Synthesis of the New Saccharin Derivatives Containing Imidazolidine-2,4,5-trione or 2-Thio-imidazolidine-4,5-dione Group

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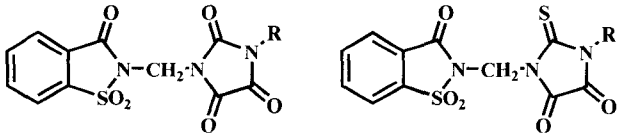
Saccharin derivatives were synthesized by means of 4 reaction steps involved the reaction of 1-methylurea (or 1-methylthiourea) and oxalyl chloride. 1-Alkyl(or phenyl)-3-(1,1,3-trioxo-1,3-dihydro-1^6-benzo[*d*]isothiazol-2-ylmethyl)-imidazolidine-2,4,5-trione **5** and 1-alkyl(or phenyl)-2-thioxo- 3-(1,1,3-trioxo-1,3-dihydro-1^6-benzo-[*d*]isothiazol-2-ylmethyl)-imidazolidine-4,5-dione **12** were obtained by means of 4 reaction steps involved the reaction of 1-methyl-urea(or 1-methylthiourea) and oxalyl chloride.

Key words – agrochemical, benzisothiazole, imidazolidine-2,4,5-trione, 2-thio-imidazolidine-4,5-dione, saccharin derivatives

Saccharin derivatives have been widely studied for the use of phytocides, herbicides, and insecticides[3,4,6]. Imidazolidine-2,4,5-triones are known for their herbicide, plant-growth regulator, and fungicide properties [5,7,8,9].

In the development of new agrochemical, we chose to associate benzisothiazole and imidazoli- dine-2,4,5-trione or 2-thio-imidazolidine-4,5-dione groups as a new structure in which each part would serve as an active component for the desired property (Scheme 1).

In order to obtain a new agrochemical, we planned first to synthesize a chlorinated precursor **4** or **11** to introduce 1,2-benz-isothiazole-3- one-1,1-dioxide (Saccharin).



Materials and Methods

Melting points were determined on an electrothemal capillary melting point apparatus and uncorrected. TLC was performed on glass plates coated with silicon oxide (silica gel $60F_{254}$) and compounds were visualized using a uv lamp. Proton nuclear magnetic resonance and ^{13}C NMR spectra were obtained with Bruck AC 200 (200MHz) and Varian Gemini (200MHz) spectrometers. Mass specta were measured with HP 5890 II GC/Mass (70eV, EI). The organic solvents and chemicals were obtained from commercial products and purified by the appropriate methods before use.

The typical experimental procedure for 1-phenyl-3-(1,1,3-trioxo-1,3-dihydro-1^6-benzo-[*d*]isothiazol-2-ylmethyl)-imidazolidine-2,4,5-trione **5c** is as follows : To a solution of 1-chloromethyl-3-phenylimidazolidine-2,4,5- trione **4c** (2.38 g, 10 mmol) in dry THF (15 mL) under nitrogen at room temperature was added solution of saccharin (2.01 g, 11 mmol) and triethylamine (1.2 mL) in dry THF (15 mL). The reaction mixture was stirred at room temperature for 30 minutes. After 30 minutes, the reaction mixture was refluxed at 55~60℃ for 5hrs. The reaction mixture was cooled again to room temperature and THF (50 mL) was added. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluted with only CH_2Cl_2, to provide the 1-phenyl-3-(1,1,3-trioxo-1,3-dihydro-1^6-benzo[*d*]isothiazol-2-ylmethyl)-imidazolidine-2,4,5-trione **5c** as a white crystalline solid (1.93 g, 50%). mp 191-192℃; ^1H NMR(200 ㎒, $CDCl_3$) 5.84 (s, 2H, CH_2), 7.4~8.1 (m, 9H, phenyl); Mass m/z (rel. intensity, %) 385 ($[M]^+$, 40), 196 (100), 91, 77. And the typical experimental procedure for 1-ethyl-2-thioxo-3-(1,1,3-trioxo-1,3-dihydro-1^6-benzo[*d*]isothiazol-2-ylmethyl)-imidazolidine-4,5-dione **12b** is as follows: To a solution of 1-ethyl-2-thioxo-imidazolidine-4,5-dione **9b** (1 g, 4.8 mmol) in the dry THF (10 mL) under nitrogen at room temperature was added solution of saccharin (1.5 g, 8.2 mmol) and triethylamine

