[Chem. Pharm. Bull. 33(3) 982—988 (1985)]

# Synthesis of Pyrazolo[3,4-*d*]pyridazines from 5-(1-Methylhydrazino)-pyridazines by Means of the Vilsmeier–Haack Reaction

KENJI KAJI, HIROMU NAGASHIMA, YOSHIHIKO HIROSE and HIROHISA ODA*

*Gifu College of Pharmacy, 5–6–1, Mitahora-higashi, Gifu 502, Japan*

(Received June 13, 1984)

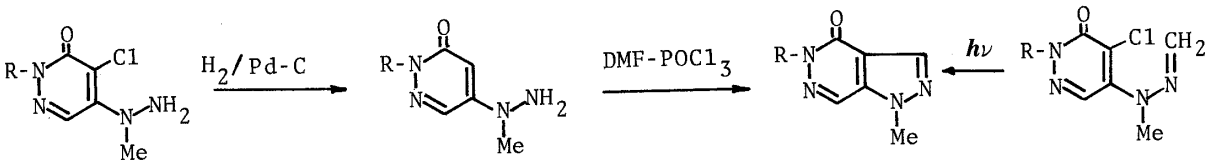
Reaction of 2-substituted 5-(1-methylhydrazino)-3(2*H*)-pyridazinones (**2a**—**d**) with dimethylformamide-phosphorus oxychloride afforded 5-substituted 1,5-dihydro-1-methyl-4*H*-pyrazolo[3,4-*d*]pyridazin-4-ones (**3a**—**d**) in good yields. However, concurrent formation of 5-substituted 2,5-dihydro-2-(2-substituted 1-chlorovinyl)-4*H*-pyrazolo[3,4-*d*]pyridazin-4-ones (**6a**—**c**, **12**, **13**) (minor products) and the 1-methyl-4*H*-derivatives (**3a**—**c**) (major ones) was observed, when starting with the corresponding 2-substituted 5-(2-acetyl-1-methylhydrazino)-3(2*H*)-pyridazinones (**5a**—**c**, **9**, **10**) under similar reaction conditions. A plausible mechanism for the reaction is proposed.

**Keywords**——pyridazine; pyrazolo[3,4-*d*]pyridazine; Vilsmeier reagent; tri-*n*-butyltin chloride; sodium borohydride; stereoisomer; photoisomerization; vinyl radical

Synthetic approaches to the pyrazolo[3,4-*d*]pyridazines, which are of great interest to chemists from chemical and biological viewpoints,[1,2] can be divided into two types:[3] one of them starts from the pyrazole and the other from the pyridazine. Most workers have used the former approach, and only a few papers have appeared on the latter one.[4] Recent papers from our laboratory have dealt with the synthesis of the title compounds by photochemical cyclization of 2-substituted 5-(1-alkyl-2-alkylidenehydrazino)-4-chloro-3(2*H*)-pyridazinones[5] and by the ring contraction of pyridazino[4,5-*e*][1,3,4]thiadiazines *via* extrusion of sulfur.[6–8]

The Vilsmeier–Haack–Arnold reaction[9] is also well known as an efficient method for the introduction of a one-carbon unit into aromatic and heteroaromatic rings.[10,11] We would like here to report a convenient synthesis of pyrazolo[3,4-*d*]pyridazines through the Vilsmeier reaction of 5-(1-methylhydrazino)-3(2*H*)-pyridazinones, as well as a novel concurrent formation of 2-chlorovinylpyrazolo[3,4-*d*]pyridazines and the 1-methyl derivatives, by starting from the 5-(2-acyl-1-methylhydrazino)-3(2*H*)-pyridazinones, under similar reaction conditions.

A solution of 2-methyl-5-(1-methylhydrazino)-3-(2*H*)-pyridazinone (**2a**)[8] was heated




**1a–d** **2a–d** **3a–d** **4a**

**a** : R=Me **b** : R=Ph **c** : R=PhCH$_2$ **d** : R=H

Chart 1

with phosphorus oxychloride in an excess of dimethylformamide (DMF) at 100 °C for 3 h, followed by treatment with water, to afford 1,5-dihydro-1,5-dimethyl-4*H*-pyrazolo[3,4-*d*]-pyridazin-4-one (**3a**) in 88% yield. The structure of **3a** was confirmed by comparison of **3a** with an authentic specimen prepared from 4-chloro-2-methyl-5-(1-methyl-2-methylidene-hydrazino)-3(2*H*)-pyridazinone (**4a**) by photocyclization.[5] Similar reaction of compounds **2b**—**d**, derived from compounds **1b**—**d**[8] by catalytic dechlorination, gave the corresponding pyrazolo[3,4-*d*]pyridazine derivatives (**3b**—**d**) in 88%, 71% and 59% yields, respectively.

