Preparation of *N'*-[2-(5,6-Dimethylbenzothiazolyl)]-*N*-furfuryloxamide with Plant Growth Regulatory Activity

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The reaction of the *N*-furfuryloxamic acid sodium salt (12) with 1,1'-oxalyldiimidazole (ODI) yielded the imidazolide (13) as an intermediate, and this directly reacted with 2-aminothiazole derivatives (14) or 2-aminobenzothiazole derivatives (15) under essentially neutral conditions to afford the *N'*-[2-(substituted thiazolyl)]- or *N'*-[2-(substituted benzothiazolyl)]-*N*-furfuryloxamides (6 or 7).

The prepared compounds (6 and 7) were examined for plant growth regulatory activity in a seed germination assay. The examination resulted in the discovery of some new revelations that *N'*-[2-(5,6-dimethylbenzothiazlyl)]-*N*-furfuryloxamide (7c) at the concentration of 1.0×10^{-3} M completely inhibited the radicle growth of both rape and leek seedlings.

Key words furan derivative; oxamide derivative; plant growth regulator; seedling; benzothiazole derivative; herbicide

Thiazole and benzothiazole derivatives have attracted much attention from both botanical and plant physiological viewpoints.[1] For example, the 5-thiazolecarboxamide derivative (**1**) at 50 ppm showed 75% control of the fungus *Pseudoperonospora cubenis*.[2] Compound (**2**) totally protected wood against *Coniophora puteana*.[3] Compound (**3**) gave ≧90% control of *Amaranthus viridis* at 0.05 kg/ha and caused no damage to beets. The herbicidal activity of **3** is greater than that of triflusulfuron-methyl.[4] The benzothiazole derivative (**4**) showed 90—100% control against *Sesbania exaltata*, *Abutilon theophrasti*, *Solanum* sp. and *Viola* sp. at 0.1 kg/ha.[5] The 2-(2-benzothiazolyloxy)acetamide derivative (**5**) inhibited the growth of barnyard grass and *Cyperaceae* weeds.[6]

In previous papers, we showed that *N'*-(2-thiazolyl)-*N*-furfuryloxamide (**6a**) induced about a 23% promotion in rooting in a seed germination assay using rape and leek.[7] As part of our efforts to identify more effective plant growth regulators among the derivatives of **6a**, we were prompted to examine the effect of the structural changes of the thiazole ring on plant physiology. Namely, our attention focused on the expectation that the modest promotion property mentioned above may vary with the structure of thiazole ring either to be reduced or to be strengthened. Here we describe the preparation of the thiazole and benzothiazole derivatives (**6b—f** and **7a—c**) and the examination of their activity as plant growth regulators in a seed germination assay.

We synthesized the thiazole derivatives (**6a—f**) and benzothiazole derivatives (**7a—c**) as follows. Furfurylamine (**9**) was condensed with the potassium salt (**10**) of the oxalic acid monomethyl ester using 1,1'-oxalyldiimidazole (ODI) to afford methyl *N*-furfuryloxamate (**11**), which was hydrolyzed in sodium hydroxide solution at room temperature to give the sodium salt (**12**) of *N*-furfuryloxamic acid.

The carboxyl group of **12** was activated with ODI to form the imidazolide intermediate (**13**), which was subjected to amidation with the 2-aminothiazole derivatives (**14**) or 2-aminobenzothiazole derivatives (**15**) to afford the corresponding *N'*-substituted *N*-furfuryloxamides (**6** or **7**) in yields of 40% to 83%.

The plant growth regulatory property was assayed according to the method reported by Inamori *et al.*[8] using seeds of rape, *Brassica campestris* L. (Brassicaceae), as a dicotyledon and leek, *Allium tuberosum* ROTTLER (Liliaceae), as a monocotyledon. 2,4-Dichlorophenoxyacetic acid (2,4-D) was used as the positive control. The results are summarized in Tables 1 and 2.

