Retro-Ene Reaction. VI. Functionalization of 4,5-Dihalopyridazin-6-ones Using 1-Acetyloxymethyl-4,5-dihalopyridazin-6-ones as the 1-O, 3-N, 5-O Ene-Adduct

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Received September 22, 1998

Functionalization of 1-acetyloxymethyl-4,5-dihalopyridazin-6-ones *via* retro-ene reaction with some nucleophiles gave regioselectively only 5-halo-4-substitutedpyridazin-6-ones.

J. Heterocyclic Chem., **36**, 413 (1999).

The functionalization of 4,5-dihalopyridazin-6-ones using 1-hydroxymethyl-4,5-dihalopyridazin-6-ones as the 1-O, 3-N, 5-O ene-adduct *via* a retro-ene reaction has reported [1]. The retro-ene reaction of a 1-O, 3-N, 5-O ene-adduct is promoted by heat and/or a base [2]. For that reason, the synthesis and storage of 1-hydroxymethyl-4,5-dihalopyridazin-6-ones are difficult. Thus, we attempted to develop a novel 1-O, 3-N, 5-O ene-adduct for the functionalization of 4,5-dihalopyridazin-6-ones.

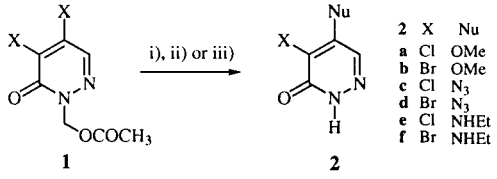
In a previous paper [3], we also reported the transformation of 1-acetyloxymethyl-5-chloro-4-phenoxypyridazin-6-one to 5-chloro-4-phenoxypyridazin-6-one by aqueous potassium carbonate solution. This transformation occurs easily *via* the retro-ene fragmentation. The retro-ene reaction of 1-acetyloxymethylpyridazinone is slower than it of 1-hydroxymethylpyridazinone. Therefore, we investigated the functionalization of 4,5-dihalopyridazin-6-ones using 1-acetyloxymethylpyridazinone as the 1-O, 3-N, 5-O ene-adduct.

In this paper, we reported the results for the title reaction.

Methoxylation [4] of **1** with potassium carbonate (2 equivalents) and methanol gave regioselectively the corresponding 4-methoxy-5-halopyridazin-6-ones **2a** or **2b** in excellent yields. Azidation of **1** with sodium azide (2 equivalents) in methanol also afforded the corresponding 4-azido-5-halo derivatives **2c** or **2d** in good yields. Reaction of **1** with ethylamine hydrochloride (4 equivalents) in the presence of potassium carbonate (4 equivalents) in acetonitrile yielded the corresponding 4-ethylamino-5-halo derivatives **2e** (77%) or **2f** (78%). The structures of **2a-2f** were established by ir, nmr and elemental analyses.

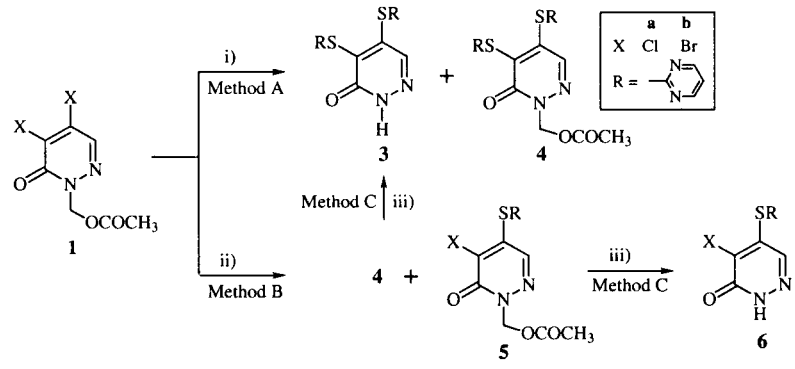
Compound **1** was allowed to react with 2-mercaptopyrimidine (2 equivalents) in the presence of potassium carbonate in acetonitrile at room temperature to give **3** (35%) and **4** (58%) (Method A). Whereas, reaction of **1a** with 2-mercaptopyrimidine (1 equivalent) and potassium carbonate (1 equivalent) in acetonitrile at room temperature afforded compound **4** (8%) and **5a** (76%) (Method B). Treatment of **1b** with 2-mercaptopyrimidine (1 equivalent) and potassium carbonate (1 equivalent) in acetonitrile at room temperature also yielded only **5b** in 91% yield

Scheme 1



i) MeOH, K_2CO_3 (2 equivalents), reflux for **2a** and **2b.**
ii) NaN_3 (2 equivalents), MeOH, reflux for **2c** and **2d.**
iii) $EtNH_2.HCl$ (4 equivalents), K_2CO_3 (4 equivalents), CH_3CN, reflux for **2e** and **2f.**

Scheme 2



i) Method A: 2-Mercaptopyrimidine (2 equivalents), K_2CO_3 (2 equivalents), CH_3CN, room temperature. ii) Method B: 2-Mercaptopyrimidine (1 equivalent), K_2CO_3 (1 equivalent), CH_3CN, room temperature. iii) Method C: K_2CO_3 (2 equivalents), H_2O, reflux.

(Method B). Treatment of compounds **4** or **5** with aqueous potassium carbonate (2 equivalents) gave the corresponding **3** (74%) or **6** (50% for **6a** or 84% for **6b**) (Method C). The structures of **3-6** were also established by ir, nmr and elemental analyses.

On the other hand, reaction of **1** with phenol (1 equivalent) and potassium carbonate (1 equivalent) in acetonitrile and then with aqueous potassium carbonate furnished regioselectively **7** in excellent yield (Method D). Whereas, treatment of **1** with phenol (2 equivalents) and potassium carbonate (2 equivalents) in acetonitrile gave **7** as main product and **8** in low yield (Method E). The formation of **8** in this system is similar the Chung's results for 1-hydroxymethyl-4,5-dihalopyridazin-6-ones [1].

