Reaction of *N*-Hydroxymethylsaccharin with Aliphatic Carboxylic Acid Derivatives: Synthesis of *N*-Acylsaccharins and *N*-(Saccharinylmethyl) Aliphatic Carboxylates

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N-Acylsaccharins and *N*-(saccharinylmethyl)aliphatic carboxylates were synthesized from *N*-hydroxymethylsaccarin and aliphatic carboxylic acid chlorides (or anhydrides).

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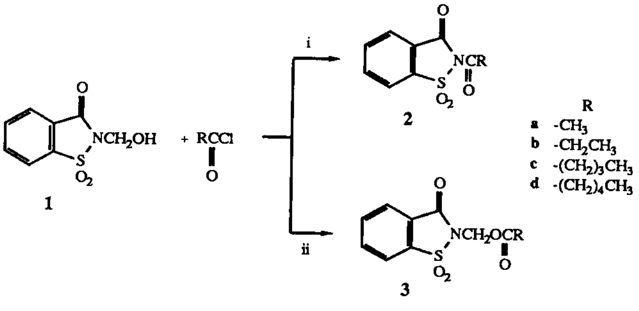
As a part of a continuous program to develop novel fungicides, we attempted to synthesize *N*-substituted saccharins, such as *N*-acylsaccharins and *N*-(saccharinylmethyl)carboxylates.

In this paper, we would like to report the synthesis of *N*-acylsaccharins and *N*-(saccharinylmethyl)aliphatic carboxylates from *N*-hydroxymethylsaccharin (**1**) and aliphatic carboxylic acid chlorides and anhydrides.

N-Hydroxymethylsaccharin (**1**) was prepared by a slight modification of the method reported by Böhme [1]. Reaction of **1** with aliphatic acyl chlorides in the presence of pyridine in acetone gave the corresponding *N*-acylsaccharins **2a-2d** as unusual products instead of the corresponding ester compounds **3a-3d** in good yield.

Scheme I



1

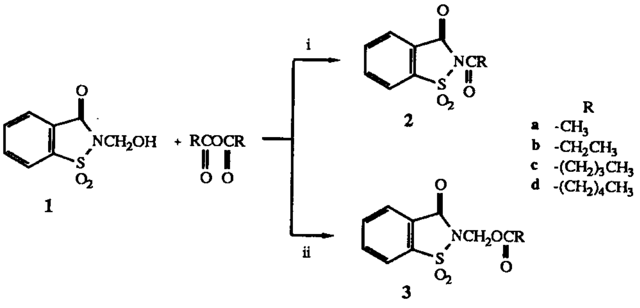
2

3

i) Method A, ii) Method D.

On the other hand, the reaction of **1** with acid chlorides without pyridine in acetone gave the corresponding ester compounds **3a-3d** as the major product. We have also attempted to synthesize compounds **2a-2d** and **3a-3d** from **1** and aliphatic carboxylic acid anhydrides. Reaction of **1** with the corresponding aliphatic acid anhydrides in the presence of pyridine in acetone gave *N*-acylsaccharins **2a-2d**, whereas reaction of **1** with the corresponding aliphatic carboxylic acid anhydrides in the presence of phosphoric acid afforded the corresponding esters **3a-3d**.

Scheme II



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i) Method B, ii) Method C.

It was easy to distinguish between *N*-acylsaccharins and *N*-(saccharinylmethyl)carboxylates on the proton nuclear magnetic resonance spectra. The peak as a singlet of two protons of the methylene for *N*-(saccharinylmethyl)carboxylates were at 5.76 to 6.30 ppm.

In order to prove the mechanistic aspects for the synthesis of *N*-acylsaccharins from **1** and acid chlorides (or anhydrides) in the presence of pyridine, *N*-hydroxymethylsaccharin (**1**) was treated with pyridine in acetone to give saccharin in good yield. Reaction of saccharin with acetic anhydride or acetyl chloride in acetone also gave *N*-acetylsaccharin (**2a**) in good yield. The formation of *N*-acylsaccharin from **1** and an acid chloride (or an anhydride) may be regarded that they occur *via* a saccharin anion or saccharin itself that are generated by the decomposition of *N*-hydroxymethylsaccharin (**1**). Many examples of the synthesis of *N*-acylsaccharins from the saccharin anion and an acid chloride or anhydride are actually known [2].

On the other hand, we attempted to convert *N*-(saccharinylmethyl) acetate (**3a**) to the corresponding *N*-acetylsaccharin (**2a**) in the presence of pyridine in acetone, but we did not obtain *N*-acetylsaccharin (**2a**).

