Synthesis of Alkyl or Aryl Pyridazinyl Ethers

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Received December 21, 2004

This paper presents the synthesis of some alkyl or aryl pyridazinyl ethers from 2-alkyl-4-halo-5-hydroxy- and 2-alkyl-4,5-dichloropyridazin-3(2*H*)-ones or 3,6-dichloropyridazine. Reaction of 2-alkyl-4-halo-5-hydroxypyridazin-3(2*H*)-ones **1** with 1,2-dibromoethane or 1,3-dibromopropane gave the corresponding monopyridazin-5-yl ethers **2** and α,ω-[di(pyridazin-5-oxy)]alkanes **3**. Treatment of **4** with 4-substituted-phenol afforded 5-(4-substituted-phenoxy)-2-(4-substituted-phenoxymethyl) derivatives **5**. Reaction of 2-alkyl-4,5-dichloro derivatives **7** with **1** gave the corresponding di(pyridazin-5-yl) ethers **8** in good yields. Compound **10** was reacted with catechol to give monopyridazin-3-yl ether **11** and/or di(pyridazin-3-yl) ether **12**. Also we described the results for the reaction of 2-alkyl-4-chloro-5-(4-substituted-phenoxy)pyridazin-3(2*H*)-ones with nucleophiles.

J. Heterocyclic Chem., **42**, 639 (2005).

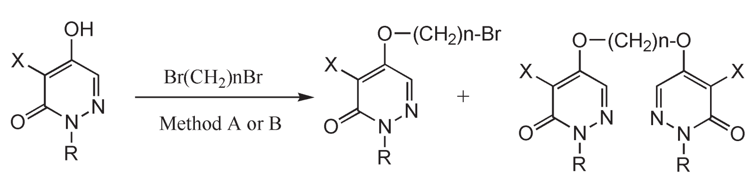
As part of our research program for the development of novel pyridazin-3(2*H*)-one derivatives as potential agrochemicals, we synthesized some new alkyl or aryl pyridazinyl ethers containing a halogen atom at C-4 position of pyridazinone ring.

Although some methods for direct synthesis of 4,5-dialkoxy, and 4(or 5)-monoalkoxypyridazin-3(2*H*)-one derivatives from the corresponding 4,5-dihalo derivatives have been reported, [1-4] they are nonselective for the alkoxylation of 4,5-dichloropyridazin-3(2*H*)-ones [4]. Therefore, we selected 5-hydroxy-4-halopyridazin-3(2*H*)-ones **1** and 2-chloromethyl-4,5-dichloropyridazin-3(2*H*)-one (**4**) as starting materials for the synthesis of 4-halo-5-alkoxy derivatives. Compounds **1** [5] and **4** [6] were prepared by literature methods.

Reaction of **1** with 1,2-dibromoethane or 1,3-dibromopropane in the presence of potassium carbonate (mole ratio; **1**/$Br(CH_2)_nBr/K_2CO_3$ = 1:1:1) gave compounds **2** as the main product and **3**. The results are summarized in Table 1. Whereas, treatment of **1a** with 1,2-dibromoethane or 1,3-dibromopropane in the presence of potassium carbonate (mole ratio; **1**/$Br(CH_2)_nBr/K_2CO_3$ = 2:1:2) also gave **3** as the main product. The structures of **2** and **3** were established by ir, nmr and elemental analyses. The proton magnetic resonance spectra of **2** showed proton signals of CH_2Br (δ 3.59-3.68 ppm range) and CH_2O (δ 4.35-4.54 ppm range) involving other proton signals of the proposed structures, while the proton magnetic resonance spectra of **3** showed proton signals of two CH_2O (δ 4.11-4.75 ppm range) involving other proton signals of the proposed structures.

According to the literature [6b], the reaction of **4** with nucleophiles such as CH_3O^- and N_3^- selectively afford the corresponding 4-chloro-5-substituted-2-methoxy(or

Scheme 1



1 **2** **3**

Method A: **1**/$Br(CH_2)_nBr/K_2CO_3$ (1:1:1 mole ratio) in DMF
Method B: **1**/$Br(CH_2)_nBr/K_2CO_3$ (2:1:2 mole ratio) in DMF
Method C: **1**/$Br(CH_2)_nBr/K_2CO_3$ (1:2:2 mole ratio) in DMF

1	**a**	**b**	**c**	**d**	**e**
R	Et	*n*-Pr	*n*-Pr	Me	$PhCH_2$
X	Cl	Cl	Br	Cl	Cl

2,3	**a**	**b**	**c**	**d**	**e**	**f**
R	Et	*n*-Pr	*n*-Pr	Me	Et	$PhCH_2$
n	2	2	2	3	3	3
X	Cl	Cl	Br	Cl	Cl	Cl

Table 1

Yields, Melting Points and Infrared Spectral Data for **2**, **3**, **5**, **8**, **11**, **12**, **14** and **17**

