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Synthesis and Activity Evaluation of Imidazolidinetrionylsaccharin Derivatives

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Abstract

1-Methyl-3-(1,1,3-trioxo-1,3-dihydro-1 λ^6-benzo[*d*]isothiazol-2-ylmethyl)-imidazolidine-2,4,5-triones **5a,** 1-ethyl-3-(1,1,3-trioxo-1,3-dihydro-1 λ^6-benzo[*d*]isothiazol-2-ylmethyl)-imidazolidine-2,4,5-triones **5b,** 1-phenyl-3-(1,1,3-trioxo-1,3-dihydro-1 λ^6-benzo [*d*]isothiazol-2-ylmethyl)-imidazolidine-2,4,5-triones **5c** were obtained by means of 4 reaction steps involved the reaction of 1-methyl-urea and oxalyl chloride. Biological tests(Plant Response Screening Result, Insect Primary Screening Result and Fungicide Primary Screening Result) of synthesized sacccarin derivatives were executed.

Key words – agrochemicals, saccharin, imidazolidinetrione group, biological activity

Introduction

Saccharin derivatives have been widely studied for the use of phytocides, herbicides and insecticides. Imidazolidine-2,4,5-triones are known for their herbicide, plantgrowth regulator and fungicide properties[1,4-6]. In the development of new agrochemical, we chose to associate benzisothiazole and imidazolidine-2,4,5-trione 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** to introduce 1,2-benzisothiazole-3-one-1,1-dioxide (Saccharin). The unstability of **3** made its isolation very difficult and R_f value is the same for 2 and 3. So the next chlorination step was realized starting directly from a mixture of 2 and 3.

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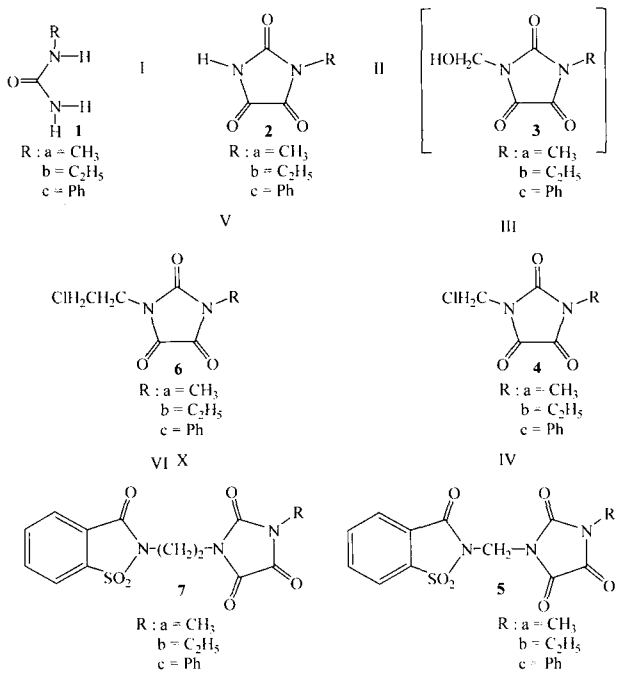
Materials and Methods

The typical experimental procedure for 1-phenyl-3-(1,1,3-trioxo-1,3-dihydro-1 λ^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 temprature for 30 minutes. After 30 minutes, the reaction mixture was refluxed at 55~60℃ for 5 hrs. 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 chro-matography on silica gel eluted with only CH_2Cl_2, to provide the 1-phenyl-3-(1,1,3-trioxo-1,3-dihydro-1 λ^6-benzo[*d*]isothiazol-2-ylmethyl)-imidazolidine-2,4,5-trione **5c** as a white crystalline solid (1.93 g, 50%). mp 191-192



Reagents and reaction conditions; (I) Benzene, r.t, COCICICO (II) $(CH_2O)a$, K_2CO_3 (III) $SOCl_2$ (IV) saccharin, THF, TEA (V) $ClCH_2CH_2Cl$, TEA (VI) saccharin, THF, TEA.

Scheme 1. Synthesis of saccharin derivatives 5 using 1-chloromethyl precursor 4.

℃; ^{1}H NMR (200 ㎒, $CDCl_3$) δ 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.

The yield , mp, IR, and ^{1}H NMR of the synthesized products 2a~5a are as follows.

