SYNTHESIS OF 2,4-DIOXOIMIDAZOLIDINES FROM 2-ARYLIMINO-1,3-THIAZINES AND THEIR ANTIFUNGAL ACTIVITY

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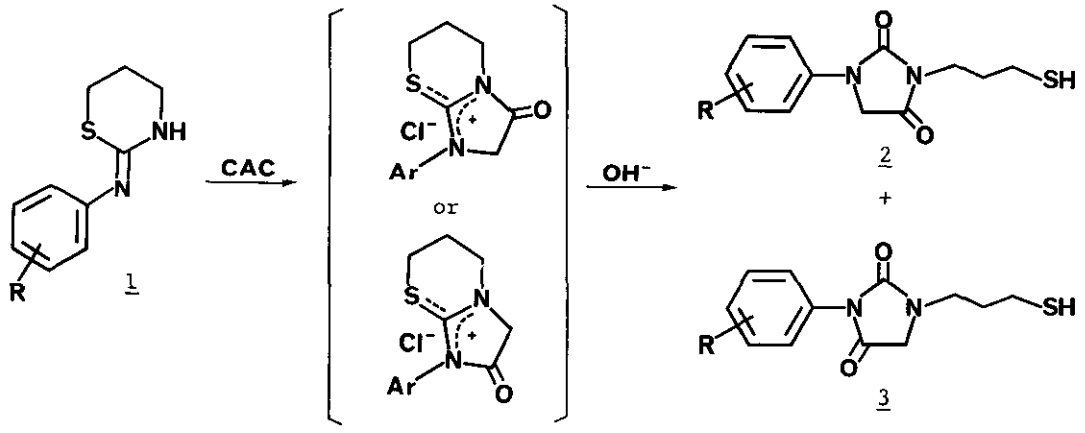
Abstract —— 2,4-Dioxoimidazolidines were obtained by the reaction of 2-arylimino-1,3-thiazines with chloroacetyl chloride (CAC) under aqueous alkaline conditions. Some derivatives of 2,4-dioxoimidazolidines exhibited antifungal activity against downy mildew.

In a previous paper[1], we reported that two regioisomers of mesoionic imidazolones were obtained by the reaction of 2-arylimino-1,3-thiazines 1 with CAC.
Here we wish to report another type of the reaction which gave 2,4-dioxoimidazolidines 2 and 3 under aqueous alkaline conditions (Scheme 1).



Scheme 1

The reaction of 1 with CAC gave oxoimidazolinium salt intermediates which were converted to either 2 and 3 by hydrolysis or mesoionic imidazolones by base-catalyzed deprotonation and subsequent electrophilic attack of CAC. Generally, trihetero-substituted carbonium ions have two reactive sites toward nucleophiles, i.e., the electron-deficient central carbon atom and the ring methylene carbon atom[2-4].

In this case, OH^- attacked the central carbon atom of the intermediates to give 2 and 3 in the yields shown in Table 1. Table 2 shows the yields of 2a and 3a under various conditions, indicating that the yield of 2a increases under weaker basic conditions. The reaction time was not so important; vigorous stirring increased the yields of 2 and 3. Two mesoionic regioisomers were formed under aqueous sodium or potassium hydroxide conditions. For example, 2-chloroacetyl-6,7-dihydro-1-phenyl-5H-imidazolo-[2,3-b][1,3]thiazinylium-3-olate and 3-chloroacetyl-2-olate[1] were formed under aqueous sodium hydroxide conditions (Run 5) in 15% and 16% yields, respectively.

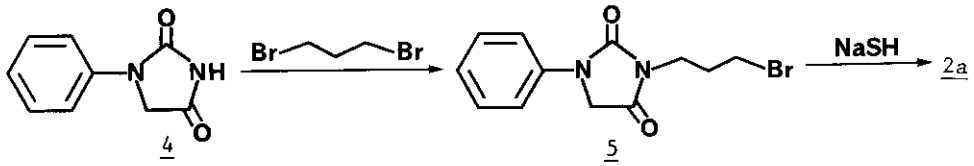
Table 1. Reactions of 1a-c with CAC under aqueous potassium carbonate conditions

Compound	R	K_2CO_3 (eq)	Reaction time, h	Yield (%) 2	3
1a	H	3	1	39	7
1b	4-F	2	48	41	14
1c	4-Me	2	1	22	10

