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A Synthesis of 4-Thiomethylbenzisothiazolone-1,1-dioxide using HDPT

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Abstract: 4-Thiomethylbenzisothiazolone-1,1-dioxides were synthesized *via* the corresponding 4-methylbenzisothiazolone-1,1-dioxides by a regioselective benzylic bromination, followed by conversion of the bromide to the thiol moiety under mild and neutral reaction conditions using 1-(2-hydroxyethyl)-4,6-diphenylpyridine-2-thione (HDPT). © 1998 Elsevier Science Ltd. All rights reserved.

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Benzisothiazolone-1,1-dioxide is a class of heterocycle that has been continuing to be investigated in pharmaceutical research. Compounds containing the benzisothiazolone-1,1-dioxide nucleus have been explored for use as anti-inflammatory agents,[1] anti-fungal agents,[2] inhibitors of blood platelet aggregation[3] and inhibitors of aldehyde dehydrogenase.[4] *N*-Acyl benzisothiazolone-1,1-dioxides have been examined as potent inhibitors of the serine proteases, trypsin, chymotrypsin, cathepsin G and elastase.[5] Recently, 4,6-disubstituted 2-acyloxymethylbenzisothiazolone-1,1-dioxide has been used as potent and selective mechanism-based inhibitor of human leukocyte elastase.[6] Current literature procedures are mostly limited to the preparation of alkyl and alkoxy substituted benzisothiazolone-1,1-dioxides.[7] Methods to introduce substituents, by functionalization at the benzylic carbon with heteroatoms, that can serve as the side chains of hydrophilic amino acids (*e.g.* those of arginine, serine, threonine, cysteine) are lacking. We have reported the synthesis of 4-hydroxymethylbenzisothiazolone-1,1-dioxide *via* the Diels-Alder reaction between furfuryl alcohol and 2-(*tert*-butyl)-isothiazolone-1,1-dioxide.[8] In this letter we report a method to prepare the related thiol analogues, 2-acyloxymethyl-4-thiomethylbenzisothiazolone-1,1-dioxides **5**.

We envisaged that a fast entry to such compounds would be by derivatization at the benzylic position of 2-acyloxymethyl-4-methylbenzisothiazolone-1,1-dioxides **1** which could be readily prepared by known procedures.[9] Since the arylsulfonamide of **1** is base sensitive, mild and neutral reaction conditions would be preferred for the transformations. As shown in the general sequence in **Scheme 1**, 4-methylsaccharin **1** was brominated using NBS under standard conditions to provide the 4-bromomethyl derivative **2** which was then reacted with 1-(2-hydroxyethyl)-4,6-diphenylpyridine-2-thione **3** (HDPT) using a modification of the protocol developed by Molina and Katritzky[10] to form the pyridinium bromide **4**. Treatment of this salt with silica gel in ethyl acetate gave the desired 4-thiomethylsaccharin **5**. The results of the reactions are summarized in **Table 1**.

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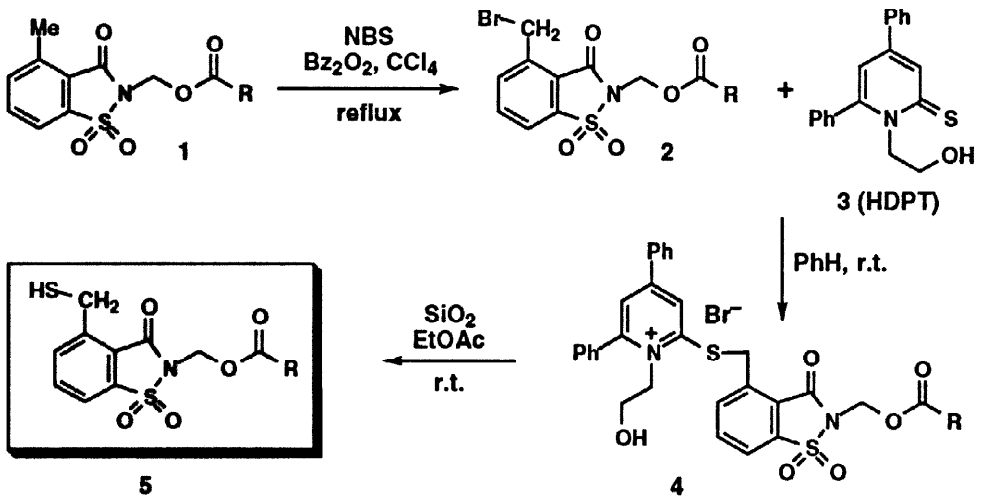
NBS was found to be the most effective for the bromination of 4-methylsaccharin **1** and in general moderate to good yields could be obtained (**Table 1**). Unreacted starting materials were always recovered and in most cases about 10-20% of dibrominated side-products also isolated. Bromination at the formyl carbon was not observed under these conditions and no α-bromination in the reaction of **1a**. The optimal reaction concentration of substrate was found to be about 1 M except that of compound **1f** which was fairly soluble in carbon tetrachloride. Other commonly used radical initiators, like AIBN, did not offer any obvious advantage over benzoyl peroxide.



