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N-Benzoylsaccharins, *N*-(saccharinylmethyl) benzoates and *N*-alkylsaccharins were synthesized from *N*-hydroxymethylsaccharin and the corresponding benzoyl chlorides or alkyl halides under different conditions. The reaction mechanisms are also discussed.

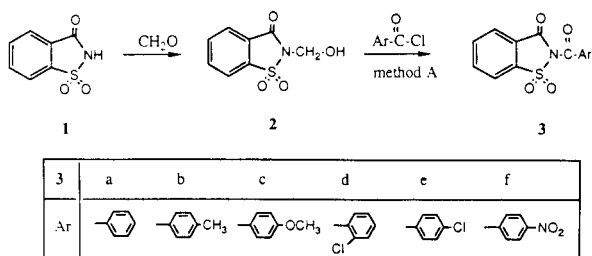
J. Heterocyclic Chem., **30**, 353 (1993).

We previously described [1] the reaction of *N*-hydroxymethylsaccharin (**2**) with aliphatic carboxylic acid derivatives in basic and neutral media. Reaction of **2** with aliphatic carboxylic acid derivatives in basic medium gave the corresponding *N*-acyl derivatives. Therefore, as a part of a continuous program to study the novel reaction of *N*-hydroxymethyl heterocycles containing a carbonyl group at the vicinal position, we investigated the reaction of **2** with benzoyl chlorides and alkyl halides.

In this paper, we would like to report our observations on the title reaction.

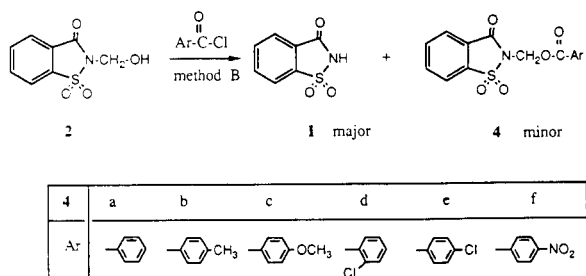
N-Hydroxymethylsaccharin **2** was prepared by a slight modification of the method reported by Böhme [2]. Reaction of **2** with benzoyl chlorides in the presence of pyridine or potassium carbonate in acetone gave the corresponding *N*-benzoylsaccharins **3a-3f** in 80-90% and the unusual products instead of the corresponding ester compounds.

Scheme I



On the other hand, reaction of **2** with benzoyl chlorides under neutral conditions in acetone at reflux temperature [3] gave saccharin (**1**) as the major product and the corresponding ester compounds **4a-4f** as minor products.

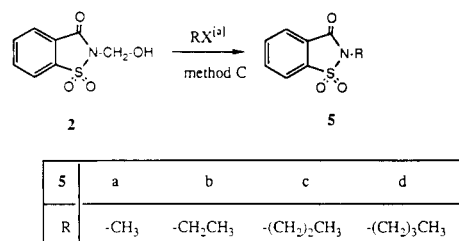
Scheme II



It was easy to distinguish between *N*-benzoylsaccharins **3a-3f** and *N*-(saccharinylmethyl) benzoates **4a-4f** by the proton magnetic resonance spectra. The peak as a singlet of two protons of the methylene for *N*-(saccharinylmethyl) benzoates **4a-4f** was at 5.5 to 6.2 ppm, whereas it was not detected by the proton magnetic resonance spectra for the *N*-benzoyl compounds **3a-3f**.

We also investigated the reaction of **2** with some alkyl halides such as methyl iodide, ethyl bromide, propyl bromide and *n*-butyl chloride. Reaction of **2** with alkyl halides in the presence of potassium carbonate gave the corresponding *N*-alkylsaccharins **5a-5d** in 80-82% yield instead of the corresponding ethers. The proton signal as a singlet of the two protons of the methylene for *N*-CH₂-O was not detected by proton magnetic resonance spectra for compounds **5a-5d**.