First, we chose a bromine group as the substituent on the thiazole ring because agrochemicals containing this halogen atom, such as bromacil or diquat, often cause a negative mode of action. The 5-bromothiazole derivative (**6b**) at high concentrations of 1.0×10^{-3} M then exhibited a marked inhibitory effect, whereas the parent 2-thiazole derivative (**6a**) showed about 23% promotion of root growth for the rape and leek seedlings. On the other hand, the 4,5-dimethylthiazole derivative (**6e**) showed about 45% inhibition, which suggest that a small alkyl group such as a methyl group did not have a great effect on the inhibition activity.

We are continuously interested in the more bulky substituent such as the phenyl ring. For example, the thiazole de-

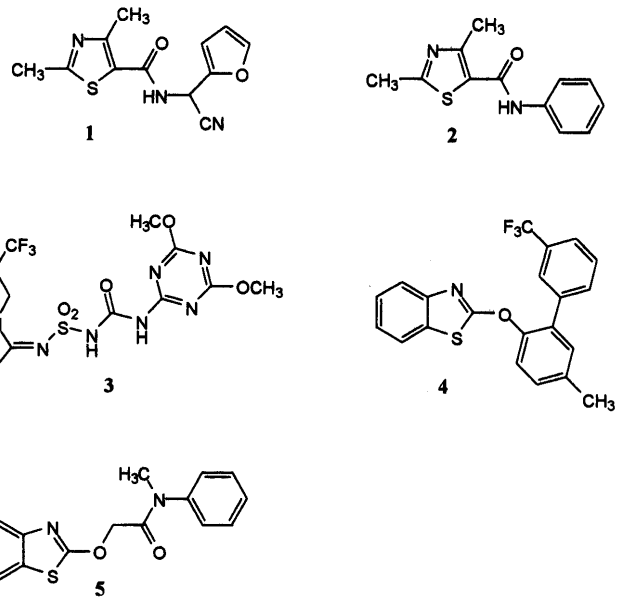

Chart 1

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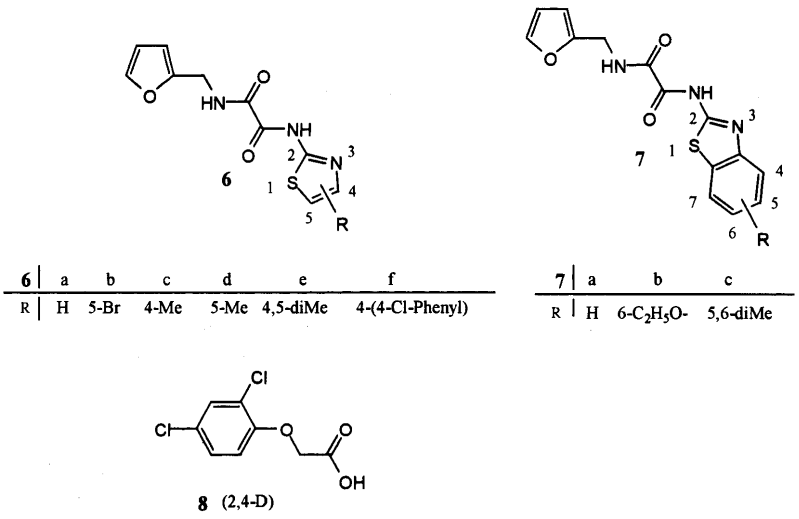
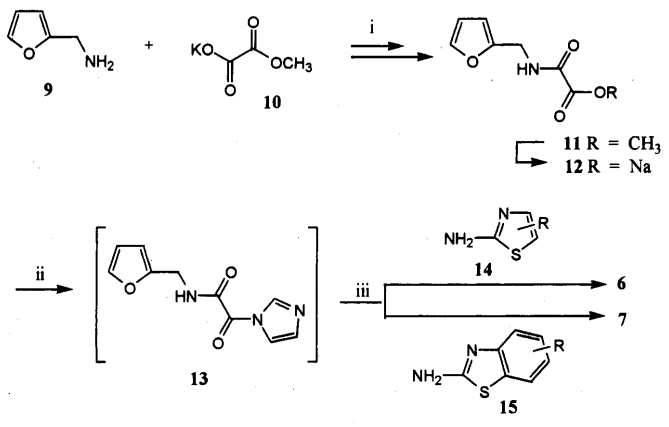


Chart 2



i, condensation using 1,1′-oxalyldiimidazole (ODI) to give an amide-ester, and the hydrolysis using NaOH. ii, activation using ODI. iii, amidation.