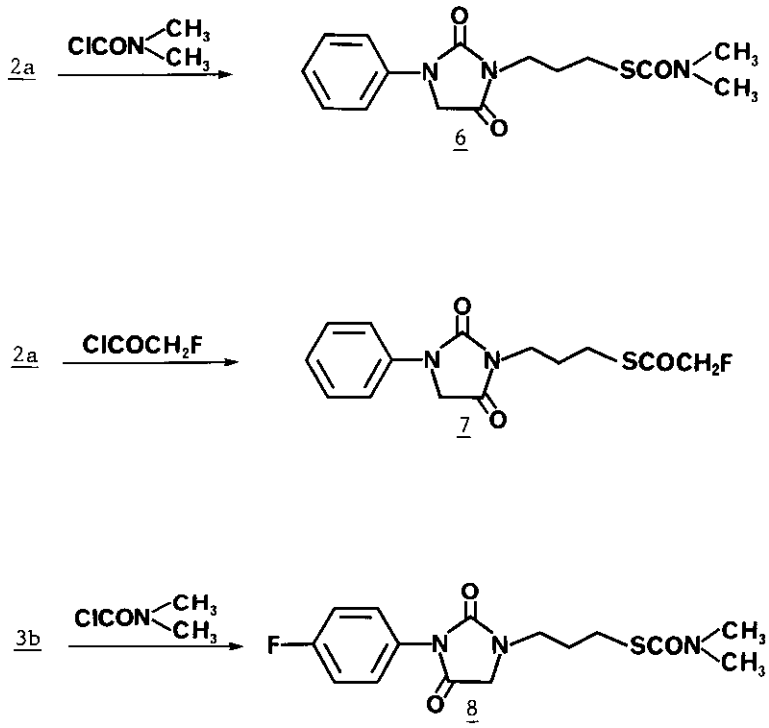
Table 2. Reactions of 1a with CAC under various conditions

Run	Base (eq)	Reaction time, h	Yield (%) 2a	3a
1	$NaHCO_3$ (4)	1	41	Trace
2	Na_2CO_3 (3)	1	33	2
3	K_2CO_3 (2)	0.05	37	Trace
4	K_2CO_3 (2)	1	35	Trace
5	NaOH (4)	1	7	Trace
6	KOH (4)	1	7	1

The structures of 2 and 3 were assigned on the basis of their ^1H nmr spectra. 2,4-Dioxoimidazolidines 2 and 3 showed markedly different ^1H nmr chemical shifts for the C_5-proton: 4.23-4.26 ppm and 3.96-4.00 ppm, respectively. The distinct downfield shifts of the C_5-proton signal in 2 were due to the anisotropic deshielding of the aromatic ring. Furthermore, the physical properties of 2a were identical with those of the product prepared by an independent route (Scheme 2).



Scheme 2



Scheme 3

Some 2,4-dioxoimidazolidines act as fungicides[5], but they are not very effective against Phycomycetes pathogens. Some of the derivatives (Scheme 3) that were prepared by the reaction with N,N-dimethylcarbamoyl chloride or fluoroacetyl chloride exhibited antifungal activity against Pseudoperonospora cubensis (Table 3). Compounds 6 and 7 had not only preventive activity, but also curative activity.

Table 3. Antifungal activity against P. cubensis (downy mildew of cucumber)

Compound	Protective values (%)[a]					
	Preventive activity			Curative activity		
(ppm)	125	31.3	7.8	125	31.3	7.8
6	75	75	20[b]	75	55	30
7	60	50	40[b]	75	-	70
	100	100	100[c]			
8	40	0	0[b]	0	0	0

[a] Protective value (%)=(1-(A/B))x100, where A represents the percentage of disease on treated plants (each chemical was treated on upper leaf surface) and B represents that on untreated plants.

[b] Inoculation of fungus to the under leaf surface.

[c] Inoculation of fungus to the upper leaf surface.

EXPERIMENTAL

All melting points are uncorrected. ^{1}H and ^{13}C nmr spectra were obtained on a JEOL JNM-PMX 60Si spectrometer with TMS as the internal standard. Ir spectra were measured on a Hitachi 260-10 infrared spectrometer. Mass spectra were measured on a Hitachi RMU-8GN mass spectrometer. Satisfactory elemental analyses were obtained for all new compounds.

