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단 신

3-알콕시-6-알릴싸이오피리다진의 효과적 합성

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An Efficient Synthesis of 3-Alkoxy-6-allylthiopyridazines

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Recently 3-alkoxy-6-allylthiopyridazines have attracted many interests in the chemistry of the substituted pyridazines[1] because they exhibit a superior effect for prevention and treatment of hepatic diseases induced by toxic substances and for protection of human tissues from radiation.[2] It was found that allylthio group in garlic oil plays an important role for inhibiting oncogenesis and protecting liver from hepatotoxicity by increasing the intracellular expression rate of microsomal epoxide hydrolase (mEH) and glutathione S-transferase (GST).[3] Pyridazines were not thoroughly investigated because they don't occur as natural products and thus allylthio group was introduced into pyridazine nucleus as a pharmacologically active group for drug development. 3-Alkoxy-6-allylthiopyridazines have been prepared from 3,6-dichloropyridazine, prepared from maleic anhydride,[4] by two steps. The treatment of maleic anhydride with hydrazine monohydrate in aqueous HCl at reflux temperature affords maleic hydrazide, a tautomer of 3,6-pyridazinediol. Maleic hydrazide undergoes chlorination on heating with phosphorus oxychloride[5] or thionyl chloride methanesulfonic acid[6] to give 3,6-dichloropyridazine. The reaction of 3,6-dichloropyridazine with alcoholic sodium alkoxides affords the corresponding 3-alkoxy-6-chloropyridazines with the selective substitution of the first chlorine atom,[7] which are further converted into the corresponding 3-alkoxy-6-allylthiopyridazines with 2-propene-1-thiol/sodium ethoxide by two steps.[8] However, the nucleophilic displacement of chlorine atom in 3-alkoxy-6-chloropyridazines requires for prolonged reaction time at reflux temperature and yields are moderate to low. In the present study we report an efficient procedure which would give good yields of 3-alkoxy-6-allylthiopyridazine derivatives under mild conditions.

EXPERIMENTAL

Preparation of 3-ethoxy-6-chloropyridazine (3b) <typical procedure>. To a 3,6-dichloropyridazine (298.0 mg, 2.0 mmol) in THF (8.0 mL) was slowly added sodium ethoxide (21 wt.% in EtOH, 0.75 mL, 2.0 mmol) at room temperature. After being stirred for 0.2 h, THF and EtOH were evaporated *in vacuo* and the reaction mixture was dissolved in methylene chloride, followed by filtering off sodium chloride. The concentration of filtrate afforded **3b** (276.0 mg, 87%) as a solid. M.p. 60-62 °C (lit.[8b] 60-62 °C); FT-IR(KBr) 3055, 2983, 1587, 1427, 1389, 1140, 1031, 839, 737 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 7.36 (d, J=9.3 Hz, 1H), 6.94(d, J=9.3 Hz, 1H), 4.55(q, J=7.2 Hz, 2H), 1.44(t, J=7.2 Hz, 3H). Spectral data, **3a**: M.p. 88-90 °C (lit.[7c] 90-91 °C); FT-IR(KBr) 3064, 2991, 2953, 1590, 1462, 1399, 1139, 1008, 846, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37(d, J=9.3 Hz, 1H), 6.97(d, J=