Chart 3

rivative (**6f**), which has a 4-chlorophenyl group at the 4-position of the thiazole ring, exhibited a 98% inhibition for rape and 95% for leek at the concentration of 1.0×10^{-3} M.

It would appear quite reasonable to us that increasing the steric crowding on the *b*-side of the thiazole ring enhances the inhibitory effect on root growth. Therefore, by postulating that all the oxamide groups, thiazole rings and 4-chlorophenyl rings lie on the same plane, it may be useful to speculate that the more the coplanarity is increased, the more clearly the inhibition property will appear. This idea is supported by the finding that the 5,6-dimethylbenzothiazole derivative (**7c**) showed complete inhibition at the concentration of 1.0×10^{-3} M for both rape and leek seedlings, while the 6-ethoxybenzothiazole derivatives (**7b**) showed only about a 70% inhibition at the same concentration because the whole coplanarity formed by oxamide-benzothiazole groups is slightly broken by bonding of the 6-ethoxy group with the benzene ring. As shown in Table 2, the activity of **7c** is similar to that of 2,4-D (**8**) as the positive control. Therefore, **7c** appears to be a new seed compound available as a growth retardant.

In summary, we synthesized the *N*′-[2-(substituted thiazolyl)] and *N*′-[2-(substituted benzothiazolyl)]-*N*-furfuryloxamides (**6** and **7**). The *N*′-[2-(5,6-dimethylbenzothiazolyl)]-*N*-furfuryloxamide (**7c**) at the concentration of 1.0×10^{-3} M completely inhibited the rooting of the rape and leek seedlings.

Experimental

Methyl oxalate, oxalyl chloride, imidazole, dimethyl sulfoxide (DMSO), furfurylamine, the 2-aminothiazole derivatives (**14b**—**f**), the 2-aminobenzothiazole derivatives (**15a**—**c**), and 2,4-D were purchased from commercial sources and used as received. *N*′-Thiazolyl-*N*-furfuryloxamide (**6a**) and the *N*-furfuryloxamic acid sodium salt (**12**) were prepared according to the reported procedures.[7a] *N*-Furfuryloxamic acid is very hygroscopic; therefore, for convenience, it was converted into the corresponding sodium salt. When compounds **14c**, **14d**, **14f**, **15a**—**15c** were chosen as the free amine components, no triethylamine was used as a scavenger for hydrogen halide. Melting points were taken on a Yanagimoto melting point apparatus. All melting points are uncorrected. The IR spectra were measured using a Hitachi model 270-30 IR spectrophotometer. The NMR spectra were measured on a Bruker DPX-400 spectrometer (400 MHz) with tetramethylsilane as the internal reference, and chemical shifts were recorded as δ-values.

***N*′-[2-(5-Bromothiazolyl)]-*N*-furfuryloxamide (6b)** A solution of oxalyl chloride (1.28 g, 10 mmol) in acetonitrile (10 ml) was added dropwise to an ice-cold, stirred solution of imidazole (2.7 g, 40 mmol) in acetonitrile (150 ml). The mixture was stirred at room temperature for 5 min, then a suspension of the *N*-furfuryloxamic acid sodium salt (**12**) (1.8 g, 10 mmol) and methanesulfonic acid (1 g, 10 mmol) in acetonitrile (10 ml) was rapidly added as a single portion. The mixture was stirred at room temperature for 20 min, and then a suspension of 2-amino-5-bromothiazole mono hydrobromide (**14b**) (1.14 g, 10 mmol) and triethylamine (1.0 g, 10 mmol) in acetonitrile (10 ml) was added in a single portion. The resultant mixture was stirred for 3 h at 40 °C. The solvent was removed *in vacuo*, and the remaining residue was poured onto ice and extracted with ethyl acetate. Washing of the ethyl acetate extract with 5% hydrochloric acid and water, followed by drying and evaporation of the solvent left 2.3 g (69%) of the crude product (**6b**). Recrystallization from toluene gave **6b** with a mp of 210—212 °C. IR (KBr) cm^{-1}: 1662 (CO). ^{1}H-NMR (DMSO-d_6) δ: 4.3 (d, 2H, J=6.1 Hz, CH_2), 6.2—7.5 (m×3, 1H×3, furan-4H, -3H and -5H), 7.6 (s, 1H, thiazole-4H), 9.5—9.6 (t, 1H, $CH_2\underline{NH}$), 13.4 (s, 1H, CONH). *Anal.* Calcd for $C_{10}H_8BrN_3O_3S$: C, 36.38; H, 2.44; N, 12.73. Found: C, 36.12; H, 2.31; N, 12.72.