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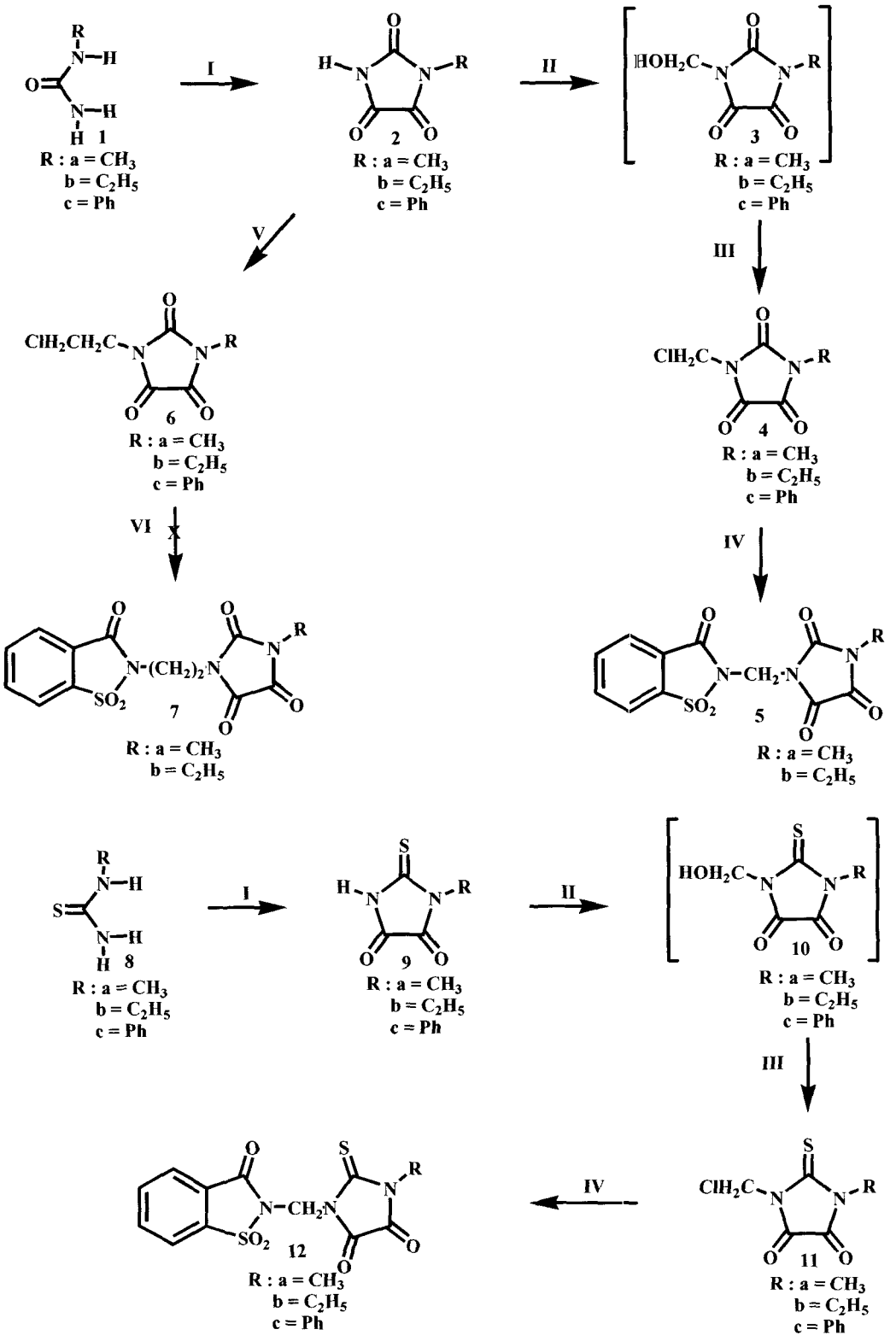

Scheme 1. Synthesis of saccharin derivatives 5 and 12 using 1-chloromethyl precursor 4 and 1-chloromethyl-2-thioxo precursor 11.

