# Studies in Vilsmeier-Haack Reaction. IX. Synthesis and Application of Novel Heterocyclo-Substituted Furo[2,3-*c*:5,4-*c*']dipyrazole Derivatives

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The Vilsmeier–Haack reaction on 4,4'-bi-4*H*-pyrazole-5,5'(1*H*,1'*H*)-dione brought about the formation of one methyl group, chloro substitution of a carbonyl group in the 5-position, and the cyclization of the 5-chloro-3-(2-amino-1-formylethenyl)derivative in one step to give the corresponding furo[2,3-*c*:5,4-*c*']dipyrazole (**3**). Treatment of **3** with some secondary heterocyclic amines gave the aminomethylene derivatives **6**—**8**. Interaction of **3** with hydroxylamine hydrochloride, hydrazine hydrate and phenylhydrazine afforded the corresponding isoxazolyl and pyrazolyl derivatives **9**—**11** which have been screened in vitro for antibacterial and antifungal activities.

In view of the current interest in the pharmacological activity of pyrazolones and their activities, as germicides,[1] antifungal,[2–5] and antibacterial agents,[6] it was intended to synthesize a wide variety of heterocyclic compounds containing a 4,4'-bi-4*H*-pyrazole-5,5'(1*H*, 1'*H*)-dione[7] moiety for studying their utility as pharmacological agents. Thus, the present paper describe the application of the Vilsmeier[8–15] reaction to 4,4'-bi-4*H*-pyrazole-5,5'(1*H*, 1'*H*)-dione to prepare several hitherto unreported heterocycle-fused pyrazole derivatives with several heterocyclic substituents at the 3-position in the hope that some of them might show improved pharmacological properties.

## Results and Discussion

The Vilsmeier–Haack reaction on 3,3'-dimethyl-1,1'-diphenyl-4,4'-bi-4*H*-pyrazole-5,5'(1*H*, 1'*H*)-dione (**1**) in equal molar ratio with Vilsmeier reagent on cold at 5—10 °C for 2 h giving 4-[5-chloro-3-(1-formyl-2-dimethylaminoethenyl)-1-phenyl-1*H*-pyrazol-4-yl]-2,4-dihydro-5-methyl-2-phenyl-3*H*-pyrazol-3-one (**2**). This means that the Vilsmeier reagent attacked only one methyl group of the two pyrazole rings and the another methyl group with carbonyl function still intact. However, when the reaction mixture of an equimolar ratio of Vilsmeier reagent and 4,4'-bipyrazolone was carried out on hot at 70—80 °C for 7—8 h (usual condentions), a

Table 1. Physicochemical Characteristics of Compounds (**2**—**12**)

| Compd No. | Mp °C | Yield % | Formula (M.W.) | Calcd/% C | H | N | Cl | Found/% C | H | N | Cl |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 320[d] | 82 | $C_{20}H_{18}N_4O_2$ (346.40) | 69.35 | 5.24 | 16.17 | — | 68.95 | 5.19 | 16.20 | — |
| **2** | 345 | 70 | $C_{24}H_{22}N_5O_2Cl$ (447.98) | 64.35 | 4.95 | 15.63 | 7.92 | 64.52 | 5.15 | 15.28 | 8.18 |
| **3** | 240 | 80 | $C_{24}H_{21}N_5O_2$ (412.48) | 69.89 | 5.38 | 16.98 | — | 69.20 | 5.40 | 16.19 | — |
| **4** | 220 | 85 | $C_{20}H_{17}N_4OCl$ (364.55) | 65.84 | 4.70 | 15.36 | 9.72 | 65.13 | 4.79 | 15.92 | 9.01 |
| **5** | 260 | 75 | $C_{22}H_{16}N_4O_3$ (383.41) | 68.92 | 4.21 | 14.61 | — | 69.00 | 4.18 | 14.28 | — |
| **6** | 302 | 65 | $C_{27}H_{25}N_5O_2$ (451.53) | 71.82 | 5.58 | 15.51 | — | 71.95 | 5.49 | 15.48 | — |
| **7** | 330 | 68 | $C_{26}H_{23}N_5O_3$ (453.51) | 68.86 | 5.11 | 15.44 | — | 68.10 | 1.19 | 15.37 | — |
| **8** | 290 | 72 | $C_{26}H_{24}N_6O_2$ (452.52) | 69.01 | 5.35 | 18.57 | — | 69.55 | 5.40 | 18.17 | — |
| **9** | 338 | 70 | $C_{22}H_{15}N_5O_2$ (381.41) | 69.28 | 3.96 | 18.36 | — | 69.01 | 3.80 | 18.59 | — |
| **10** | 240 | 78 | $C_{22}H_{16}N_6O$ (380.41) | 69.46 | 4.24 | 22.09 | — | 69.62 | 4.29 | 21.88 | — |
| **11** | 287 | 58 | $C_{28}H_{20}N_6O$ (456.51) | 73.67 | 4.42 | 18.41 | — | 73.20 | 4.49 | 18.48 | — |
| **12** | 370 | 70 | $C_{48}H_{38}N_{10}O_4$ (829.98) | 70.04 | 4.94 | 17.31 | — | 69.87 | 5.15 | 17.98 | |