However, in the reaction of 5-(2-acetyl-1-methylhydrazino)-2-methyl-3-(2*H*)-pyridazinone (**5a**) under similar conditions, concurrent formation of the compound **3a** (major product, 48% yield) and 2-(1-chlorovinyl)-2,5-dihydro-5-methyl-4*H*-pyrazolo[3,4-*d*]pyridazin-4-one (**6a**) (minor product, 18% yield) was observed. The assigned structure for **6a** was confirmed by the elemental analysis ($C_8H_7ClN_4O$), mass spectrum (MS) (*m/e*: 210, $M^+$) and proton nuclear magnetic resonance ($^1$H-NMR) spectrum, in which vinyl protons were observed at $\delta$ 5.51 and 6.28 (each doublet, $J=3$ Hz). Other 2-(1-chlorovinyl)-4*H*-pyrazolo[3,4-*d*]pyridazinone derivatives (**6b**, 15%; **6c**, 24%) were also obtained and could be separated from the major products (**3b**, 63%; **3c**, 58%) by column chromatography on silica gel when starting with the pyridazine derivatives (**5b**, **c**) under the same reaction conditions. Dechlorination of **6a** with sodium borohydride in EtOH in the presence of 0.2 equivalent of tri-*n*-butyltin chloride[12] gave the 2-vinyl derivative (**7**) (65% yield) together with a small amount of the 2-ethyl derivative (**8**) (9% yield). Compound **8** was also obtained from **6a** by catalytic hydrogenation with palladium on carbon in MeOH in 61% yield.

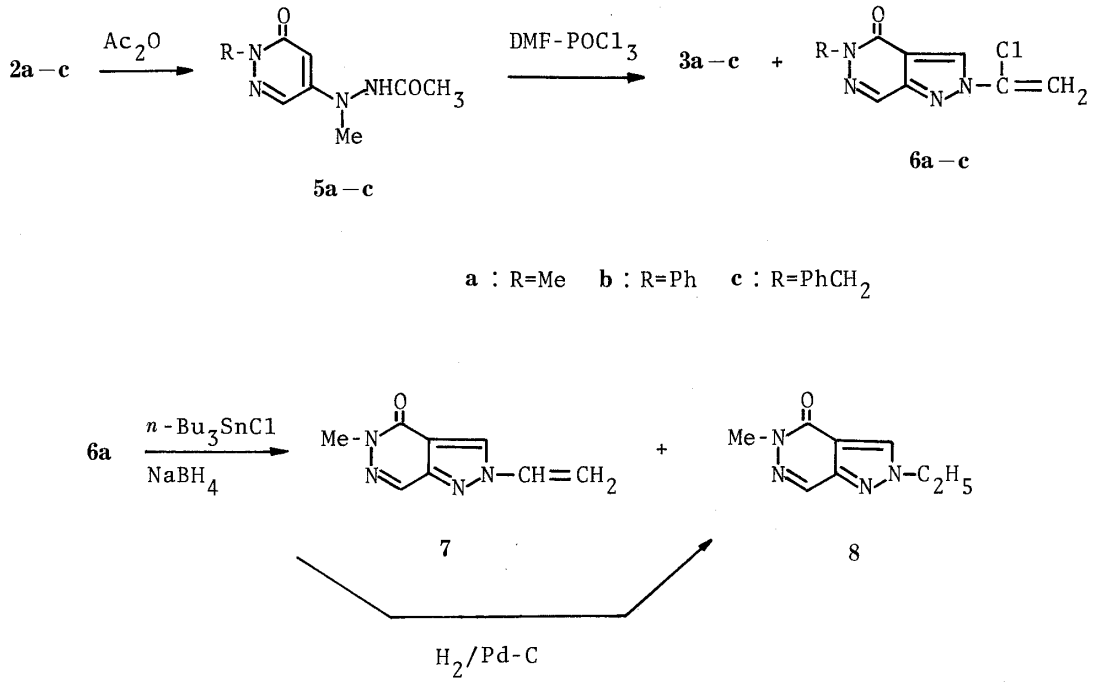



Chart 2

A possible reaction pathway for the concurrent formation of **3a**—**c** and **6a**—**c** *via* an intermediacy (A) is shown in Chart 3. The acetyl group is eliminated from the intermediate (A) to afford **3a**—**c** (path a), while demethylation, assisted by the $\beta$-aminoenone moiety, with subsequent chlorination of the acetyl group, also proceeds to give **6a**—**c** (path b).

Vilsmeier–Haack reactions of the acylhydrazinopyridazine derivatives **9** (R=isopropyl) and **10** (R=ethyl) under similar reaction conditions also afforded the 2-(1-chloro-2,2-dimethylvinyl)-pyrazolo[3,4-*d*]pyridazine derivative (**12**) (22% yield) and the 2-(1-chloro-2-