1-Methyl-imidazolidine-2,4,5-trione 2a. yield 92%; mp 146-147℃; IR (ν, 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 (ν, 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 (ν, KBr, cm^{-1}) 3245, 3066, 1793, 1736; ^{1}H NMR (200 ㎒, DMSO-d_6) δ 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 (ν, 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 ㎒, $CDCl_3$) δ 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 (ν, 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 ㎒, $CDCl_3$) δ 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 (ν, 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 ㎒, $CDCl_3$) δ 5.6 (s, 2H, CH_2Cl), 7.4-7.5 (m, 5H, phenyl). **1-Methyl-3-(1,1,3-trioxo- 1,3-dihydro-1 λ^6-benzo [*d*]isothiazol-2-ylmethyl)-imidazolidine-2,4,5-trione 5a.** yield 40%; mp 192-193℃; IR (ν, 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) δ 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 λ^6-benzo[*d*]isothiazol-2-yl-methyl)-imidazolidine-2,4,5-trione 5b.** yield 54%; mp 182-183℃; IR (ν, 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) δ 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 λ^6-benzo[*d*] isothiazol-2-ylmethyl)-imidazolidine-2,4,5-trione 5c**: yield 50%; mp 191- 192℃; IR (ν, 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 ㎒, $CDCl_3$) δ 5.84 (s, 2H, CH_2), 7.4-8.1 (m, 9H, phenyl).

Result and Discussion

In the development of new agrochemical, we chose to

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.

associate benzisothiazole and imidazolidine- 2,4,5-trione groups as a new structure in which each part would serve as an active component for the desired property. In order to obtain a new agrochemical, we planned first to synthesize a chlorinated precursor **4** to introduce 1,2-benzisothiazole-3-one-1,1-dioxide.

The base-catalyzed condensation between 1-alkyl(or phenyl) imidazolidine-2,4,5-trione **2**[2,3] and para-formaldehyde 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.

We also tried to obtain various saccharin derivatives, but the reaction of saccharin and N-chloroethyl-N'-methylimidazolidinetrione **6** synthesized by using dichloroethane with triethyamine did not occur. It was found that compound **4** is more reactive than compound **6**.

Biological activities such as plant response screening result, insect primary screening result, and fungicide primary screening result of the new sacchrin derivatives (5a-c) containing 2,4,5-imidazolidinethrione group are as follows.

Biological tests were executed at Dongbu Agropharma Research Institute. As shown in Table 2~4, we didn't

Table 2. Plant Response Screening Result

CHEMICAL REF.	RATE (Kg/HA)	ORYSA (3LEAF)	ORYSA (SEED)	ECHOR	SCPJU	MOOVA	CYPSE	SAGPY
5a	4.00	0	0	0	0	0	0	0
5b	4.00	0	0	0	60	60	80	0
5c	4.00	0	0	0	0	0	0	0

Table 3. Insect Primary Screening Result

CHEMICAL REF.	CONC. (PPM)	BPH	GPA	RW	DBM	TCW	TSSM	REMARK
5a	500	0	10	-	0	20	16	·
5b	500	0	0	-	0	0	0	·
5c	500	5	10	-	0	20	0	·

Table 4. Fungicide Primary Screening Result

CHEMICAL REF.	CONC. (PPM)	BPH	GPA	RW	DBM	TCW	TSSM	REMARK
5a	100	25	0	0	0	13	0	·
5b	100	8	0	0	0	0	0	·
5c	100	0	10	0	0	26	0	·

obtain results of good biological activity. However, to obtain new agrochemical having good biological activity, continually we will try synthesis of saccharin derivatives containing 2,4,5-imidazolidine-trione group.

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초록 : Imidazolidinetrionylsaccharin 유도체의 합성 및 활성평가

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새로운 농약을 창출하기 위해, thiazole 유도체 등에서 살균력이 존재하는 구조를 가진 1,2-benzisothiazole-3-one-1,1-dioxide를 선도물질로 imidazolidinetrionyl 기를 가진 새로운 화합물을 합성하였다. 1-methylurea와 oxalyl chloride의 반응으로부터 4단계 반응을 거쳐 1-methyl-3-(1,1,3-trioxo-1,3-dihydro-1 λ^6-benzo [*d*]isothiazol-2-ylmethyl)-imidazolidine-2,4,5-triones **5a,** 1-ethyl-3-(1,1,3-trioxo-1,3-dihydro-1 λ^6-benzo[*d*] isothiazol-2-ylmethyl)-imidazolidine-2,4,5-triones **5b,** 1-phenyl-3-(1,1,3- trioxo-1,3-dihydro-1 λ^6-benzo[*d*] isothiazol-2-ylmethyl)-imidazolidine-2,4,5-triones **5c**를 합성하였다. 합성된 **5a, 5b, 5c**를 식물반응, 곤충 그리고 살균제 등에 대한 생물학적 반응검색을 하였다. 생물학적 반응검색 결과(식물반응 검색은 5b, 곤충검색은 5a, 그리고 살균제 검색은 5a에서 생물활성이 조금 나타남) 썩 좋은 반응결과를 얻지 못했다. 하지만 계속해서 2,4,5-imidazolidinetrionyl기를 가진 saccharin유도체를 합성하여 새로운 농약을 창출하고자 한다.