General Method for Preparation of 1-Aryl-3-(3-mercaptopropyl)-2,4-dioxoimidazolidine (2a-c) and 3-Aryl-1-(3-mercaptopropyl)-2,4-dioxoimidazolidine (3a-c). The results are summarized in Table 1. CAC (30 mmol) was added dropwise to a mixture of 2-aryl-imino-1,3-thiazines 1a-c (10 mmol), methylene chloride (30 ml) and aqueous alkaline solution (K_2CO_3 (30 mmol)/H_2O (20 ml)) at 0°C with vigorous stirring. Stirring was continued at room temperature for each reaction time then the reaction mixture was extracted with methylene chloride, and dried over anhydrous sodium sulfate. The extract was concentrated, and the residue was chromatographed on silica gel. The fraction eluted with methylene chloride gave 2a-c. The second fraction eluted with methylene chloride-methanol (30:1) gave 3a-c. The reactions of 1a (0.01 mol) with CAC (0.02 mol) under various conditions were carried out in the same procedure as described above, and the results are shown in Table 2.

3-(3-Mercaptopropyl)-1-phenyl-2,4-dioxoimidazolidine (2a) ——— Mp 87-90°C (from benzene); ir ($CHCl_3$) 1770, 1710 (C=O) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.56 (1H,t,J=8Hz), 2.02 (2H,m), 2.56 (2H,m), 3.70 (2H,t,J=6Hz), 4.27 (2H,s), 7.0-7.6 (5H,m); ms m/z: 250 (M^+).

1-(3-Mercaptopropyl)-3-phenyl-2,4-dioxoimidazolidine (3a) ——— $n^{22.4}_D$=1.5860; ir ($CHCl_3$) 1775, 1720 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$)δ 1.53 (1H,t,J=8Hz), 1.89 (2H,m), 2.53 (2H,m), 3.57 (2H,t,J=7Hz), 3.98 (2H,s), 7.58 (5H,s); ms m/z: 250 (M^+).

1-(4-Fluorophenyl)-3-(3-mercaptopropyl)-2,4-dioxoimidazolidine (2b) ——— Mp 56-57°C (from benzene-n-hexane); ir ($CHCl_3$) 1775, 1715 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$)δ 1.59 (1H, t,J=8Hz), 2.01 (2H,m), 2.57 (2H,m), 3.70 (2H,t,J=7Hz), 4.28 (2H,s), 6.9-7.7 (4H,m); ms m/z: 268 (M^+).

3-(4-Fluorophenyl)-1-(3-mercaptopropyl)-2,4-dioxoimidazolidine (3b) ——— Mp 49-51°C (from benzene-n-hexane); ir ($CHCl_3$) 1775, 1715 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$)δ 1.54 (1H, t,J=8Hz), 1.93 (2H,m), 2.58 (2H,m), 3.57 (2H,t,J=7Hz), 4.00 (2H,s), 7.0-7.6 (4H,m); ms m/z: 268 (M^+).

3-(3-Mercaptopropyl)-1-(4-methylphenyl)-2,4-dioxoimidazolidine (2c) ——— Mp 87-89°C (from benzene-n-hexane); ir ($CHCl_3$) 1765, 1710 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$)δ 1.55 (1H, t,J=8Hz), 1.89 (2H,m), 2.33 (3H,s), 2.53 (2H,m), 3.70 (2H,t,J=7Hz), 4.28 (2H,s), 6.9-7.4 (4H,m); ms m/z: 264 (M^+).

1-(3-Mercaptopropyl)-3-(4-methylphenyl)-2,4-dioxoimidazolidine (3c) ——— $n^{21.0}_D$=1.5602; ir ($CHCl_3$) 1775, 1710 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$)δ 1.55 (1H,t,J=8Hz), 1.89 (2H,m), 2.33 (3H,s), 2.53 (2H,m), 3.56 (2H,t,J=7Hz), 3.96 (2H,s), 7.26 (4H,s); ms m/z: 264 (M^+).

