Pyridazines with Heteroatom Substituents in Positions 3 and 5. 6 [1]. S_N Reactions in Position 5 of 2-Aryl-5-hydroxypyridazin-3(2*H*)-ones

Bernt D. Schober [2], Gabor Megyeri and Thomas Kappe*

Institut für Organische Chemie, Karl-Franzens-Universität Graz,
A-8010 Graz, Austria

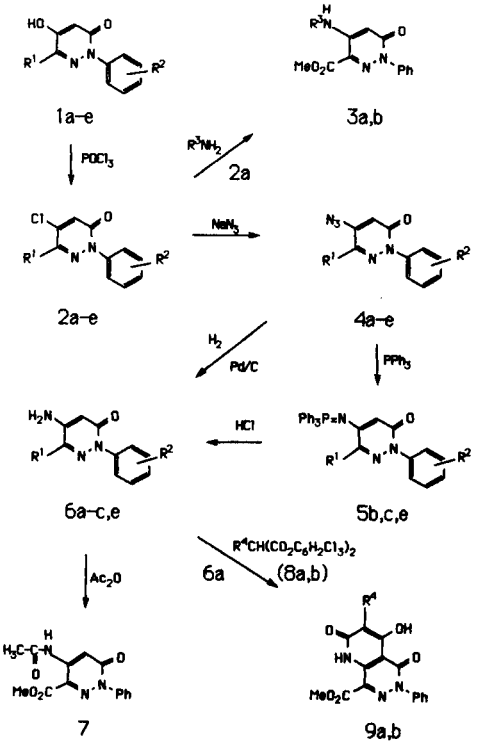
Received May 4, 1989

The nucleophilic introduction of chloro- (**2**), azido- (**4**), (substituted) amino (**3**, **6**), mercapto (**10**) and hydrazino-groups (**13**) into 2-aryl-5-hydroxypyridazin-3(2*H*)-ones [3] is described. The 5-aminopyridazin-3(2*H*)-one (**6**) also reacts with activated malonates **8** [4] to give pyrido[2,3-*d*]pyridazines **9**. Hydrazino compounds **13** can be treated with aldehydes to yield compounds **14**. Iodine can be introduced into position 4 of 5-amino-(**15**) and 5-hydroxypyridazin-3(2*H*)-ones (**17**) by electrophilic substitution to afford compounds **18**.

J. Heterocyclic Chem., **27**, 471 (1990).

Nucleophilic substitution of the 5-hydroxy group of **1a-e** [3] with chlorine can be achieved by reaction with phosphorus oxychloride [5,6,7,8]. Compounds **1a-e** are *N*-substituted malonyl systems therefore chlorination in this way leads only to the monochloro products **2a-e**, chlorination at the oxo group in position 3 is not possible [9,10]. This reaction should be carried out at 95 to 100°, working at reflux temperature of phosphorus oxychloride leads to lower yields and impure products.

Scheme 1



Chloro compounds **2a-e** are the starting materials for further reactions as for the introduction of substituted amino groups. Attempts to obtain **3a,b** from **1a** and aniline or benzylamine, respectively, failed. The addition of the corresponding amine hydrochloride as it was described for some substitution reactions of hydroxy versus amino groups in malonyl systems [11,12] did not lead to any improvement. The reaction of **2a** with aniline or benzylamine to **3a,b** should be performed in a solvent, without solvent we obtained only poor yields.

Unsubstituted amino compounds **6** are accessible from chloro compounds **2** *via* azido compounds **4** in two ways. The latter can be obtained in high yields from **2a-e** by reaction with sodium azide in dimethylformamide. Catalytic hydrogenation of **4** in glacial acetic acid leads to **6** just as a two step process using triphenylphosphine for yielding the triphenylphosphoranylidene compounds **5** [13-22] which can be treated with acids like hydrochloric acid or acetic acid to yield the amino compounds **6**.

Hydrogenation of **4a** in glacial acetic acid does not give the acetylamino compound **7** as it was described for a similar reaction recently [23] but **7** can be obtained by refluxing **6a** in acetic anhydride.

Using **6a** as starting material pyrido[2,3-*d*]pyridazines **9** can be obtained. This system is known indeed for some time [24-27] but analogous malonyl systems have only been described recently [23]. The reaction must be performed with active malonic esters **8** (2,4,6-trichlorophenyl esters) [4], using alkyl malonates does not yield **9a,b** but only decomposition.

Scheme 2

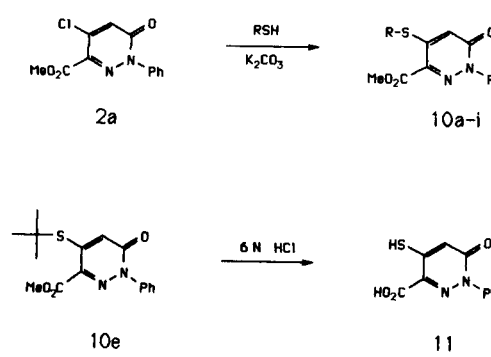


Table 1

2–Aryl-5-chloropyridazin-3(2*H*)-ones **2a-e**

No.	R^1	R^2	Formula (Moleweight)	Yield (%)	mp (recrystallization)	Analysis (Calcd./Found) C	H	N	C	IR (cm^{-1})
2a	CO_2CH_3	H	$C_{12}H_9ClN_2O_3$ (264.7)	91	105-106° (methanol/water)	54.45 54.43	3.43 3.56	10.59 10.52		3600-3300 w, b, 1735 s, 1700 sh, 1675 s, 1650 sh, 1635 sh, 1600 w
2b	CO_2CH_3	3-Trifluro-methyl	$C_{13}H_8ClF_3N_2O_3$ (332.7)	71	98-99° (methanol)	46.93 46.75	2.42 2.33	8.42 8.37		3100 w, 2980 w, 1745 s, 1680 s, 1660 sh, 1580 w
2c	CO_2CH_3	4-Chloro	$C_{12}H_9Cl_2N_2O_3$ (299.1)	66	162-163° (methanol)	48.18 47.90	2.70 2.40	9.37 9.20		3100 w, 1740 s, 1685 sh, 1580 w
2d	H	3-Trifluro-methyl	$C_{11}H_6ClF_3NO_2$ (274.6)	91	76-77° (methanol)	48.10 48.02	2.21 2.00	10.20 10.18		3070 m, 1685 s, 1670 sh, 1655 s, 1645 sh, 1590 m
2e	H	4-Chloro	$C_{10}H_6Cl_2N_2O$ (241.1)	92	147-148° (methanol)	49.82 49.89	2.51 2.22	11.62 11.57	29.41 29.14	3080 w, 1700 sh, 1690 sh, 1680 sh, 1660 s, 1640 sh, 1590 m