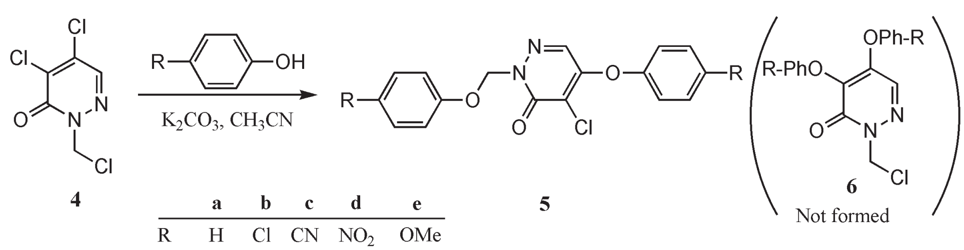
Compound No	Isolated Yield(%)	Mp (°C) (Lit. mp)	IR (potassium bromide, cm^{-1})
2a	47 [a] 0.3 [b]	116-117	3110, 3070, 3000, 2890, 1642, 1605, 1450, 1420, 1330, 1299, 1200, 1100, 955, 850, 745
2b	11 [a]	79-80	3130, 3100, 3000, 2900, 1660, 1620, 1460, 1430, 1340, 1300, 1218, 1120, 1000, 880, 780
2c	26 [a]	118-120	3070, 2980, 2900, 1650, 1605, 1420, 1320, 1300, 1200, 1100, 840
2d	15 [a]	78-80	3120, 3060, 2960, 1645, 1610, 1398, 1330, 1305, 1215, 1102, 1000, 880
2e	18 [a]	70-71	3075, 2999, 1650, 1420, 1358, 1320, 1282, 1200, 1105, 990, 890, 850
2f	52 [a]	82-84	3100, 3060, 3000, 2930, 1660, 1618, 1420, 1400, 1330, 1285, 1220, 1100, 880, 738
3a	10 [a] 40 [b]	145-146	3090, 3000, 2955, 2890, 1640, 1610, 1420, 1365, 1320, 1282, 1195, 1102, 905, 860, 760
3b	27 [a]	108-109	3140, 3080, 2950, 2880, 1650, 1600, 1410, 1370, 1315, 1280, 1190, 1100, 1030, 890, 860
3c	17 [a]	157-158	2998, 2900, 1660, 1610, 1480, 1420, 1350, 1320, 1280, 1200, 1100, 999, 858, 780, 760
3d	13 [a]	188-190	3130, 3100, 2999, 2930, 1655, 1610, 1403, 1340, 1300, 1218, 1110, 1030, 880
3e	11 [a] 67 [b]	225-228	3070, 3000, 2970, 1640, 1618, 1505, 1400, 1380, 1200, 1090, 860
3f	20 [a]	198-200	3150, 3100, 2999, 1660, 1620, 1420, 1310, 1198, 1100, 1038, 878, 680
5a	98	76-78	3090, 3000, 1689, 1605, 1507, 1400, 1290, 1235, 1180, 1170, 1085, 1050, 1030, 760
5b	81	155-156	3100, 3070, 2980, 2930, 1670, 1605, 1495, 1380, 1278, 1232, 1220, 1090, 1040, 840, 820
5c	81	133-135	3060, 3000, 2250, 1680, 1500, 1460, 1420, 1385, 1280, 1230, 1180, 1030, 850
5d	77	177-179	3140, 3100, 2950, 2900, 1690, 1630, 1605, 1540, 1520, 1368, 1330, 1290, 1240, 1122, 1030, 880
5e	88	73-75	3100, 3045, 3000, 2940, 2870, 1665, 1525, 1402, 1300, 1265, 1222, 1050, 860, 802, 765
8a	72	148-149	3070, 3002, 2952, 1662, 1610, 1405, 1303, 1270, 1190, 1100, 860
8b	82	133-134	3070, 2960, 2870, 1655, 1600, 1380, 1310, 1265, 1190, 1095
8c	83	177-179	3070, 3050, 2975, 1665, 1630, 1600, 1405, 1310, 1260, 1090, 880
11	87 [a]	148-150	3500-2900(br), 1620, 1600, 1520, 1445, 1300, 1240, 1160, 1110, 1100, 860, 760
12	10 [a] 88 [b]	166-168	3150, 3075, 1585, 1500, 1419, 1300, 1190, 1150, 860, 760
14a	86 [c] 86 [d] 94 [e]	154-155 (154-155) [8]	3125, 3070, 3020, 2990, 1645, 1610, 1400, 1332, 1300, 1221, 1105, 962, 880
14b	89 [f] 24 [g]	99-100 (99-100) [5a]	3140, 3090, 3025, 2990, 1658, 1620, 1489, 1465, 1428, 1340, 1300, 1200, 1120, 970, 870
14c	52 [h]	109-110 (109-110) [5a]	3100, 3060, 3000, 2955, 2900, 1650, 1605, 1468, 1440, 1365, 1275, 1210, 1210, 1180, 1100, 959, 820
17	74	84-85	3100, 3045, 3000, 2900, 2140, 1639, 1415, 1362, 1320, 1300, 1225, 1140, 1015, 980, 855

[a] Method A in Scheme 4; [b] Method B in Scheme 4; [c] From compound **13a**; [d] From compound **13b**; [e] From compound **13c**. [f] From compound **13d**; [g] From compound **17**; [h] From compound **13e**.

azido)methyl derivatives. Therefore, we attempted the synthesis of 4-chloro-5-phenoxy-2-phenoxymethylpyridazin-3(2*H*)-one **5** from **4**. Reaction of **4** with *p*-substituted-phenol in the presence of potassium carbonate in acetonitrile gave only compounds **5** in good yield instead of 4,5-di(4-substituted-phenyl)-2-chloromethyl derivatives **6**.

The structures of **5** were established by ir, nmr and elemental analyses. The proton magnetic resonance spectra of

Scheme 2



5 showed protons signals of CH_2O at the N-2 position in the δ 5.95-6.17 ppm range as singlet, as well as other proton signals corresponding to the proposed structures.

