SYNTHESIS OF PYRAZOLO[3,4-d]PYRIDAZINES —— THIONATION FOLLOWED BY ALKYLATION OF PYRAZOLO[3,4-d]PYRIDAZIN-4(5H)-ONE

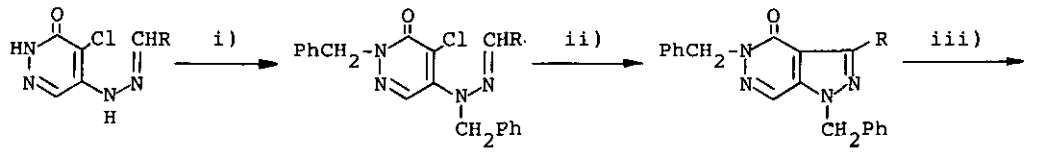
Kenji Kaji, Hiromu Nagashima, Keizo Tabashi, and Hirohisa Oda*
Gifu College of Pharmacy, 5-6-1, Mitahora-higashi, Gifu 502, Japan

Abstract —— Alkylation of the pyrazolo[3,4-d]pyridazine-4(5H)-thiones are described. Employment of an equivalent of alkylating agent afforded only S-alkylated products, while S,N-dialkyl compounds were formed when an excess of alkylating agent was used. An unequivocal synthesis and ^{1}H-NMR spectroscopic studies of 1- and 2-alkyl-4-alkylthiopyrazolo[3,4-d]pyridazines are also discussed.

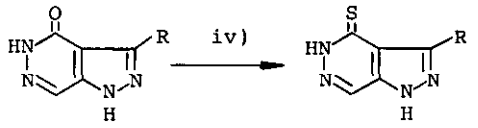
The synthetic approaches to pyrazolo[3,4-d]pyridazines, which are of chemical and biological interest,[1,2] have utilized the pyrazoles with appropriate ortho-functional groups as starting material,[3] except one report.[4] As a comparable synthetic approaches to this, we have presented hitherto a series of papers[5-9] concerned with the synthesis of pyrazolo[3,4-d]pyridazines starting with pyridazines utilizing such as photocyclization of alkylidenehydrazinopyridazines,[5] Vilsmeier reaction of hydrazinopyridazines[6] and ring contraction of pyridazino[4,5-e][1,3,4]thiadiazines.[7-9] Furthermore, some of them have been found to exhibit interesting biological activities.[1] In this connection, we wish to describe here the synthesis and reactions of some alkylthio derivatives of pyrazolo[3,4-d]pyridazines, involving a photochemical cyclization.

5-(2-Alkylidenehydrazino)-4-chloro-3(2H)-pyridazinones (1a,b) were converted into the dibenzyl derivatives (2a: 56%, 2b: 46%) using two equivalents of benzyl chloride because no photocyclization proceeded when the nitrogen of hydrazino moiety is unsubstituted.[5] Irradiation on 2a,b in benzene afforded the corresponding pyrazolo-[3,4-d]pyridazines (3a,b) in 87% and 68% yields, respectively. The benzene extract of 2a,b, obtained from 1a,b, was irradiated to give also 3a,b in over all yields of 40-50% without isolation of 2a,b. 4-Oxo derivatives (4a,b) were derived from

compounds 3a,b by debenzylation with $AlCl_3$ in warm toluene[10] in good yields.[11] Thionation of 4a,b with phosphorus pentasulfide in pyridine gave the 4-thioxo derivatives (5a,b) in 75% and 76% yields, respectively.[12]



1a,b 2a,b 3a,b

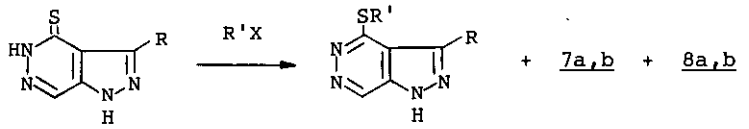


4a,b 5a,b

a: R=Ph
b: R=H

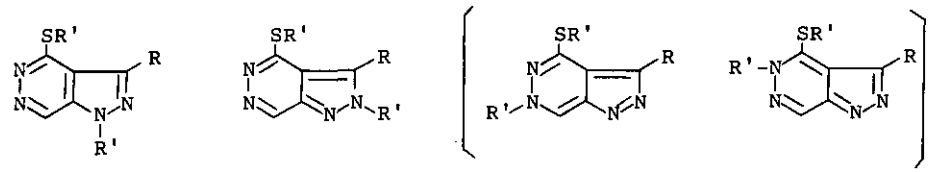
i) $PhCH_2Cl$, K_2CO_3 in DMF
ii) hν in benzene
iii) $AlCl_3$ in toluene
iv) P_2S_5 in pyridine