Table 2

^{1}H-NMR Spectral Data of **2** (measured in deuteriochloroform)

2a: δ = 3.9 (s, CH_3), 7.1 (s, H at C-4), 7.3-7.7 (m, 5 ArH)
2b: δ = 3.9 (s, CH_3), 7.2 (s, H at C-4), 7.5-8.0 (m, 4 ArH)
2c: δ = 4.0 (s, CH_3), 7.1 (s, H at C-4), 7.4-7.6 (m, 4 ArH)
2d: δ = 7.1 (d, J = 2 Hz, H at C-4), 7.65 (d, J = 2 Hz, H at C-6), 7.8-7.95 (m, 4 ArH)
2e: δ = 6.95 (d, J = 2 Hz, H at C-4), 7.3-7.5 (m, 4 ArH), 7.75 (d, J = 2 Hz, H at C-6)

Mercapto groups can be introduced into position 5 by treating **2a** with mercaptanes as it was described most recently for similar pyridazines [28] but elimination of a *t*-butylthio group with Lewis acids [28] cannot be performed without complete decomposition, use of hydrochloric acid yields the thiol **11** in 74% yield.

Reaction of **2a** with hydrazinium hydrate affords up to two different products according to the amount of hydrazinium hydrate used for the reaction. Using equimolar amounts of the latter with **2a** leads to **12** whereas use of an excess of hydrazinium hydrate yields **13** which can be treated with aldehydes in ethanolic solution to give the hydrazones **14a-e**.

Scheme 3

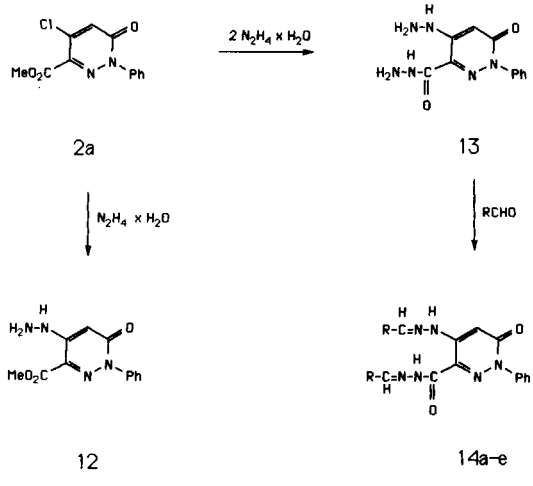


Table 3

2–Aryl-5-azidopyridazin-3(2*H*)-ones **4a-e**

No.	R^1	R^2	Formula (Moleweight)	Yield (%)	mp (recrystallization)	Analysis (Calcd./Found) C	H	N	C	IR (cm^{-1})
4a	CO_2CH_3	H	$C_{12}H_9N_5O_3$ (271.2)	85	129-130° (methanol)	53.14 53.38	3.34 3.30	25.82 25.42		3040 w, 2140 s, 1750 s, 1690 s, 1660 sh, 1600 s, 1585 w
4b	CO_2CH_3	3-Trifluoro-methyl	$C_{13}H_8F_3N_5O_3$ (339.2)	92	118° (methanol)	46.02 45.71	2.37 2.23	20.64 20.26		3040 w, 2150 m, 1740 s, 1680 s, 1620 w, 1590 w
4c	CO_2CH_3	4-Chloro	$C_{12}H_8Cl_2N_5O_3$ (305.7)	95	154° (methanol)	47.71 47.05	2.63 2.51	22.91 25.15		3040 w, 2160 s, 1750 s, 1685 s, 1600 w, 1585 w
4d	H	3-Trifluoro-methyl	$C_{11}H_6F_3N_5O$ (281.2)	91	111-112° (ethanol)	46.05 47.11	2.08 2.15	24.91 25.15		3040 w, 2160 s, 2100 sh, 1690 sh, 1675 s, 1660 sh, 1600 m
4e	H	4-Chloro	$C_{10}H_6ClN_5O$ (247.6)	87	189-190° (acetone)	48.50 48.39	2.44 2.28	28.28 28.43	14.30 14.29	2140 s, 1680 s, 1660 sh, 1605 w, 1600 w

Table 4

5-amino-2-arylpyridazin-3(2*H*)-ones **6a-c,e**

No.	R^1	R^2	Formula (Molweight)	Method	Yield (%)	mp (recrystallization)	Analysis (Calcd./Found) C	H	N	IR (cm^{-1})
6a	CO_2CH_3	H	$C_{12}H_{11}N_3O_3$ (245.2)	A	89	233-234° (tolulene)	58.77 58.50	4.52 4.63	17.13 16.96	3440 m, 3420 m, 3300 m, 3220 m, 3180 m, 1720 s, 1700 sh, 1665 s, 1620 s
6b	CO_2CH_3	3-Trifluoro-methyl	$C_{13}H_{10}F_3N_{32}O_3$ (313.2)	B	56	216-217° (acetoneacetone)	49.84 49.98	3.21 3.20	13.41 13.36	3430 s, 1720 m, 1660 ss, 1645 s, 1620 s,
6c	CO_2CH_3	4-Chloro	$C_{12}H_{10}ClN_3O_3$ (279.7)	B	89	245-247° (acetone)	51.53 51.68	3.60 3.62	15.02 14.91	3440 s, 1730 s, 1670 s, 1645 ss, 1630 s
6e	H	4-Chloro	$C_{10}H_8ClN_3O$ (221.6)	B	48	242-243° (acetonitrile)	54.19 54.25	3.64 3.58	18.96 19.09	3480 m, 3200 m, 1660 m, 1630 s, 1620 sh