Scheme III



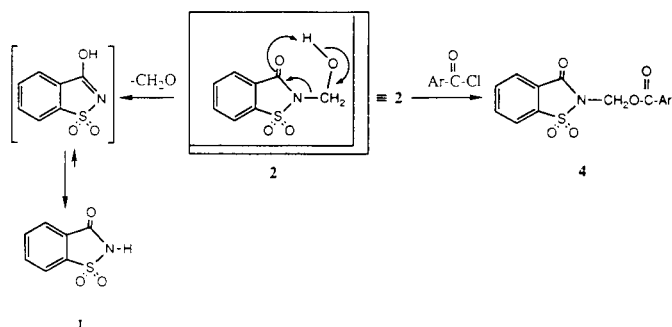
[a] -X : -I for 5a ; -Br for 5b and 5c ; -Cl for 5d

It has already been described by us [1] that the reactions of **2** with aliphatic carboxylic acid derivatives in the presence of base occurs in two steps. The reactions of **2** with benzoyl chlorides and alkyl halides in the presence of base also occur *via* two steps. The first step of these reactions may be regarded as a fragmentation of the retro-ene type in which facile carbon-nitrogen cleavage occurs and the leaving enophile is formaldehyde. Similar fragmentations of the retro-ene type have been reported [4-7]. The second step is the formation of a new nitrogen-carbon bond.

On the other hand, the reaction of **2** with aliphatic carboxylic acid derivatives under neutral condition gave only

ester products [1], whereas the reaction of **2** with benzoyl chlorides under the same conditions afforded saccharin (**1**) as the major product and the corresponding ester compounds as minor products, but *N*-benzoylsaccharins **3** were not detected.

Scheme IV



In order to provide evidence of a mechanism for the results of reaction of **2** with benzoyl chlorides under basic or neutral conditions, we attempted to convert *N*-(saccharinylmethyl) benzoates **4** to saccharin (**1**) or *N*-benzoylsaccharins **3**. According to our previous results [1], treatment of **2** with pyridine in acetone at room temperature gave saccharin (**1**) in good yield. Reaction of **2** with a base such as potassium carbonate or pyridine in acetone at reflux temperature during a short period gave saccharin (**1**) in good yield. The conversion rate of compound **2** to saccharin (**1**) under neutral conditions was also faster at higher temperature than at lower temperatures. Thus, this fragmentation of **2** may be regarded as a base and/or heat promoted retro-ene type reaction. Treatment of *N*-(saccharinylmethyl) benzoates **4** with or without hydrochloric acid in acetone at room or reflux temperature did not give com-

Table 1

Physical and Analytical Data of *N*-Benzoylsaccharins **3a-3f**

Compound	Yield %	Mp °C	Formula	Analysis %		
				Calcd./Found	C	H
3a	87	163-165 [a]	C ₁₄ H ₉ NO ₄ S	58.53	3.16	4.88
				58.23	3.56	4.28
3b	83	179-181 [b]	C ₁₅ H ₁₁ NO ₄ S	59.79	3.68	4.65
				60.04	3.62	4.80
3c	90	136-137 [b]	C ₁₅ H ₁₁ NO ₅ S	56.78	3.49	4.41
				56.38	3.36	4.38
3d	86	163-164 [d]	C ₁₄ H ₈ NO ₄ SCI	52.27	2.51	4.35
				52.62	2.80	4.31
3e	87	203-205 [e]	C ₁₄ H ₈ NO ₄ SCI	52.27	2.51	4.35
				52.61	2.77	4.21
3f	80	182-183	C ₁₄ H ₈ N ₂ O ₆ S	50.61	2.43	8.43
				50.93	2.83	8.35

[a] Lit [8] mp 165°. [b] Lit [8] mp 182°. [c] Lit [8] mp 138°. [d] Lit [8] mp 196°. [e] Lit [8] mp 205°.

Table 2

Physical and Analytical Data of *N*-(Saccharinylmethyl)benzoates **4a-4f**

Compound	Yield %	Mp °C	Formula	Analysis %		
				Calcd./Found	C	H
4a	23	109-110	C ₁₅ H ₁₁ NO ₅ S	56.78	3.49	4.41
				56.85	3.50	4.42
4b	25	102-103	C ₁₆ H ₁₃ NO ₅ S	58.00	3.95	4.23
				58.35	3.95	4.36
4c	22	282-284	C ₁₆ H ₁₃ NO ₆ S	55.33	3.77	4.03
				55.63	3.96	4.21
4d	28	139-140	C ₁₅ H ₁₀ NO ₅ SCI	51.22	2.87	3.98
				51.43	3.03	3.72
4e	22	149-150	C ₁₅ H ₁₀ NO ₅ SCI	51.22	2.87	3.98
				51.52	2.99	3.85
4f	25	141-142	C ₁₅ H ₁₀ N ₂ O ₇ S	49.73	2.78	7.73
				49.87	3.04	7.71

[a] Yield of saccharin as major product was 65-73%.