***N*′-2-(4-Methylthiazolyl)-*N*-furfuryloxamide (6c)** **6c** was prepared as described for **6b**, through the reaction of **12** with 2-amino-4-methylthiazole (**14c**) in 68% yield. Recrystallization from ethanol gave **6c**, mp 172—173 °C. IR (KBr) cm^{-1}: 1665 (CO). ^{1}H-NMR (DMSO-d_6) δ: 2.2 (s, 3H, CH_3), 4.3—4.4 (d, 2H, J=6.1 Hz, CH_2), 6.2—7.5 (m×3, 1H×3, furan-4H, -3H and -5H), 6.9 (s, 1H, thiazole-5H), 9.5 (t, 1H, $CH_2\underline{NH}$), 12.4 (s, 1H, CONH). *Anal.* Calcd for $C_{11}H_{11}N_3O_3S$: C,49.8; H, 4.18; N, 15.84. Found: C, 49.97; H, 4.24; N, 15.86.

***N*′-2-(5-Methylthiazolyl)-*N*-furfuryloxamide (6d)** **6d** was prepared as described for **6b**, through the reaction of **12** with 2-amino-5-methylthiazole (**14d**) in 66% yield. Recrystallization from ethanol gave **6d**, mp 195—

Table 1. Plant Growth-Modulating Activities of *N'*-Substituted *N*-(2-Furfuryl)oxamides (**6** and **7**)

Compound	*N'*-Subs. groups	Dicotyledoneae Rape; *Brassica campestris* L.				Monocotyledoneae Leek; *Allium tuberosum* Rottler			
		Growth (mm)[a]		Promotion	Inhibition	Growth (mm)[a]		Promotion	Inhibition
		Control	1.0×10^{-3} (M)	(%)[b]	(%)[b]	Control	1.0×10^{-3} (M)	(%)	%)
6a	2-Thiazolyl	57±17.5	70±10.5**	21	—	8±5.0	10±5.7*	25	—
6b	2-(5-Bromothiazolyl)	57±15.4	1±0.9**	—	99	7±3.9	0**	—	100
6c	2-(4-Methylthiazolyl)	52±16.3	31±19.1**	—	41	7±3.7	2±1.9**	—	71
6d	2-(5-Methylthiazolyl)	59±16.9	28±19.2**	—	5	7±3.9	3±2.2**	—	57
6e	2-(4,5-Dimethylthiazolyl)	60±16.1	32±18.9**	—	47	7±5.1	4±3.3*	—	42
6f	2-[4-(4-Chlorophenyl)thiazolyl]	58±17.2	0.8±0.9**	—	98	7±4.9	0.3±0.4**	—	95
7a	2-Benzthiazolyl	57±15.2	4±4.7**	—	92	6±3.5	0.9±0.5**	—	85
7b	2-(6-Ethoxybenzthiazolyl)	62±15.7	21±9.7**	—	67	6±3.6	1±1.1**	—	83
7c	2-(5,6-Dimethylbenzthiazolyl)	53±15.6	0**	—	100	7±3.4	0**	—	100
	2,4-D[c]	64±25.7	0**	—	100	10±2.2	0**	—	100

a) The values represent mean±S.D. of 40 seeds after seven days (*A. tuberosum*: 10 d). Significant differences from the corresponding control level are indicated, * and ** show $p<0.05$ and $p<0.01$, respectively. Quantity of light: 127 μmol·m^{-2}·s^{-1}. Temperature 25 °C. Relative humidity of 60%. Experimental size: 20 seeds/group, 2 groups. *b*) [(The mean value of the control−the mean value at the concentration (M) of 1.0×10^{-3})/the mean value of control]×100=*P* (%); when *P* shows a positive value, the absolute value of *P* corresponds to the promotion effect, and in the case of *P* showing a negative value, the absolute value of that corresponds to the inhibition effect. *c*) 2,4-Dichlorophenoxyacetic acid (2,4-D) was used as a positive control.