In order to establish the synthetic mechanism for **8**, we attempted to react **9** with phenol under the different conditions. Compound **9** was prepared from **1** and phenol (1 equivalent) in the presence of potassium carbonate in acetonitrile. Decomposition of **9** with aqueous potassium carbonate (2 equivalents) afforded the corresponding **7** (Method F). Whereas, treatment of **9** with phenol (2 equivalents) and potassium carbonate (2 equivalents) furnished **7** as main product and **8**. The synthesis of **8** occurs *via* two steps; *i.e*, i) the substitution of nucleophile at C-4 position on the ring occurs in the first step, ii) the Mannich condensation of **9** with phenol *via* the immonium intermediate to give **8** progress in the second step [1]. This reaction process was also observed by tlc during the reaction. The

Table 1

Yields, Melting Points and IR Spectral Data for **2-8**

Compound No.	Method	Yield (%)	mp(°C) (lit. mp)	IR (potassium bromide) (cm^{-1}) [d]
2a		90	230-231 (232-233) [1] (233-235) [5]	3300-2950 (m), 1660, 1600, 1470, 1410, 1280, 1120, 950, 900
2b		89	213-214 (213-214) [1] (212-213) [5]	3300-2900 (m), 1650, 1610, 1400, 1280, 1100, 960, 890
2c		81	172-173 (172-173) [1] (170-172) [5]	3300-2900 (m), 2200, 2150, 1665, 1620, 1410, 1350, 1310, 1100
2d		81	173-175 (173-175) [1] (174-175) [5]	3300-2900 (m), 2200, 2150, 1660, 1610, 1410, 1340, 1300, 1070
2e		77	203-204 (203-204) [1] (198-200) [6]	3350, 3150-2950 (m), 1680, 1660, 1620, 1460, 1350, 1320, 1030
2f		78	197-198 (197-198) [1]	3350, 3000-2900, 1660, 1620, 1450, 1340, 1300, 1020, 560
3	A	35 [a]	174-175 (174-175) [1]	3200-2900 (m), 1640, 1570, 1400, 1180
	C	74 [b]		
4	A	58 [a]	102-103	3000, 1760, 1680, 1560, 1380, 1200, 1180, 760
	B	8 [c]		
	A	96 [c]		
5a	B	76	121-122	3000-2900 (m), 1760, 1680, 1565, 1400, 1260, 1040
5b	B	91	141-142	3100-2900 (m) , 1760, 1680, 1580, 1400, 1260
6a	C	50	222 dec (222 dec) [1]	3200-2900 (m), 1680, 1580, 1400, 1180, 1080
6b	C	84	236 dec	3200-2850 (m), 1660, 1560, 1400, 1170, 1140, 1060, 810, 730
7a	D	89	178-179	3250-2900 (m), 1680, 1620, 1600, 1500, 1400,
	E	43	(178-179)	1280, 1100, 780
	F	62	[1,5]	
	G	53		
7b	D	91	194-196	3200-2900 (m) , 1660, 1600, 1500, 1410, 1280
	E	32	(195-196) [1]	
	F	67	(197) [5]	
	G	44		
8a	E	20	140-142	3150-3050 (m), 1640, 1620, 1600, 1580, 1500,
	G	12	(140-142) [1]	1400, 1220, 1160, 760
8b	E	23	157-158	3200-3000 (m), 1640, 1600, 1500, 1220, 760
	G	9	(157-158) [1]	

[a] From **1a**. [b] From **4**. [c] From **1b**. [d] m = multiplet.

Table 2
Yields, Melting Points and IR Spectral Data for **9, 11** and **12**

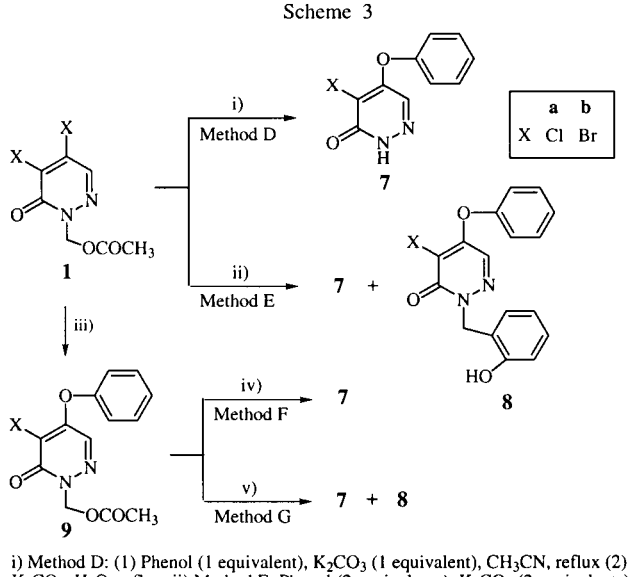
Compound No.	Method	Yield (%)	mp (°C) (lit mp)	IR (potassium bromide) (cm^{-1}) [a]
9a		78	125 (124-125) [3]	3100, 1780, 1760, 1690, 1610, 1510, 1410, 1340, 1300, 1230, 1150, 840, 770
9b		54	139-141	3100-2900 (m), 1780, 1760, 1690, 1610, 1500, 1400, 1290, 1220, 1050, 760
11a	H	84	146-147	3100-3000 (m), 1780, 1700, 1680, 1630, 1600, 1540, 1500, 1400, 1370, 1290, 1220, 1040
11b	H	78	154-155	3100-3000 (m), 1780, 1680, 1600, 1540, 1500, 1360, 1280, 1040, 870, 760
11c	H	96	147-148	3100, 2250, 1760, 1680, 1600, 1520, 1300, 1220, 1040
11d	H	33	152-153	3100-3000 (m), 2250, 1770, 1680, 1600, 1520, 1400, 1220, 1040, 880
12a	I	64	248-249 (249-250) [5]	3400, 3100-2900 (m), 1660, 1630, 1600, 1540, 1500, 1360, 1280, 880
12b	I	94	276-277 (275-276) [5]	3150-2850 (m), 1680, 1630, 1600, 1540, 1500, 1360, 1280, 880, 760
12c	I	72	217-218 (218-220) [5]	3350-2900 (m), 2250, 1700, 1670, 1640, 1620, 1520, 1400, 1260, 1100, 860
12d	H	37	245-246 (247-248) [5]	3150-2900 (m), 2250, 1680, 1600, 1510, 1400, 1260, 860
12e	H	60	162-164 (163-164) [5]	3300-3000 (m), 1660, 1640, 1520, 1260, 1220, 1040
12f	H	72	172-173 (173-174) [5]	3300-2900 (m), 1660, 1620, 1600, 1520, 1410, 1280, 1200, 1040, 860
12g	H	45	205-207 (206-207) [5]	3150-2900 (m), 1680, 1640, 1600, 1500, 1400, 1280, 1100, 850, 780
12h	H	71	249-250 (249-251) [5]	3150-2850 (m), 1680, 1640, 1600, 1500, 1400, 1260, 1200, 850, 780

[a] m = multiplet.

retro-ene reaction for **9** is more favorable than the Mannich condensation under our reaction condition.