Condensation of **1** with **7** in the presence of potassium carbonate in dimethylsulfoxide furnished the corresponding dipyridazinyl ethers **8** in good yields. The formation of **9** by the intermolecular reaction of **1**, however, was not detected under the same condition. The structures of **8** were established by ir, nmr and elemental analyses. The proton magnetic resonance spectra of **8** revealed the proton signal of C-6 in the δ 7.60-7.66 ppm range, as well as other protons signals corresponding to the proposed structures. The carbon-13 magnetic resonance spectra of **8** showed carbon signals of the carbonyl at C-3 (for **8a**: δ 158.1; for **8b**: δ 181.3; for **8c**: δ 157.8 ppm), as well as other carbons signals corresponding to the proposed structures.

Reaction of 3,6-dichloropyridazine (**10**) [7] with catechol in the presence of potassium carbonate in acetonitrile (mole ratio; **10**/catechol/K_2CO_3 = 1:1:1) also afforded **11** in 87% yield and **12** in 10% yield. Whereas, treatment of **10** with catechol in the presence of potassium carbonate in acetonitrile (mole ratio; **10**/catechol/K_2CO_3 = 2:1:2) afforded only **12** in 88% yield. The structures of **11** and **12** were established by ir, nmr and elemental analyses. The infrared spectrum of **11** showed an absorption band of OH (3500-2900 cm^{-1}), whereas that of **12** did not show the absorption band of OH. The proton magnetic resonance spectrum of **11** showed the proton signal of OH at δ 9.55 ppm.

We also attempted the synthesis of 4-methoxy-5-(4-substituted-phenyl) derivatives **15** from **13**. Methoxylation of **13** [8] with potassium carbonate/methanol system gave only the corresponding 4-chloro-5-methoxy derivatives **14**

Scheme 3

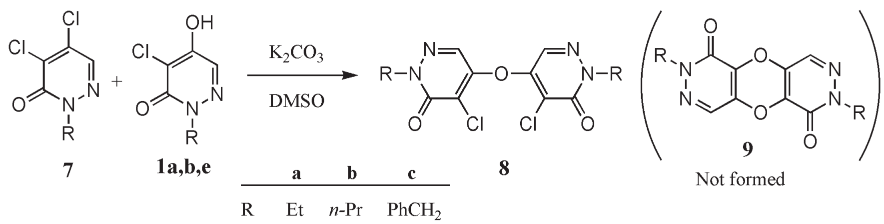


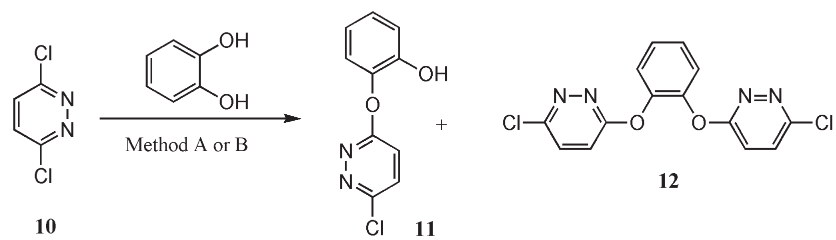
Table 2

^{1}H Nmr Spectral Data for **2**, **3**, **5**, **8**, **11**, **12**, **14** and **17**