d=decomp without melting.

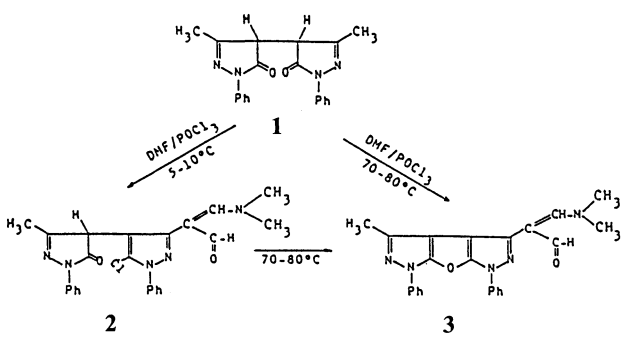
Table 2. Characteristic IR Bands of the Synthesized Compounds in $cm^{-1}$

| Assignment Compd No. | $\nu$ >C=O | Acrolein-CHO | $\nu$ >C=C | $\nu$ >C=N | $\nu$ >C–$CH_3$ | $\nu$ C–O–C | $\nu$ C–Cl | $\nu$ OH | $\nu$ NH |
|---|---|---|---|---|---|---|---|---|---|
| **2** | 1710 | 1620 | 1600 | 1590 | 1400 | — | 745 | — | — |
| **3** | — | 1615 | 1605 | 1580 | 1395 | 1078, 1020 | — | — | — |
| **4** | 1715 | — | 1600 | 1585 | 1400 | — | 750 | — | — |
| **5** | — | 1625 | 1600 | 1585 | 1405 | 1080, 1025 | — | 3250 | — |
| **6** | — | 1615 | 1605 | 1590 | 1400 | 1075, 1025 | — | — | — |
| **8** | — | 1625 | 1605 | 1595 | 1390 | 1085, 1020 | — | — | 3280 |
| **9** | — | — | 1600 | 1585 | 1400 | 1080, 1025 | — | — | — |
| **10** | — | — | 1600 | 1585 | 1400 | 1078, 1025 | — | — | 3285 |

Table 3. $^1H$ NMR Spectra of Representative Examples of the Synthesized Compounds (Chemical Shifts in $\delta$/ppm)

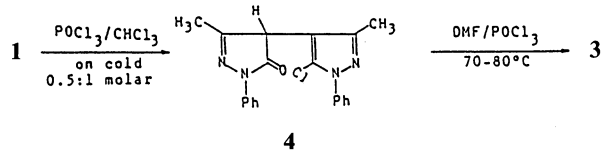
| Compound No. | Aromatic protons (m) | /$CH_3$ –N \$CH_3$ (s) | –$CH_3$ (s) | $\alpha,\beta$-Unsaturated CHO (s) | Enolic OH malonaldehyde (s) | Side-chain methine =CH–N< (s) | /$CH_2$– –N \$CH_2$– (t) | >NH (s) |
|---|---|---|---|---|---|---|---|---|
| **2** | 7.00—8.20 (10 H) | 2.82—2.92 (6 H) | 2.35 (3 H) | 9.15 (1 H) | — | 8.45 (1 H) | — | — |
| **3** | 7.15—8.35 (10 H) | 2.85—2.90 (6 H) | 2.40 (3 H) | 9.20 (1 H) | — | 8.50 (1 H) | — | — |
| **5** | 7.20—8.15 (10 H) | — | 2.35 (3 H) | 9.25 (1 H) | 4.80 (1 H) | 8.35 (1 H) | — | — |
| **6** | 7.10—8.30 (10 H) | — | 2.38 (3 H) | 9.24 (1 H) | — | 8.45 (1 H) | 2.80 (2t, 4H, 2$\alpha CH_2$), 3.68 (2t, 4H, 2$\beta CH_2$), 3.72 ( t, 2H, $\gamma CH_2$), | — |
| **7** | 7.20—8.25 (10 H) | — | 2.33 (3 H) | 9.23 (1 H) | — | 8.44 (1 H) | 2.86 (2t, 4H, 2$\alpha CH_2$), 3.70 (2t, 4H, 2$\alpha CH_2$), | — |
| **8** | 7.22—8.30 (10 H) | — | 2.32 (3 H) | 9.25 (1 H) | — | 8.46 (1 H) | 2.84 (2t, 4H, 2$\alpha CH_2$), 3.70 (2t, 4H, 2$\beta CH_2$). | 9.85 (1 H) |
| **9** | 7.10—8.20 (10 H) | — | 2.36 (3 H) | — | — | — | — | — |
| **10** | 7.15—8.20 (10 H) | — | 2.36 (3 H) | — | — | — | — | 10.60 (1 H) |