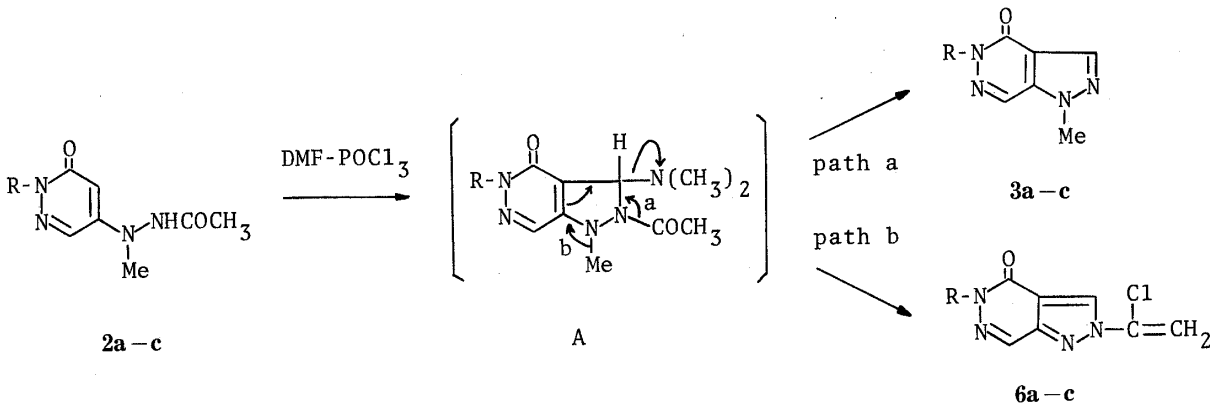



Chart 3

methylvinyl) derivative (**13**) (19% yield) together with **3a** (51% yield from **9**; 48% yield from **10**), respectively. Though compound **13** appeared to be a single compound on thin-layer chromatography (TLC) (silica gel), it was found to be a mixture of stereoisomers ($E/Z$= 80:20) from the $^1$H-NMR spectrum in deuteriochloroform. The $E/Z$ ratio changed to 35:65 through photoisomerization,[13] upon irradiation of **13** in EtOH for 10 h with a 100 W high-pressure mercury lamp. The $E$ and $Z$ stereochemistries were assigned by comparison of the chemical shift of the vinyl proton. The vinyl proton signal of $E$-isomer appears at lower field ($\delta$ 6.68) than that of the $Z$-isomer ($\delta$ 6.17) due to the magnetic anisotropy of the pyrazole ring. The $^1$H-NMR spectrum of compound **14** (a mixture of $E/Z$=78:22), obtained by dechlorination of **13** with tri-*n*-butyltin chloride and sodium borohydride as described for **7**, offered more definite information, *i.e.*, the proton spin–spin-coupling constant ($J$ value) of the $E$-isomer is 14 Hz and that of the $Z$-isomers is 9 Hz, as determined by a decoupling experiment. Compound **14** was also obtained from the photoisomerized product **13′** with the same reagents (*n*-$Bu_3SnCl$ and $NaBH_4$) in almost the same ratio ($E/Z$=75:25) as from **13**.

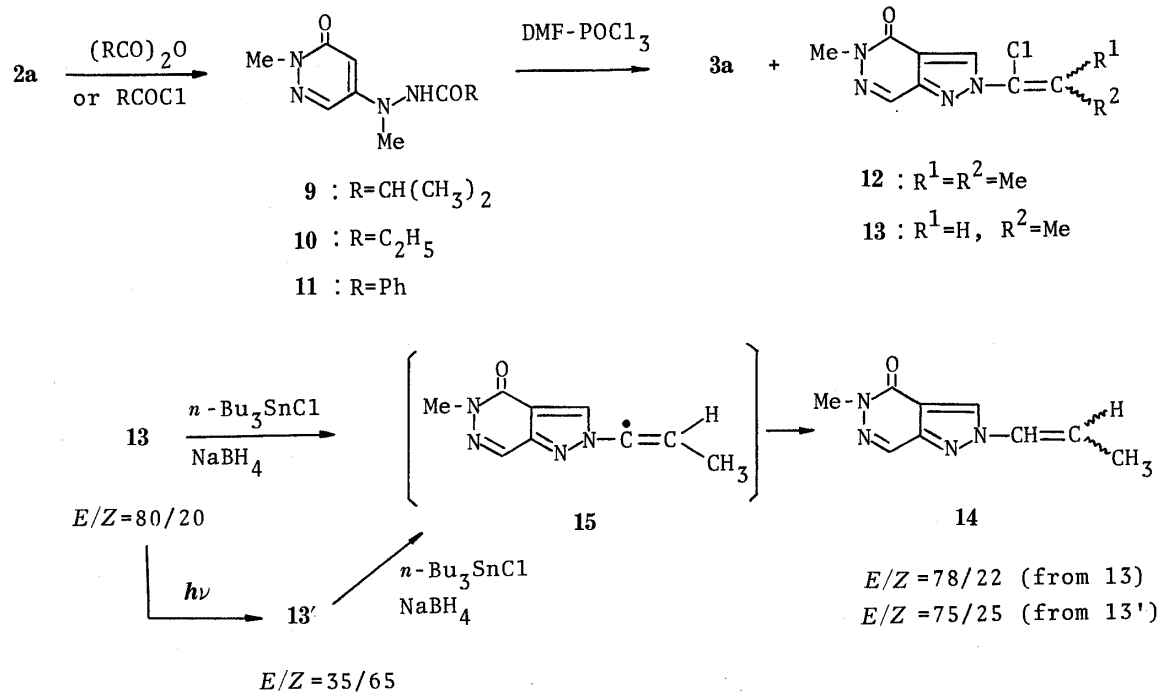
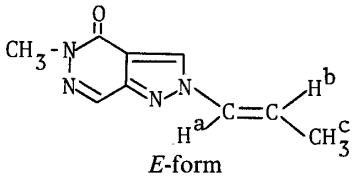
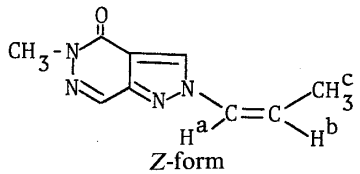