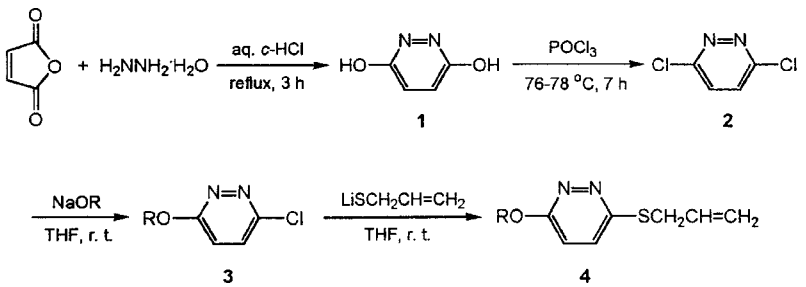
9.3 Hz, 1H), 4.12(s, 3H). **3c**: M.p. 70-72 °C (lit.[9] 72-73 °C); FT-IR(KBr) 3056, 2968, 2882, 1590, 1428, 1382, 1137, 998, 854, 737 cm^{-1}; ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.36(d, *J*=9.2 Hz, 1H), 6.95(d, *J*=9.2 Hz, 1H), 4.44(t, *J*=6.7 Hz, 2H), 1.78-1.88(m, 2H), 1.04(t, *J*=7.4 Hz, 3H). **3d**: M.p. 84-86 °C (lit.[9] 83-85 °C); FT-IR(KBr) 3060, 2981, 1587, 1423, 1374, 1145, 1109, 858, 738 cm^{-1}; ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.34(d, *J*=9.3 Hz, 1H), 6.89 (d, *J*=9.3 Hz, 1H), 5.52(septet, *J*=6.3 Hz, 1H), 1.40(d, *J*=6.3 Hz, 6H). **3e**: M.p. 90-93 °C (lit.[9] 86-89 °C); FT-IR (KBr) 3061, 2976, 1583, 1418, 1367, 1141, 854, 703 cm^{-1}; ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.32(d, *J*=9.0 Hz, 1H), 6.84(d, *J*=9.0 Hz, 1H), 1.65(s, 9H). **3f**: M.p. 35- 37 °C; FT-IR(KBr) 3065, 2979, 2938, 1585, 1460, 1382, 1367, 1161, 1072, 852, 733 cm^{-1}; ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.31(d, *J*=9.3 Hz, 1H), 6.84(d, *J*=9.3 Hz, 1H), 2.04(q, *J*=7.5 Hz, 2H), 1.61(s, 6H), 0.91(t, *J*=7.5 Hz, 3H). **3g**: M.p. 114-116 °C; FT-IR(KBr) 3054, 1591, 1491, 1425, 1265, 1196, 739, 701 cm^{-1}; ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.47(d, *J*=9.0 Hz, 1H), 7.34-7.44(m, 2H), 7.16-7.27(m, 3H), 7.15(d, *J*=9.0 Hz, 1H).

Preparation of 3-ethoxy-6-allylthiopyridazine (4b) <typical procedure>. To a 2-propene-1-thiol (tech., 80%, 220 μL, 2.2 mmol) in THF (4 mL) was slowly added *n*-butyllithium (1.6 M in hexane, 1.38 mL, 2.2 mmol) at 0 °C. After being stirred for 10 min, this resulting solution was added to 3-ethoxy-6-chloropyridazine (317.2 mg, 2.0 mmol) in THF (4 mL) at room temperature. After being stirred for 4 h, THF was evaporated *in vacuo* and the reaction mixture was dissolved in *n*-hexane, followed by filtering off lithium chloride. The concentrated residue was subjected to silica gel column chromatography using 10% EtOAc *n*-hexane as an eluant to give **4b** (365 mg, 93%). FT-IR(film) 3080, 2979, 1636, 1591, 1425, 1387, 1141, 1032, 915, 836 cm^{-1}; ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.20(d, *J*=9.3 Hz, 1H), 6.80(d, *J*=9.3 Hz, 1H), 5.94-6.06(m, 1H), 5.32(d, *J*=17.0 Hz, 1H), 5.13(d, *J*=9.6 Hz, 1H), 4.52(q, *J*=7.2 Hz, 2H), 3.95(d, *J*=6.9 Hz, 2H), 1.44(t, *J*=7.2 Hz, 3H). **4a**: FT-IR(film) 3062, 2947, 1637, 1595, 1461, 1399, 1147, 1011, 930, 841 cm^{-1}; ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.21(d, *J*=9.0 Hz, 1H), 6.83 (d, *J*=9.0 Hz, 1H), 5.89-6.07(m, 1H), 5.33(dd, J_1=3.0 Hz, J_2=18.0 Hz, 1H), 5.14(dd, J_1=3.0 Hz, J_2=9.0 Hz, 1H), 4.09(s, 3H), 3.95(d, *J*=6.0 Hz, 2H). **4c**: FT-IR(film) 3047, 2963, 1596, 1427, 1383, 1139, 1000, 928, 845 cm^{-1}; ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.20(d, *J*=9.3 Hz, 1H), 6.81(d, *J*=9.3 Hz, 1H), 5.98-6.07(m, 1H), 5.32(d, *J*=17.0 Hz, 1H), 5.13(d, *J*=9.4 Hz, 1H), 4.41(t, *J*=6.7 Hz, 2H), 3.95(d, *J*=6.9 Hz, 2H), 1.78-1.87(m, 2H), 1.03(t, *J*=7.2 Hz, 3H). **4d**: FT-IR(film) 3081, 2979, 2934, 1637, 1591, 1422, 1385, 1142, 1108, 989, 939, 834 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20(d, *J*=9.3 Hz, 1H), 6.76(d, *J*=9.3 Hz, 1H), 5.97-6.06(m, 1H), 5.50(septet, *J*=6.3 Hz, 1H), 5.31(d, *J*=17.0 Hz, 1H), 5.13(d, *J*=10.2 Hz, 1H), 3.95(d, *J*=6.9 Hz, 2H), 1.40(d, *J*=6.3 Hz, 6H). **4e**: FT-IR (film) 3080, 2977, 2928, 1636, 1587, 1423, 1316, 1171, 988, 901, 835 cm^{-1}; ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.17 (d, *J*=9.3 Hz, 1H), 6.70(d, *J*=9.3 Hz, 1H), 5.94-6.06(m, 1H), 5.28(d, *J*=17.0 Hz, 1H), 5.12(d, *J*=9.4 Hz, 1H), 3.96(d, *J*=6.9 Hz, 2H), 1.64(s, 9H). **4f**: FT-IR(film) 3081, 2975, 2928, 1636, 1590, 1423, 1366, 1317, 1162, 989, 895, 835 cm^{-1}; ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.17(d, *J*=9.3 Hz, 1H), 6.71(d, *J*=9.3 Hz, 1H), 5.93-6.08(m, 1H), 5.30(d, *J*=17.1 Hz, 1H), 5.13(d, *J*=9.9 Hz, 1H), 3.96(d, *J*=6.9 Hz, 2H), 2.02(q, *J*=7.5 Hz, 2H), 1.60 (s, 6H), 0.92 (t, *J*=7.5 Hz, 3H). **4g**: M.p. 75-76 °C; FT-IR(KBr) 3059, 1637, 1581, 1491, 1413, 1289, 1199, 989, 871, 764, 738 cm^{-1}; ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.38-7.43 (m, 2H), 7.31(d, *J*=9.3 Hz, 1H), 7.17-7.24(m, 3H), 7.01(d, *J*=9.3 Hz, 1H), 5.92-6.06(m, 1H), 5.30(d, *J*=17.0 Hz, 1H), 5.12(d, *J*=10.2 Hz, 1H), 3.94(d, *J*=6.9 Hz, 2H).