tricyclic fused compound 3-(1-formyl-2-dimethylaminoethenyl)-4-methyl-1,6-diphenyl furo[2,3-*c*: 5,4-*c'*] dipyrazole (**3**) was obtained. On the other hand, when the reaction mixture was carried in 2:1 molar ratio of Vilsmeier reagent and 4,4'-bipyrazolone on cold at 5—10 °C for 3 h and/or on hot at 70—80 °C gave the same cyclized compound **3**. This means that the reaction proceeds via formylation of one 3-methyl group only, chloro substitution of a carbonyl group on 5-position, followed by ring closure with elimination of HCl giving the corresponding fused furan compound **3**. This was fully confirmed by the correct elemental analysis and the spectroscopic data (Tables 1—3).



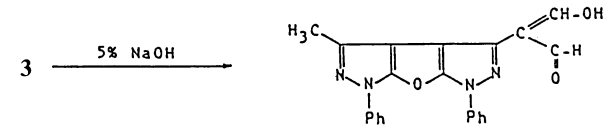

An alternative route for the formation of compound **3** from 4,4'-dipyrazolone may be assumed to through the intermediate compound **4**, followed by ring closure. It is quite clear by the action of $POCl_3$ in chloroform used 1:0.5 molar ratio of 4,4'-bipyrazolone and $POCl_3$ gave the corresponding 4-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2,4-dihydro-5-methyl-2-phenyl-3*H*-pyrazol-3-one (**4**). Vilsmeier reaction on the chloro derivative **4**, simultaneously leads to the diformylation

on the methyl group and ring closure giving a cyclized compound furo[2,3-*c*: 5,4-*c'*]dipyrazole (**3**) according to the following Scheme:



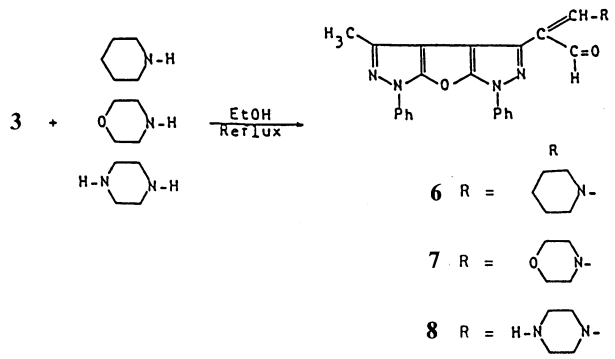

**4**

2-Amino-1-formylethenyl derivative **3** was readily hydrolyzed by heating with 5% sodium hydroxide solution giving the corresponding malonaldehyde **5** with evolution of dimethylamine, which gave a pale brown coloration with iron (III) chloride due to the formation of enolic malonaldehyde group.