Table 2. Plant Growth Activities of Compounds **6b**, **6f**, **7a**, **7c** and **8**

Compound	*N'*-Subs. groups	Dicotyledoneae Rape; *Brassica campestris* L.				Monocotyledoneae Leek; *Allium tuberosum* Rottler			
		Inhibition (%)[a]				Inhibition (%)[a]			
		1.0×10^{-3} (M)	5.0×10^{-4} (M)	1.0×10^{-4} (M)	5.0×10^{-5} (M)	1.0×10^{-3} (M)	5.0×10^{-4} (M)	1.0×10^{-4} (M)	5.0×10^{-5} (M)
6b	2-(5-Bromothiazolyl)	99	79	20	2	100	85	27	5
6f	2-[4-(4-Chlorophenyl)thiazolyl]	98	90	85	72	96	96	68	57
7a	2-Benzthiazolyl	92	70	41	3	85	64	43	19
7c	2-(5,6-Dimethyl)benzthiazolyl	100	100	95	62	100	98	95	53
8	2,4-D[b]	100	99	98	98	100	100	99	97

a) See the footnotes *a*) and *b*) of Table 1. *b*) 2,4-Dichlorophenoxyacetic acid (2,4-D) was used as a positive control.

198 °C. IR (KBr) cm^{-1}: 1663 (CO). ^{1}H-NMR (DMSO-d_6) δ: 2.1(s, 3H, CH_3), 4.2—4.3 (d, 2H, J=6.1 Hz, CH_2), 6.1—7.4 (m×3, 1H×3, furan-4H, -3H and -5H), 7.1 (s, 1H, thiazole-5H), 9.3 (t, 1H, $CH_2\underline{NH}$), 12.1 (s, 1H, CONH). *Anal.* Calcd for $C_{11}H_{11}N_3O_3S$: C, 49.8; H, 4.18; N, 15.84. Found: C, 49.65; H, 4.23; N, 15.80.

***N'*-[2-(4,5-Dimethylthiazolyl)]-*N*-furfuryloxamide (6e)** **6e** was prepared as described for **6b**, through the reaction of **12** with 2-amino-4,5-dimethylthiazole hydrochloride (**14e**) in 83% yield. Recrystallization from toluene gave **6e**, mp 168—169 °C. IR (KBr) cm^{-1}: 1659 (CO). ^{1}H-NMR (DMSO-d_6) δ: 2.1 (s, 3H, CH_3), 2.2 (s, 3H, CH_3), 4.3 (d, 2H, J=6.1 Hz, CH_2), 6.2—7.5 (m×3, 1H×3, furan-4H, -3H and -5H), 9.4 (t, 1H, $CH_2\underline{NH}$), 12.4 (br s, 1H, CONH). *Anal.* Calcd for $C_{12}H_{13}N_3O_3S$: C, 51.61; H, 4.69; N, 15.04. Found: C, 51.59; H, 4.69; N, 15.09.

***N'*-[2-[4-(4-Chlorophenyl)thiazolyl]]-*N*-furfuryloxamide (6f)** **6f** was prepared as described for **6b**, through the reaction of **12** with 2-amino-4-(4-chlorophenyl)thiazole (**14f**) in 46% yield. Recrystallization from methanol gave **6f**, mp 205—207 °C. IR (KBr) cm^{-1}: 1662 (CO). ^{1}H-NMR (DMSO-d_6) δ: 4.4 (d, 2H, J=6.1 Hz, CH_2), 6.3—7.6 (m×3, 1H×3, furan-4H, -3H and -5H), 7.5—7.9 (two d, each 2H, J=8.0 Hz, phenyl -2H, -6H and phenyl-3H, -5H), 7.8 (s, 1H, thiazole-5H), 9.5 (t, 1H, $CH_2\underline{NH}$), 12.6 (s, 1H, CONH). *Anal.* Calcd for $C_{16}H_{12}ClN_3O_3S$: C, 53.12; H, 3.34; N,11.61. Found: C,53.33; H,3.43; N,11.51.