[a] Corresponding to **4a-c,e.**

Table 5

^{1}H-NMR Spectral Data of **6** (measured in hexadeuteriodimetyl sulfoxide unless otherwise stated)

6a: (deuteriochloroform): δ = 3.9 (s, CH_3), 5.9 (s, H at C-4), 7.5 (s, 5 ArH)

6b: δ = 3.8 (s, CH_3), 5.8 (s, H at C-4), 7.0 (s, NH_2), 7.4-7.9 (s, 4 ArH)

6c: δ = 3.7 (s, CH_3), 5.8 (s, H at C-4), 7.0 (s, NH_2), 7.5 (s, 4 ArH)

6d: δ = 5.65 (d, J = 2 Hz, H at C-4), 7.3-7.7 (m, 4 ArH, NH_2 and H at C-6)

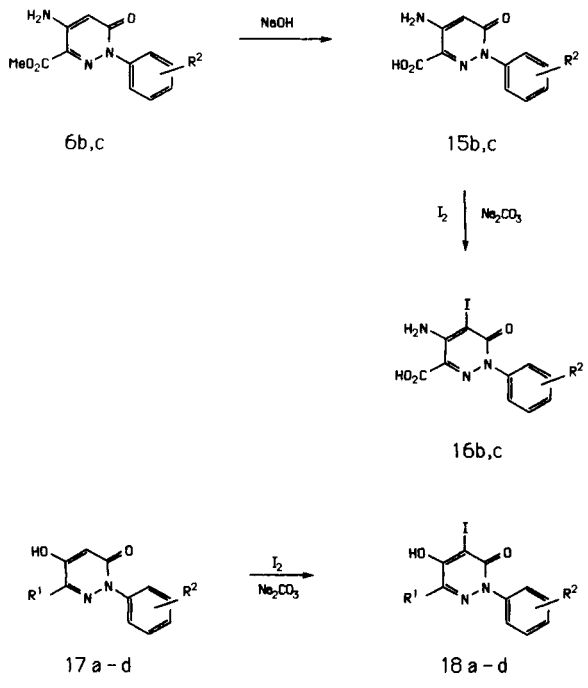
Some 2-aryl-pyridazin-3(2*H*)-ones are also topics for the electrophilic introduction of iodine into position 4. For better solubility in an aqueous solution of sodium carbonate, esters have first to be saponificated. 6-Unsubstituted 5-hydroxy-pyridazinones **17a,b** are also soluble under these conditions whereas the corresponding 5-amino compound **6c** cannot be used.

Table 6

5-(Alkyl aryl)thio-6-methoxycarbonyl-2-phenylpyridazin-3(2*H*)-ones **10a-i**

No.	R	Formula (Molweight)	Yield (%)	mp (recrystallization)	Analysis (Calcd./Found) C	H	N	IR (cm^{-1})
10a	Ethyl	$C_{14}H_{14}N_2O_3S$ (290.3)	74	140-142° (methanol)	57.91 57.85	4.86 4.80	9.65 9.57	3100 w, 2960 w, 1730 s, 1670 s, 1650 sh, 1550 m, 1490 m
10b	*n*–Propyl	$C_{15}H_{16}N_2O_3S$ (304.3)	72	146-148° (methanol)	59.19 59.09	5.30 5.39	9.21 9.14	3070 w, 2960 w, 1720 s, 1670 s, 1655 sh, 1590 m, 1550 m, 1490 m
10c	*i*–Propyl	$C_{15}H_{16}N_2O_3S$ (304.3)	87	118-120° (methanol/water)	59.19 59.32	5.30 5.38	9.21 9.17	3070 w, 2960 w, 1730 m, 1670 s, 1665 sh, 1655 sh, 1550 m, 1490 m
10d	*n*–Butyl	$C_{16}H_{18}N_2O_3S$ (318.4)	96	125-127° (methanol)	60.35 60.28	5.70 5.68	8.80 8.71	3080 w, 2960 w, 1730 m, 1720 m, 1670 s, 1660 s, 1650 sh, 1550 m, 1490 m
10e	*t*–Butyl	$C_{16}H_{18}N_2O_3S$ (318.4)	87	128-130° (methanol/water)	60.35 59.96	5.70 5.72	8.80 8.63	3120 w, 2960 w, 1730 s, 1720 sh, 1660 s, 1650 sh, 1550 m, 1490 m
10f	Cyclohexyl	$C_{18}H_{19}N_2O_3S$ (343.4)	87	141-143° (methanol)	62.76 62.63	5.85 5.75	8.14 8.10	3070 w, 2950 sh, 2940 m, 2850 m, 1730 s, 1670 s, 1550 m, 1490 m
10g	Benzyl	$C_{19}H_{16}N_2O_3S$ (352.4)	95	206-207° (tolulene)	64.75 64.90	4.58 4.78	7.95 7.80	3070 w, 2960 w, 1720 s, 1660 s, 1650 sh, 1550 m, 1490 w
10h	Phenyl	$C_{18}H_{14}N_2O_3S$ (338.4)	89	170-172° (methanol)	63.89 63.72	4.17 4.25	8.28 8.26	3060 w, 2950 w, 1730 s, 1670 s, 1650 sh, 1550 m, 1490 w
10i	2-Hydroxy-ethyl	$C_{14}H_{14}N_2O_4S$ (306.4)	55	164-166° (methanol)	54.89 54.67	4.61 4.66	9.15 9.06	3500-3250 m, b, 3060 w, 2960 w, 1730 s, 1670 s, 1655 sh, 1640 s

Scheme 4



17, 18	R^1	R^2
a	H	2-CF_3
b	H	4-Cl
c	CO_2H	3-CF_3
d	CO_2H	4-Cl

EXPERIMENTAL

The melting points were determined in open capillary tubes on a Gallenkamp melting point apparatus Model MFB-595 and are uncorrected. The ir spectra were recorded on a Perkin Elmer 298 spectrophotometer using samples in potassium bromide disks. The ^{1}H-nmr spectra were recorded in hexadeuteriodimethyl sulfoxide (unless otherwise indicated) and with TMS as an internal standard; the instrument used was the Varian EM 360 at 60 MHz. Elemental analyses were performed with an C,H,N-automat Carlo Erba 1106.