Alkylation of 4-thioxo derivative (5a) using 1.5 equivalents of methyl iodide in dil. aq. KOH solution afforded mono-S-methyl derivative 6a and two kinds of S,N-dimethyl compounds 7a and 8a as minor products. The possible structures of dimethyl compounds may be A and B, however, the structure C and D are not excluded, according to the report of Chen and Panzica.[13] Another alkylation reaction of 5b with ethyl bromide afforded also 4-ethylthio derivative (6a) as well as 7b and 8b.



5a,b 6a,b

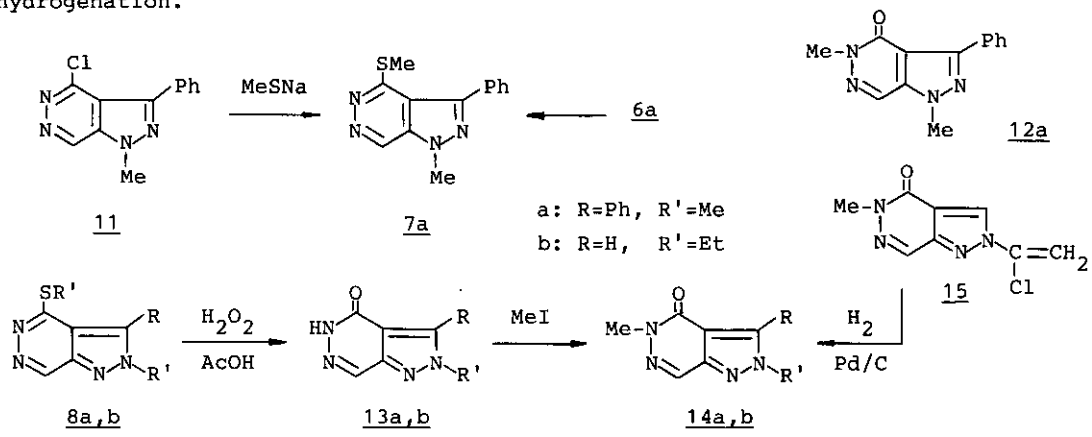
a: R=Ph, R'=Me
b: R=H, R'=Et



A B C D

The structure of 7a,b and 8a,b were established by the following unequivocal synthesis and conversion into the known compound. Reaction of 4-chloro-1-methyl-3-phenyl-1H-pyrazolo[3,4-d]pyridazine (11)[5] with sodium methyl mercaptide gave the 4-methylthio derivative which was identical in every respect (mp, TLC, IR and ^{1}H-NMR) with compound 7a. As the postulated structure for the other products 8a,b is a tentative structure B, they were converted into the 4-oxo derivatives (13a,b) on

exposure to H_2O_2 in AcOH. Subsequent methylation of 13a,b afforded compounds 14a,b, one of which (14b) was identical with a sample obtained from by catalytic hydrogenation.[6]



^{1}H-NMR spectra ($CDCl_3$) of 7a and 8a show the almost same chemical shifts except signals due to phenyl protons. Phenyl protons in 7a appear at δ 7.21-7.86 (broader multiplet) and those of 8a appear at δ 7.35-7.63 (narrower multiplet). This phenomenon is remarkably noticed in compounds 12a[8] and 14a. Phenyl protons in 12a appear as multiplet at δ 7.21-7.69 (3H) and δ 8.12-8.45 (2H), while those of 14a appear as singlet at δ 7.52 (5H). Therefor, it might be rationalized that coplanarity between pyrazole and benzene rings causes the magnetic anisotropy effect on the ortho-protons in benzene, whereas a steric hindrance of a methyl group at 2-position of pyrazole lowers such an effect on the benzene ring.[14,15]

EXPERIMENTAL

Melting points are uncorrected. IR, ^{1}H-NMR and MS spectra were taken on a JASCO IRA-I, a Hitachi R-20B (60 Mz) and a JEOL JMS-D300 spectrometers, respectively. Irradiation was carried out with a Riko-UVL 400 W high-pressure mercury lamp.