Table 3

Physical and Analytical Data of *N*-Alkylsaccharins **5a-5d**

Compound	Yield %	Mp °C	Formula	Analysis %		
				Calcd./Found	C	H
5a	80	129-130 [a]	C ₈ H ₇ NO ₃ S	48.72	3.58	7.10
				48.63	3.60	7.21
5b	81	92-93 [b]	C ₉ H ₉ NO ₃ S	51.17	4.29	6.63
				51.36	4.48	6.62
5c	87	71-72	C ₁₀ H ₁₁ NO ₃ S	53.32	4.92	6.22
				53.37	4.98	6.21
5d	82	38-39 [c]	C ₁₁ H ₁₃ NO ₃ S	55.21	5.48	5.85
				55.02	6.30	5.78

[a] Lit [10] mp 131-132°. [b] Lit [10] mp 93.5-94.5°. [c] Lit [10] mp 39-40°.

pond **1** or the corresponding *N*-benzoylsaccharins **3**. Reaction of **1** with benzoyl chlorides in the presence of base afforded the corresponding *N*-benzoylsaccharins **3** in low yields, whereas treatment of **1** with benzoyl chlorides under neutral conditions did not give the corresponding *N*-benzoylsaccharins **3**. An example of the synthesis of *N*-benzoylsaccharins **3** from saccharin sodium salt and benzoyl chlorides is known [8]. We also attempted to convert *N*-benzoylsaccharins **3** to **1**. When *N*-benzoylsaccharins **3** were treated with a catalytic amount of hydrochloric acid at room or at reflux temperature in acetone, we detected saccharin (**1**) and carboxylic acid derivatives on tlc plates.

On the other hand, treatment of **2** with alkyl halides in the presence of potassium carbonate gave the corresponding *N*-alkylsaccharins **5**. Many examples of the synthesis of *N*-alkylsaccharins **5** from the saccharin anion and alkyl

halides are actually known [9].

Finally, reaction of **2** with aliphatic carboxylic acid derivatives, benzoyl chlorides and alkyl halides in the presence of base occurs *via* two steps. The first step is a fragmentation of the *N*-hydroxymethyl groups by a retro-ene type reaction, and the second step is the formation of a new nitrogen-carbon bond. Whereas, the formation reaction of esters from **2** and benzoyl chlorides or aliphatic carboxylic acid derivatives under neutral condition occur *via* one step. The retro-ene type fragmentation of compound **2** occurs to a greater extent than the formation of an ester when compound **2** is reacted with benzoyl chlo-

Table 4
Spectral Data of *N*-Benzoylsaccharins **3a-f**

Compound	(Solvent)	¹ H-NMR (ppm)	IR (cm ⁻¹) (Potassium bromide disk)
3a	A	7.4-8.3 (m, 9H)	3100, 1780, 1710, 1600, 1380, 1190
3b	A	2.5 (s, 3H) 7.2-8.2 (m, 8H)	3100, 1760, 1700, 1600, 1360, 1180
3c	B	3.8 (s, 3H) 7.0-8.7 (m, 8H)	3100, 2900, 1780, 1700, 1600, 1360, 1190
3d	A	7.6-8.8 (m, 8H)	3100, 1780, 1710, 1600, 1380, 1190
3e	A	7.6-8.4 (m, 8H)	3100, 1800, 1740, 1600, 1240, 1080
3f	B	7.8-8.2 (m, 8H)	3100, 1780, 1700, 1600, 1550, 1380, 1330, 1190

A = Deuteriochloroform, B = Deuteriochloroform + DMSO-d₆.

Table 5
Spectral Data of *N*-(Saccharinylmethyl)benzoates **4a-4f**

Compound	(Solvent)	¹ H-NMR (ppm)	IR (cm ⁻¹) (Potassium bromide disk)
4a	A	6.2 (s, 2H) 7.4-8.2 (m, 9H)	3100, 2960, 1749, 1720, 1600, 1350, 1250, 1100
4b	A	2.4 (s, 3H) 6.2 (s, 2H) 7.2-8.2 (m, 8H)	3100, 2950, 1750, 1720, 1600, 1350, 1220, 1080
4c	A	3.7 (s, 3H) 6.0 (s, 2H) 7.0-8.3 (m, 8H)	3100, 2950, 1750, 1720, 1600, 1350, 1250, 1080
4d	A	6.2 (s, 2H) 7.3-8.3 (m, 8H)	3100, 2950, 1780, 1710, 1600, 1370, 1200, 1080
4e	A	5.5 (s, 2H) 7.7-8.2 (m, 8H)	3100, 1760, 1700, 1620, 1370, 1210, 1080
4f	A	6.2 (s, 2H) 7.4-8.3 (m, 8H)	3100, 2950, 1790, 1720, 1550, 1370, 1300, 1220, 1080

A = Deuteriochloroform.