Table 7

^{1}H-NMR Spectral Data of **10**

(measured in deuteriochloroform unless otherwise stated)

10a: δ = 1.45 (t, J = 7 Hz, ethyl-CH_3), 2.95 (q, J = 7 Hz, CH_2), 3.9 (s, ester-CH_3), 6.8 (s, H at C-4), 7.2-7.9 (m, 5ArH)

10b: δ = 1.0 (t, J = 7 Hz, propyl-CH_3), 1.75 (q, J = 7 Hz, CH_2), 2.8 (t, J = 7 Hz, S-CH_2), 3.9 (s, ester-CH_3), 6.7, (s, H at C-4), 7.3-7.8 (m, 5ArH)

10c: δ = 1.55 (t, J = 7 Hz, 2 CH_3), 3.2-3.8 (m, CH), 4.0 (s, ester-CH_3), 6.8 (s, H at C-4), 7.3-7.8 (m, 5ArH)

10d: δ = 0.8-1.2 (m, butyl-CH_3), 1.3-2.0 (m, 2 CH_2), 2.9 (t, J = 7 Hz, S-CH_2), 4.0 (s, ester-CH_3), 6.8 (s, H at C-4), 7.4-7.9 (m, 5ArH)

10e: δ = 1.6 (s, 3 CH_3), 3.9 s, ester-CH_3), 7.1 (s, H at C-4), 7.3-7.9 m, 5ArH)

10f: δ = 1.2-2.3 (m, 5 CH_2), 3.9 (s, CH_3), 6.8 (s, H at C-4), 7.3-7.8 (m, 10 ArH)

10g: δ = 3.9 (m, CH_3), 4.1 (s, CH_2), 6.8 (s, H at C-4), 7.2-7.7 (m, 10 ArH)

10h: δ = 4.0 (s, CH_3), 6.3 (s, H at C-4), 7.2-7.9 (m, 10 ArH)

10i: (hexadeuteriodimethyl sulfoxide): δ = 3.25 (q, J = 7 Hz, S-CH_2), 3.5-3.9 (m, O-CH_2 and CH_3) , 7.1 (s, H at C-4), 7.5 (s, 5 ArH)

Table 8

5-(Alkylidene or arylidene)hydrazino-6-(alkylidene or arylidene)hydrazinocarbonyl-2-phenylpyridazin-3(2*H*)-ones **14a-e**

No.	R	Formula (Molweight)	Method	Yield (%)	mp (recrystallization)	Analysis (Calcd./Found) C	H	N	IR (cm^{-1})
14a	Methyl	$C_{15}H_{16}N_6O_2$ (312.3)	A	95	176-178° dec (ligroin)	57.68 57.29	5.16 5.27	26.91 26.31	3300-3100 w, b, 1660 s, 1650 sh, 1590 m, 1530 m, 1490 m
14b	Phenyl	$C_{25}H_{20}N_6O_2$ (436.5)	B	100	262° dec (dioxane)	68.79 68.44	4.62 4.71	19.26 19.24	3220-3140 w, b, 1670 s, 1640 w, 1605 m, 1585 m, 1520 m, 1490 m
14c	4-Methoxy-phenyl	$C_{27}H_{24}N_6O_4$ (496.5)	B	86	226-227° (dioxane)	65.31 64.94	4.87 4.95	16.93 16.59	3260-3120 w, b, 3060-3000 w, b, 1665 s, 1640 s, 1605 s, 1585 m, 1500 m, 1490 sh
14d	2.5-Dimeth-oxyphenyl	$C_{29}H_{28}N_6O_6$ (556.6)	B	53	216-217° (dioxane)	62.57 62.17	5.07 5.17	15.10 14.92	3300-300 w, b, 1680 w, 1600 s, 1595 m, 1540 s, 1500 s
14e	4-Hydroxy-3-methoxy-phenyl	$C_{27}H_{24}N_6O_6$ (528.5)	B	83	171° (dioxane)	61.36 61.29	4.58 4.66	15.90 15.87	3600-2800 m, b, 1665 s, 1640 s, 1600 s, 1585 s, 1530 m, 1510 s, 1490 s

General Procedure for 2-Aryl-5-chloro-6-methoxycarbonylpyridazin-3(2*H*)-ones (**2a-e**).

A solution of **1a-e** (20 mmoles) in 20 ml of phosphorus oxychloride was heated to 95 to 100° for three hours. After cooling it was poured into 300 ml of ice water. The precipitate was filtered and recrystallized from methanol.

5-Anilino-6-methoxycarbonyl-2-phenyl-pyridazin-3(2*H*)-one (**3a**).

A solution of 1.32 g (5 mmoles) of **2a** and 1.86 g (20 mmoles) of aniline in 20 ml of 1,2-dichlorobenzene was refluxed for 2.5 hours. Then the solution was cooled to room temperature and diluted with 50 ml of hexane. The product precipitated within the following 18 hours and was filtered. The yield was 1.05 g (65%), mp 157-158° (ligroin); ir: 3340 w, 1710 m, 1700 m, 1670 s, 1660 sh, 1640 sh, 1590 m, 1580 m, 1540 m, 1535 sh, 1520 sh, 1490 m cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 4.0 (s, CH_3), 6.4 (s, H at C-4), 7.2-7.9 (m, 10 ArH), 9.3 (s, NH).

Anal. Calcd. for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.20; H, 4.61; N, 13.06.

5-Benzylamino-6-methoxycarbonyl-2-phenylpyridazin-3(2*H*)-one (**3b**).