RESULTS AND DISCUSSION

3,6-Dichloropyridazine **2**, a pivotal intermediate for the synthesis of 3-alkoxy-6-allylthiopyridazines **4**, was prepared from maleic anhydride by two steps. The reaction of maleic anhydride with hydrazine monohydrate in aqueous *conc*-HCl afforded 3,6-dihydroxypyridazine **1**, a tautomer of maleic hydrazide, in 83% yield after 3 h at reflux temperature (*Scheme* 1). The chlorination of **1** was accomplished by heating with phosphorus oxychloride at 76-78 °C for 7 h. After the reaction to completion, the mixture was neutralized with 28% ammonium hydroxide until slightly basic and extraction with methylene chloride gave **2** in 94% yield. Alternatively, **1** could be also chlorinated by the treatment with thionyl chloride (9 eq) methanesulfonic acid (3 eq) at 70-75 °C for 48 h and **2** was obtained in 90% yield.

The effect of solvents and metal alkoxides was exam-



Scheme 1

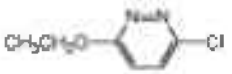
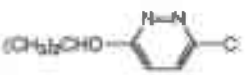
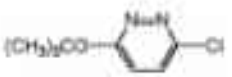
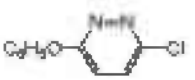
ined for the displacement of the first chlorine atom in **2**. The reaction of **2** and lithium ethoxide in THF proceeded sluggish at room temperature, yielding 3-ethoxy-6-chloropyridazine **3b** in 48% yield after 48 h with the recovery of starting material in 35% yield. The chlorine displacement of **2** with copper(II) ethoxide, generated from the transmetalation of lithium ethoxide and half equivalent of copper(II) bromide in THF, was not effective and thus **3b** was obtained in only 3% yield, together with 87% yield of starting material after 24 h. However, the treatment of **2** with sodium ethoxide (21 wt.% in EtOH) in THF at room temperature afforded **3b** in 87% yield after only 0.2 h with the formation of sodium chloride as a precipitate. When diethyl ether and acetonitrile were employed as a solvent, the corresponding reaction went to completion in 0.3 h and 0.4 h, respectively, and **3b** was obtained in 90% and 89% yield, respectively. The use of EtOH as a solvent instead of THF required somewhat longer reaction time (1.5 h), showing decreased nucleophilicity by hydrogen bonding between ethoxide anion and EtOH.