Chart 4

TABLE I. $^1$H-NMR Chemical Shifts of **14** ($CDCl_3$: $\delta$ in ppm)



*E*-form



*Z*-form

| Isomer | $CH_3^c$ | N–$CH_3$ | Vinyl-H | Ring-H | $J_{ab}$ | $J_{bc}$ | $J_{ac}$ |
|---|---|---|---|---|---|---|---|
| *E* | 1.95 (dd) | 3.79 (s) | $H^a$: 7.07 (dd)<br>$H^b$: 6.56 (dd) | 8.22 (s)<br>8.29 (s) | 14 Hz | 7 Hz | 1.5 Hz |
| *Z* | 2.05 (dd) | 3.79 (s) | $H^a$: 6.99 (dd)<br>$H^b$: 5.86 (dd) | 8.25 (s)<br>8.31 (s) | 9 Hz | 7 Hz | 3 Hz |

This suggests that the dechlorination of **13** or **13′** proceeds *via* a common intermediate, such as the vinyl radical (**15**).[14] Several attempts to separate the *E*- and *Z*-isomers of **13** and **14** were not successful. Vilsmeier reaction of the benzoylhydrazino derivative (**11**) gave **3a** as the sole product (63%), as expected.

## Experimental

All melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (IR) spectra were taken in potassium bromide disks on a JASCO IRA-I spectrophotometer. $^1$H-NMR spectra were taken on a Hitachi R-20B spectrometer (60 MHz) with tetramethylsilane (TMS) as an internal standard. MS were recorded on a JEOL JMS-D300 mass spectrometer. Irradiation was carried out with a Riko-UVL 100 W high-pressure mercury arc lamp.

**4-Chloro-5-(1-methylhydrazino)-2-phenyl-3(2*H*)-pyridazinone (1b)**——Methylhydrazine (2.76 g, 60 mmol) was added dropwise to a solution of 4,5-dichloro-2-phenyl-3(2*H*)-pyridazinone[15] in MeOH (50 ml) with stirring at room temperature. The stirring was continued for 6 h, then the separated product was collected. Recrystallization from EtOH gave 3.1 g (61%) of **1b** as colorless needles, mp 153—154 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3320, 3200 (NH), 1620 (CO). $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.48 (3H, s, $NCH_3$), 4.54 (2H, br, $NH_2$), 7.26—7.57 (5H, m, $C_6H_5$), 8.42 (1H, s, $C^6$-H). *Anal.* Calcd for $C_{11}H_{11}ClN_4O$: C, 52.69; H, 4.43; N, 22.35. Found: C, 52.81; H, 4.35; N, 22.40.

**2-Benzyl-4-chloro-5-(1-methylhydrazino)-3(2*H*)-pyridazinone (1c)**——2-Benzyl-4,5-dichloro-3(2*H*)-pyridazinone[16] (5.10 g, 20 mmol) was reacted with methylhydrazine (2.76 g, 60 mmol) in MeOH (30 ml) in the same manner as described for **1b** to afford 3.00 g (57%) of **1c** as colorless needles (EtOH), mp 130 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3305, 3190 (NH), 1640 (CO). $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.31 (3H, s, $NCH_3$), 4.76 (2H, br, $NH_2$), 5.25 (2H, s, $NCH_2$), 7.31 (5H, s, $C_6H_5$), 8.36 (1H, s, $C^6$-H). *Anal.* Calcd for $C_{12}H_{13}ClN_4O$: C, 54.44; H, 4.95; N, 21.17. Found: C, 54.40; H, 5.02; N, 21.23.

**5-(1-Methylhydrazino)-2-phenyl-3(2*H*)-pyridazinone (2b)**——A solution of **1b** (1.25 g, 5 mmol) and KOH (340 mg, 6 mmol) in MeOH (100 ml) was hydrogenated catalytically using 5% palladium on carbon (200 mg) at atmospheric pressure and room temperature. After the uptake of an equimolar amount of hydrogen, the catalyst was filtered off and the solvent was removed *in vacuo*. The residue was treated with water and extracted with $CHCl_3$. The crude product obtained upon removal of $CHCl_3$ was recrystallized from ethyl acetate to give 0.73 g (68%) of **2b** as colorless needles, mp 192—194 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3290, 3180 (NH), 1620 (CO). $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.13 (3H, s, $NCH_3$), 4.26 (2H, br, $NH_2$), 5.67 (1H, d, $J$=3 Hz, $C^4$-H), 7.11—7.69 (5H, m, $C_6H_5$), 8.24 (1H, d, $J$=3 Hz, $C^6$-H). *Anal.* Calcd for $C_{11}H_{12}N_4O$: C, 61.09; H, 5.59; N, 25.91. Found: C, 61.19; H, 5.68; N, 26.04.