A solution of 2.64 g (10 mmoles) of **2a** and 2.14 g (20 mmoles) of benzylamine in 40 ml of 1,2-dichlorobenzene was refluxed for three hours. The product precipitated at cooling, was filtered and washed with hexane. The yield was 3.30 g (99%), mp 150-152° (ligroin), ir: 3380 m, 3060-3020 w, b, 1720 sh, 1710 s, 1700 sh, 1670 s, 1650 s, 1640 sh, 1630-1615 sh, b, 1590 m, 1580 s, 1540 sh, 1530 m, 1520 sh, 1490 m, ^{1}H-nmr (deuteriochloroform): δ = 3.9 (s, CH_3), 4.3 (d, J = 6 Hz, CH_2), 5.8 (s, H at C-4), 7.2-7.7 (m, 10 ArH).

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.45; H, 5.15; N, 12.87.

General Procedure for 2-Aryl-5-azidopyridazin-3(2*H*)-ones (**4a-e**).

The 5-chloropyridazines **2a-e** (50 mmoles) were dissolved in 100 ml of dimethylformamide and stirred in suspension with 100 mmoles of sodium azide at room temperature for two hours, then poured into 300 ml of ice water. The precipitate was filtered and dried at temperatures below 50°.

Compound **4b** had ^{1}H-nmr: δ = 3.9 (s, CH_3), 7.1 (s, H at C-4), 7.8 (s, 4 ArH).

Compound **4d** had ^{1}H-nmr (deuteriochloroform): δ = 6.65 (d, J = 2 Hz, H at C-4), 7.5-8.0 (m, 4 ArH and H at C-6).

Compound **4e** had ^{1}H-nmr: δ = 6.75 (d, J = 2 Hz, H at C-4), 7.6 (s, 4 ArH), 7.95 (d, J = 2 Hz, H at C-6).

General Procedure for 2-Aryl-5-phosphoranylideneiminopyridazin-3(2*H*)-ones (**5b,c,e**).

The 5-azidopyridazines **4b,c,e** (25 mmoles) were suspended in 100 ml of benzene and treated with 30 mmoles of triphenylphosphine at room temperature. Within 30 minutes of stirring a clear solution resulted from this procedure. The solvent was removed at low pressure, the residue was heated in cyclohexane for 10 minutes, filtered and recrystallized.

6-Methoxycarbonyl-5-phosphoranylideneimino-2-(3-trifluoromethyl)phenylpyridazin-3(2*H*)-one (**5b**).

The yield was 10.90 g (76%), mp 207-208° (methanol); ir: 3070 w, 2960 w, 1755 s, 1655 s, 1585 m, 1580 m, 1520 m, 1490 w cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 3.9 (s, CH_3), 5.5 (s, H at C-4), 7.1-7.9 (m, 19 ArH).

Anal. Calcd. for $C_{31}H_{23}F_3N_3O_3P$: C, 64.92; H, 4.04; N, 7.32. Found: C, 65.08; H, 4.02; N, 7.35.

2-(4-Chlorophenyl)-6-methoxycarbonyl-5-triphenylphosphoranylideneiminopyridazin-3(2*H*)-one (**5c**).

The yield was 8.91 g (66%), mp 194-196° (acetone); ir: 3060 w, 2960 w, 1750 sh, 1740 s, 1730 m, 1660 sh, 1650 s, 1600 sh, 1590 sh, 1580 sh, 1570 s, 1510 sh, 1495 s cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 4.0 (s, CH_3), 5.6 (s, H at C-4), 7.2-8.0 (m, 19 ArH).

Anal. Calcd. for $C_{30}H_{23}ClN_3O_3P$: C, 66.73; H, 4.29; N, 7.78. Found: C, 66.43; H, 4.10; N, 7.71.

2-(4-Chlorophenyl)-5-triphenylphosphoranylideneiminopyridazin-3(2*H*)-one (**5e**).

The yield was 8.31 g (69%), mp 197-198° (methanol); ir: 3060 w, 1660 sh, 1645 sh, 1640 s, 1600 m, 1590 m, 1580 m, 1530 sh, 1520 m, 1490 m cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 5.55 (d, J = 2 Hz, H at C-4), 7.1-7.9 (m, 19 ArH and H at C-6).

Anal. Calcd. for $C_{25}H_{21}ClN_3OP$: C, 67.37; H, 4.75; N, 9.42. Found: C, 67.12; H, 4.72; N, 9.13.

5-Amino-6-methoxycarbonyl-2-phenylpyridazin-3(2*H*)-one (**6a**). (Method A).

To a solution of 6.78 g (25 mmoles) of **4a** in 200 ml of glacial acetic acid about 100 mg of charcoal with 5% of palladium were added. At 60° this solution was treated with hydrogen. The charcoal was filtered and the solvent removed to yield 5.46 g (89%).

General Procedure for 2-Aryl-5-aminopyridazin-3(2*H*)-ones (Method B) (**6b,c,e**).

A well stirred solution of 10 mmoles of **5b,c,e** in 250 ml of acetone was treated with 5 ml of concentrated hydrochloric acid. The solvent was removed at low pressure to give a crude product still containing triphenylphosphine oxide, which could be removed by recrystallization.

5-Acetylamino-6-methoxycarbonyl-2-phenylpyridazin-3(2*H*)-one (**7**).

The 5-aminopyridazine **6a** (0.62 g, 2.5 mmoles), dissolved in 10 ml of acetic anhydride, was refluxed for four hours. The solution was allowed to cool to room temperature, then poured into 50 ml of water. The precipitate was filtered. The yield was 0.63 g (88%), mp 175-177° (ligroin), ir: 3180 m, 3140 sh, 3100 sh, 1725-1710 s, b, 1700 s, 1665 s, 1655 sh, 1650 sh, 1640 sh, 1560 sh, 1540 sh, 1535 s, 1520 sh, 1490 m cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 2.3 (s, acetyl-CH_3), 4.0 (s, ester-CH_3), 7.3-7.7 (m, 5 ArH), 8.2 (s, H at C-4).

Anal. Calcd. for $C_{14}H_{13}N_3O_4$: C, 58.53; H, 4.56; N, 14.63. Found: C, 58.30; H, 4.71; N, 14.45.

