18; Cl, 19.12; N, 14.99.

3-Methoxycarbonyl-1-(*o*-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **9**.

A solution of **8** (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 **9**, 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: $\nu$ $cm^{-1}$ 1720; pmr (deuteriodimethylsulfoxide): 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 **10**.

A suspension of **9** (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 **10**, which were collected by suction filtration (8.40 g). Evaporation of the filtrate *in vacuo* gave additional yellow needles **10** (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: $\nu$ $cm^{-1}$ 3320, 3260, 1680; pmr (deuteriodimethylsulfoxide): 8.57-7.20 (m, 8H, aromatic), 4.00 (br, $-NHNH_2$ and $H_2O$).

*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 **10** (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 [9].

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 **11**.

A suspension of **10** (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 **11**, 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: $\nu$ $cm^{-1}$ 1640, 1570, 1500, 1490; pmr (deuteriodimethylsulfoxide): 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 **12a,b**.

A suspension of **10** (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 **12a,b**, which were triturated with ethanol/water and then collected by suction filtration [**12a** (1.84 g, 89%), **12b** (1.94 g, 93%)]. Recrystallization from *N,N*-dimethylformamide/ethanol provided yellow needles **12a,b**.

Compound **12a** had mp 269-270°; ms: m/z 348 ($M^+$), 350 ($M^+ + 2$); ir: $\nu$ $cm^{-1}$ 3080, 1601, 1582, 1570, 1540; pmr (deuteriodimethylsulfoxide): 9.65 (s, 1H, $C_2$-H), 8.67-7.20 (m, 8H, aromatic).

*Anal.* Calcd. for $C_{17}H_9ClN_6O$: 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 **12b** had mp 256-257°; ms: m/z 362 ($M^+$), 364 ($M^+ + 2$); ir: $\nu$ $cm^{-1}$ 1601, 1584, 1570, 1540; pmr (deuteriodimethylsulfoxide): 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.

3-Amino-1-(*o*-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **13**.

A solution of sodium nitrite (2.04 g, 0.0296 mole) in water (30 ml) was added to a suspension of **10** (10 g, 0.0296 mole) in acetic acid (150 ml) and water (20 ml) with stirring in an ice-water bath. The mixture was heated on a boiling water bath for 2 hours with an initial stirring to precipitate yellow crystals **13**. After the mixture was cooled to room temperature, the yellow crystals **13** were collected by suction filtration (5.03 g). The filtrate was evaporated *in vacuo* to afford yellow crystals, which were triturated with water to provide additional yellow crystals **13** (3.43 g), total yield, 8.46 g (97%). Recrystallization from ethanol gave yellow

needles, mp 187-188°; ms: m/z 295 ($M^+$), 297 ($M^+ + 2$); ir: $\nu$ $cm^{-1}$ 3440, 3270, 3200, 3160, 1620; pmr (deuteriodimethylsulfoxide): 8.40-7.00 (m, 8H, aromatic), 6.58 (s, 2H, $NH_2$).

*Anal.* Calcd. for $C_{15}H_{10}ClN_5$: C, 60.92; H, 3.41; Cl, 11.99; N, 23.68. Found: C, 60.73; H, 3.41; Cl, 11.91; N, 23.48.

1-(*o*-Chlorophenyl)-3-(*p*-chlorophenylmethylenehydrazinocarbonyl)-1*H*-pyrazolo[3,4-*b*]quinoxaline **14**.

A solution of **10** (2 g, 5.92 mmoles) and *p*-chlorobenzaldehyde (0.998 g, 7.10 mmoles) in 1-butanol (50 ml) and *N,N*-dimethylformamide (20 ml) was refluxed in an oil bath for 2 hours. The solution was cooled to room temperature to precipitate yellow crystals **14**, which were collected by suction filtration (1.46 g). The filtrate was evaporated *in vacuo* gave additional yellow crystals **14** (1.0 g). Total yield, 2.46 g (90%). Recrystallization from *N,N*-dimethylformamide/ethanol afforded yellow needles, mp 213-214°; ms: m/z 460 ($M^+$), 462 ($M^+ + 2$); ir: $\nu$ $cm^{-1}$ 1700; pmr (deuteriodimethylsulfoxide): 12.28 (s, 1H, NH), 8.67 (s, 1H, benzylidene CH), 8.57-7.00 (m, 12H, aromatic).

*Anal.* Calcd. for $C_{23}H_{14}Cl_2N_6O$: C, 59.88; H, 3.06; Cl, 15.37; N, 18.22. Found: C, 59.74; H, 3.35; Cl, 15.13; N, 18.24.

1-(*o*-Chlorophenyl)-3-(*p*-chlorophenylmethyleneamino)-1*H*-pyrazolo[3,4-*b*]-quinoxaline **15**.

A solution of **13** (2 g, 6.77 mmoles) and *p*-chlorobenzaldehyde (1.14 g, 8.12 mmoles) in 1-butanol (50 ml) was refluxed in an oil bath for 2 hours. The solution was cooled to room temperature to precipitate yellow crystals **15**, which were collected by suction filtration (2.33 g). The filtrate was evaporated *in vacuo* to give additional yellow crystals **15**, which were triturated with ethanol and then collected by suction filtration (0.27 g), total yield, 2.60 g (94%). Recrystallization from *N,N*-dimethylformamide/ethanol provided yellow needles, mp 202-203°; ms: m/z 417 ($M^+$), 419 ($M^+ + 2$); ir: $\nu$ $cm^{-1}$ 1605, 1590, 1562, 1490; pmr (deuteriodimethylsulfoxide): 9.92 (s, 1H, benzylidene CH), 8.50-7.57 (m, 12H, aromatic).

*Anal.* Calcd. for $C_{22}H_{13}Cl_2N_5$: C, 63.17; H, 3.13; Cl, 16.95; N, 16.74. Found: C, 63.19; H, 3.12; Cl, 17.04; N, 16.81.

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