(1.1 mL) in the dry THF (10 mL). The reaction mixture was stirred at room temperature for 30 minutes. After 30 minutes, the mixture was refluxed at 55~60℃ for 5hrs. The reaction mixture was cooled again to room temperature and THF (50 mL) was added. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluted with only CH_2Cl_2, to provide the 1-ethyl-2-thioxo-3-(1,1,3-trioxo-1,3-dihydro-1^6-benzo-[*d*]isothiazol-2-ylmethyl)-imidazolidine-4,5-dione **12b** as a yellow crystalline solid (1.68 g, 49%). mp 157-158℃; ^{1}H NMR (200 ㎒, Acetone-d_6) 1.17 (t, 3H, -CH_3), 3.99- 4.06 (q, 2H, -CH_2), 6.04 (s, 2H, N-CH_2-N), 8.05 -8.20 (m, 4H, phenyl); IR (, KBr, ㎝$^{-1}$) 1780, 1740, 1720, 1390, 1330, 1280, 1240, 1175; Mass m/z(rel. intensity, %) 352 ([M]$^+$).

1-Methyl-imidazolidine-2,4,5-trione 2a. yield 92%; mp 146-147℃; IR (, KBr, cm^{-1}) 3230, 2732, 1748, 1620, 1460, 1320, 1120; Mass, *m/z*(rel. intensity, %) 128 ([M]$^+$, 100), 100 (55), 70 (35), 56 (60). **1-Ethyl-imidazolidine- 2,4,5-trione 2b**. yield 85%; mp 121-123℃; IR (, KBr, cm^{-1}) 3160, 2990, 2850, 1782, 1422, 1351, 1064; Mass, *m/z* (rel. intensity, %) 142 ([M]$^+$, 100), 114 (30), 86 (5), 70 (30), 56 (50). **1-Phenyl-imidazolidine-2,4,5- trione 2c**. yield 90%; mp 203-204℃; IR (, KBr, cm^{-1}) 3245, 3066, 1793, 1736; ^{1}H NMR (200 ㎒, DMSO-d_6) 7.3-7.56 (m, 5H, phenyl), 12.27 (s, 1H, NH). **1-Chloromethyl-3-methyl-imidazolidine-2,4,5-trione 4a**. yield 50%; mp 149-150℃; IR (, KBr, cm^{-1}) 1731.7, 1459, 1407, 1306, 1129; Mass *m/z* (rel. intensity, %) 179 ([M+2]$^+$, 5), 176 ([M]$^+$, 20), 141 (100) 113 (30), 94 (5), 70 (35), 56 (85); ^{1}H NMR (200 ㎒, $CDCl_3$) 3.23 (s, 3H, CH_3), 5.40 (s, 2H, CH_2Cl). **1-Chloromethyl-3-ethyl-imidazolidine-2,4,5-trione 4b**. yield 64%; mp 83-84℃; IR (, KBr, cm^{-1}) 2982, 2865, 1735, 1409, 1298, 1208, 1128; Mass *m/z*(rel. intensity, %) 192 ([M+1]$^+$, 5), 190 ([M-1]$^+$, 10), 175 (2), 162 (1), 154 (30), 127 (15), 99 (10), 70 (45), 56 (100). ^{1}H NMR (200 ㎒, $CDCl_3$) 1.27-1.34 (t, 3H, CH_3), 3.70-3.81 (q, 2H, CH_2Cl), 5.39 (s, 2H, CH_2Cl). **1-Chloromethyl-3-phenyl-imidazolidine-2,4,5-trione 4c**. yield 70%; mp 130-131℃; IR (, KBr, cm^{-1}) 1780, 1730, 1500, 1440, 1295, 1190; Mass *m/z*(rel. intensity, %) 238 ([M]$^+$, 27), 119 (100), 91 (23); ^{1}H NMR (200 ㎒, $CDCl_3$) 5.6 (s, 2H, CH_2Cl), 7.4-7.5 (m, 5H, phenyl). **1-Methyl-3-(1,1,3-trioxo-1,3-dihydro-1^6-benzo [*d*]-isothiazol-2-yl-methyl)-imidazolidine-2,4,5-trione 5a**. yield 40%; mp 192-193℃; IR (, KBr, cm^{-1}) 1749, 1453, 1340, 1291, 1245, 1179; Mass *m/z* (rel. intensity, %) 323 ([M]$^+$, 1), 259 (15), 223 (4), 196 (100), 174 (20), 169 (17), 132 (20), 121 (5), 104 (22), 76 (15), 70 (9); ^{1}H NMR (200 ㎒, Acetone-d_6) 3.14 (s, 3H, CH_3), 5.70 (s, 2H, CH_2), 8.05-8.21 (m, 