Table 6
Spectral Data of *N*-Alkylsaccharins **5a-5d**

Compound	(Solvent)	¹ H-NMR (ppm)	IR (cm ⁻¹) (Potassium bromide disk)
5a	A	3.2 (s, 3H) 7.6-8.2 (m, 4H)	3100, 2895, 1750, 1600, 1320, 1180
5b	A	2.4 (t, 3H) 3.8 (q, 2H) 7.6-8.2 (m, 4H)	3100, 2990, 1750, 1560, 1380, 1200
5c	A	1.0 (t, 3H) 1.8 (m, 2H) 4.7 (t, 2H) 7.6-8.2 (m, 4H)	3100, 2950, 1750, 1600, 1320, 1190
5d	A	1.0 (t, 3H) 1.2-2.2 (m, 4H) 3.7 (t, 2H) 7.7-8.2 (m, 4H)	3100, 2980, 2900, 1740, 1600, 1350, 1190

A = Deuteriochloroform.

rides under neutral conditions. These results are due to the difference in reactivity of the carbonyl carbon with benzoyl chlorides or with aliphatic carboxylic acid derivatives.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Proton 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. Elemental analyses were performed with a LECO Micro Carbon Hydrogen Determinator (CHN-800). Open-bed column chromatography was carried out silica gel 60 (70-230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent.

Reaction of *N*-Hydroxymethylsaccharin (**2**) with Benzoyl Chlorides.

Method A. Synthesis of *N*-Benzoylsaccharins **3a-3f**.

A mixture of *N*-hydroxymethylsaccharin (**2**, 0.01 mmoles), benzoyl chlorides (0.01 mmoles), pyridine or potassium carbonate (0.01 mmoles) and acetone (30-50 ml) was refluxed for 2 hours with stirring. The reaction mixture was cooled to room temperature and then poured into ice water (200 ml) with stirring. The precipitate was filtered, washed with cold water (100 ml x 2) and dried in air. The crude products were recrystallized from *n*-hexane/chloroform (1:1, v/v) to give the corresponding *N*-benzoylsaccharins **3a-3f**.

Method B. Synthesis of *N*-(Saccharinylmethyl) Benzoates **4a-4f**.

A mixture of compound **2** (0.5 mmole), benzoyl chlorides (0.5 mmole) and acetone (or DMF, THF) (20-30 ml) was refluxed for 4 hours. After cooling to room temperature, the reaction mixture was poured into ice water (100 ml) with stirring. The resulting

precipitate was filtered, washed with water (50 ml x 2) and dried in air. The crude product was dissolved in methanol (2 ml). The solution was applied to an open-bed silica gel column (3.0 x 25 cm). The column was eluted with *n*-hexane/methanol (9.5:0.5, v/v). The fractions containing saccharin (detection using tlc) were combined, and the solvent was evaporated under reduced pressure to give saccharin **1**. The fractions containing the corresponding esters (detection using tlc) were combined, and the solvent was evaporated under reduced pressure to give the corresponding esters **4a-4f**. The crude ester products were recrystallized from ether/cyclohexane (1:1, v/v) to give pure ester compounds **4a-4f**.

Reaction of *N*-Hydroxymethylsaccharin (**2**) with Alkyl Halides.

Method C. Synthesis of *N*-Alkylsaccharins **5a-5d**.

A mixture of *N*-hydroxymethylsaccharin (**2**, 10.3 mmoles), alkyl halide (15.5 mmoles), potassium carbonate (15.5 mmoles) and acetone (40 ml) was refluxed for 5 hours. After cooling to room temperature, the reaction mixture was poured into ice water (500 ml) with stirring. The precipitate was filtered, and dried in air. The crude products were recrystallized from *n*-hexane/chloroform (1:1, v/v) to give pure *N*-alkylsaccharins **5a-5d**.

Reaction of Saccharin (**1**) with Benzoyl Chlorides.

A mixture of saccharin (**1**, 5.5 mmoles, 1 g), benzoyl chlorides (6.0 mmoles) and acetone (15-20 ml) was stirred for 2-3 hours at

room temperature. The reaction mixture was poured into ice-water (50-100 ml) with stirring. The precipitate was filtered, washed with cold water (10 ml x 2) and dried in air to give *N*-benzoylsaccharins **3a-3f** in low yield (7-15%). These products were identical with the compound **3a-3f** which were prepared by method A.

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