Because of our interest in the effect of the substituents on the phenyl ring, we attempted to synthesize **12** from **1** and **10**. Reaction of **1** with **10a** (2 equivalents) and potassium carbonate (2 equivalents) in acetonitrile gave regioselectively **11a** (84%) or **11b** (78%) (Method H). Decomposition of **11a** and **11b** with aqueous potassium carbonate (2 equivalents) yielded **12a** (64%) and **12b** (94%) (Method I). Treatment of **1a** with **10b** (2 equivalents) and potassium carbonate (2 equivalents) in acetonitrile afforded **11c** in excellent yield (Method H). Fragmentation of **11c** with aqueous potassium carbonate (2 equivalents) gave **12c** in 72% yield (Method I). Compound **1b** was also reacted with **10b** in the presence of potassium carbonate in acetonitrile to give **11d** (33%) and **12d** (37%) (Method H). Whereas, reaction of **1** with **10c** (2 equivalents) and potassium carbonate (2 equivalents) in acetonitrile afforded only **12e** (60%) or **12f** (72%) (Method H). Treatment of **1** with **10d** (2 equivalents) and potassium carbonate (2 equivalents) yielded only **12g** (45%) or **12h** (71%) (Method H). The structures of **11** and **12** were established by ir, nmr and elemental analyses.

Scheme 3



i) Method D: (1) Phenol (1 equivalent), K_2CO_3 (1 equivalent), CH_3CN, reflux (2) K_2CO_3, H_2O, reflux. ii) Method E: Phenol (2 equivalents), K_2CO_3 (2 equivalents), CH_3CN, reflux. iii) Phenol (1 equivalent), K_2CO_3 (1 equivalent), CH_3CN, reflux. iv) Method F: K_2CO_3 (2 equivalents), H_2O, reflux. v) Method G: Phenol (2 equivalents), K_2CO_3 (2 equivalents), CH_3CN, reflux.

According to our observations, the *p*-substituents on the phenyl ring affect the retro-ene fragmentation of the ene-adduct. The reaction of **1** with **10a** and **10b** gave the corresponding compound **11**, whereas the reaction of **1** with **10c** and **10d** furnished the corresponding **12**. Retro-ene fragmentation of **11e-11h** containing electron donating groups such as methoxy and chloro groups is faster than that of **11a-11d** containing electron withdrawing groups such as nitro and cyano groups. This was easily observed by tlc during the reaction. These results are different from our previous results [5] about the reaction of 1-(1,1-dibromo-

Table 3

^{1}H NMR Spectral Data for **2 -9, 11** and **12**

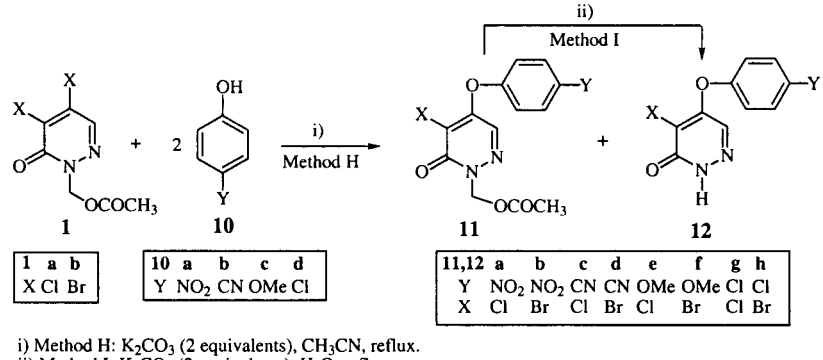
Compound No.	Solvent [a]	^{1}H nmr (δ ppm) [b] N-1 1H (bs)	C-3 1H (s)	Others
2a	D	13.26	8.10	4.06 (s, 3H)
2b	D	13.24	8.10	4.07 (s, 3H)
2c	D	13.26	8.08	-
2d	D	13.32	8.04	-
2e	C	12.42	7.63	1.32 (t, 3H), 3.41 (quin, 2H), 5.19 (bs, NH)
2f	C	12.42	7.42	1.12 (t, 2H), 3.21 (quin, 2H), 4.98 (bs, NH)
3	D	13.40	8.16	8.60 (d, 2H, J = 8), 8.70 (d, 2H, J = 8.2)
4	C	-	8.10	2.12 (s, 3H), 6.06 (s, 2H), 7.06 (t, 1H), 7.17 (t, 1H), 8.49 (d, 2H, J = 4.3), 8.59 (d, 2H, J = 5.1)
5a	C	-	8.03	2.13 (s, 3H), 6.09 (s, 2H), 7.17 (t, 1H), 8.59 (d, 2H, J = 3)
5b	C	-	7.99	2.16 (s, 3H), 6.11 (s, 2H), 7.21 (t, 1H), 8.63 (d, 2H, J = 5.4)
6a	D	13.59	8.14	7.42 (t, 1H), 8.74 (d, 2H, J = 4.5)
6b	D	13.48	8.06	7.42 (t, 1H), 8.74 (d, 2H, J = 4.5)
7a	C	No detection	7.54	7.26-7.48 (m, Ar, 5H)
7b	D	13.43	7.53	7.23-7.51 (m, Ar, 5H)

[a] D = dimethyl-d_6 sulfoxide-d_6, C = Deuteriochloroform. [b] Abbreviations used: bs = broad singlet, s = singlet, d = doublet, t = triplet, quin = quintet, m = multiplet and Ar = aromatic. J = Hz unit. The proton signals of all NH were exchangeable with deuterium oxide.