4H, phenyl). **1-Ethyl-3-(1,1,3-trioxo-1,3-dihydro-1^6-benzo[*d*]-isothiazol-2-ylmethyl)-imi- dazolidine-2,4,5-trione 5b**. yield 54%; mp 182-183℃; IR (, KBr, cm^{-1}) 2981, 2885, 1746, 1425, 1340, 1293, 1251, 1180, 1115, ; Mass *m/z* (rel. intensity, %) 337 ([M]$^+$, 2), 273 (8), 223 (4), 196 (100), 174 (15), 169 (14), 132 (20); ^{1}H NMR (200 ㎒, Acetone-d_6) 1.18-1.28 (t, 3H, CH_3), 3.64- 3.75 (q, 2H, CH_2), 5.70 (s, 2H, N-CH_2-N), 8.02-8.22 (m, 4H, phenyl). **1-Phenyl- 3-(1,1,3-trioxo-1,3-dihydro-1^6-benzo[*d*]-isothiazol-2-ylmethyl)-imidazolidine- 2,4,5-trione 5c**: yield 50%; mp 191-192℃; IR (, KBr, cm^{-1}) 1785, 1750, 1410, 1330, 1290, 1250; Mass *m/z*(rel. intensity, %) 385 ([M]$^+$, 40), 196 (100), 169 (20), 119 (80), 91 (45), 77 (33); ^{1}H NMR (200 ㎒, $CDCl_3$) 5.84 (s, 2H, CH_2), 7.4-8.1 (m, 9H, phenyl). **1-Methyl-2-thioxo-imidazolidine-4,5-dione 9a**: yield 60%; mp 108-109℃; IR (, KBr, cm^{-1}) 3150, 2920, 1780, 1750, 1430, 1320, 1190; Mass *m/z*(rel. intensity, %) 144 ([M]$^+$); ^{1}H NMR (200 ㎒, DMSO-d_6) 3.17 (s, 3H, -CH_3), 12.98 (s, 1H, -NH). **1-Ethyl-2-thioxo-imidazolidine-4,5-dione 9b**: yield 70%; mp 77-78℃; IR (, KBr, cm^{-1}) 3250, 2910, 1680, 1550, 1400, 1290, 1270, 1125, 1100; Mass *m/z*(rel. intensity, %) 158([M]$^+$); ^{1}H NMR (200 ㎒, DMSO-d_6) 1.10-1.17 (t, 3H, -CH_3), 3.71-3.82 (q, 2H, -CH_2), 12.98 (s, 1H, -NH). **1-Phenyl-2- thioxo-imidazolidine-4,5-dione 9c**: yield 70%; mp 168-169℃; IR (, KBr, cm^{-1}) 3280, 3075, 1790, 1750, 1650, 1500, 1410, 1220, 1080; Mass *m/z* (rel. intensity, %) 204 ([M]$^+$); ^{1}H NMR (200 ㎒, DMSO-d_6) 7.3-7.5 (m, 5H, -phenyl), 12.27 (s, 1H, -NH). **1-Chloro-methyl-3-methyl-2-thioxo-imidazolidine-4,5-dione 11a**: yield 45%; mp 97-98℃; IR (, KBr, cm^{-1}) 1784, 1772, 1405, 1378, 1354; Mass *m/z* (rel. intensity, %) 192 ([M]$^+$); ^{1}H NMR (200 ㎒, Acetone- d_6) 3.38 (s, 3H, -CH_3), 5.76 (s, 2H, -CH_2). **1-Chloromethyl-3-ethyl-2-thioxo-imi-dazolidine-4,5-dione 11b**: yield 45%; mp 108-109℃; IR (, KBr, cm^{-1}) 1780, 1740, 1402, 1370, 1230, 1135; Mass *m/z* (rel. intensity, %) 206 ([M]$^+$); ^{1}H NMR (200 ㎒, Acetone- d_6) 1.21-1.28 (t, 3H, -CH_3), 3.95- 4.06 (q, 2H, -CH_2), 5.75 (s, 2H, -CH_2Cl). **1-Chloromethyl-3-phenyl-2-thioxo-imidazolidine-4,5-dione 11c**: yield 40%; mp 215-216℃; IR (, KBr, cm^{-1}) 1780, 1650, 1520, 1500, 1400, 1230; Mass *m/z* (rel. intensity, %) 254 ([M]$^+$); ^{1}H NMR (200 ㎒, Acetone-d_6) 5.87 (s, 2H, -CH_2Cl), 7.43-7.60 (m, 5H, -phenyl). **1-Methyl-2-thioxo-3-(1,1,3-trioxo-1,3-dihydro-1^6-benzo[*d*]isothiazol-2-ylmethyl)-imidazolidine-4,5-dione 12a**: yield 40%; mp 173-174℃; IR (, KBr, cm^{-1}) 1780, 1400, 1340, 1290, 1250, 1170, 1100; Mass *m/z* (rel. intensity, %) 339 ([M]$^+$); ^{1}H NMR (200 ㎒, Acetone-d_6) 3.39 (s, 3H, -CH_2), 6.04 (s, 2H, N-CH_2-N), 8.10-8.17 (m, 4H, phenyl). **1-Ethyl-2-thioxo-3-(1,**