Table 1

Physical and Analytical Data of *N*-Acylsaccharins **2a-2d**

Compound	Yield %	Method	mp °C [a]	Formula	Analysis % Calcd./Found C	H	N
2a	95	A	194-195	$C_9H_7NO_4S$	47.99	3.13	6.22
	95	B	[b]		48.01	3.65	6.35
	81	E					
	94	F					
2b	77	A	212-214	$C_{10}H_9NO_4S$	50.20	3.79	5.85
	82	B	[c]		50.32	3.90	6.01
2c	82	A	113-114	$C_{12}H_{13}NO_4S$	53.92	4.90	5.24
	81	B	[d]		53.88	5.10	5.75
2d	80	A	92-93	$C_{13}H_{15}NO_4S$	55.50	5.37	4.97
	90	B	[e]		55.68	5.82	5.25

[a] Recrystallization from carbon tetrachloride/dichloromethane. [b] Lit [4] mp 196°. [c] Lit [4] mp 212°. [d] Lit [4] mp 215°. [e] Lit [4] mp 92°.

Table 2

Physical and Analytical Data of *N*-(Saccharinylmethyl)carboxylates **3a-3d**

Compound	Yield %	Method	mp °C	Formula	Analysis % Calcd./Found C	H	N
3a	90	C	186-188	$C_{10}H_9NSO_5$	47.05	3.55	5.48
	92	D	[a]		47.36	3.53	5.72
3b	58	C	81-82	$C_{11}H_{11}NSO_5$	49.06	4.12	5.20
	66	D	[a]		49.53	4.50	5.68
3c	67	C	oil	$C_{13}H_{15}NSO_5$	52.51	5.08	4.71
	79	D			52.98	5.68	5.12
3d	50	C	oil	$C_{14}H_{17}NSO_5$	54.01	5.50	4.49
	75	D			54.62	6.10	4.88

[a] Recrystallization from dichloromethane/carbon tetrachloride.

Table 3

Spectral Data of *N*-Acylsaccharins **2a-2d**

Compound	^{1}H-NMR Solvent	(ppm)	IR (cm^{-1}) Potassium bromide disk
2a	Deuteriochloroform	2.8 (s, 3H), 8.3 (m, 4H)	1740, 1715, 1350, 1080
2b	DMSO-d_6	1.00 (t, 3H), 2.96 (q, 2H), 7.66 (m, 4H)	1752, 1730, 1368, 1196
2c	DMSO-d_6	0.64 (t, 3H), 1.28 (m, 4H), 2.50 (t, 2H), 7.86 (m, 4H)	1756, 1740, 1362, 1196
2d	Deuteriochloroform	0.66 (t, 3H), 1.26 (m, 6H), 2.60 (t, 2H), 7.80 (m, 4H)	1754, 1740, 1360, 1196

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were obtained on a Bruker 80 MHz spectrometer with chemical shift values reported in δ units (part per million) relative to an internal standard (tetramethylsilane). Infrared spectral data were obtained on a Hitachi 270-50 spectrophotometer.

Table 4

Spectral Data of *N*-(Saccharinylmethyl)carboxylates **3a-3d**

Compound	^{1}H-NMR (ppm) [a]	IR (cm^{-1})
3a	2.62 (s, 3H), 6.3 (s, 2H), 8.0 (m, 4H)	[b] 1750, 1730, 1370, 1190
3b	1.10 (t, 3H), 2.35 (q, 2H), 5.80 (s, 2H), 7.96 (m, 4H)	[b] 1750, 1729, 1350, 1194
3c	1.10-1.90 (m, 5H), 2.16 (m, 2H), 5.76 (s, 2H), 7.9 (m, 4H)	[c] 1756, 1342, 1200
3d	0.8 (t, 3H), 1.3 (m, 4H), 1.6 (m, 2H), 2.36 (t, 2H), 5.76 (s, 2H), 7.9 (m, 4H)	[c] 1748, 1350, 1194

[a] Solvent, deuteriochloroform. [b] Potassium bromide disk. [c] Neat.

Synthesis of *N*-Hydroxymethylsaccharin (**1**).

