Direct Preparation of Saccharin Skeletons from *N*-Methyl(*o*-methyl)arenesulfonamides with (Diacetoxyiodo)arenes

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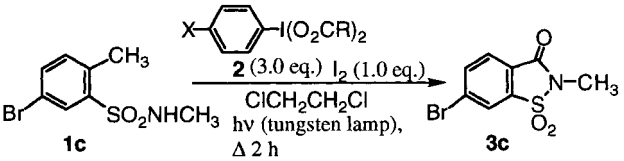
Abstract: Various *N*-methylsaccharins were easily prepared in moderate to good yields by the reaction of *N*-methyl(*o*-methyl)arenesulfonamides with (diacetoxyiodo)arene in the presence of iodine under irradiation with a tungsten lamp. The present method is very useful for the direct preparation of saccharins with *N*-methyl(*o*-methyl)arenesulfonamides containing various substituents on the aromatic ring.

It is well known that many isothiazole derivatives exhibit biological activity in the medicinal and agrochemical fields.[1] Among them, saccharin derivatives, *i.e.*, α-ethyl[3-oxo-1,2-benzisothiazole-2(3H)]-acetamide 1,1-dioxide and 2-[4-[4-(2-pyrimidinyl)piperazinyl]butyl]-3-oxo-1,2-benzisothiazole-2(3H) 1,1-dioxide (Ipsapirone), have potent antibacterial, sedative-hypnotic, anti-anxiety and anticonvulsant activities.[1] Recently, as an orally active bioavailable human leukocyte elastase (HLE) inhibitor, [6-methoxy-4-isopropyl-3-oxo-1,2-benzisothiazole-2(3H)-yl]methyl 2,6-dichloro-3-[2-(4-morpholinyl)-ethoxy]benzoate S,S-dioxide (WIN) series,[2] saccharin-based inhibitors, were found to have potent HLE inhibitory activity. Therefore, extensive studies on the preparation of these skeletons have been carried out, mainly by ortho-lithiation and the subsequent sulfonation of amides or ortho-lithiation and the subsequent carbonation of sulfonamides.[3] Recently, it has been well recognized that radical reactions are quite useful for organic synthesis.[4] However, study on the radical cyclization via nitrogen-centered radicals is limited except the Hofmann-Loeffler-Freytag reaction, *i.e.*, the photolysis of *N*-nitroamine, *N*-cyanamide, and *N*-phosphoramidate derivatives of steroidal compounds[5] and lactams[6] to give the corresponding cyclized compounds via the Hofmann-Loeffler-Freytag type reaction, in the presence of (diacetoxyiodo)benzene and iodine. Thus, a simple and practical synthetic method of various types of saccharin derivatives via a sulfonamidyl radical has been required, in view of their potential as biologically active agents.

Here, as a part of our study on the reactivity of (diacetoxyiodo)arenes as radical precursors,[7] we report the direct preparation of a saccharin skeleton from various *N*-methyl(*o*-methyl)arenesulfonamides with (diacetoxyiodo)arene in the presence of iodine. As a typical procedure, to a solution of *N*-methyl(*o*-methyl)arenesulfonamide (0.5 mmol) in 1,2-dichloroethane (7 ml) were added (diacetoxyiodo)benzene (1.5 mmol) and iodine (0.5 mmol). The mixture was irradiated with a tungsten lamp (500 W) at refluxing temperature for 2 h under an argon atmosphere. After the reaction, the mixture was poured into chloroform and washed with aq. sodium sulfite solution and subsequently with water.

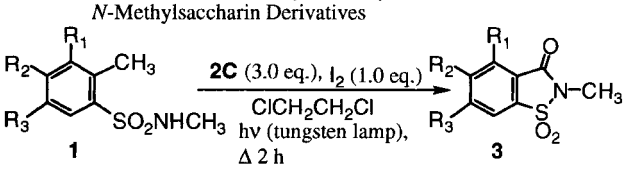
The organic layer was dried over sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel by preparative thin layer chromatography to give the *N*-methylsaccharin in 61% yield. Table 1 shows the substituent effect of (diacetoxyiodo)arenes **2** in the formation of *N*-methylsaccharin **3c** from the compound **1c**. Here, (diacetoxyiodo)benzene (**2C**) showed the best reactivity, while [bis(trifluoroacetoxy)iodo]benzene (**2E**) did not work at all. Table 2 shows the formation of various *N*-methylsaccharins with (diacetoxyiodo)benzene (**2C**) under the same conditions.[8] The reaction also proceeds in ethyl acetate which is a less toxic solvent; however, the

Table 1. Substituent Effect of (Diacyloxyiodo)arenes



Entry	-X	R	**3c** / Yield (%)
1	(**2A**) -OCH_3	-CH_3	29
2	(**2B**) -CH_3	-CH_3	28
3	(**2C**) -H	-CH_3	80
4	(**2D**) -Cl	-CH_3	63
5	(**2E**) -H	-CF_3	0
6	(**2F**) -H	-CH_2CH_3	29

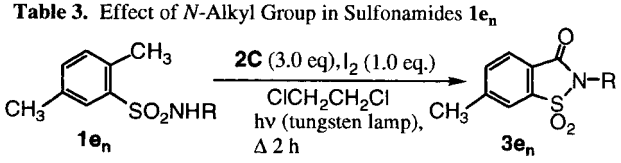
Table 2. Conversion of *N*-Methyl(*o*-methyl)arenesulfonamides to the *N*-Methylsaccharin Derivatives