Compound No.	Solvent [a]	^{1}H nmr (δ ppm) [b] N-1 1H (bs)	C-3 1H (s)	N1-CH_2O (s)	Others
8a	C	-	7.55	5.32	6.85-7.55 (m, Ar, 9H), 9.07 (bs, OH)
8b	C	-	7.45	5.33	6.83-7.48 (m, Ar, 9H), 9.14 (bs, OH)
9a	C	-	8.10	6.04	2.12 (s, 3H), 7.05 (t, 1H), 7.16 (t, 2H), 8.49 (d, 1H, J = 4.8), 8.59 (d, 1H, J = 4.8)
9b	C	-	7.47	6.08	2.11 (s, 3H), 7.13-7.49 (m, Ar, 5H)
11a	C	-	7.65	6.10	2.13 (s, 3H), 7.18 (d, 2H, J = 9.0), 8.34 (d, 2H, J = 9.0)
11b	C	-	7.55	6.11	2.14 (s, 3H), 7.18 (d, 2H, J = 9.0), 8.36 (d, 2H, J = 9.0)
11c	C	-	7.63	6.10	2.14 (s, 3H), 7.18 (d, 2H, J = 9.0), 7.76 (d, 2H, J = 9.0)
11d	C	-	7.51	6.10	2.13 (s, 3H), 7.20 (d, 2H, J = 8.1), 7.77 (d, 2H, J = 8.4)
12a	D	13.64	7.96	-	7.47 (d, 2H, J = 15.5), 8.32 (d, 2H, J = 15.5)
12b	D	13.51	7.86	-	7.43 (d, 2H, J = 16.0), 8.31 (d, 2H, J = 16.0)
12c	D	13.60	7.90	-	7.43 (d, 2H, J = 8.7), 7.95 (d, 2H, J = 8.7)
12d	D	13.49	7.79	-	7.41 (d, 2H, J = 8.7), 7.94 (d, 2H, J = 8.7)
12e	D	13.42	7.53	-	3.78 (s, 3H), 7.02 (d, 2H, J = 7.8), 7.22 (d, 2H, J = 7.8)
12f	D	13.34	7.43	-	3.78 (s, 3H), 7.02 (d, 2H, J = 9.0), 7.20 (d, 2H, J = 9.0)
12g	C	12.64	7.52	-	7.23 (d, 2H, J = 9.0), 7.45 (d, 2H, J = 9.0)
12h	D	13.42	7.63	-	7.28 (d, 2H, J = 8.9), 7.52 (d, 2H, J = 8.8)

[a] D = dimethyl-d_6 sulfoxide, C = Deuteriochloroform. [b] Abbreviations used: bs = broad singlet, s = singlet, d = doublet, t = triplet, quin = quintet, m = multiplet and Ar = aromatic. J = Hz unit. The proton signals of all NH were exchangeable with deuterium oxide.

Scheme 4



i) Method H: K_2CO_3 (2 equivalents), CH_3CN, reflux.
ii) Method I: K_2CO_3 (2 equivalents), H_2O, reflux.

Table 4

^{13}C Nmr Spectral Data of **2 -9, 11** and **12**

Compound No	Solvent [a]	^{13}C nmr (δ ppm)
2a	D	58.2, 106.0, 127.9, 157.5, 159.4
2b	D	58.0, 105.4, 128.2, 157.8, 159.7
2c	D	119.2, 131.6, 141.1, 157.8
2d	D	111.1, 131.0, 143.4, 158.1
2e	C	14.8, 37.4, 105.8, 126.2, 144.2, 158.5
2f	C	14.5, 37.2, 97.3, 125.4, 145.6, 158.1
3	D	118.6, 119.4, 135.9, 138.8, 142.7, 142.8, 158.0, 158.1, 158.2, 158.7, 167.5, 168.1
4	C	20.6, 43.1, 73.6, 117.9, 118.6, 136.7, 138.8, 143.4, 157.6, 157.9, 168.4, 168.8, 169.6, 174.2
5a	C	13.0, 20.6, 27.7, 73.6, 118.8, 136.6, 138.7, 158.2, 169.6, 206.8
5b	C	20.7, 23.9, 38.2, 73.8, 99.8, 118.9, 130.5, 138.3, 158.2, 167.5, 194.2
6a	D	119.4, 135.6, 137.9, 139.3, 156.6, 158.8, 167.0
6b	D	119.4, 131.8, 138.7, 139.1, 157.0, 158.8, 167.0
7a	C	119.7, 126.2, 130.5, 131.1, 153.8, 154.6, 160.5
7b	D	111.6, 119.1, 125.6, 130.4, 130.5, 153.8, 155.7, 159.5
8a	C	53.7, 118.6, 119.7, 120.1, 120.5, 121.3, 126.6, 130.8, 131.1, 131.9, 153.5, 154.6, 156.2, 160.1, 194.2
8b	C	53.7, 98.6, 118.5, 119.9, 120.3, 121.1, 126.5, 130.2, 130.6, 130.9, 131.7, 137.3, 147.3, 147.7, 156.0, 178.1, 185.3
9a	C	20.6, 53.2, 63.0, 73.4, 119.7, 121.0, 126.2, 130.5, 130.7, 153.7, 158.5, 169.5
9b	C	20.7, 39.9, 73.6, 98.2, 99.4, 118.9, 131.0, 138.2, 158.2
11a	C	20.6, 73.4, 118.5, 126.4, 131.6, 151.8, 158.0, 158.4, 169.5
11b	C	21.0, 73.9, 115.8, 119.1, 126.8, 131.6, 131.7, 145.3, 154.6, 158.7, 158.8, 170.0
11c	C	20.6, 70.9, 73.4, 109.5, 117.7, 119.1, 131.5, 134.7, 151.9, 157.0, 158.2, 163.2, 169.5, 191.1
11d	C	21.0, 73.9, 109.9, 115.3, 118.1, 119.7, 131.5, 134.9, 135.2, 154.7, 157.3, 158.8, 169.9
12a	D	118.9, 123.0, 126.6, 132.6, 144.3, 152.3, 159.3, 159.4
12b	D	116.7, 120.0, 127.7, 133.4, 145.3, 155.5, 160.5, 160.9
12c	D	30.0, 104.9, 109.8, 118.0, 119.4, 132.2, 135.0, 157.4, 159.9
12d	D	107.4, 114.8, 118.3, 119.0, 131.7, 134.9, 154.1, 157.5 159.4
12e	D	55.7, 115.4, 121.2, 129.3, 130.3, 146.7, 154.9, 155.2, 157.7
12f	D	55.5, 115.3, 120.9, 129.5, 146.9, 156.1, 156.9, 159.4
12g	C	120.7, 130.4, 130.5, 131.3, 152.1, 153.9, 158.9, 172.9
12h	D	112.2, 120.8, 129.4, 130.2, 130.6, 152.6, 155.2, 159.4

[a] D = Dimethyl-d_6 sulfoxide, C = Deuteriochloroform.