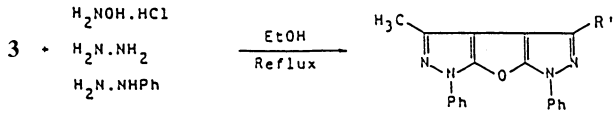


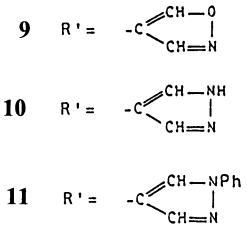

**5**

On the other hand, condensation of the 2-amino-1-formylethenyl derivative **3** with some secondary heterocyclic amines (piperidine, morpholine, and piperazine) in boiling ethanol afforded the expected aminomethylene derivatives **6**—**8**. The structures of these compounds were established from the correct microanalysis (cf. Table 1). The IR spectra were in agreement with their structures indicating the presence of a sharp absorption band at 1620 $cm^{-1}$ (side-chain CHO). $^1H$ NMR spectrum of compound **7** in $CF_3COOH$ showed the presence of signals at $\delta$=4.00—2.88 (t.>N-$CH_2$-) due to the piperidine ring, besides signals due to the other protons (cf. Table 3).




Also, interaction of **3** with hydroxylamine, hydrazine hydrate, and phenylhydrazine afforded the corresponding 4-isoxazolyl, 4-pyrazolyl, and 1-phenyl-4-pyrazolyl derivatives at the 3-position of furo[2,3-*c*: 5,4-*c'*] dipyrazole **9**—**11**.



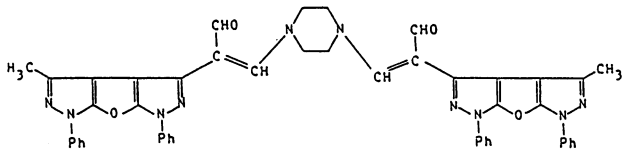




When piperazine was reacted with two moles of compound **3**, a 1,4-piperazinediyl compound **12** was obtained. The IR, $^1H$ NMR and microanalysis of this compound were in accordance with the structural formula.

Table 4. Antibacterial and Antifungal Activities of **1**—**12** Compounds (Inhibition Zones/mm)

| Compd No. | Antibacterial activity | | | | Antifungal activity | | |
|---|---|---|---|---|---|---|---|
| | *Staphylococcus aureus* | *Bacillus cereus* | *Serratia rhodnii* | *Pseudomonas aeruginosa* | *Altrnaria alternata* | *Penicillium chrysogenum* | *Aspergillus flavus* |
| **1** | 30 | 60 | 20 | 40 | 30 | 40 | 30 |
| **2** | 105 | 65 | 95 | 100 | 65 | 55 | 70 |
| **3** | 120 | 70 | 105 | 95 | 75 | 110 | 75 |
| **4** | 110 | 30 | 105 | 120 | 80 | 75 | 45 |
| **5** | 80 | 30 | 60 | 65 | 50 | 140 | 30 |
| **6** | 70 | 100 | 80 | 85 | 40 | 70 | -ve |
| **7** | 95 | 50 | 90 | 75 | 30 | 50 | 40 |
| **8** | 65 | 20 | 60 | 30 | 40 | -ve | -ve |
| **9** | 80 | 50 | 75 | 80 | 80 | -ve | 50 |
| **10** | 90 | 40 | 110 | 35 | 120 | 50 | -ve |
| **11** | 85 | 45 | 90 | 65 | 40 | 55 | 35 |
| **12** | 80 | 40 | 120 | 70 | 60 | 40 | -ve |

-ve. Compound not effective.



12

The results obtained from antibacterial effects indicated that all compounds exhibit variable activities against all bacteria used (inhibition zones ranged from 20—120 mm). It seems that 2-amino-1-formylethenyl, piperidino, morpholino, 4-pyrazolyl compounds **3**, **6**, **7**, **10**, and chloro derivatives **2**, **4** compounds are comparatively more active against the test bacteria than the other compounds, especially with the starting compound **1**.

The antifungal results indicate that all compounds synthesized in this series possess good antifungal activities (inhibition zones ranged from 30—140 mm). All synthesized compounds showed strong effects against *Alternaria alternata* except compound **8**. Also, compounds **3**, **4**, and **5** showed potent effects against *Penicillium chrysogenum*. Furthermore, compounds **2**, **3**, **4**, **5**, **7**, and **11** are highly active against all fungi used than other compounds especially with the starting material compound **1** (cf. Table 4).

## Experimental

All melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were recorded on a PYE-UNICAM SP3-100 Infrared Spectrophotometer using KBr disc techniques. $^1$H NMR spectra were recorded on Varian EM-390 90 MHz NMR spectrometer using trifluoroacetic acid (TFA) as solvent and TMS as internal standard. Elemental analysis was carried out by elemental analyser 240C.