1,5-Dibenzyl-3-phenyl-1H-pyrazolo[3,4-d]pyridazin-4(5H)-one (3a) and 1,5-Dibenzyl-1H-pyrazolo[3,4-d]-pyridazin-4(5H)-one (3b) ---- To a suspension of 10 mmol of 1a,b[5] and K_2CO_3 (5 g, 36 mmol) in DMF (100 ml) was added benzyl chloride (3.1 g, 24 mmol) and the whole was heated at 80°C for 4 h. The reaction mixture was poured into ice-water and extracted with benzene (300 ml). The benzene extract was irradiated with a 400 W high-pressure mercury lamp for 5 h and evaporated in vacuo. Recrystallization from EtOH gave 2.0 g (52%) of 3a and 1.3 g (41%) of 3b, which were identical with an authentic sample.[5]

3-Phenyl-1H-pyrazolo[3,4-d]pyridazin-4(5H)-one (4a) ---- To a solution of 3a (1.57 g, 4 mmol) in

toluene (100 ml) was added $AlCl_3$ (2.4 g, 16 mmol) with stirring and the whole was kept at 50°C for 3 h. The reaction mixture was evaporated in vacuo and the residue was poured into ice-water. The precipitated solid was collected and recrystallized from EtOH to afford 0.68 g (80%) of 4a as colorless needles, mp>300°C. IR (KBr) cm^{-1}: 3180 (NH), 1630 (C=O). MS m/e: 212 (M^+). Anal. Calcd. for $C_{11}H_8N_4O$: C, 62.26; H, 3.80; N, 26.40. Found: C, 62.38; H, 4.01; N, 26.38.

1H-Pyrazolo[3,4-d]pyridazin-4(5H)-one (4b) ---- From 1.25 g (4 mmol) of 3b in a similar procedure as that for 4a, 0.49 g (90%) of 4b was obtained, colorless needles (EtOH), mp>300°C (lit. 298-310°C).[12] IR (KBr) cm^{-1}: 3250 (NH), 1645 (C=O). MS m/e: 136 (M^+). Anal. Calcd. for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.16. Found: C, 44.20; H, 3.05; N, 41.09.

3-Phenyl-1H-pyrazolo[3,4-d]pyridazine-4(5H)-thione (5a) and 1H-Pyrazolo[3,4-d]pyridazine-4(5H)-thione (5b) ---- Compounds 4a,b (5 mmol) were thionated with phosphorus pentasulfide (3.33 g, 15 mmol) in pyridine (50 ml) according to the usual procedure.[5,12] 5a: 0.87 g (76%), mp 255-257°C. IR (KBr) cm^{-1}: 3140 (NH), 1200 (C=S). MS m/e: 228 (M^+). Anal. Calcd. for $C_{11}H_8N_4S$: C, 57.88; H, 3.53; N, 24.54. Found: C, 57.71; H, 3.68; N, 24.63. 5b: 0.57 g (75%), mp 298-301°C (lit. 305°C).[12] IR (KBr) cm^{-1}: 3160 (NH), 1220 (C=S). MS m/e: 152 (M^+). Anal. Calcd. for $C_5H_4N_4S$: C, 39.46; H, 2.65; N, 36.82. Found: C, 39.51; H, 2.49; N, 36.99.

Alkylation of Pyrazolo[3,4-d]pyridazine-4(5H)-thiones (5a,b) ---- To a suspension of 5a or 5b (5 mmol) in 0.5N aq. KOH (12 ml) was added 5.5 mmol of methyl iodide or ethyl bromide. The reaction mixture was stirred at room temperature for 2.5 h. The resulting solution was acidified with dil. HCl. The deposited product was collected and recrystallized from EtOH to give S-methyl (6a) or S-ethyl derivative (6b). 6a: 746 mg (62%), colorless needles, mp 285-286°C. IR (KBr) cm^{-1}: 3190 (NH). ^{1}H-NMR (DMSO-d_6) δ: 2.65 (3H, s, SCH_3), 7.40-7.82 (5H, m, C_6H_5), 9.37 (1H, s, 7-H). Anal. Calcd. for $C_{12}H_{10}N_4S$: C, 59.48; H, 4.16; N, 23.12. Found: C, 59.32; H, 4.12; N, 22.95. 6b: 540 mg (60%), colorless needles, 243-245°C. IR (KBr) cm^{-1}: 3150 (NH). ^{1}H-NMR (DMSO-d_6) δ: 1.42 (3H, t, J=7.5Hz, CH_2CH_3), 3.41 (2H, q, J=7.5Hz, SCH_2CH_3), 8.16 (1H, s, ring-H), 9.25 (1H, s, ring-H). Anal. Calcd. for $C_7H_8N_4S$: C, 46.65; H, 4.47; N, 31.09. Found: C, 46.73; H, 4.40; N, 31.11.