**2-Benzyl-5-(1-methylhydrazino)-3(2*H*)-pyridazinone (2c)**——Compound **1c** (1.32 g, 5 mmol) was hydrogenated catalytically with 5% palladium on carbon (200 mg) and KOH (340 mg, 6 mmol) in MeOH (100 ml) by the same method as described for **2b** to give 1.00 g (65%) of **2c** as colorless needles (ethyl acetate), mp 146—147 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3280, 3175 (NH), 1620 (CO). $^1$H-NMR ($CDCl_3$) $\delta$: 3.06 (3H, s, $NCH_3$), 3.54 (2H, br, $NH_2$), 5.23 (2H, s, $NCH_2$), 5.72 (1H, d, $J$=3 Hz, $C^4$-H), 7.30 (5H, s, $C_6H_5$), 8.07 (1H, d, $J$=3 Hz, $C^6$-H). *Anal.* Calcd for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.50; H, 5.99; N, 24.45.

**5-(1-Methylhydrazino)-3(2*H*)-pyridazinone (2d)**——A solution of **1d**[5] (0.87 g, 5 mmol) and KOH (340 mg, 6 mmol) in MeOH was hydrogenated with 5% palladium on carbon (200 mg) as described for compound **2b** to afford 0.42 g (60%) of **2d** as colorless needles (EtOH), mp 230—231 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3290, 3150 (NH), 1640 (CO). $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.05 (3H, s, $NCH_3$), 4.67 (2H, br, $NH_2$), 5.52 (1H, d, $J$=3 Hz, $C^4$-H), 8.04 (1H, d, $J$=3 Hz, $C^6$-H), 12.00 (1H, br, NH). *Anal.* Calcd for $C_5H_8N_4O$: C, 42.85; H, 5.75; N, 39.98. Found: C, 42.76; H, 5.82; N, 40.04.

**Reaction of 2a—d with the Vilsmeier Reagent. Formation of 5-Substituted 1,5-Dihydro-1-methyl-4*H*-pyrazolo-[3,4-*d*]pyridazin-4-one (3a—d)**——A solution of one of **2a—d** (2 mmol) in DMF (10 ml) was added in portions to the Vilsmeier reagent [prepared from phosphorus oxychloride (770 mg, 5 mmol) and DMF (2 ml)] under ice-cooling and the whole was heated at 100 °C for 3 h. The reaction mixture was poured into water (50 ml) to yield crystals. Recrystallization from EtOH gave the corresponding product, **3a—d**. Compounds **3a** and **3d** were identical with samples obtained by the reported procedure.[5]

**3a**: 289 mg (88%), colorless needles, mp 208—210 °C.

**3b**: 398 mg (88%), colorless needles, mp 216—217 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1655 (CO). $^1$H-NMR ($CDCl_3$) $\delta$: 4.14 (3H, s, $NCH_3$), 7.38—7.69 (5H, m, $C_6H_5$), 8.28 (2H, s, $C^3$-H and $C^7$-H). *Anal.* Calcd for $C_{12}H_{10}N_4O$: C, 63.70; H, 4.46; N, 24.77. Found: C, 63.99; H, 4.44; N, 24.77.

**3c**: 339 mg (71%), colorless needles, mp 170—171 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1650 (CO). $^1$H-NMR ($CDCl_3$) $\delta$: 4.07 (3H, s, $NCH_3$), 5.40 (2H, s, $NCH_2$), 7.22—7.58 (5H, m, $C_6H_5$), 8.10 (1H, s, ring-H), 8.20 (1H, s, ring-H). *Anal.* Calcd for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 65.21; H, 5.05; N, 23.29.

**3d**: 176 mg (59%), colorless needles, mp 244—245 °C.

**2-Substituted 5-(2-Acetyl-1-methylhydrazino)-3(2*H*)-pyridazinone (5a—c)**——A solution of one of **2a—c** (5 mmol) and acetic anhydride (620 mg, 6 mmol) in dry pyridine (30 ml) was stirred at room temperature for 10 h. The reaction mixture was evaporated *in vacuo*. The residue was collected and recrystallized from ethyl acetate to give the corresponding product, **5a—c**.

**5a**: 826 mg (84%), colorless needles, mp 186—187 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3180 (NH), 1680, 1620 (CO), $^1$H-NMR ($CDCl_3$) $\delta$: 2.04 (3H, s, $COCH_3$), 3.18 (3H, s, $NCH_3$), 3.65 (3H, s, $NCH_3$), 5.79 (1H, d, $J$=3 Hz, $C^4$-H), 7.59 (1H, d, $J$=3 Hz, $C^6$-H). *Anal.* Calcd for $C_8H_{12}N_4O_2$: C, 48.97; H, 6.17; N, 28.56. Found: C, 49.25; H, 6.20; N, 28.57.