3-*n*-Butyl-4-hydroxy-8-methoxycarbonyl-6-phenylpyrido[2,3-*d*]pyridazine-2,5(1*H*,6*H*)-dione (**9a**).

A well triturated mixture of 0.81 g (3.3 mmoles) of **6a** and 1.70 g (3.3 mmoles) of bis(2,4,6-trichlorophenyl) *n*-butylmalonate **8a** was heated to 240° for 20 minutes. The product was allowed to cool to room temperature and treated with hexane/diethyl-ether 1:1 to remove 2,4,6-trichlorophenol. The yield was 0.99 g (81%), mp 150-151° (ligroin); ir: 3200-2700 m, b, 1740 m, 1690 sh, 1660 sh, 1650 s, 1640 sh, 1600 m, 1590 m, 1570 sh, 1530 w, 1490 w cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 0.7-1.1 (m, butyl-CH_3), 1.1-1.8 (m, 2 CH_2), 2.4-2.8 (m, CH_2 at C-3), 4.0 (s, ester-CH_3), 7.6 (s,

5 ArH), 11.5-11.7 (s, b, NH).

Anal. Calcd. for $C_{19}H_{19}N_3O_5$: C, 61.78; H, 5.88; N, 11.38. Found: C, 62.12; H, 5.54; N, 11.37.

4-Hydroxy-8-methoxycarbonyl-3,6-diphenylpyrido[2,3-*d*]pyridazine-2,5(1*H*,6*H*)-dione (**9b**).

A well triturated mixture of 0.61 g (2.5 mmoles) of **6a** and 1.35 g (2.5 mmoles) of bis(2,4,6-trichlorophenyl)phenylmalonate **8b** was treated as described for **9a**. The yield was 0.78 g (80%), mp 176° (ligroin); ir: 3340-3240 m, b, 1750 sh, 1710 s, 1680-1620 s, b, 1600 m, 1560 sh, 1540 sh, 1490 m cm^{-1}; ^{1}H-nmr: δ = 3.9 (s, CH_3), 7.2-7.6 (m, 10 ArH), 12.2-12.4 (s, b, NH).

Anal. Calcd. for $C_{21}H_{15}N_3O_5$: C, 64.78; H, 3.88; N, 10.79. Found: C, 64.38; H, 4.15; N, 10.58.

General Procedure for 5-(Alkyl or aryl)thio-6-methoxycarbonyl-2-phenylpyridazin-3(2*H*)-ones (**10a-i**).

A solution of 1.32 g (5 mmoles) of **2a** in 15 ml of dry dimethylformamide was treated with 5 mmoles of the according mercaptane and 2.07 g (15 mmoles) of potassium carbonate. The suspension was stirred for one hour, then poured into 40 ml of ice water. The product precipitated, was filtered and recrystallized.

5-Mercapto-3-oxo-2-phenyl-2,3-dihydropyridazine-6-carboxylic Acid (**11**).

A suspension of 0.5 g (1.6 mmoles) of **10e** in 40 ml of 6 *N* hydrochloric acid was refluxed for six hours. The precipitate was filtered after cooling. The yield was 0.29 g (74%), mp 219° dec (methanol); ir: 3100-2300 w, b, 1920-1800 w, b, 1740 sh, 1720 m, 1700 sh, 1660 sh, 1640 sh, 1630 sh, 1610 s, 1595 sh, 1580 sh, 1560 sh, 1540 m, 1490 m cm^{-1}; ^{1}H-nmr: δ = 7.1 (s, H at C-4), 7.5 (s, 5 ArH).

Anal. Calcd. for $C_{11}H_8N_2O_3S$: C, 53.21; H, 3.25; N, 11.29. Found: C, 52.83; H, 3.53; N, 11.08.

5-Hydrazino-6-methoxycarbonyl-2-phenylpyridazin-3(2*H*)-one (**12**).

The 5-chloropyridazine **2a** (3.56 g, 13.5 mmoles) was dissolved in 150 ml of ethanol and treated with 0.68 g (13.5 mmoles) of hydrazine hydrate. That solution was warmed to 40° for 10 minutes. The product precipitated forming long needles. The yield was 3.30 g (94%), mp 205° dec (methanol); ir: 3380 s, 3360 sh, 3320 w, 3180 w, 3060 w, 2940 w, 1720 m, 1710 sh, 1655 s, 1650 sh, 1640 sh, 1610 m, 1580 w, 1515 w, 1510 w, 1490 w cm^{-1}; ^{1}H-nmr (trifluoroacetic acid): δ = 4.0 (s, CH_3), 7.05 (s, H at C-4), 7.5 (s, 5 ArH).

Anal. Calcd. for $C_{12}H_{12}N_4O_3$: C, 55.38; H, 4.65; N, 21.53. Found: C, 55.16; H, 4.50; N, 21.23.

5-Hydrazino-3-oxo-2-phenyl-2,3-dihydropyridazine-6-carboxylic Hydrazide (**13**).

A solution of 13.2 g (50 mmoles) of **2a** in 1000 ml of ethanol was treated with 12.5 g (250 mmoles) of hydrazine hydrate and refluxed for 15 minutes. The product precipitated at cooling. The yield was 10.96 g (84%), mp 212-213° (ethanol); ir: 3360 m, 3320 s, 3310 s, 3280 m, 3220-3180 m, b, 3020 w, 1685 m, 1660 s, 1640 s, 1620 s, 1610 s, 1590 m, 1580 sh, 1550 w, 1520 w, 1500 w, 1490 m cm^{-1}; ^{1}H-nmr (trifluoroacetic acid): δ = 7.0 (s, H at C-4), 7.3-7.6 (m, 5 ArH).

Anal. Calcd. for $C_{11}H_{12}N_6O_2$: C, 50.76; H, 4.65; N, 32.29. Found: C, 50.52; H, 4.62; N, 32.31.

5-Ethylidenehydrazino-6-ethylidenehydrazinocarbonyl-2-phenylpyridazine-3(2*H*)-one (**14a**).