Compound No	Solvent [a]	^{1}H Nmr (δ, ppm) [b]
2a	C	1.30(t, 3H, *J* = 7.2), 3.60 (t, 2H, *J* = 6.2), 4.17 (q, 2H, *J* = 7.2), 4.47(t, 2H, *J* = 6.2), 7.70(s, 1H)
2b	C	0.95(t, 3H, *J* = 7.5), 1.82(m, 2H), 3.68(t, 2H, *J* = 6.6), 4.15(t, 2H, *J* = 7.5), 4.55(t, 2H, *J* = 6.6), 7.77(s, 1H)
2c	C	0.95(t, 3H, *J* = 7.5), 1.82(q, 2H, *J* = 7.5), 3.68(t, 2H, *J* = 6.3), 4.16 (t, 2H, *J* = 7.5), 4.54(t, 2H, *J* = 6.3), 7.67(s, 1H)
2d	C	2.29(m, 2H), 3.65(t, 2H, *J* = 6.5), 3.69(s, 3H), 4.45(t, 2H, *J* = 6.5), 8.23(s, 1H)
2e	C	1.37(t, 3H, *J* = 7.2), 2.38(t, 2H, *J* = 6.0), 3.63(t, 2H, *J* = 6.0), 4.25(q, 2H, *J* = 7.2), 4.39(t, 2H, *J* = 6.0), 7.8(s, 1H)
2f	C	2.34(m, 2H), 3.59(t, 2H, *J* = 7.2), 4.35(t, 2H, *J* = 7.2), 5.33(s, 2H), 7.35(m, 5H), 7.80(s, 1H)
3a	C	1.37(t, 6H, *J* = 7.2), 4.24(q, 4H, *J* = 7.2), 4.66(s, 4H), 7.90(s, 2H)
3b	C	0.94(t, 6H, *J* = 7.5, 7.0), 1.82(m, 4H), 4.15(t, 2H, *J* = 7.5, 7.0), 4.66(s, 4H), 7.89(s, 2H)
3c	D	0.86(t, 6H, *J* = 7.5), 1.71(m, 4H), 4.06(t, 2H, *J*= 7.5), 4.75(s, 4H), 8.18(s, 2H)
3d	D	2.24(m, 2H), 3.68(s, 6H), 4.49(t, 4H, *J* = 6.2), 8.21(s, 2H)
3e	D	1.25(t, 6H, *J* = 7.1), 2.25(t, 2H, *J* = 6.0), 4.11(m, 4H), 4.51(t, 4H, *J* = 7.1), 8.26(s, 2H)
3f	D	2.24(m, 2H), 4.50(t, 4H, *J* = 6.0), 5.28(s, 4H), 7.30(m, 10H), 8.29(s, 2H)
5a	C	6.05(s, 2H), 7.44(m, 10H), 8.25(s, 1H)
5b	C	6.01(s, 2H), 7.22(m, 8H), 7.52(s, 1H)
5c	C	6.11(s, 2H), 7.20(m, 4H), 7.61(t, 2H, *J* = 1.9), 7.62(s, 1H), 7.76(t, 2H, *J* = 1.9)
5d	C+D	6.17(s, 2H), 7.26(m, 4H), 7.74(s, 1H), 8.21(s, 2H, *J* = 9.2), 8.33(d, 2H, *J* = 9.2)
5e	C	3.75(s, 3H), 3.82(s, 3H), 5.95(s, 2H), 6.92(m, 8H), 7.47(s, 1H)
8a	C	1.41(t, 6H, *J* = 7.0), 4.29(m, 4H), 7.66(s, 2H)
8b	D	0.86(t, 6H, *J* = 7.2), 1.72(m, 4H), 4.06(t, 4H, *J* = 7.2), 8.19 (s, 2H)
8c	C	5.35(s, 4H), 7.38(m, 10H), 7.60(s, 2H)
11	D	6.69(m, 4H), 7.32(d, 1H, *J* = 9.5), 7.71(d, 1H, *J* = 9.5), 9.55(bs, 1H)
12	C	7.01(d, 2H, *J* = 9.0), 7.23(m, 4H), 7.36(d, 2H, *J* = 9.0)
14a	C	3.84(s, 3H), 4.09(s, 3H), 7.80(s, 1H)
14b	D	1.40(t, 3H, *J* = 7.2), 4.10(s, 3H), 4.20(q, 2H, *J* = 7.2), 7.80(s, 1H)
14c	D	1.28(d, 6H, *J* = 6.0), 4.08(s, 3H), 5.14(m, 1H), 8.31(s, 1H)
17	C	1.37(t, 3H, *J* = 7.2), 4.23(q, 2H, *J* = 7.2), 7.62(s, 1H)

[a] Solvent: C=$CDCl_3$, D=DMSO-d_6; [b] Abbreviations used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, *J* = Hz unit.

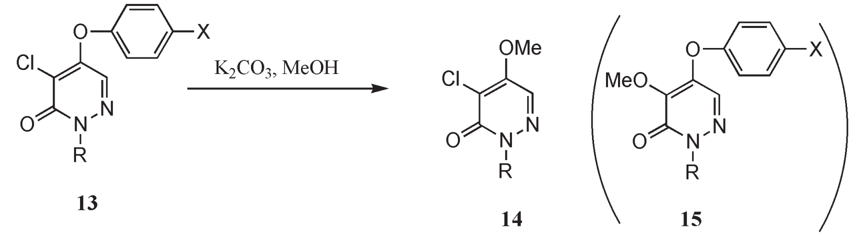
Scheme 4



Method A: **10**/Catechol/K_2CO_3 (1:1:1 mole ratio) in CH_3CN
Method B: **10**/Catechol/K_2CO_3 (2:1:2 mole ratio) in CH_3CN

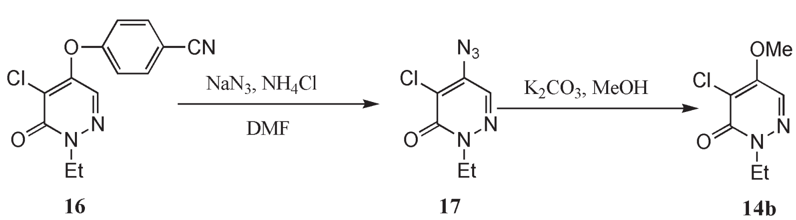
instead of compound **15**. The alkyl groups at the N-2 position of pyridazin-3(2*H*)-one has an effect on the methoxylation of **13** based on our results. Compound **16** [8] was also treated with NaN_3/NH_4Cl in dimethylformamide to give 5-azido-4-chloro derivative **17** instead of the 4-azido-5-(4-cyanophenyl) derivative. Treatment of **17** with potassium carbonate/methanol also gave the corresponding 4-chloro-5-methoxy derivative **14b** instead of the 4-methoxy-5-azido derivative. The structures of **14** and **17** were established by ir, nmr and elemental analyses. And compounds **14** and **17** were also identical to authentic compounds.

Scheme 5



13	a	b	c	d	e
R	Me	Me	Me	Et	*i*-Pr
X	Cl	OMe	CN	OMe	CN

14	a	b	c
R	Me	Et	*i*-Pr



Finally, 2-Alkyl-4-halo-5-hydroxypyridazin-3(2*H*)-ones **1** proved to be useful precursors for the synthesis 4-halo-5-alkoxy or aryloxypyridazin-3(2*H*)-ones. The conversion of 5-phenoxy or azido derivatives to 5-azido or methoxy derivatives may also be useful for the regioselective functionalization.

Further work is under way in our laboratory including the biological characterization, other chemical transformation of new derivatives and the regioselective functionalization using 5-azido or 5-phenoxy derivatives.