Alkylation of 5a with 1.5 eq. of Methyl Iodide ---- To a suspension of 5a (1.14 g, 5 mmol) in 0.5N aq. KOH (18 ml) was added 1.10 g (7.5 mmol) of methyl iodide. The reaction mixture was stirred at room temperature for 5 h. The resulting solution was extracted with $CHCl_3$. The aqueous layer was acidified with dil. HCl to precipitate a white crystals (6a) (479 mg, 41% yield), which was identical with a sample obtained above. The $CHCl_3$ extract was chromatographed on column of silica gel with $CHCl_3$ as an eluent. From the first fractions, 102 mg (8%) of 7a was isolated as colorless needles (EtOH), mp 147-148°C. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (3H, s, SCH_3), 4.19 (3H, s, NCH_3), 7.21-7.86 (5H, m, C_6H_5), 9.91 (1H, s, 7-H). Anal. Calcd. for $C_{13}H_{12}N_4S$: C, 60.92; H, 4.72; N, 21.86. Found: C, 61.06; H, 4.80; N, 21.70. From the second fractions, 282 mg (22%) of 8a was obtained as colorless needles

(EtOH), mp 211-212°C. ^{1}H-NMR ($CDCl_3$) δ: 2.59 (3H, s, SCH_3), 4.00 (3H, s, NCH_3), 7.35-7.63 (5H, m, C_6H_5), 9.25 (1H, s, 7-H). Anal. Calcd. for $C_{13}H_{12}N_4S$: C, 60.92; H, 4.72; N, 21.86. Found: C, 60.97; H, 4.69; N, 22.01.

Alkylation of 5b with 1.5 eq. of Ethyl Bromide ---- From 761 mg (5 mmol) of 5b and 820 mg (7.5 mmol) of ethyl bromide in a similar manner as that for 5a was obtained compounds 6b, 7b and 8b. 6b: 396 mg (44%). This compound was identical with a sample obtained above. 7b: 62 mg (6%), colorless needles (hexane), mp 48°C. ^{1}H-NMR ($CDCl_3$) δ: 1.49 (3H, t, J=7.5Hz, CH_2CH_3), 1.59 (3H, t, J=7.5Hz, CH_2CH_3), 3.54 (2H, q, J=7.5Hz, SCH_2CH_3), 4.61 (2H, q, J=7.5Hz, NCH_2CH_3), 8.12 (1H, s, ring-H), 9.30 (1H, s, ring-H). Anal. Calcd. for $C_9H_{12}N_4S$: C, 51.90; H, 5.81; N, 26.90. Found: C, 51.99; H, 5.72; N, 26.89. 8b: 156 mg (15%), colorless needles (EtOH), mp 63-64°C. ^{1}H-NMR ($CDCl_3$) δ: 1.48, (3H, t, J=7.5Hz, CH_2CH_3), 1.66 (3H, t, J=7.5Hz, CH_2CH_3), 3.51 (2H, q, J=7.5Hz, SCH_2CH_3), 4.61 (2H, q, J=7.5Hz, NCH_2-CH_3), 8.21 (1H, s, ring-H), 9.35 (1H, s, ring-H). Anal. Calcd. for $C_9H_{12}N_4S$: 51.90; H, 5.81; N, 26.90. Found: C, 51.85; H, 5.90; N, 26.82.

An Unequivocal Synthesis of 7a ---- To a solution of 4-chloro-1-methyl-3-phenyl-1H-pyrazolo[3,4-d]-pyridazine[5] (245 mg, 1 mmol) in EtOH (10 ml) was added 15% sodium methyl mercaptide solution (600 mg, 1.5 mmol). The reaction mixture was stirred at room temperature for 10 h and evaporated in vacuo. The residue was extracted with CH_2CH_2. The crude product obtained upon removal of CH_2Cl_2 was recrystallized from EtOH to give 154 mg (60%) of 7a. This compound was identical with the sample obtained from 6a with methyl iodide.

2-Methyl-3-phenyl-2H-pyrazolo[3,4-d]pyridazin-4(5H)-one (13a) ---- A solution of 8a (256 mg, 1 mmol) and 30% H_2O_2 (1.13 g, 10 mmol) in AcOH (25 ml) was warmed at 50°C for 10 h. The reaction mixture was evaporated in vacuo and extracted with CH_2Cl_2. The residue obtained upon removal of CH_2Cl_2 was recrystallized from EtOH to give 182 mg (80%) of 13a as colorless needles, mp 265-268°C. IR (KBr) cm^{-1}: 3160 (NH), 1650 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 4.04 (3H, s, NCH_3), 7.49-7.75 (5H, m, C_6H_5), 8.30 (1H, s, 7-H). Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 24.76. Found: C, 63.67; H, 4.45; N, 24.74.