1,3-trioxo-1,3-dihydro-1^6-benzo[*d*]isothiazol-2-ylmethyl)-imidazolidine-4,5-dione 12b: yield 49%; mp 157-158℃; IR (, KBr, cm^{-1}) 1780, 1740, 1720, 1390, 1330, 1280, 1240, 1175; Mass *m/z* (rel. intensity, %) 353 ([M]$^+$); ^{1}H NMR (200 ㎒, Acetone-d_6) 1.17 (t, 3H, -CH_2), 3.99-4.06 (q, 2H, -CH_2), 6.04 (s, 2H, N-CH_2-N), 8.05-8.20 (m, 4H, phenyl). **1-Phenyl-2-thioxo-3-(1,1,3-trioxo-1,3-dihydro-1^6-benzo[*d*]isothiazol-2-ylmethyl)-imidazolidine-4,5-dione 12c**: yield 30%; mp 170-171℃; IR (, KBr, cm^{-1}) 1785, 1720, 1400, 1370, 1360, 1300, 1250, 1180; Mass *m/z* 402 ([M]$^+$); ^{1}H NMR (200 ㎒, Acetone-d_6) 6.58 (s, 2H, -CH_2), 7.84-8.63 (m, 9H, phenyl).

Result and Discussion

The base-catalyzed condensation between 1-alkyl (or phenyl) imidazolidine-2,4,5-trione **2**[1,2] and paraformaldehyde in aqueous solution allowed us a mixture of the expected 1-hydroxymethyl derivative **3** and **2**. However, the unstability of **3** made its isolation very difficult. The use of column chromatography as a method of purification failed, whatever the eluent or support (silica gel, alumina) used, because the R_f value is the same for the two compounds. For this reason, the next chlorination step, using a large excess of thionyl chloride, was realized starting directly from a mixture of **3** and **2**. The chlorinated precursor **4** was easily isolated by column chromatography (silica gel, CH_2Cl_2) and the product has a much higher R_f value than the starting material. When chlorinated products **4** were allowed to react with 1,2-benzisothiazole-3-one-1,1-dioxide, saccharin derivatives **5** containing imidazolidine-2,4,5-trione group were obtained in good yields as shown in the Table 1.