A solution of 1.30 g (5 mmoles) of **13** in 50 ml of dimethylformamide was treated with 0.5 ml (0.39 g, 8.9 mmoles) of acetaldehyde and was stirred at room temperature for 24 hours. Then the solution was heated to reflux temperature for five minutes and the solvent removed under low pressure. The remaining oil crystallized within a few days to yield 1.48 g (95%), mp 176-178° (ligroin); ir: 3300-3100 w, b, 1685 sh, 1660 s, 1650 sh, 1640 sh, 1620 sh, 1590 m, 1540 sh, 1530 m, 1520 sh, 1490 m cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 1.7-2.1 (m, 2 CH_3), 6.6 (s, H at C-4), 7.2-7.6 (m, 5 ArH), 9.9-10.1 (s, b, NH).

Anal. Calcd. for $C_{15}H_{16}N_6O_2$: C, 57.68; H, 5.16; N, 26.91. Found: C, 57.28; H, 5.27; N, 27.31.

General Procedure for 5-Arylidenehydrazino-6-arylidenehydrazinocarbonyl-2-phenylpyridazin-3(2*H*)-ones (**14b-e**).

Compound **13** (1.30 g, 5 mmoles) was dissolved in 350 ml of ethanol at reflux temperature and treated with 5 mmoles of the corresponding aldehyde in 5 ml of ethanol. The solution was refluxed for another ten minutes. The product precipitated at cooling.

5-Amino-3-oxo-2-(3-trifluoromethyl)phenyl-2,3-dihydropyridazine-6-carboxylic Acid (**15b**).

Compound **6b** (4.68 g, 15 mmoles) was dissolved in 100 ml of water containing 10 g of sodium hydroxide at 50°. The solution was allowed to cool to room temperature and then acidified to *p*H 5 by the addition of hydrochloric acid. The product precipitated. The yield was 4.00 g (89%), mp 249-250° (acetonitrile); ir: 3520 w, 3480 m, 3460 sh, 3370 w, 3340 w, 1730-1715 m, b, 1630 s, 1600-1585 sh, b, 1560 sh, 1530 w, 1495 w cm^{-1}; ^{1}H-nmr: δ = 5.8 (s, H at C-4), 6.9-7.3 (s, b, NH_2), 7.5-8.0 (m, 4 ArH).

Anal. Calcd. for $C_{12}H_8F_3N_3O_3$: C, 48.17; H, 2.70; N, 14.04. Found: C, 48.01; H, 2.56; N, 13.87.

5-Amino-2-(4-chlorophenyl)-3-oxo-2,3-dihydropyridazine-6-carboxylic Acid (**15c**).

Compound **6c** (4.20 g, 15 mmoles) was treated as described for **15b**. The yield was 3.67 g (92%), mp 259-260° (methanol); ir: 3370 m, 3400 w, 3380-3300 w, b, 3250-3160 w, b, 3080 w, 1740-1720 m, b, 1665 sh, 1650-1630 s, b, 1495 m cm^{-1}; ^{1}H-nmr: δ = 5.7 (s, H at C-4), 6.8-7.2 (s, b, NH_2), 7.4 (s, 4 ArH).

Anal. Calcd. for $C_{11}H_8ClN_3O_3$: C, 49.73; H, 3.04; N, 15.82. Found: C, 49.45; H, 2.83; N, 15.66.

General Procedure for 5-(Amino or hydroxy)-2-aryl-4-iodo-3-oxo-2,3-dihydropyridazines (**16b,c**, **18a-d**).

The carboxylic acids **15b,c,17a-d** (5 mmoles) were dissolved in 100 ml of water containing 1.59 g (15 mmoles) of sodium carbonate. At reflux temperature 1.27 g (5 mmoles) of iodine in 15 ml of dioxane were added, the solution cooled and acidified to *p*H 5 with hydrochloric acid. The product precipitated at cooling.

5-Amino-4-iodo-3-oxo-2-(3-trifluoromethyl)phenyl-2,3-dihydropyridazine-6-carboxylic Acid (**16b**).

The yield was 1.95 g (92%), mp 236° (acetone); ir: 3480 m, 3340 m, 3200-2400 m, b, 1720 m, 1635 sh, 1625 sh, 1610 s, 1550 m, 1500 sh, 1490 m cm^{-1}; ^{1}H-nmr: δ = 6.9-7.5 (s, b, NH_2), 7.6-8.1 (m, 4 ArH).

Anal. Calcd. for $C_{12}H_7F_3IN_3O_3$: C, 33.91; H, 1.66; N, 9.88. Found: C, 33.71; H, 1.62; N, 9.70.

5-Amino-2-(4-chlorophenyl)-4-iodo-3-oxo-2,3-dihydropyridazine-6-carboxylic Acid (**16c**).

The yield was 1.82 g (93%), mp 278-281° (methanol); ir: 3460 m, 3330 m, 3300 sh, 3100 w, 1740 s, 1725 sh, 1640 s, 1615 s, 1590 sh, 1560 m, 1550 sh, 1505 sh, 1490 m cm^{-1}; ^1H-nmr: δ = 7.0-7.4 (s, b, NH_2), 7.5 (s, 4 ArH).

Anal. Calcd. for $C_{11}H_7ClIN_3O_3$: C, 33.74; H, 1.80; N, 10.73. Found: C, 33.47; H, 1.56; N, 10.60.

5-Hydroxy-4-iodo-2-(2-trifluoromethyl)phenylpyridazin-3(2*H*)-one (**18a**).

Treating 5-hydroxy-2-(2-trifluoromethyl)phenylpyridazin-3(2*H*)-one (**17a**) according to the general procedure afforded 1.17 g (61%), mp 237-238° (acetonitrile); ir: 3200-2500 m, b, 1625 s, 1605 s, 1500 w cm^{-1}; ^1H-nmr: δ = 7.6-8.0 (m, 4 ArH, 2 H at C-4 and C-6).

Anal. Calcd. for $C_{11}H_6F_3IN_2O_2$: C, 34.58; H, 1.58; N, 7.33. Found: C, 34.56; H, 1.51; N, 7.32.