EXPERIMENTAL

TLC was performed on silica gel (60 F^{254} Merck). The spots were located by UV light. Open-bed chromatography was carried out on silica gel (70 ~ 230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent. Melting points were determined with a capillary apparatus and uncorrected. ^1H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer with chemical shift values reported in δ units (ppm) relative to an internal standard (TMS). IR spectra were obtained on an IR spectrophotometer. Elemental analyses were performed with a Perkin Elmer 240C.

Table 3

^{13}C Nmr Spectral Data for **2**, **3**, **5**, **8**, **11**, **12**, **14** and **17**

Compound No	Solvent [a]	^{1}H Nmr (δ, ppm)
2a	C	13.9, 28.3, 48.4, 70.5, 118.5, 127.7, 154.2, 158.7
2b	C	11.4, 22.0, 28.3, 54.6, 70.5, 118.5, 127.5, 154.1, 158.9
2c	C	11.1, 21.7, 27.8, 54.4, 70.1, 109.6, 126.6, 155.7, 158.8
2d	C	30.3, 31.7, 68.4, 114.6, 127.4, 127.7, 154.4, 157.6
2e	C	13.5, 29.0, 32.0, 47.9, 67.9, 117.4, 126.8, 154.2, 158.4
2f	C	28.9, 32.0, 55.9, 68.0, 117.6, 127.2, 128.1, 128.6, 129.0, 135.7, 154.2, 158.5
3a	C	13.5, 47.9, 69.0, 118.1, 127.3, 154.0, 158.2
3b	C	11.4, 22.0, 54.6, 69.3, 118.4, 127.5, 154.3, 158.8
3c	D	10.8, 21.2, 53.2, 69.0, 107.0, 127.9, 156.2, 157.8
3d	D	29.5, 41.2, 66.5, 117.6, 126.9, 154.7, 159.1
3e	D	13.3, 28.5, 46.8, 66.9, 114.7, 127.9, 154.3, 157.1
3f	D	29.0, 55.2, 67.5, 99.4, 115.2, 128.0, 128.3, 128.9, 136.8, 154.9, 157.9
5a	C	78.2, 116.7, 120.4, 120.7, 123.2, 126.9, 130.3, 131.0, 131.2, 154.0, 154.3, 157.2, 159.3
5b	C	77.9, 117.6, 120.8, 120.9, 127.7, 129.6, 130.4, 130.7, 131.7, 152.0, 153.2, 155.2, 158.6
5c	C	77.3, 106.1, 109.7, 116.5, 117.7, 118.7, 119.3, 123.4, 131.6, 134.2, 134.8, 152.1, 156.9, 158.4, 159.8
5d	C+D	77.9, 116.1, 116.3, 119.1, 123.8, 126.2, 126.7, 132.2, 142.9, 145.2, 152.3, 158.6, 161.8
5e	C	55.6, 55.7, 78.8, 114.7, 115.6, 117.7, 118.9, 121.2, 129.8, 146.7, 150.6, 154.2, 155.2, 157.8, 158.7
8a	C	13.7, 48.8, 123.1, 129.8, 150.7, 158.1
8b	D	34.4, 44.6, 77.3, 144.8, 154.0, 174.3, 181.3
8c	C	56.5, 123.0, 128.5, 129.0, 129.3, 129.6, 135.0, 150.3, 157.8
11	D	117.5, 119.9, 120.8, 123.1, 127.0, 132.4, 140.8, 149.2, 151.7, 165.2
12	C	119.9, 123.6, 127.5, 132.0, 145.2, 152.9, 164.9
14a	C	41.2, 58.0, 117.0, 126.3, 155.4, 159.2
14b	D	13.5, 47.8, 57.6, 116.7, 126.1, 154.9, 158.4
14c	D	21.0, 50.7, 57.5, 116.4, 125.9, 154.4, 158.4
17	C	13.4, 48.1, 122.7, 129.3, 139.1, 156.9

[a] Solvent: C=$CDCl_3$, D=DMSO-d_6.

Table 4

Elemental Analysis of **2**, **3**, **5**, **8**, **11**, **12**, **14** and **17**.

Compound No	Molecular Formula	Calcd./Found(%) C	H	N
2a	$C_8H_{10}N_2O_2BrCl$	34.13	3.58	9.95
		34.08	3.51	9.89
2b	$C_9H_{12}N_2O_2BrCl$	36.57	4.09	9.48
		36.44	4.01	9.37
2c	$C_9H_{12}N_2O_2Br_2$	31.79	3.56	8.24
		32.00	3.68	8.22
2d	$C_8H_{10}N_2O_2BrCl$	34.13	3.58	9.95
		34.01	3.66	10.01
2e	$C_9H_{12}N_2O_2BrCl$	36.57	4.09	9.48
		36.50	4.19	9.29
2f	$C_{14}H_{14}N_2O_2BrCl$	47.02	3.95	7.83
		47.12	4.01	7.79
3a	$C_{14}H_{16}N_4O_4Cl_2$	44.82	4.30	14.93
		44.88	4.33	14.79
3b	$C_{16}H_{20}N_4O_4Cl_2$	47.65	5.00	13.89
		47.70	5.01	13.90
3c	$C_{16}H_{20}N_4O_4Br_2$	39.05	4.10	11.38
		39.09	4.13	11.39
3d	$C_{13}H_{14}N_4O_4Cl_2$	43.23	3.91	15.51
		43.31	4.01	15.55
3e	$C_{15}H_{18}N_4O_4Cl_2$	46.29	4.66	14.39
		46.12	4.43	14.16
3f	$C_{25}H_{22}N_4O_4Cl_2$	58.49	4.32	10.91
		58.51	4.39	10.98
5a	$C_{17}H_{13}N_2O_3Cl$	62.11	3.99	8.52
		62.17	4.02	8.60