**3,3′-Dimethyl-1,1′-diphenyl-4,4′-bi-4*H*-pyrazole-5,5′(1*H*, 1′*H*)-dione (1):** This compound was prepared as reported previously.[7]

**3-(-1-Formyl-2-dimethylaminoethenyl)-4-methyl-1,6-diphenyl-furo[2,3-*c*: 5,4-*c*′]dipyrazole (3):** To *N*,*N*-dimethylformamide (5 ml) cooled to 0 °C, phosphoryl chloride (1.8 ml, 0.04 mol) was added and the mixture left to stand for 15 min. To this with stirring, the bipyrazolone **1** (0.02 mol) dissolved in *N*,*N*-dimethylformamide (5 ml) was added. The reaction mixture was left to stand for 10 min, then heated to 60—80 °C for 6 h with stirring. The cooled reaction mixture poured into ice-water and treated with $NaHCO_3$ to pH 9. The deep orange yellow solid separated was filtered, washed thoroughly with cold water and crystallized from methanol. The physical and chemical data are depicted in Table 1.

**4-(5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2,4-dihydro-5-methyl-2-phenyl-3*H*-pyrazol-3-one (4):** To chloroform (20 ml) solution of 4,4′-bipyrazolone (0.01 mol) cooled to 10 °C, phosphoryl chloride (0.05 mol) was added dropwise with stirring for 2 h at 30 °C. The yellow precipitate that seperated was filtered, washed thoroughly with chloroform and crystallized from ethanol to afford compound **4**.

**3-(1-Formyl-2-hydroxyethenyl)-1,6-diphenyl-4-methyl-furo[2,3-*c*: 5,4-*c*′]dipyrazole (5):** The aminoacrylaldehyde derivative **3** (1 g) taken in 5% NaOH (20 ml) was heated to 50 °C (20 min). It was then filtered off, cooled, and acidified. The solid that separated was filtered, washed well with cold water, and crystallized from aq ethanol. The physical and chemical data are quoted in Table 1.

**3-[1-Formyl-2-(piperidinyl, morpholinyl and piperazinyl)-ethenyl]-4-methyl-1,6-diphenyl-furo[2,3-*c*: 5,4-*c*′]dipyrazoles (6—8):** To compound **3** (0.01 mol) taken in ethanol (30 ml) was added (0.01 mol) quantity of the amine and the mixture gently heated on a water bath for half hour. The solid that separated after concentration and pouring onto ice-cold water was filtered, washed with cold water and crystallized from methanol. The physical and chemical data are recorded in Table 1.

**3-(4-Isoxazolyl, 4-pyrazolyl, and 1-phenyl-4-pyrazolyl)-4-methyl-1,6-diphenyl-furo[2,3*c*: 5,4-*c*′]dipyrazoles (9—11):** To a solution of compound **3** in ethanol (40 ml) was added an equimolar quantity of hydroxylamine hydrochloride, hydrazine hydrate, or phenylhydrazine, respectively. The reaction mixture was refluxed for 2 h, cooled, concentrated, and poured onto crushed ice. The precipitate solid was filtered, washed with cold water, and crystallized from ethanol. The physical and chemical data are presented in Table 1.

**Formation of Dimer (12):** To compound **3** (0.02 mol) taken in ethanol (30 ml) was added (0.01 mol) quantity of piperazine and the mixture gently heated on a water bath. The solid that separated was filtered, washed with cold water, then with cold ethanol and crystallized from ethanol. The physical and chemical data are listed in Table 1.

**Biological Activity:** All the newly synthesized compounds were tested in vitro for antibacterial activity against *Staphylococcus aureus, Serratia rhodnii, Bacillus cereus, and Pseudomonas aeruginosa* and also were tested for antifungal activity against (*Alternaria alternata, Penicillium chrysogenum,* and *Aspergillus flavus*). The culture medium was normal nutrient agar (NA), supplement with 1 g-yeast $dm^{-3}$, the tested compounds were dissolved in sterile *N*,*N*-dimethylformamide at a concentration of 0.5% (w/v) solutions were prepared. The antibacterial and antifungal activities were evaluated by the classical cupplate agar diffusion technique.[16,17] The dishes were allowed to stand in a refrigerator at 4—8 °C for 0.5 h to allow diffusion of the solutions and were then incubated at 37±1 °C for 28 h. The inhibition zones were measured with callipers.

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