A mixture of saccharin (0.1 mole, 18.3 g), 8 ml of formalin (37%) and 60 ml of water was refluxed for 1 hour. The reaction mixture was then cooled to room temperature. The resulting precipitate was filtered and washed with water (20 ml x 3), and dried in air to give compound **1** in 90% (19.2 g), mp 126-127° (lit [1] mp 128°); ^{1}H-nmr (acetone-d$_6$): δ 5.3 (s, 2H), 6.0 (s, 1H), 7.9 ppm (s, 4H).

Synthesis of *N*-Acylsaccharins **2a-2d**.

Method A.

To a solution of *N*-hydroxymethylsaccharin (4.69 mmoles, 1 g) in 10 ml of acetone, an acid chloride (50 mmoles) and pyridine (50 mmoles, 0.4 ml) were added. The mixture was stirred at room temperature for 1 hour. The solvent was evaporated under reduced pressure. The residue was poured into water (20 ml) and basified with potassium carbonate to *p*H 11. The precipitate was filtered and dried in air to give the products **2a-2d**.

Method B.

To a solution of *N*-hydroxymethylsaccharin (**1**, 4.69 mmoles, 1 g) in 10 ml of acetone, a carboxylic acid anhydride (50 mmoles) and pyridine (50 mmoles) were added. The mixture was stirred at room temperature for 1 hour. The solvent was evaporated under reduced pressure. The residue was poured into water (20 ml) and basified with potassium carbonate to *p*H 11. The precipitate was filtered and dried in air to give the products **2a-2d**.

Synthesis of *N*-(Saccharinylmethyl)carboxylates **3a-3d**.

Method C.

A mixture of *N*-hydroxymethylsaccharin (**1**, 4.69 moles, 1 g), a carboxylic acid anhydride (5 ml) and phosphoric acid (85%, 3 drops) were refluxed for 10 minutes with stirring. The reaction mixture was cooled to room temperature, and then poured into water (30 ml). The resulting solution was basified with potassium carbonate to *p*H 11. The product was extracted with methylene chloride (20 ml x 3). After the organic layer was dried with anhydrous potassium carbonate, the solvent was evaporated under reduced pressure to give compounds **3a-3d**.

Method D.

A mixture of *N*-hydroxymethylsaccharin (**1**, 4.69 mmoles, 1 g), the corresponding acid chloride (9.36 moles) and acetone (10 ml) was refluxed for 6-7 hours under a nitrogen atmosphere. After cooling to room temperature, the solvent and excess acid chloride were distilled off under reduced pressure. The residue was poured into water (20 ml). For **3a** and **3b**, the resulting precipitate was filtered, washed with water (10 ml x 5) and dried in air to give compounds **3a** and **3b**. For **3c** and **3d**, the solution was basified with potassium carbonate to *p*H 11. The product was extracted with chloroform or methylene chloride (20 ml x 3). After drying with potassium carbonate (anhydrous), the solvent was evaporated under reduced pressure to give compounds **3c** and **3d** as oils.

Synthesis of Saccharin from *N*-Hydroxymethylsaccharin (**1**).

A mixture of *N*-hydroxymethylsaccharin (**1**, 4.69 mmoles, 1 g), pyridine (5.2 mmoles) and acetone (10 ml) was stirred for 30 minutes at room temperature. The solvent was evaporated under reduced pressure. The residue was poured into cold water (20 ml). The solution was acidified with concentrated hydrochloric acid (1.5 ml). The resulting precipitate was filtered, washed with cold water (10 ml x 3) and dried in air to give saccharin 85% (0.74 g) yield, mp 224-225° (lit [3] mp 224°). The product was identical with an authentic sample.

Synthesis of *N*-Acetylsaccharin from Saccharin.

Method E.

A mixture of saccharin (**4**, 5.5 mmoles, 1 g), acetic anhydride (6.1 mmoles, 0.58 ml) and acetone (15 ml) was refluxed for 1 hour. After cooling to room temperature, the reaction mixture was poured into ice water (50 ml) with stirring. The precipitate was filtered, washed with cold water (10 ml x 3) and dried in air to give *N*-acetylsaccharin (**2a**) in 81% (1.0 g) yield. This product was identical with the compound **2a** which was prepared by methods A and B.

Method F.

A mixture of saccharin (**4**, 5.5 mmoles, 1 g), acetyl chloride (6.05 mmoles, 0.43 ml) and acetone (15 ml) was stirred for 1 hour at room temperature. The reaction mixture was poured into ice water (50 ml) with stirring. The precipitate was filtered, washed with cold water (10 ml x 3) and dried in air to give *N*-acetylsaccharin (**2a**) in 94% (1.16 g) yield.

REFERENCES AND NOTES

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