**5b**: 865 mg (67%), colorless needles, mp 226—227 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3200 (NH), 1680 1625 (CO). $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.00 (3H, s, $COCH_3$), 3.19 (3H, s, $NCH_3$), 5.84 (1H, d, $J$=3 Hz, $C^4$-H), 7.27—7.66 (5H, m, $C_6H_5$), 7.80 (1H, d, $J$=3 Hz, $C^6$-H), 10.31 (1H, br, NH). *Anal.* Calcd for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.70. Found: C, 60.47; H, 5.44; N, 21.64.

**5c**: 979 mg (72%), colorless needles, mp 204—205 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3175 (NH), 1675, 1625 (CO). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.96 (3H, s, $COCH_3$), 3.11 (3H, s, $NCH_3$), 5.29 (2H, s, $NCH_2$), 7.77 (1H, d, $J$=3 Hz, $C^4$-H), 7.38 (5H, s, $C_6H_5$), 7.63 (1H, d, $J$=3 Hz, $C^6$-H), 10.19 (1H, br, NH). *Anal.* Calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.71; H, 6.11; N, 20.49.

**Reaction of 5a—c with the Vilsmeier Reagent. Concurrent Formation of 5-Substituted 2-(1-Chlorovinyl)-2,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyridazin-4-ones (6a—c) and 5-Substituted 1,5-Dihydro-1-methyl-4*H*-pyrazolo[3,4-*d*]-pyridazin-4-ones (3a—c)**——A solution of one of **5a—c** (1 mmol) in DMF (6 ml) was added to the Vilsmeier reagent [prepared from phosphorus oxychloride (460 mg, 3 mmol) and DMF (2 mmol)] under ice-cooling and the whole was heated at 100 °C for 3 h. The reaction mixture was poured into ice-water and extracted with $CHCl_3$. The extract was chromatographed on a column of silica gel with $CHCl_3$ to afford the corresponding products (first **6a—c** and then **3a—c**). Compounds **3a—c** were identical with the samples obtained from **2a—c** by use of the Vilsmeier reagent.

a) **6a**: 37 mg (18%), colorless needles (EtOH), mp 162—163 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1670 (CO). $^1$H-NMR ($CDCl_3$) $\delta$: 3.78 (3H, s, $NCH_3$), 5.51, 6.28 (each 1H, each d, $J$=3 Hz, vinyl-H). 8.27 (1H, s, ring-H), 8.70 (1H, s, ring-H). *Anal.* Calcd for $C_8H_7ClN_4O$: 45.61; H, 3.36; N, 26.60. Found: C, 45.64; H, 3.34; N, 26.85. **3a**: 79 mg (48%), cololress needles (EtOH).

b) **6b**: 40 mg (15%), colorless needles (EtOH), mp 186—188 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1680 (CO). $^1$H-NMR ($CDCl_3$) $\delta$: 5.50, 6.29 (each 1H, each d, $J$=3 Hz, vinyl-H), 7.30—7.73 (5H, m, $C_6H_5$), 8.39 (1H, s, ring-H), 8.78 (1H, s, ring-H). *Anal.* Calcd for $C_{13}H_9ClN_4O$: C, 57.25; H, 3.33; N, 20.55. Found: C, 57.11; H, 3.33; N, 20.52. **3b**: 142 mg (63%), colorless needles (EtOH).

c) **6c**: 70 mg (24%), colorless needles (EtOH), mp 143—144 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1675 (CO). $^1$H-NMR ($CDCl_3$) $\delta$: 5.33 (2H, s, $NCH_2$), 5.47, 6.23 (each 1H, each d, $J$=3 Hz, vinyl-H), 7.47 (5H, s, $C_6H_5$), 8.25 (1H, s, ring-H), 8.67 (1H, s, ring-H). *Anal.* Calcd for $C_{14}H_{11}ClN_4O$: C, 58.64; H, 3.87; N, 19.54. Found: C, 58.60; H, 3.99; N, 19.62. **3c**: 165 mg (58%), colorless needles (EtOH).

**Reaction of 6a with Tri-*n*-butyltin Chloride and Sodium Borohydride**——Sodium borohydride (23 mg, 0.6 mmol) dissolved in EtOH (5 ml) was rapidly added, *via* a syring, to a solution of **6a** (105 mg, 0.5 mmol) and tri-*n*-butyltin chloride (36 mg, 0.1 mmol) in EtOH (15 ml) under a nitrogen atmosphere. The reaction mixture was refluxed for 5 h[17] then evaporated *in vacuo*. The residue was extracted with $CHCl_3$ and the extract was chromatographed on a column of silica gel with $CHCl_3$. From the first fractions, 2,5-dihydro-5-methyl-2-vinyl-4*H*-pyrazolo[3,4-*d*]pyridazin-4-one (**7**) (57 mg, 65% yield) was isolated as colorless needles (EtOH), mp 166—168 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1650 (CO). $^1$H-NMR ($CDCl_3$) $\delta$: 3.78 (3H, s, $NCH_3$), 5.27 (1H, dd, $J$=2 Hz, $J'$=9 Hz, vinyl-H), 5.99 (1H, dd, $J$=2 Hz, $J'$=16 Hz, vinyl-H), 7.26 (1H, dd, $J$=9 Hz, $J'$=16 Hz, vinyl-H), 8.25 (1H, s, ring-H), 8.38 (1H, s, ring-H). *Anal.* Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.68; H, 4.49; N, 31.89.