Scheme 1

To convert the benzylic bromide **2** to the desired 4-thiomethylsaccharin **5**, methods that involving strong basic hydrolysis, *e.g.* those using thiourea,[11] 1-methylpyridine-2-thione,[12] were excluded. The uses of other nucleophilic sulfur reagents, *e.g.* thioacetate,[13] sodium hydrosulfide,[14] were also avoided. We found that the thiolating reagent, HDPT,[15] introduced by Molina and Katritzky[10] ideally served the purpose in that the thiol group was introduced under mild and neutral conditions (PhH, r.t.) without affecting the sensitive arylsulfonamide group. It should be noted that the use of this thiol reagent in organic synthesis is relatively unexplored. Addition of HDPT to the benzyl bromide **2** in benzene at r.t. generated the pyridinium bromide **4** which could be easily isolated as a white solid (**Table 1**). However, unlike the protocol, the salt did not undergo an intramolecular nucleophilic displacement *in situ* to liberate the desired compound **5.** It was found that stirring a mixture of the pyridinium bromide **4** and silica gel in ethyl acetate provided the 4-thiomethylsaccharin **5**.[16] Generally, good yields (**Table 1**) could be obtained except in the reaction of **1f** which was complicated by disulfide formation. Although intramolecular nucleophilic displacement by the appendant hydroxyl group in **4** could operate under these conditions, it is reasonable to assume that the more acidic silanol of the silica gel could also act as the nucleophile to generate thiol **5**.[17]

In summary, we have shown that 2-acyloxymethyl-4-methylbenzisothiazolone-1,1-dioxides could be selectively brominated at the benzylic position and the benzyl bromide could be displaced by using HDPT to provide 2-acyloxymethyl-4-thiomethylbenzisothiazolone-1,1-dioxides.

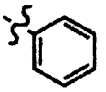
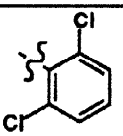
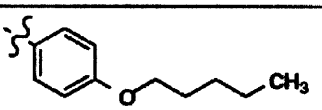
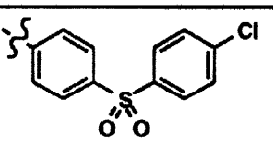
1, R =	2 (yield, %)[a]	4 (yield, %)	5 (yield, %)
a, CH_3	45 (58)[b]	65	40
b, 	59 (69)	71	87
c, 	58 (78)	66	64
d, 	47 (64)	80	67
e, 	34 (55)	65	73
f, 	23 (62)[c]	69	27[d]

Table 1: All yields in this table are isolated yields. a) reaction concentration of substrate ~1 M; yields in parenthesis were based on unreacted starting materials; in most cases about 10-20% of dibrominated side-products were also isolated; bromination at the formyl carbon was not observed. b) no α-bromination. c) substrate concentration ~0.25M. d) disulfide formation also observed.

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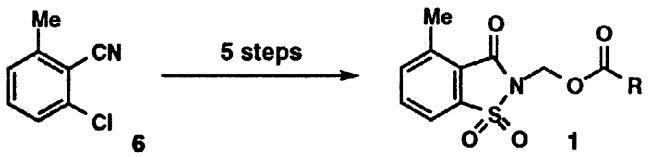
(9) 4-methylbenzisothiazolone-1,1-dioxides **1a-f** were prepared from 2-chloro-6-methylbenzonitrile **6** in 5 steps by a modification of literature procedures: (a) Hirokazu, K.; Hiroshi, G. *Patent*, EP 702008-A2 (Mar. 20, **1996**); (b) Court, J. J.; Lessen, T. A.; Hlasta, D. J. *Synlett* **1995**, 423 and Ref. 7(a).



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(15) HDPT was prepared according to the procedures described in Ref. 10.

(16) **Representative Procedure:** To a solution of the 4-bromomethylsaccharin **2b** (0.95 g, 2.43 mmol) in PhH (86 ml) at ambient temperature under N_2 was added HDPT (0.84 g, 2.73 mmol) and the resulting mixture stirred for 19 h. The precipitate formed was filtered, washed with benzene and dried to give the pyridinium bromide **4b** (1.21 g, 71%) as a white solid. The bromide **4b** was then stirred in EtOAc (40 ml) at ambient temperature under N_2 and silica gel (2.0 g, 230-400 mesh) was added. After stirring for 21 h, the mixture was filtered and the filtrate evaporated *in vacuo*. The crude product was purified by flash column chromatography (50% EtOAc/hexane) to give the 4-thiomethlysaccharin **5b** as a colourless crystalline solid (0.52 g, 87%); R_f = 0.28 (30% EtOAc/hexane); m.p. (uncorrected) 89-90°C; ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.83-7.73 (3H, m, ArH), 5.82 (2H, s, NCH_2), 4.23 (2H, d, J = 8.7 Hz, SCH_2), 2.19 (1H, t, J = 8.7 Hz, SH), 1.21 (9 H, s, ^{t}Bu); $C_{14}H_{17}NO_5S_2$ (343.4120) Calcd. C, 48.97; H, 4.99; N, 4.08. Found C, 49.24; H, 4.86; N, 4.08.

(17) No reaction was observed by TLC analysis when a mixture of **4** in MeCN was stirred at elevated temperature (50°C).