2-(4-Chlorophenyl)-5-hydroxy-4-iodopyridazine-3(2*H*)-one (**18b**).

Treating 2-(4-chloro)phenyl-5-hydroxypyridazin-3(2*H*)-one (**17b**) according to the general procedure afforded 1.34 g (77%), mp 285-286° (methanol); ir: 3200-2400 m, b, 1645 sh, 1630 m, 1610 s, 1600 sh, 1580 s, 1565 sh, 1545 sh, 1495 s cm^{-1}; ^1H-nmr: δ = 7.4 (s, 4 ArH), 7.6 (s, H at C-6).

Anal. Calcd. for $C_{10}H_6ClIN_2O_2$: C, 34.46; H, 1.74; N, 8.04. Found: C, 34.50; H, 1.69; N, 7.92.

5-Hydroxy-4-iodo-3-oxo-2-(3-trifluoromethyl)phenyl-2,3-dihydropyridazine-6-carboxylic Acid (**18c**).

Starting from 5-Hydroxy-3-oxo-2-(3-trifluoromethyl)phenyl-2,3-dihydropyridine-6-carboxylic acid (**17c**) the yield was 1.81 g (85%), mp 262-263° (methanol); ir: 3300-2600 m, b, 2520 w, 1705 m, 1620 s, 1600 sh, 1590 m, 1565 sh, 1500 w cm^{-1}; ^1H-nmr: δ 7.6-8.0 (m, 4 ArH), 10.5-10.9 (b, OH and COOH).

Anal. Calcd. for $C_{12}H_6F_3IN_2O_4$: C, 33.82; H, 1.42; N, 6.57. Found: C, 34.01; H, 1.40; N, 6.45.

2-(4-Chloro)phenyl-5-hydroxy-4-iodo-3-oxo-2,3-dihydropyridazine-6-carboxylic Acid (**18d**).

Starting from 2-(4-chloro)phenyl-5-hydroxy-3-oxo-2,3-dihydropyridazine-6-carboxylic acid (**17d**) the yield was 1.47 g (75%), mp 245-246° (methanol); ir: 3300-2600 m, b, 1700 m, 1640 s, 1600 sh, m, 1495 s, cm^{-1}; ^1H-nmr: δ = 7.4 (s, 4 ArH), 10.5-10.9 (b, OH and COOH).

Anal. Calcd. for $C_{11}H_6ClIN_2O_4$: C, 33.66; H, 1.54; N, 7.14. Found: C, 33.40; H, 1.43; N, 7.02.

REFERENCES AND NOTES

[1] For part **5** see: W. Stadlbauer, A. Pfaffenschlager and Th. Kappe, *Synthesis*, 781 (1989).

[2] B. D. Schober, Diss. University of Graz 1988.

[3] B. D. Schober, G. Megyeri and Th. Kappe, *J. Heterocyclic Chem.*, **26**, 169 (1989).

[4] Th. Kappe, *Monatsh. Chem.*, **98**, 874 (1967).

[5] P. Friedländer and F. Müller, *Ber.*, **20**, 2009 (1887).

[6] R. E. Lutz, J. F. Kodington, R. J. Rowlett, A. J. Deineth and B. S. Baily, *J. Am. Chem. Soc.*, **68**, 1810 (1946).

[7] Y. Kawase, S. Yamaguchi, M. Morita and T. Uesugi, *Bull. Chem. Soc. Japan*, **53**, 1055 (1980).

[8] F. J. Buchmann and S. Hamilton, *J. Am. Chem. Soc.*, **64**, 1352 (1942).

[9] H. J. Knops and B. Born, *Tetrahedron Letters*, 2973 (1983).

[10] E. Schrötter, H. Niedrich and H. Schick, *Pharmazie*, **39**, 155 (1984).

[11] W. Stadlbauer and Th. Kappe, *Monatsh. Chem.*, **113**, 751 (1982).

[12] Ng. C. Hung and E. Bisagni, *Synthesis*, 765 (1984).

[13] H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 635 (1919).

[14] H. Staudinger and E. Hauser, *Helv. Chim. Acta*, **4**, 861 (1921).

[15] J. Bödecker, B. Richter and P. Köckritz, *Z. Chem.*, **20**, 417 (1980).

[16] H. M. Blatter and H. Lukaszewski, *Tetrahedron Letters*, 1087 (1964).

[17] U. V. Gizycki and G. Oertel, *Angew. Chem.*, **80**, 363 (1968).

[18] J. Bödecker, P. Köckritz and R. Kraft, *Z. Chem.*, **17**, 371 (1977).

[19] J. Bödecker, K. Courault and P. Köckritz, *Z. Chem.*, **20**, 211 (1980).

[20] M. Sakamota, K. Miyazawa and T. Tomimatsu, *Chem. Pharm. Bull.*, **24**, 2532 (1976).

[21] J. Bödecker and K. Courault, *Tetrahedron*, **34**, 101 (1978).

[22] N. Knouzi, M. Voultier and R. Carrié, *Bull. Soc. Chim. France*, 815 (1985).

[23] C. Kos, Diss. University of Graz 1985; Th. Kappe, A. Pfaffenschlager and W. Stadlbauer, *Synthesis*, 666 (1989).

[24] I. Maeba, K. Mori and R. N. Castle, *J. Heterocyclic Chem.*, **16**, 1559 (1979).

[25] H. A. Offe, W. Siefken and G. Domagk, *Z. Naturforsch.*, **7B**, 462 (1952).

[26] Chugai Pharmaceutical Co., Ltd. (by Y. Nitta, F. Yoneda and I. Matsuura), *Japan Patent*, 192 (1967).

[27] P. Kregar-Cadez, A. Pollak, B. Stanovnik, M. Tisler and B. Wechtersberg-Lazetic, *J. Heterocyclic Chem.*, **9**, 351 (1972).

[28] P. H. Olesen, Th. Kappe and J. Becher, *J. Heterocyclic Chem.*, **25**, 1719 (1988).