2-oxopropyl)-4,5-dihalopyridazin-6-ones with *p*-substituted phenols under similar condition.

The positions of the substitution for **2**, **6**, **7** and **8** were established by comparison of authentic compounds [1,5]. The substituent positions of **5** and **9** were also confirmed by the synthesis of **6** and **7**, respectively.

Finally, *N*-acetyloxymethylpyridazin-6-one may be useful as an ene-adduct for the functionalization of 4,5-dihalopyridazin-6-ones. Our functionalization is also regioselective and convenient.

Further work including the chemical transformation and the relationship of a substituent at N-1 and the reactivity of C-4 is under way in our laboratory.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were performed with a Perkin Elmer 240C. Magnetic resonance spectra were obtained on a Varian Unity Plus 300 spectrometer with chemical shift values reported in δ unit (part per million) relative to an internal standard (tetramethylsilane). Infrared spectral data were obtained on a Hitachi 270-50 spectrophotometer. Open-bed chromatography was carried out silica gel 60 (70-230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent.

1-Acetyloxymethyl-4,5-dihalopyridazin-6-ones **1** [3].

A mixture of 1-chloromethyl-4,5-dihalopyridazin-6-one (47 mmoles), potassium carbonate (56 mmoles) and acetic acid was refluxed for 1-2 hours. After cooling to room temperature, water (150 ml) was added to the reaction mixture. The resulting crystals were filtered, washed with excess water, then washed with *n*-hexane (20 ml) and dried in air to give **1** in excellent yield.

4-Methoxy-5-halopyridazin-6-ones **2a** and **2b**.

A mixture of **1a** or **1b** (6.33 mmoles), potassium carbonate (12.66 mmoles) and methanol (40 ml) was refluxed 48 hours for **1a** or 24 hours for **1b**. After cooling to room temperature, the solvent was evaporated under reduced pressure. Water (50 ml) was added to the residue with stirring, and the solution was then neutralized by dilute hydrochloric acid (7.4%). The resulting precipitate was filtered. The crude product was recrystallized from ethanol to give **2a** or **2b**.

4-Azido-5-halopyridazin-6-ones **2c** and **2d**.

A solution of **1a** or **1b** (4.22 mmoles), sodium azide (8.44 mmoles) and methanol (20 ml) was refluxed for 8 hours for **1a** or 6 hours for **1b**. After cooling to room temperature, the solvent

Table 5
Elemental Analytical Data of Compound **2-9**, **11** and **12**

Compound No.	Molecular Formula	Calcd./Found (%) C	H	N	S
2a	$C_5H_5N_2O_2Cl$	37.40	3.14	17.45	
		37.53	2.95	17.32	
2b	$C_5H_5N_2O_2Br$	29.29	2.46	13.66	
		29.02	2.24	13.39	
2c	$C_4H_2N_5OCl$	28.01	1.18	40.82	
		28.05	1.24	40.56	
2d	$C_4H_2N_5OBr$	22.24	0.93	32.42	
		22.14	0.94	32.06	
2e	$C_6H_8N_3OCl$	41.51	4.64	24.20	
		41.24	4.35	24.30	
2f	$C_6H_8N_3OBr$	33.05	3.70	19.27	
		32.97	3.55	18.96	
3	$C_{12}H_8N_6S_2O$	45.56	2.55	26.57	20.27
		45.71	2.62	26.46	20.61
4	$C_{15}H_{12}N_6O_3S_2$	46.38	3.11	21.64	16.51
		46.03	3.00	21.40	16.48
5a	$C_{11}H_9N_4O_3SCl$	42.25	2.90	17.92	10.25
		42.25	2.89	17.85	10.13
5b	$C_{11}H_9N_4O_3SBr$	36.99	2.54	15.69	8.98
		36.56	2.49	15.74	9.20
6a	$C_8H_5N_4OSCl$	39.93	2.09	23.28	13.32
		39.62	2.07	22.97	13.34
6b	$C_8H_5N_4OSBr$	33.70	1.77	19.65	11.24
		33.46	1.86	19.41	11.37
7a	$C_{10}H_7N_2O_2Cl$	53.95	3.17	12.58	
		53.76	3.12	12.79	
7b	$C_{10}H_7N_2O_2Br$	44.97	2.64	10.49	
		44.60	2.37	10.47	
8a	$C_{17}H_{13}N_2O_3Cl$	62.11	3.99	8.52	
		61.90	3.90	8.44	
8b	$C_{17}H_{13}N_2O_3Br$	54.71	3.51	7.51	
		55.06	3.51	7.39	
9a	$C_{13}H_{11}N_2O_4Cl$	52.98	3.76	9.51	
		52.87	3.68	9.65	
9b	$C_{13}H_{11}N_2O_4Br$	46.04	3.27	8.26	
		45.93	3.24	8.23	
11a	$C_{13}H_{10}N_3O_6Cl$	45.97	2.97	12.37	
		46.08	2.92	12.35	
11b	$C_{13}H_{10}N_3O_6Br$	40.65	2.62	10.94	
		40.60	2.63	10.95	
11c	$C_{14}H_{10}N_3O_4Cl$	52.60	3.15	13.14	
		52.43	2.99	13.07	
11d	$C_{14}H_{10}N_3O_4Br$	46.18	2.77	11.54	
		46.09	2.67	11.50	
12a	$C_{10}H_6N_3O_4Cl$	44.88	2.26	15.70	
		44.53	2.29	15.43	
12b	$C_{10}H_6N_3O_4Br$	38.49	1.94	13.46	
		38.21	1.96	13.30	
12c	$C_{11}H_6N_3O_2Cl$	53.35	2.44	16.97	
		53.07	2.40	16.61	
12d	$C_{11}H_6N_3O_2Br$	45.23	2.07	14.39	
		44.93	2.06	14.18	
12e	$C_{11}H_9N_2O_3Cl$	52.29	3.59	11.09	
		52.12	3.57	10.89	
12f	$C_{11}H_9N_2O_3Br$	44.47	3.05	9.43	
		44.26	2.92	9.36	
12g	$C_{10}H_6N_2O_2Cl_2$	46.72	2.35	10.90	
		46.73	2.30	10.80	
12h	$C_{10}H_6N_2O_2ClBr$	39.83	2.01	9.29	
		39.82	2.03	8.97	

was evaporated under reduced pressure. Water (50 ml) was added to the residue with stirring. The resulting crystals were filtered and dried in air to give **2c** or **2d**.