Table 4 (continued)

Compound No	Molecular Formula	Calcd./Found(%) C	H	N
5b	$C_{17}H_{11}N_2O_3Cl_3$	51.35	2.79	7.04
		51.46	2.82	7.20
5c	$C_{19}H_{11}N_4O_3Cl$	60.25	2.93	14.79
		60.29	2.99	14.81
5d	$C_{17}H_{11}N_4O_7Cl$	48.76	2.65	13.38
		48.97	2.69	13.43
5e	$C_{19}H_{17}N_2O_5Cl$	58.69	4.41	7.21
		58.72	4.48	7.28
8a	$C_{12}H_{12}N_4O_3Cl_2$	43.52	3.65	16.92
		43.66	3.69	16.97
8b	$C_{14}H_{16}N_4O_3Cl_2$	46.81	4.49	15.60
		46.90	4.53	15.63
8c	$C_{22}H_{16}N_4O_3Cl_2$	58.04	3.54	12.31
		58.11	3.61	12.44
11	$C_{10}H_7N_2O_2Cl$	53.95	3.17	12.58
		53.98	3.21	12.64
12	$C_{14}H_8N_4O_2Cl_2$	50.17	2.41	16.72
		50.21	2.45	16.80
14a	$C_6H_7N_2O_2Cl$	41.28	4.04	16.05
		41.31	4.12	16.12
14b	$C_7H_9N_2O_2Cl$	44.58	4.81	14.85
		44.61	4.90	14.92
14c	$C_6H_5N_2O_2Cl$	41.76	2.92	16.23
		41.82	2.99	16.31
17	$C_6H_6N_5OCl$	36.10	3.03	35.09
		36.33	3.11	35.13

4-Chloro-2-ethyl-5-(2-bromoethoxy)pyridazin-3(2*H*)-one (**2a**) and 1,2-Bis[4-chloro-2-ethyl-3-oxopyridazin-5-yl]oxy]ethane (**3a**).

Method A.

A mixture of **1a** (2.1 g, 12 mmoles), 1,2-dibromoethane (2.16 g, 12 mmoles), potassium carbonate (1.66 g, 12 mmoles) and dimethylformamide (50 mL) was stirred at room temperature for 24 hours. The mixture was poured into water (200 mL) with stirring. After extracting with chloroform (150 mL) the products, chloroform solution was washed with water (200 mL x 5) and dried over anhydrous magnesium sulfate. After evaporating the solvent under reduced pressure, the resulting residue was applied to the top of an open-bed silica gel column (2.4 x 5 cm). The column was eluted with chloroform. Fractions containing **2a** (R_f = 0.3 $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure to give **2a** in 47% yield (3 g, recrystallization solvent: diethyl ether/*n*-hexane = 1:3, v/v). Fractions containing **3a** (R_f = 0.05 $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure to give **3a** in 10% yield (0.9 g, recrystallization solvent: diethyl ether).

Method B.

A mixture of **1a** (1 g, 5.75 mmoles), 1,2-dibromoethane (0.25 g, 2.87 mmoles), potassium carbonate (0.79 g, 5.75 mmoles) and dimethylformamide (15 mL) was stirred at room temperature for 45 hours. The mixture was poured into water (200 mL) with stirring. After extracting with chloroform (50 mL) the products, chloroform solution was washed with water (100 mL x 5) and dried over anhydrous magnesium sulfate. After evaporating the solvent under reduced pressure, the resulting residue was applied to the top of an open-bed silica gel column (2.4 x 5 cm). The column was eluted with chloroform. Fractions containing **2a** (R_f = 0.3 $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure to give **2a** in 0.3% yield (0.01 g, recrystallization solvent: diethyl ether/*n*-hexane = 1:3, v/v). Fractions containing **3a** (R_f = 0.05 $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure to give **3a** in 40% yield (0.9 g, recrystallization solvent: diethyl ether).

4-Chloro-2-propyl-5-(2-bromoethoxy)pyridazin-3(2*H*)-one (**2b**) and 1,2-Bis[4-chloro-2-propyl-3-oxopyridazin-5-yl]oxy]ethane (**3b**).

Method C.

A mixture of **1b** (1.13 g, 6 mmoles), 1,2-dibromoethane (2.16 g, 12 mmoles), potassium carbonate (1.66 g, 12 mmoles) and dimethylformamide (20 mL) was stirred for 6 days at 50-60 °C. After cooling to room temperature, the mixture was poured into water (100 mL) with stirring. After extracting with chloroform (100 mL) the products, chloroform solution was washed with water (200 mL x 5) and dried over anhydrous magnesium sulfate. After evaporating the solvent under reduced pressure, the resulting residue was applied to the top of an open-bed silica gel column (2.4 x 12 cm). The column was eluted with chloroform. Fractions containing **2b** (R_f = 0.53 $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure to give **2b** in 11% yield (0.5 g, recrystallization solvent: diethyl ether/*n*-hexane = 1:2, v/v). Fractions containing **3b** (R_f = 0.17 $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure to give **3b** in 27% yield (1.7 g, recrystallization solvent: diethyl ether/*n*-hexane = 1:2, v/v).