***N'*-(2-Benzothiazolyl)-*N*-furfuryloxamide (7a)** **7a** was prepared as described for **6b**, through the reaction of **12** with 2-aminobenzothiazole (**15a**) in 40% yield. Recrystallization from toluene gave **7a**, mp 161—162 °C. IR (KBr) cm^{-1}: 1660 (CO). ^{1}H-NMR (DMSO-d_6) δ: 4.2 (d, 2H, J=6.1 Hz, CH_2), 6.3—7.7 (three m, each 1H, furan-3H, 4H and 5H), 7.3—7.5 (m, 4H, benzothiazole-4H, 5H, 6H and -7H), 9.6 (t, 1H, $CH_2\underline{NH}$), 12.3 (br s, 1H, CONH). *Anal.* Calcd for $C_{14}H_{11}N_3O_3S$: C, 55.81; H, 3.68; N, 13.95. Found: C, 56.14; H, 3.89; N, 14.18.

***N'*-[2-(6-Ethoxybenzothiazole)]-*N*-furfuryloxamide (7b)** **7b** was prepared as described for **6b**, through the reaction of **12** with 2-amino-6-ethoxybenzothiazole (**15b**) in 83% yield. Recrystallization from toluene gave **7b**, mp 172—173 °C. IR (KBr) cm^{-1}: 1668 (CO). ^{1}H-NMR (DMSO-d_6) δ: 1.3 (s, 3H, CH_3), 4.0 (q, 2H, $\underline{CH_2}CH_3$), 4.4 (d, 2H, J=6.1 Hz, $\underline{CH_2}NH$), 6.3—7.0 (three m, each 1H, furan-3H, 4H and 5H), 7.5—7.9 (m, 3H, benzothiazol-4H, 5H and 7H), 9.5 and 9.6 (t, 1H, $\underline{CH_2}NH$), 12.6 (br s, 1H, CONH). *Anal.* Calcd for $C_{16}H_{15}N_3O_4S$: C, 55.65; H, 4.34; N, 12.17. Found: C, 55.57; H, 4.27; N, 11.81.

***N'*-[2-(5,6-Dimethylbenzothiazolyl)]-*N*-furfuryloxamide (7c)** **7c** was prepared as described for **6b**, through the reaction of **12** with 2-amino-5,6-dimethylbenzothiazole (**15c**) in 81% yield. Recrystallization from toluene gave **7c**, mp 250—251 °C. IR (KBr) cm^{-1}: 1707 and 1617 (CO). ^{1}H-NMR (DMSO-d_6) δ: 2.3 (two s, each 3H, each CH_3), 4.3 (d, 2H, J=6.1 Hz, CH_2), 6.2—7.7 (three m, each 1H, furan-3H, 4H and 5H), 7.2—7.3 (m, 2H, benzothiazole-4H and 7H), 9.6 (t, 1H, each $CH_2\underline{NH}$), 12.6 (br s, 1H, CONH). *Anal.* Calcd for $C_{16}H_{15}N_3O_3S$: C, 58.35; H, 4.59; N, 12.76. Found: C, 58.22; H, 4.55; N, 12.80.

Plant Growth-Inhibitory Activity Test This test was carried out according to the method reported by Inamori *et al.*[8] The DMSO solution (1.0 ml) containing a test oxamide derivative (**6b—f** or **7a—c**), 2,4-D as the positive control, or DMSO alone (1.0 ml) as the control, was diluted in 100 ml of sterilized agar (0.8%, Nacalai Tesque, Inc.) to give concentrations of 5×10^{-5} M, 1.0×10^{-4} M, 5×10^{-4} M, and 1.0×10^{-3} M. Agar containing the test compounds (**6**, **7** and 2,4-D) or DMSO as the control was poured into a 500 ml sterilized culture jar. Twenty seeds of each plant species, sterilized with 70% ethanol and 1% NaClO, were placed on the agar and left for seven days (*A. tuberosum*; ten days) at 25 °C under a relative humidity of 60% and a light intensity of 127 μmol·m^{-2}·s^{-1}. The results are summarized in Tables 1 and 2.

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