2-Ethyl-2H-pyrazolo[3,4-d]pyridazin-4(5H)-one (13b) ---- From 316 mg (1.5 mmol) of 8b in the same procedure as that for 13a, 96 mg (40%) of 13b was obtained as colorless needles (EtOH), mp 210-212°C. IR (KBr) cm^{-1}: 3170 (NH), 1675 (C=O). Anal. Calcd. for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.39; H, 4.99; N, 33.86.

2,5-Dimethyl-3-phenyl-2H-pyrazolo[3,4-d]pyridazin-4(5H)-one (14a) ---- To a suspension of 13a (130 mg, 0.57 mmol) and K_2CO_3 (160 mg, 1.2 mmol) in DMF (10 ml) was added methyl iodide (180 mg, 1.2 mmol) and the whole was stirred at room temperature for 5 h. The reaction mixture was poured into ice-water and extracted with benzene. The extract was concentrated to dryness and the residue was recrystallized from EtOH to give 42 mg (30%) of 14a as colorless needles, mp 154-156°C. IR (KBr) cm^{-1}: 1650

(C=O). ^{1}H-NMR ($CDCl_3$) δ: 3.78 (3H, s, NCH_3), 4.08 (3H, s, NCH_3), 7.52 (5H, s, C_6H_5), 8.25 (1H, s, 7-H). Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 65.09; H, 5.07; N, 23.16.

2-Ethyl-5-methyl-2H-pyrazolo[3,4-d]pyridazin-4(5H)-one (14b) ---- From 180 mg (1.1 mmol) of 13b in a similar procedure as that for 13a, 72 mg (39%) of 14b was obtained as colorless needles (EtOH). This compound was identical with an authentic sample.[6]

ACKNOWLEDGEMENT

The authers are grateful to Dr. S. Saitoh and Dr. T. Iwakuma, Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd. for xanthine oxidase inhibitory screening tests.

REFERENCES AND NOTES

1. K. Kaji, H. Nagashima, H. Oda, S. Nagao, Y. Wakabayashi, Y. Hirose, M. Taniguchi, and T. Ikai, Japan Patent Kokai 71010 (1981) [Chem. Abstr., 95, 127428n (1981)].
2. A. Lespagnol, C. Lespagnol, and B. Willecomme, Eur. J. Med. Chem., 1974, 9, 51.
3. M. Tišler and B. Stanovnik, "The Chemistry of Heterocyclic Compounds," Vol. 27, ed. by R. N. Castle, John Wiley and Sons, Inc., New York, 1973, pp. 785-788.
4. M. Frank-Neumann and G. Leclerc, Tetrahedron Lett., 1969, 1063.
5. K. Kaji, H. Nagashima, Y. Ohta, K. Tabashi, and H. Oda, J. Heterocyclic Chem., in press.
6. K. Kaji, H. Nagashima, Y. Hirose, and H. Oda, Chem. Pharm. Bull., in press.
7. K. Kaji, H. Nagashima, Y. Ohta, S. Nagao, Y. Hirose, and H. Oda, Heterocycles, 1984, 22, 479.
8. K. Kaji, H. Nagashima, S. Nagao, K. Tabashi, and H. Oda, Chem. Pharm. Bull., in press.
9. K. Kaji, H. Nagashima, Y. Ohhata, K. Tabashi, and H. Oda, J. Heterocyclic Chem., submitted.
10. K. Kaji, H. Nagashima, and H. Oda, Chem. Pharm. Bull., 1984, 32, 1423.
11. Though compound 4b is an isostere of 4-hydroxypyrazolo[3,4-d]pyrimidine (allopurinol), it exhibited only a weak activity of xanthine oxidase inhibitor.
12. J.-P. Marquet, J.-D. Bourzat, J. André-Louisfert, and E. Bisagni, Tetrahedron, 1973, 29, 435.
13. S.-F. Chen and R. P. Panzica, J. Org. Chem., 1981, 46, 2467.
14. L. G. Tensmeyer and C. Ainsworth, J. Org. Chem., 1966, 31, 1878.
15. S. Gelin and D. Hartmann, J. Heterocyclic Chem., 1978, 15, 813.

Received, 19th June, 1984