4-Bromo-2-propyl-5-(2-bromoethoxy)pyridazin-3(2*H*)-one (**2c**) and 1,2-Bis[4-bromo-2-propyl-3-oxopyridazin-5-yl]oxy]ethane (**3c**).

Method A.

A mixture of **1c** (2.88 g, 12 mmoles), 1,2-dibromoethane (2.16 g, 12 mmoles), potassium carbonate (1.66 g, 12 mmoles) and dimethylformamide (20 mL) was stirred for 54 hours at 35-40 °C. After cooling to room temperature, the mixture was poured into water (200 mL) with stirring. After extracting with chloroform (50 mL) the products, chloroform solution was washed with water (200 mL x 5) and dried over anhydrous magnesium sulfate. After co-evaporating silica gel (4 g) under reduced pressure, the resulting residue was applied to the top of an open-bed silica gel column (2.4 x 10 cm). The column was eluted with chloroform. Fractions containing **2c** (R_f = 0.54 $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure to give **2c** in 26% yield (1.1 g, recrystallization solvent: *n*-hexane). Fractions containing **3c** (R_f = 0.18 $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure to give **3c** in 17% yield (1.1 g).

4-Chloro-2-methyl-5-(3-bromopropyloxy)pyridazin-3(2*H*)-one (**2d**) and 1,3-Bis[4-chloro-2-methyl-3-oxopyridazin-5-yl]oxy]-propane (**3d**).

Method A.

A mixture of **1d** (3 g, 19 mmoles), 1,3-dibromopropane (3.8 g, 19 mmoles), potassium carbonate (2.63 g, 19 mmoles) and dimethylformamide (20 mL) was stirred for 77 hours at 40-50 °C. After cooling to room temperature, the mixture was poured into water (150 mL) with stirring. After extracting with chloroform (50 mL x 3) the products, chloroform solution was washed with water (200 mL x 5) and dried over anhydrous magnesium sulfate. After evaporating the solvent under reduced pressure, the resulting residue was applied to the top of an open-bed silica gel column (2.4 x 10 cm). The column was eluted with chloroform. Fractions containing **2d** (R_f = 0.53 $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure to give **2d** in 15% yield (1.5 g, recrystallization solvent: chloroform/*n*-hexane = 1:5, v/v). Fractions containing **3d** (R_f = 0.14 $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure to give **3d** in 13% yield (1.8 g).

4-Chloro-2-ethyl-5-(3-bromopropyloxy)pyridazin-3(2*H*)-one (**2e**) and 1,3-Bis[4-chloro-2-ethyl-3-oxopyridazin-5-yl]oxy]-propane (**3e**).

Method A.

A mixture of **1a** (5 g, 29 mmoles), 1,3-dibromopropane (7 g, 29 mmoles), potassium carbonate (4.01 g, 29 mmoles) and acetonitrile (120 mL) was refluxed for 24 hours. After cooling to room temperature, the mixture was filtered. After evaporating the solvent under reduced pressure, the resulting residue was applied to the top of an open-bed silica gel column (2.4 x 20cm). The column was eluted with chloroform. Fractions containing **2a** (R_f = 0.54 $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure to give **2e** in 18% yield (1.5 g, recrystallization solvent: *n*-hexane). Fractions containing **3e** (R_f = 0.16 $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure to give **3e** in 11% yield (2.5 g, recrystallization solvent: diethyl ether).

Method B.

A mixture of **1a** (1 g, 5.74 mmoles), 1,3-dibromopropane (0.58 g, 2.87 mmoles), potassium carbonate (0.79 g, 5.75 mmoles) and dimethylformamide (15 mL) was refluxed for 79 hours. After cooling to room temperature, the mixture was filtered. After evaporating the solvent under reduced pressure, the resulting residue was applied to the top of an open-bed silica gel column (2 x 20 cm). The column was eluted with chloroform. Fractions containing **3e** (R_f = 0.16 $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure to give **3e** in 67% yield (1.4 g, recrystallization solvent: diethyl ether).

2-Benzyl-4-Chloro-5-(3-bromopropyloxy)pyridazin-3(2H)-one (**2f**) and 1,3-Bis[2-benzyl-4-chloro-3-oxopyridazin-5-yl]oxy]propane (**3f**).

Method A.

A mixture of **1e** (5 g, 20 mmoles), 1,3-dibromopropane (4.24 g, 21 mmoles), potassium carbonate (2.9 g, 21 mmoles) and acetonitrile (120 mL) was refluxed for 22 hours. After cooling to room temperature, the mixture was filtered. After evaporating the solvent under reduced pressure, the resulting residue was applied to the top of an open-bed silica gel column (3 x 20 cm). The column was eluted with chloroform. Fractions containing **2f** (R_f = 0.58 $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure to give **2f** in 52% yield (1.8 g, recrystallization solvent: diethyl ether/*n*-hexane = 1:2, v/v). Fractions containing **3f** (R_f = 0.21 $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure to give **3f** in 20% yield (1 g).

4-Chloro-5-phenoxy-2-phenoxymethylpyridazin-3(2*H*)-ones **5**.