From the next fractions, 8 mg (9%) of 2,5-dihydro-2-ethyl-5-methyl-4*H*-pyrazolo[3,4-*d*]pyridazin-4-one (**8**) was isolated as colorless needles (EtOH). This compound was identical with an authentic sample obtained from **6a** by

hydrogenation with palladium on carbon.

**2,5-Dihydro-2-ethyl-5-methyl-4*H*-pyrazolo[3,4-*d*]pyridazin-4-one (8)**——A solution of **6a** (105 mg, 0.5 mmol) and triethylamine (70 mg, 0.7 mmol) in tetrahydrofuran (20 ml) was hydrogenated over 5% palladium on carbon (50 mg). After hydrogen absorption had ceased, the catalyst was removed by filtration. The residue obtained upon removal of the solvent was extracted with chloroform. Recrystallization of the product from EtOH gave 54 mg (61%) of **8** as colorless needles, mp 124—125 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1655 (CO). $^1$H-NMR ($CDCl_3$) $\delta$: 1.62 (3H, t, $J$=7.5 Hz, $CH_2C\underline{H}_3$), 3.78 (3H, s, $NCH_3$), 4.44 (2H, q, $J$=7.5 Hz, $NC\underline{H}_2CH_3$), 8.22 (2H, s, C$^3$-H and C$^7$-H). *Anal.* Calcd for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.45. Found: C, 54.11; H, 5.51; N, 31.51.

**5-(2-Isobutyryl-1-methylhydrazino)-2-methyl-3(2*H*)-pyridazinone (9)**——A solution of **2a** (628 mg, 4 mmol) and isobutyric anhydride (950 mg, 6 mmol) in dry pyridine (30 ml) was stirred for 12 h at room temperature. The reaction mixture was evaporated under reduced pressure. The residue was collected and washed with water. Recrystallization from ethyl acetate gave 760 mg (85%) of **9** as colorless prisms, mp 204—205 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3160 (NH), 1680, 1620 (CO). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.14 (6H, d, $J$=7.5 Hz, $CH(C\underline{H}_3)_2$), 2.42 (1H, q, $J$=7.5 Hz, $C\underline{H}(CH_3)_2$), 3.11 (3H, s, $NCH_3$), 3.16 (3H, s, $NCH_3$), 5.74 (1H, d, $J$=3 Hz, C$^4$-H), 7.52 (1H, d, $J$=3 Hz, C$^6$-H), 10.10 (1H, br, NH). *Anal.* Calcd for $C_{10}H_{16}N_4O_2$: C, 53.55; H, 7.19; N, 24.99. Found: C, 53.60; H, 7.30; N, 24.96.

**2-Methyl-5-(1-methyl-2-propionylhydrazino)-3(2*H*)-pyridazinone (10)**——Reaction of **2a** (628 mg, 4 mmol) with propionic anhydride (780 mg, 6 mmol) in dry pyridine (30 ml) gave the crude compound **10** in the same manner as described for **9**. Recrystallization from ethyl acetate afforded 685 mg (81%) of **10** as colorless prisms, mp 181—182 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3160 (NH), 1685, 1620 (CO). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.10 (3H, t, $J$=7.5 Hz, $CH_2C\underline{H}_3$), 2.22 (2H, q, $J$=7.5 Hz, $COC\underline{H}_2CH_3$), 3.10 (3H, s, $NCH_3$), 3.58 (3H, s, $NCH_3$), 5.71 (1H, d, $J$=3 Hz, C$^4$-H), 7.58 (1H, d, $J$=3 Hz, C$^6$-H), 10.18 (1H, br, NH). *Anal.* Calcd for $C_9H_{14}N_4O_2$: C, 51.42; H, 6.71; N, 26.65. Found: C, 51.37; H, 6.66; N, 26.63.

**5-(2-Benzoyl-1-methylhydrazino)-2-methyl-3(2*H*)-pyridazinone (11)**——Compound **11** was prepared as described for compound **9**, starting from **2a** (1.1 g, 7 mmol) and benzoyl chloride (1.2 g, 8.5 mmol) in dry pyridine (20 ml). Recrystallization from EtOH yielded 1.48 g (80%) of **11** as colorless needles, mp 244—245 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3150 (NH), 1670, 1625 (CO). $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.29 (3H, s, $NCH_3$), 3.67 (3H, s, $NCH_3$), 5.89 (1H, d, $J$=3 Hz, C$^4$-H), 7.38—7.67 (3H, m, aromatic H), 7.63 (1H, d, $J$=3 Hz, C$^6$-H), 7.87—8.06 (2H, m, aromatic H), 10.90 (1H, br, NH). *Anal.* Calcd for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.70. Found: C, 60.66; H, 5.49; N, 21.71.