4-Ethylamino-5-halopyridazin-6-ones **2e** and **2f**.

A mixture of **1a** or **1b** (5.91 mmoles), ethylamine hydrochloride (0.024 moles), potassium carbonate (0.024 moles) and acetonitrile (20 ml) was refluxed for 3 hours for **1a** or 5 hours for **1b**. After cooling to room temperature, the precipitate was filtered. The filtrate was evaporated under reduced pressure. The resulting residue was recrystallized from ethyl acetate/*n*-hexane (1:3, v/v) for **2e** or ethyl acetate for **2f** to give **2e** or **2f**.

Reaction of **1a** and 2-Mercaptopyrimidine.

Method A.

A mixture of **1a** (1.5 g, 6.33 mmoles), 2-mercaptopyrimidine (1.42 g, 12.66 mmoles), potassium carbonate (1.75 g, 12.66 mmoles) and acetonitrile (20 ml) was refluxed for 2 hours. After cooling to room temperature, the precipitate was filtered. The solution was evaporated under reduced pressure, and the residue was applied to the top of an open-bed silica gel column (2.5 x 15 cm). The column was eluted with methylene chloride/diethyl ether (1:1, v/v). Fractions containing **3** (Rf = 0.7, ethyl acetate) were combined and evaporated under reduced pressure. The resulting residue was recrystallized from ethyl acetate to furnish **3** in 35% (0.42 g) yield. Fractions containing **4** (Rf = 0.6, ethyl acetate) were combined and evaporated under reduced pressure. The resulting residue was recrystallized from ethyl acetate/*n*-hexane (1:1, v/v) to give **4** in 58% (1.44 g) yield.

Method B.

A mixture of **1a** (0.81 g, 3.4 mmoles), 2-mercaptopyrimidine (0.38 g, 3.4 mmoles), potassium carbonate (0.47 g, 3.4 mmoles) and acetonitrile (20 ml) was refluxed for 2.5 hours. After cooling to room temperature, the precipitate was filtered. The solution was evaporated under reduced pressure, and the residue was applied to the top of an open-bed silica gel column (2.5 x 15 cm). The column was eluted with ethyl acetate/*n*-hexane (1:1, v/v). Fractions containing **5a** were combined and evaporated under reduced pressure. The resulting residue was recrystallized from ethyl acetate to furnish **5a** in 76% (0.81 g) yield.

Reaction of **1b** and 2-Mercaptopyrimidine.

Method A.

A solution of **1b** (0.6 g, 1.84 mmoles), 2-mercaptopyrimidine (0.42 g, 3.68 mmoles), potassium carbonate (0.5 g, 3.68 mmoles) and acetonitrile (20 ml) was stirred for 7-8 hours at room temperature. The precipitate was filtered, and the filtrate was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2.5 x 10 cm). The column was eluted with ethyl acetate. Fractions containing the product were combined and evaporated under reduced pressure. The residue was recrystallized from ethyl acetate to give **4** as yellow crystal in 96% (0.68 g) yield.

Method B.

A mixture of **1b** (0.7 g, 2.15 mmoles), 2-mercaptopyrimidine (0.24 g, 2.15 mmoles), potassium carbonate (0.3 g, 2.15 mmoles) and acetonitrile (20 ml) was stirred for 22 hours at room temperature. The precipitate was filtered. The solution was coevaporated with silica gel (1.5 g) under reduced pressure, and the

residue was applied to the top of an open-bed silica gel column (2.5 x 15 cm). The column was eluted with ethyl acetate/*n*-hexane (1:4, v/v). Fractions containing **5b** (Rf = 0.8, ethyl acetate) were combined and evaporated under reduced pressure. The resulting residue was recrystallized from chloroform/*n*-hexane (1:2, v/v) to furnish **5b** in 91% (0.437 g) yield. Fractions containing **4** (Rf = 0.6, ethyl acetate) were combined and evaporated under reduced pressure. The resulting residue was recrystallized from ethyl acetate to give **4** in 8% (0.05 g) yield.

4,5-Di(pyrimidin-2-ylsulfanyl)pyridazin-6-one (**3**)

Method C.

A mixture of **4** (0.5 g, 1.29 mmoles), potassium carbonate (0.36 g, 2.58 mmoles) and water (20 ml) was refluxed for 40 minutes. After cooling to room temperature, the resulting crystal was filtered and dried in air to afford compound **3** in 74% (0.302 g) yield.

5-Halo-4-(pyrimidin-2-ylsulfanyl)pyridazin-6-ones **6a** and **6b**.

Method C.

A solution of **5** (0.96 mmole), potassium carbonate (1.44 mmoles) and water (15 ml) was refluxed for 20 minutes. After cooling to room temperature, the solution was neutralized by dilute hydrochloric acid (7.4%). The resulting crystal was filtered, washed with water (200 ml) and dried in air to give **6**.

Reaction of **1a** with Phenol.

Method D.

A mixture of **1a** (0.3 g, 1.36 mmoles), phenol (0.13 g, 1.36 mmoles), potassium carbonate and acetonitrile (15 ml) was refluxed for 1.5 hours. The solution was evaporated under reduced pressure. Water (30 ml) was added to the residue with stirring. The resulting crystals were filtered and dried in air to give **7a** in 89% (0.266 g) yield.

Method E.

A mixture of **1a** (0.5 g, 2.11 mmoles), phenol (0.4 g, 4.22 mmoles), potassium carbonate (0.58 g, 4.22 mmoles) and acetonitrile (20 ml) was refluxed for 5.5 hours. The solution was evaporated under reduced pressure, and the mixture of water/chloroform (70 ml/30 ml) was added with stirring. The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3 x 10 cm). The column was eluted with chloroform. Fractions containing **8a** (Rf = 0.93, chloroform/diethyl ether = 9:1, v/v) were combined and evaporated under reduced pressure. The resulting residue was recrystallized from diethyl ether/*n*-hexane (1:2, v/v) to furnish **8a** in 20% (0.14 g) yield. Fractions containing **7a** (Rf = 0.23, chloroform/diethyl ether = 9:1, v/v) were combined and evaporated under reduced pressure to give **7a** in 43% (0.2 g) yield.