A mixture of **4** (2.99 g, 14 mmoles), phenol (2.64 g, 28 mmoles), potassium carbonate (3.87 g, 28 mmoles) and acetonitrile (15 mL) was refluxed until **4** was disappeared (**5a** for 3 hours, **5b** for 1 hour, **5c** for 2 hours, **5d** for 19 hours, **5e** for 8 hours). After cooling to room temperature, the mixture was filtered. The work-up processes were the following: For **5a** and **5b**: After evaporating the solvent under reduced pressure, the resulting residue was triturated in water (50 mL) with stirring. The resulting precipitates was filtered, washed with *n*-hexane and dried in air to give **5** (**5a** = 98%, **5b**=81%). For **5c** and **5d**: After evaporating the solvent under reduced pressure, the resulting residue was applied to the top of an open-bed silica gel column (2 x 12 cm). The column was eluted with chloroform. Fractions containing **5** (**5c** R_f = 0.33, **5d** R_f =0.36; $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure to give **5** (**5c** in 81% yield, **5d** in 77% yield; recrystallization solvent: $CHCl_3$/*n*-hexane = 1:1, v/v). For **5e**: After evaporating the solvent under reduced pressure, the resulting residue was recrystallized from water/methanol (5:2, v/v) to give **5e** in 88% yield.

Bis(4-chloro-2-alkyl-3-oxopyridazin-5-yl)ethers **8**.

A mixture of **7** (27 mmoles), **1** (27 mmoles), potassium carbonate (4.4 g, 30 mmoles) and solvent (for **8a** DMSO, 20 mL; for **8b** acetonitrile, 20 mL; for **8c** DMSO/acetonitrile=15:50 mL) was stirred at suitable temperature until **7** and **1** were no longer present by tlc monitoring (**8a** for 58 hours at 60-70 °C, **8b** for 8 hours at room temperature, **8c** for 8 days at 80-90 °C). After cooling to room temperature, chloroform (100 mL) and water (200 mL) were added to the mixture with stirring. After separating, the organic layer was washed with excess water and dried over anhydrous magnesium sulfate. After evaporating the solvent under reduced pressure, the resulting residue was applied to the top of an open-bed silica gel column (2.4 x 8 cm). The column was eluted with chloroform/diethyl ether (9.5:0.5, v/v, for **8a**) or chloroform (for **8b** and **8c**). Fractions containing **8** (**8a** R_f = 0.18, **8b** R_f =0.20, **8c** R_f = 0.21; $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure to give **8** (**8a** in 72% yield, **8b** in 82% yield, **8c** in 83% yield; recrystallization solvent: diethyl ether/*n*-hexane = 1:2, v/v).

6-Chloropyridazin-3-yl-2-hydroxyphenyl ether (**11**) and 1,2-Bis[6-chloropyridazin-3-yl]oxy]benzene (**12**).

A solution of 3,6-dichloropyridazine (**10**, 1 g, 7.61 mmoles), catechol (1.43 g, 13 mmoles), potassium carbonate (1.9 g, 13 mmoles) and acetonitrile (30 mL) was refluxed for 25 hours. After cooling to room temperature, the mixture was filtered and washed with methanol (10 mL). The combined filtrate was co-evaporated with silica gel (4 g) under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.4 x 12 cm). The column was eluted with chloroform. Fractions containing **12** (R_f = 0.32, $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined. After evaporating under reduced pressure, the residue was washed with diethyl ether and dried in air to give **12** in 10% (0.4 g) yield. Fractions containing **11** (R_f = 0.18, $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined. After evaporating under reduced pressure, the residue was recrystallized from diethyl ether/*n*-hexane (1:1.5, v/v) and dried in air to give **11** in 87% (1.7 g) yield.

Synthesis of 2-Alkyl-4-chloro-5-methoxypyridazin-3(2*H*)-ones **14** from **13** and **17**.

A mixture of 2-alkyl-4-chloro-5-(4-substituted-phenoxy)pyridazin-3(2*H*)-ones **13** or **17** (2.8 mmoles), potassium carbonate (0.58 g, 4.19 mmoles) and methanol (20 mL) was refluxed until the 5-phenoxy derivative was no longer present by tlc monitoring (**13a** for 2.5 hours, **13b** for 2 hours, **13c** for 20 hours, **13d**, **13e** and **17** for 1 hour). The work-up processes were the followings: For **13a**, **13b**, **13d** and **17**: After evaporating the solvent under reduced pressure, water (20 mL) was added to the residue with stirring. The precipitate was collected by filtration and dried in air to give **14a** or **14b**. For **13c** and **13e**: After cooling to room temperature, the mixture was filtered. The filtrate was co-evaporated with silica gel (2 g) under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2.4 x 10 cm). The column was eluted with methylene chloride. Fractions containing **14a** (R_f = 0.56, $CHCl_3$/diethyl ether = 9.5:0.5, v/v) or **14c**(R_f = 0.60, $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure to give **14a** (recrystallization solvent: diethyl ether) or **14c** (recrystallization solvent: diethyl ether/*n*-hexane = 1:2, v/v).

5-Azido-4-chloro-2-ethylpyridazin-3(2*H*)-one (**17**).

A mixture of **16** (1.5 g, 5.45 mmoles), sodium azide (0.7 g, 10 mmoles), ammonium chloride (0.54 g, 10 mmoles) and dimethylformamide (20 mL) was stirred for 122 hours at room temperature. Chloroform (150 mL) and water (100 mL) were added to the mixture. The resulting mixture was stirred for an additional 5 hours. The organic layer was separated, washed with excess water and dried over anhydrous magnesium sulfate. After evaporating the solvent under reduced pressure, the resulting residue was applied to the top of an open-bed silica gel column (2 x 15 cm). The column was eluted with chloroform. Fractions containing **17** (R_f = 0.62 $CHCl_3$/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure to give **17** in 74% yield (0.8 g, recrystallization solvent: *n*-hexane).

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