Preparation of 2a from 1-Phenyl-2,4-dioxoimidazolidine (4). To a solution of 1-phenyl-2,4-dioxoimidazolidine 4 (3.52 g, 20 mmol) in DMF (100 ml), 60% sodium hydride (0.88 g, 22 mmol) was added at 0°C under argon atmosphere. After stirring was continued at room temperature for 30 min, a solution of 1,3-dibromopropane (4.44 g, 22 mmol) in DMF (30 ml) was added dropwise to the mixture at room temperature during 2 min and the mixture was stirred for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was treated with 1 N hydrochloric acid and extracted with chloroform. The extract was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated. The residue was chromatographed on silica gel with chloroform and gave a solid which was recrystallized from benzene-n-hexane to afford 5 (2.84 g, 48%), mp 102.5-104°C; ir ($CHCl_3$) 1775, 1715 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$)δ 2.25 (2H,m), 3.43 (2H,t,J=7Hz), 3.75 (2H,t,J=7Hz), 4.28 (2H,s), 7.0-7.7 (5H,m).

To a solution of 70% sodium hydrosulfide hydrate (0.54 g, 6.7 mmol) in DMF (30 ml), compound 5 (1.00 g, 3.4 mmol) was added and the mixture was stirred for 30 min at room temperature under argon atomosphere. After addition of 1 N hydrochloric acid the solution was extracted with methylene chloride. The extract was washed with saturated

sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated. The residue was chromatographed on silica gel with chloroform and gave a solid which was recrystallized from benzene to afford 2a (0.48 g, 56%).

Preparation of S-3-(1-Phenyl-2,4-dioxoimidazolidin-3-yl)propyl Dimethylthiocarbamate (6). To a solution of 2,4-dioxoimidazolidine 2a (0.45 g, 1.8 mmol) and pyridine (1 ml) in methylene chloride (5 ml), N,N-dimethylcarbamyl chloride (0.29 g, 2.7 mmol) was added at room temperature with stirring. After 17 h, the reaction mixture was acidified with 1 N hydrochloric acid and extracted with methylene chloride. The extract was washed with water, dried over anhydrous sodium sulfate, and concentrated. The residue was chromatographed on silica gel. The fraction eluted with chloroform gave 6 (0.51 g, 88%), mp 117-119°C (from benzene-n-hexane); ir ($CHCl_3$) 1772, 1715, 1650 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.00 (2H,m), 2.96 (1H,t,J=7Hz), 2.97 (6H,s), 3.70 (2H,t, J=7Hz), 4.28 (2H,s), 7.1-7.7 (5H,m); ms m/z: 321 (M^+).

S-3-(3-(4-Fluorophenyl)-2,4-dioxoimidazolidin-1-yl)propyl Dimethylthiocarbamate (8). Compound (8) was obtained by the same procedure as described above in 80% yield, $n_D^{24.0}$=1.5592; ir ($CHCl_3$) 1775, 1720, 1650 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$)δ 1.93 (2H,m), 2.95 (2H,t,J=7Hz), 3.00 (6H,s), 3.56 (2H,t,J=7Hz), 4.07 (2H,s), 7.0-7.6 (4H,m); ms m/z: 339 (M^+).

Preparation of 3-(3-Fluoroacetylthiopropyl)-1-phenyl-2,4-dioxoimidazolidine (7). To a solution of 2,4-dioxoimidazolidine 2a (0.50 g, 2 mmol) and triethylamine (0.40 g, 4 mmol) in THF (10 ml), fluoroacetyl chloride (0.30 g, 3 mmol) in THF solution (5 ml) was added at room temperature with stirring. After 30 min, the reaction mixture was poured into water and extracted with chloroform. The extract was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated. The residue was recrystallized from benzene-n-hexane to afford 7 (0.55 g, 89%), mp 104-105°C; ir ($CHCl_3$) 1770, 1715 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.02 (2H,m), 3.03 (2H,t, J=7Hz), 3.72 (2H,t,J=7Hz), 4.33 (2H,s), 4.90 (2H,d,J=47Hz), 7.2-7.7 (5H,m); ms m/z: 310 (M^+).

ACKNOWLEDGEMENT

We wish to express our thanks to Dr. Y. Hayashi, Director of Aburahi Laboratories, for his support and encouragement. We also wish to express our thanks to Dr. T. Hatta for his invaluable discussion and encouragement. We are also indebted to Mr. T. Murashi for his skilled technical assistance.

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Received, 1st July, 1988