Reaction of **1b** with Phenol.

Method D.

A mixture of **1b** (1.4 g, 4.30 mmoles), phenol (0.4 g, 4.30 mmoles), potassium carbonate (0.6 g, 4.30 mmoles) and acetonitrile (50 ml) was refluxed for 4 hours. The solvent was evaporated under reduced pressure. To the residue was added water (30 ml) and potassium carbonate (1.2 g, 8.68 mmoles). The reaction mixture was refluxed for 1.5 hours. After cooling to room temperature, the solution was neutralized by dilute hydrochloric acid (7.4%). The resulting precipitate was filtered and then dissolved in chloroform. The solution was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The resulting crystal was recrystallized from chloroform/*n*-hexane (1:1.5, v/v) to give **7b** in 91% (1.05 g) yield.

Method E.

A mixture of **1b** (1 g, 3.07 mmoles), phenol (1.15 g, 6.14 mmoles), potassium carbonate (0.85 g, 6.14 mmoles) and acetonitrile (50 ml) was refluxed for 4 hours. After cooling to room temperature, the precipitate was filtered. The solid was washed with water (30 ml) and dried in air to give **7b** in 32% (0.26 g) yield. The filtrate was evaporated under reduced pressure to furnish **8b** in 23% (0.23 g) yield.

1-Acetyloxymethyl-5-chloro-4-phenoxypyridazin-6-one (**9a**).

A mixture of **1a** (1.01 g, 4.26 mmoles), phenol (0.8 g, 8.52 mmoles), potassium carbonate (1.18 g, 8.52 mmoles) and acetonitrile (50 ml) was refluxed for 1 hour. After cooling to room temperature, the solvent was evaporated under reduced pressure. Diethyl ether (10 ml) was added to the residue with stirring. The resulting crystal was filtered and dried in air to give **9a** in 78% (0.98 g) yield.

1-Acetyloxymethyl-5-bromo-4-phenoxypyridazin-6-one (**9b**).

A solution of **1b** (2.8 g, 8.59 mmoles), phenol (0.81 g, 8.59 mmoles), potassium carbonate (1.19 g, 8.59 mmoles) and acetonitrile (50 ml) was stirred for 24 hours at room temperature. The solvent was evaporated under reduced pressure. A mixture of water/chloroform (1:1, v/v, 100 ml) was added to the residue with stirring. The organic layer was seperated and evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3 x 7 cm). The column was eluted with chloroform. Fractions were combined and evaporated under reduced pressure. The resulting crystals were recrystallized from water to give **9b** in 54% (1.571 g) yield.

Synthesis of **7** from **9**.

Method F.

A solution of **9** (1.02 mmoles), potassium carbonate (2.04 mmoles) and water (20 ml) was refluxed for 0.5 hours for **9a** or 2 hours for **9b**. After cooling to room temperature, the resulting crystals were filtered and dried in air to give **7**.

Reaction of **9a** with Phenol.

Method G.

A mixture of **1** (0.75 g, 2.55 mmoles), phenol (0.48 g, 5.09 mmoles), potassium carbonate (0.7 g, 5.09 mmoles) and acetonitrile (30 ml) was refluxed for 9 hours. The solvent was evaporated under reduced pressure. Water (30 ml) was added to the residue with stirring. The solution was neutralized by dilute hydrochloric acid (7.4%). The resulting precipitate was filtered and applied to the top of an open-bed silica gel column (2 x 7 cm). The column was eluted with chloroform. Fractions containing **8a** (Rf = 0.23; chloroform/diethyl ether = 9:1, v/v) were combined and evaporated under reduced pressure. The resulting residue was recrystallized from diethyl ether/*n*-hexane (1:2, v/v) to give **8a** in 12% (0.1 g) yield. Fractions containing **7a** (Rf = 0.23, chloroform/diethyl ether = 9:1, v/v) were combined, evaporated under reduced pressure to give **7a** in 53% (0.3 g) yield.

Reaction of **9b** with Phenol.

Method G.

A mixture of **1b** (0.94 g, 2.77 mmoles), phenol (0.52 g, 5.55 mmoles), potassium carbonate (0.77 g, 5.55 mmoles) and acetonitrile (50 ml) was refluxed for 12 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. Water (30 ml) was added to the residue with stirring. The solution was neutralized by dilute hydrochloric acid (7.4%). The resulting crystal was filtered and washed with diethyl ether (50 ml) to yield **7b** (0.2 g). The filtrate was also evaporatred under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2 x 7 cm). The column was eluted with chloroform. Fractions containing **8b** (Rf = 0.89, chloroform/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure. The resulting crystal was recrystallized from diethyl ether/*n*-hexane (1:2, v/v) to give **8b** in 9% (0.1 g) yield. Fractions containing **7b** (Rf = 0.2, chloroform/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure. The resulting crystal was recrystallized from chloroform/*n*-hexane (1:1.5, v/v) to give **7b** (0.125 g). The total yield of **7b** was 44% (0.325 g).

1-Acetyloxymethyl-5-chloro-4-(4-nitrophenoxy)pyridazin-6-one (**11a**).

Method H.

A mixture of **1a** (1.5 g, 6.33 mmoles), *p*-nitrophenol (1.76 g, 12.66 mmoles), potassium carbonate (1.75 g, 12.66 mmoles) and acetonitrile (50 ml) was refluxed for 3.5 hours. After cooling to room temperature, the solution was filtered. The filtrate was evaporated under reduced pressure, and the residue was then applied to the top of an open-bed silica gel column (2.5 x 10 cm). The column was eluted with ethyl acetate/*n*-hexane (1/4, v/v). Fractions containing the product were combined and evaporated under reduced pressure. The residue was recrystallized from ethyl acetate/*n*-hexane (1:4, v/v) to give **11a** in 84% (1.8 g) yield.