In addition, to synthesize plausible new agrochemicals containing **S** atom, we selected 1-methylthiourea **8** in behalf of 1-methylurea **1** as a starting material. As shown in **Scheme 1**, reaction of 1-alkyl(or phenyl)-2-thioxo-imidazolidine-4,5-dione **9** and paraform aldehyde in aqueous solution allowed us alkyl(or phenyl) a mixture of the expected 1-hydroxymethyl derivative **10** and **9**. After chlorination step by treatment of a large excess of thionyl chloride, 1-alkyl(or phenyl)-2-thioxo-3-(1,1,3-trioxo-1,3-dihydro-1^6-benzo[*d*]isothiazol-2-ylmethyl)-imidazolidine-4,5-dione **12** as final products was formed by reaction of synthesized chlorinated products **11** with saccharin (Table 2).

We also tried to obtain various saccharin derivatives, but the reaction of saccharin and 1-chloroethyl-4-methylimidazolidine-2,4,5-trione **6** synthesized by using dichloroethane with triethylamine did not occur. It was found that attempted the reaction of 1- alkyl(or phenyl)imidazolidine-2,4,5-trione **2** and 2-chloromethyl-1,1-dioxo-1,2-dihydro-1^6-benzo[*d*]isothiazol-3-one **13** formed by 2-(hydroxymethyl) saccharin with thionyl chloride, but we did not obtain compound **5**.

We also attempted to synthesize compound **15** from 3-chlorobenzo[*d*]isothiazole-1,1-dioxide (BID-Cl) **14** and compound **2**, but we did not gain compound **15**.

Biological tests for the phytocides, herbicides, and insecticides of the new saccharin derivatives **5** and **12** containing imidazolidine- 2,4,5-trione or 2-thio-imidazolidine-4,5-dione group are in progress.

Table 1. Physical data from imidazolidine-2,4,5-triones 2 to saccharin derivatives 5

Entry	Reactant	Product	Yield[a]/%	Mp/℃
1	**1a**	**2a**	92	146-147
2	**1b**	**2b**	85	121-123
3	**1c**	**2c**	90	203-204
4	**3a**	**4a**	62	149-150
5	**3b**	**4b**	81	83-84
6	**3c**	**4c**	70	130-131
7	**4a**	**5a**	52	192-193
8	**4b**	**5b**	54	182-183
9	**4c**	**5c**	50	191-192

[a]Yields are isolated yields

Acknowledgement

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Table 2. Physical data from 2-thio-imidazolidine-4,5-diones **9** to saccharin derivatives **12**

Entry	Reactant	Product	Yield[a]/%	Mp/℃
1	**8a**	**9a**	60	108-109
2	**8b**	**9b**	70	77-78
3	**8c**	**9c**	70	168-169
4	**10a**	**11a**	45	97-98
5	**10b**	**11b**	50	108-109
6	**10c**	**11c**	40	215-216
7	**11a**	**12a**	40	173-174
8	**11b**	**12b**	49	157-158
9	**11c**	**12c**	30	170-171

[a]Yields are isolated yields

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초록 : Imidazolidine-2,4,5-trione 혹은 2-thio-imidazolidine-4,5-dione기를 포함하는 새로운 saccharin 유도체의 합성

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활성있는 새로운 농약을 창출하기 위해, saccharin 모체에 imidazolidine-2,4,5-trione과 2-thio-imidazolidine-4,5-dione 기를 도입시켰다. 각 saccharin 유도체들은 1-치환된 urea (혹은 1-치환된 thiourea)와 oxalyl chloride의 반응을 시작으로 4단계를 거쳐 합성하였다. 1-치환된 urea를 사용해서 1-치환된-3-(1,1,3-trioxo-1,3-dihydro-1^6-benzo[d]isothiazol-2- ylmethyl)-imidazolidine-2,4,5-trione **5a**, **5b**, **5c**를 합성하였고, 1-치환된 thiourea를 사용하여 1-치환된-2-thioxo-3-(1,1,3-trioxo-1,3-dihydro-1^6-benzo[d]isothiazol-2-ylmethyl)-imidazolidine-4,5-dione **12a**, **12b**, **12c**를 합성하였다.