It is of interest to note that the first chlorine atom of **2** was selectively displaced by sodium ethoxide in THF. The treatment of **2** with an excess amount of sodium ethoxide (2 equiv) in THF for 3 h at room temperature afforded only **3b** in 89% yield and disubstituted 3,6-dimethoxypyridazine was not detected to an observable amount. This effect is ascribed to the fact that resonance interaction between the annular nitrogen and electron-donating ethoxy substituent decreases the electrophilicity of chlorine-substituted carbon atom. Thus, it is desirable to introduce in the order of alkoxy and allylthio group for the facile conversion of **2** into **4**. As shown in *Table* 1, various 3-alkoxy-6-chloropyridazines were efficiently prepared in high yields by this method. The reaction of **2** with primary secondary sodium alkoxides (**3a-3d**) gave the corresponding **3** in high yields within 1 h at room temperature. However, the reaction of **2** with sodium *tert*-butoxide (**3e**), sodium *tert*-pentoxide (**3f**), and sodium phenoxide (**3g**) required 3.3 h, 5 h, and 4 h (65 °C), respectively, for the reaction to completion, reflecting steric effect or decreased nucleophilicity of the corresponding nucleophiles.

Next, we examined the effect of solvents and metal thiolates for the introduction of allylthio group in the 6-position of **3**. The treatment of **3b** with sodium 2-propene-1-thiolate in THF at room temperature gave **4b** in 84% yield after 24 h. For diethyl ether and acetonitrile solvent, the corresponding reaction proceeded sluggish, yielding **4b** in 80% and 69% yield, respectively, after 24 h along with the recovery of **3b** in 13% and 25% yield, respectively. The reaction of **3b** with sodium 2-propene-1-thiolate in EtOH proceeded very sluggish and thus **4b** was obtained in only 14% yield even after 48 h, along with the recovery of starting material in 81% yield. The displacement of chlorine atom in **3b** by the treatment with copper(II) 2-propene-1-thiolate didn't proceed at all during 24 h and starting material was recovered in 96% yield.

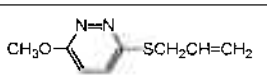
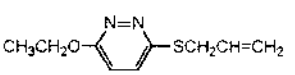
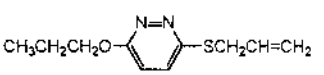
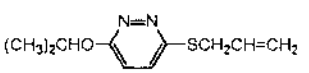
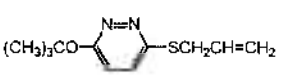
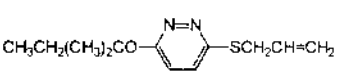
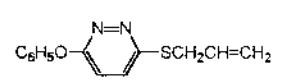
However, the reaction of **3b** with lithium 2-propene-1-thiolate, generated from 2-propene-1-thiol and *n*-butyllithium at 0 °C, proceeded smoothly in THF at room temperature. After being stirred for 4 h, THF was evaporated *in vacuo* and the mixture was dissolved in *n*-hexane. The resulting lithium chloride precipitate was filtered off and the concentrated residue was subjected to silica gel column chromatography to give **4b** in 93% yield. The synthetic results of 3-alkoxy-6-allylthiopyridazines

Table 1. Preparation of 3-alkoxy-6-chloropyridazines from 3,6-dichloropyridazine and sodium alkoxides in THF

Entry **3**	NaOR, R	Reaction time, h	Product	Isolated yield, %
a	CH_3	0.4		97
b	CH_3CH_2	0.2		87
		1[a]		86
c	$CH_3CH_2CH_2$	1		85
d	$(CH_3)_2CH$	1		88
e	$(CH_3)_3C$	3.3		99
f	$CH_3CH_2(CH_3)_2C$	5		81
g	C_6H_5	4[b]		87

[a]The reaction was carried out at 0 °C–r. t. [b]The reaction was carried out at 65 °C.

Table 2. Preparation of 3-alkoxy-6-allylthiopyridazines from 3-alkoxy-6-chloropyridazines and lithium 2-propene-1-thiolate in THF

Entry **4**	3-Alkoxy-6-chloropyridazines, R	Reaction time, h	Product	Isolated yield, %
a	CH_3	4		81
b	CH_3CH_2	4		93
c	$CH_3CH_2CH_2$	4		89
d	$(CH_3)_2CH$	4.5		93
e	$(CH_3)_3C$	4		86
f	$CH_3CH_2(CH_3)_2C$	1.4[a]		94
		24		60(31)[b]
g	C_6H_5	0.5		85

[a]The reaction was carried out at 65 °C. [b]The number in parenthesis indicates the recovery yield of 3-*tert*-pentoxy-6-chloropyridazine.

were summarized in *Table* 2. In general, **4** were obtained in high yields within 4.5 h at room temperature regardless of the structure of the alkoxy group (**4a-4e**) in the 3-position. Although the reaction of **3f** and lithium 2-propene-1-thiolate proceeded sluggish, the corresponding reaction was completed in 1.4 h at 65 °C to afford **4f** in 94% yield. The substitution of chlorine atom in **3g** proceeded rapidly to give **4g** in 85% yield because of decreased electron-donating effect of phenoxy group.

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