1-Acetyloxymethyl-5-bromo-4-(4-nitrophenoxy)pyridazin-6-one (**11b**).

Method H.

A mixture of **1b** (1.2 g, 3.68 mmoles), *p*-nitrophenol (1.02 g, 7.36 mmoles), potassium carbonate (1.02 g, 7.36 mmoles) and acetonitrile (40 ml) was refluxed for 2 hours. After cooling to room temperature, the solution was filtered. The filtrate was evaporated under reduced pressure, and the residue was then dissolved in chloroform/methanol (1:5, v/v). The solution was concentrated, and filtered to give **11b** in 78% (1.1 g) yield.

1-Acetyloxymethyl-5-chloro-4-(4-cyanophenoxy)pyridazin-6-one (**11c**).

Method H.

A mixture of **1a** (1.0 g, 4.22 mmoles), *p*-cyanophenol (1.0 g, 8.44 mmoles), potassium carbonate (1.17 g, 8.44 mmoles) and acetonitrile (30 ml) was refluxed for 4.5 hours. The solution was cooled to room temperature and filtered. The filtrate was coevaporated with silica gel (2 g) under reduced pressure, and the residue was then applied to the top of an open-bed silica gel column (2.5 x 12 cm). The column was eluted with chloroform/methanol (4:0.1, v/v). Fractions containing the product were combined and evaporated under reduced pressure. The residue was recrystallized from methanol to give **11c** in 96% (1.29 g) yield.

1-Acetyloxymethyl-5-bromo-4-(4-cyanophenoxy)pyridazin-6-one (**11d**) and 5-Bromo-4-(4-cyanophenoxy)pyridazin-6-one (**12d**).

Method H.

A mixture of **1b** (1.5 g, 4.60 mmoles), *p*-cyanophenol (1.10 g, 9.20 mmoles), potassium carbonate (1.27 g, 9.20 mmoles) and acetonitrile (30 ml) was refluxed for 4 hours. The solution was evaporated under reduced pressure, and the residue was then dissolved in methanol. The solution was filtered. The resulting precipitate was dissolved in chloroform, and the solution was coevaporated with silica gel (2 g) under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2.5 x 10 cm). The column was eluted with chloroform/methanol (4:0.1, v/v). Fractions containing **11d** (Rf = 0.68, chloroform/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure. The residue was recrystallized from methanol to give **11d** in 33% (0.545 g) yield. Fractions containing **12d** (Rf = 0.21, chloroform/diethyl ether = 9.5:0.5, v/v) were combined and evaporated under reduced pressure. The residue was recrystallized from chloroform/diethyl ether (9.5:0.5, v/v) to give **12d** in 37% (0.5 g) yield.

Synthesis of **12a**, **12b** and **12c**.

Method I.

A solution of **11a, 11b or 11c** (1.57 mmoles), potassium carbonate (0.43 g, 3.14 mmoles) and water (15 ml) was refluxed for 1 hour for **11a**, 2.5 hours for **11b** or 1.5 hours for **11c**. After cooling to room temperature, the solution was filtered. The resulting precipitate was recrystallized from ethyl acetate to give **12a, 12b** or **12c**.

5-Chloro-4-(4-methoxyphenoxy)pyridazin-6-one (**12e**).

Method H.

A solution of **1a** (1.5 g, 6.63 mmoles), *p*-methoxyphenol (1.57 g, 12.65 mmoles), potassium carbonate (1.75 g, 12.65 mmoles) and acetonitrile (30 ml) was refluxed for 14 hours. After cooling to room temperature, the solution was filtered. The resulting precipitate was dissolved in water (30 ml). The solution was neutralized by dilute hydrochloric acid (7.4%). The crystal was filtered and washed with methanol (30 ml) to give **12e** in 60% (1.11 g) yield.

5-Bromo-4-(4-methoxyphenoxy)pyridazin-6-one (**12f**).

Method H.

A mixture of **1b** (1.5 g, 4.60 mmoles), *p*-methoxyphenol (1.14 g, 9.20 mmoles), potassium carbonate (1.27 g, 9.20 mmoles) and acetonitirle (35 ml) was refluxed for 6.5 hours. After cooling to room temperature, the solution was evaporated under reduced pressure. The residue was dissolved in water/chloroform (1:1, v/v, 80 ml) with stirring. The organic layer was seperated, dried over anhydrous magnesium sulfate and coevaporated with silica gel (3 g). The residue was applied to the top of an open-bed silica gel column (2 x 10 cm). The column was eluted with chloroform. Fractions containing the product were combined and evaporated under reduced pressure. The residue was recrystallized from chloroform/*n*-hexane (1:1, v/v) to give **12f** in 72% (0.95 g) yield.

5-Chloro-4-(4-chlorophenoxy)pyridazin-6-one (**12g**).

Method H.

A mixture of **1a** (2 g, 8.44 mmoles), *p*-chlorophenol (2.17 g, 16.87 mmoles), potassium carbonate (2.33 g, 16.87 mmoles) and acetonitirle (35 ml) was refluxed for 13 hours. After cooling to room temperature, the solution was evaporated under reduced pressure. The residue was dissolved in water/chloroform (1:1, v/v, 200 ml) with stirring. The organic layer was seperated and evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2 x 10 cm). The column was eluted with chloroform. Fractions containing the product were combined and evaporated under reduced pressure to give **12g** in 45% (1.24 g) yield.

5-Bromo-4-(4-chlorophenoxy)pyridazin-6-one (**12h**).

Method H.

A mixture of **1b** (1.5 g, 4.60 mmoles), *p*-chlorophenol (1.18 g, 9.20 mmoles), potassium carbonate (1.27 g, 9.20 mmoles) and acetonitirle (35 ml) was refluxed for 6 hours. After cooling to room temperature, the solution was evaporated under reduced pressure. The residue was dissolved in water/chloroform (1:1, v/v, 100 ml) with stirring. The organic layer was seperated, dried over anhydrous magnesium sulfate and coevaporated with silica gel (3 g). The residue was applied to the top of an open-bed silica gel column (2 x 10 cm). The column was eluted with chloroform. Fractions containing the product were combined and evaporated under reduced pressure. The residue was recrystallized from diethyl ether to give **12h** in 71% (1.21 g) yield.

Acknowledgment.

This study is supported by Korean Ministry of Education through Research Fund (BSRI-97-3441).

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