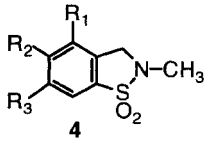
Entry	R_1	R_2	R_3	**3** / Yield (%)
1	H	H	H	61 (**3a**)
2	H	H	H	0[a] (**3a**)
3	H	CH_3	H	84 (**3b**)
4	H	H	Br	80 (**3c**)
5	H	H	NO_2	48 (**3d**)
6	H	H	CH_3	99 (**3e**)
7	H	H	SO_2CH_3	51 (**3f**)
8	H	H	$CON(C_2H_5)_2$	45 (**3g**)
9	CH_3	H	$C(CH_3)_3$	42 (**3h**)

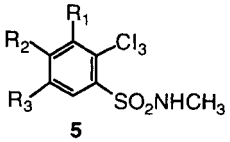
a) Galvinoxyl free radical (1.5 mmol) was added

Table 3. Effect of *N*-Alkyl Group in Sulfonamides $\mathbf{1e_n}$



Entry	-R	$\mathbf{3e_n}$ / Yield (%)
1	-H	0 (**$3e_0$**)
2	-CH_3	99 (**3e**)
3	-CH_2CH_3	33 (**$3e_2$**)
4	-$(CH_2)_3CH_3$	25 (**$3e_3$**)
5	-CH_2Ph	0 (**$3e_4$**)





yield was slightly decreased. The reaction is completely inhibited by the addition of a free galvinoxyl radical (entry 2 in Table 2), while *N*-benzyl- and other *N*-alkyl(*o*-methylarene)sulfonamides did not give the corresponding saccharin derivatives efficiently (Table 3). Here, the compound **4** is not an intermediate which is formed via the Hofmann-Loeffler-Freytag type reaction pathway, because it was not converted to the saccharin skeleton under the same conditions. However, the compound **5** is an intermediate. The reaction of *N*-methyl(*o*-methyl)benzeneamide, instead of *N*-methyl(*o*-methyl)arenesulfonamide, was not clean and gave the *N*-methyl phthalimide in only 25% yield. Thus, the present reaction is very useful for the direct preparation of various *N*-methylsaccharins from *N*-methyl(*o*-methyl)arene-sulfonamides, which are easily prepared by the chlorosulfonation of methylarenes and subsequent amidation with methylamine. Here, the *N*-methyl group in product **3** was easily removed by treatment with excess trimethylsilyl iodide. Study on further elaboration of the method and clarification of the reaction mechanism is now under way.

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References

(1) Davis, M. "Organic Compounds of Sulfur, Selenium, and Tellurium", Vol. 5, Chap 10, Ed by The Chemical Society, London (1979); Pain, D. L.; Peart, B. J.; Wooldridge, K. R. H. "Comprehensive Heterocyclic Chemistry", Eds Katritzky A. R.; Rees, C. W., Vol. 6, Pergamon Press, Oxford (1984); Svahn C. M.; Jönsson, N. Å. *Acta Chem. Scand*., (B), **1978**, 32, 137~140; *Drug of the Future*, **1986**, 11, 565.

(2) Desai. R. C.; Farrell, R. P.; Kuo, G-H.; Hlasta, D. J. *Synlett*, **1994**, 933; Court, J. J.; Lessen, T. A.; Hlasta, D. J. *ibid*., **1995**, 423; Hlasta, D. J.; Subramanyam, C.; Bell, M. R.; Carabateas, P. M.; Court, J. J.; Desai, R. C.; Drozd, M. L.; Eickhoff, W. M.; Ferguson, E. W.; Gordon, R. J.; Johnson, J. A.; Kumar, V.; Maycock, A. L.; Mueller, K. R.; Pagani, E. D.; Robinson, D. T. ; Saindane, M. T.; Silver, P. J.; Subramanian, S. *J. Med. Chem*., **1995**, 38, 739.

(3) Lombardino, J. G. *J. Org. Chem*., **1971**, 36, 1843; Watanabe, H.; Gay, R. L.; Hauser, C. R. *J. Org. Chem*., **1968**, 36, 900; Hlasta, D. J.; Court, J. J.; Desai, R. C. *Tetrahedron Lett*., **1991**, 32, 7179; Desai, R. C.; Hlasta, D. J.; Monsour, G.; Saindane, M. T. *J. Org. Chem*., **1994**, 59, 7161.

(4) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Ed. Baldwin, J. E. Pergamon Press, 1986; Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*, John Wiley & Sons, 1995.

(5) Armas P. de; Carrau, R.; Concepción, J. I.; Francisco, C. G.; Hernández, R.; Suárez, E. *Tetrahedron Lett*., **1985**, 26, 2493; Armas, P. de; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez, E. *J. Chem. Soc., Perkin Trans 1*, **1988**, 3255; Carrau, R.; Hernández, R.; Suárez, E. *J. Chem. Soc., Perkin Trans 1*, **1987**, 937.

(6) Hernández, R.; Medina, M. C.; Salazar, J. A.; Suárez, E. *Tetrahedron Lett*., **1987**, 28, 2533; Dorta, R. L.; Francisco, C. G.; Suárez, E. *J. Chem. Soc., Chem. Commun*., **1989**, 1168.

(7) Togo, H.; Muraki, T.; Yokoyama, M. *Tetrahedron Lett*., **1995**, 36, 7089; Muraki, T.; Togo, H.; Yokoyama, M. *ibid*., **1996**, 37, 2441; Togo, H.; Hoshina, Y.; Yokoyama, M. *ibid*., **1996**, 37, 6129.

(8) All the compounds gave satisfactory spectroscopic and microanalytical data.