**Reaction of 9 with the Vilsmeier Reagent**——Heating of **9** (244 mg, 1 mmol) with the Vilsmeier reagent [prepared from DMF (2 ml) and phosphorus oxychloride (460 mg, 3 mmol)] in DMF (6 ml) at 100 °C for 3 h in the same manner as described for **6a—c** yielded a mixture of **12** and **3a**, which were separated by column chromatography on silica gel with chloroform. Concentration of the first eluate gave 52 mg (22%) of 2-(1-chloro-2,2-dimethylvinyl)-2,5-dihydro-5-methyl-4*H*-pyrazolo[3,4-*d*]pyridazin-4-one (**12**) as colorless needles (EtOH), mp 155—156 °C IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1650 (CO). $^1$H-NMR ($CDCl_3$) $\delta$: 1.69 (3H, s, $CH_3$), 2.10 (3H, s, $CH_3$), 3.80 (3H, s, $NCH_3$), 8.28 (1H, s, ring-H), 8.33 (1H, s, ring-H). *Anal.* Calcd for $C_{10}H_{11}ClN_4O$: C, 50.31; H, 4.65; N, 23.48. Found: C, 50.39; H, 4.68; N, 23.57.

Concentration of the second eluate afforded 84 mg (51%) of **3a**, which was identical with the sample obtained from **2a** by reaction with the Vilsmeier reagent.

**Reaction of 10 with the Vilsmeier Reagent**——Heating of **10** (224 mg, 1 mmol) with the Vilsmeier reagent (2 ml of DMF and 460 mg of phosphorus oxychloride) in DMF (6 ml) at 100 °C for 3 h as described for **6a—c** afforded a mixture of **13** and **3a**. The resulting mixture was chromatographed on a column of silica gel with chloroform. From the first fractions, 43 mg (19%) of 2-(1-chloro-2-methylvinyl)-2,5-dihydro-5-methyl-4*H*-pyrazolo[3,4-*d*]pyridazin-4-one (**13**) was isolated as colorless needles (EtOH), mp 181—182 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1655 (CO). $^1$H-NMR ($CDCl_3$) $\delta$: *E*-isomer: 2.01 (3H, d, $J$=7 Hz, $CH_3$), 3.77 (3H, s, $NCH_3$), 6.68 (1H, q, $J$=7 Hz, vinyl-H), 8.22 (1H, s, ring-H), 8.59 (1H, s, ring-H). *Z*-isomer: 1.76 (3H, d, $J$=7 Hz, $CH_3$), 3.77 (3H, s, $NCH_3$), 6.17 (1H, q, $J$=7 Hz, vinyl-H), 8.27 (1H, s, ring-H), 8.42 (1H, s, ring-H). (*E*/*Z*=80:20 based on the integral ratio). *Anal.* Calcd for $C_9H_9ClN_4O$: C, 48.11; H, 4.05; N, 24.94. Found: C, 48.23; H, 4.09; N, 24.71.

Concentration of the second fraction afforded 79 mg (48%) of **3a**. This compound was identical with an authentic sample obtained from **2a** by reaction with the Vilsmeier reagent.

**Photoisomerization of 13**——A solution of **13** (112 mg, 0.5 mmol) in EtOH (30 ml) was irradiated with a 100 W high-pressure mercury lamp surrounded by a water-cooled Pyrex filter at room temperature for 10 h. The reaction mixture was concentrated to dryness to give **13′**, whose $^1$H-NMR spectrum showed it to be a mixture of *E*- and *Z*-isomer (*E*/*Z*=35:65).

**Reaction of 11 with the Vilsmeier Reagent**——Heating of **11** (258 mg, 1 mmol) with the Vilsmeier reagent (2 ml of DMF and 460 mg of phosphorus oxychloride) in DMF (6 ml) at 100 °C for 3 h as described above yielded 103 mg (63%) of **3a** as colorless needles (EtOH). This compound was identical with a sample obtained from **2a** by reaction with DMF–phosphorus oxychloride.

**2,5-Dihydro-5-methyl-2-(2-methylvinyl)-4*H*-pyrazolo[3,4-*d*]-pyridazin-4-one (14)**——i) Reaction of **13** (112 mg, 0.5 mmol) with tri-*n*-butyltin chloride (36 mg, 0.1 mmol) and sodium borohydride (105 mg, 0.5 mmol) in EtOH (20 ml) under a nitrogen atmosphere in a manner similar to that described for **7** gave 54 mg (57%) of **14** as colorless needles, mp 133—134 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1655 (CO). Compound **14** gave a single spot on TLC, but its $^1$H-NMR spectrum (see

Table I) showed it to be a mixture of *E*- and *Z*-isomer (*E*/*Z*=78:22 based on the integral ratio). *Anal.* Calcd for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.90; H, 5.18; N, 29.51.

ii) From **13'** (112 mg, 0.5 mmol), by using the same procedure as described for **13**, 61 mg (64%) of **14** was obtained as a mixture of stereoisomers (*E*/*Z*=75:25).

## References and Notes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17) This reaction proceeded more rapidly (within 0.5 h) under irradiation at room temperature or in the presence of azobis(isobutyronitrile) (AIBN) at 50 °C.