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Oxidative cyclization of *N*-alkyl-*o*-methyl-arenesulfonamides to biologically important saccharin derivatives

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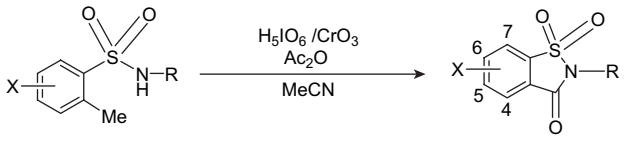
Abstract—Various biologically important saccharin skeletons and their *N*-alkyl derivatives have been efficiently prepared by chromium(VI) oxide catalyzed H_5IO_6 oxidation of *N*-alkyl-*o*-methyl-arenesulfonamides in acetonitrile. *N*-*tert*-Butyl saccharin skeletons were easily prepared by H_5IO_6–CrO_3 oxidation of *N*-*tert*-butyl-*o*-methyl arenesulfonamides in the presence of acetic anhydride. The method that furnished the novel fluoro and trifluoromethyl substituted saccharin skeletons is characterized by two steps, a simple work-up procedure, a single purification and good overall yields from substituted toluene derivatives.

1. Introduction

The H_5IO_6–CrO_3 oxidation system has been used for various C–H oxidations, such as tertiary C–H,[1] benzylic C–H,[2] alcoholic C–H,[3] aromatic C–H.[4] In recent years, our group has been studying the H_5IO_6–CrO_3 oxidation system and reported several novel C–H oxidations by using H_5IO_6–CrO_3 to oxidize *N*-alkylamides to imides,[5] *N*-alkylsulfonamides to sulfonimides,[6] benzylic silyl ethers to aldehydes or ketones.[7] Although the chromium(VI) catalyzed H_5IO_6 oxidation of toluenes to benzoic acids has been described by Yamazaki,[2] the application of this oxidation system to oxidize *N*-alkyl-*o*-methyl-arenesulfonamides to saccharin skeletons has not been reported.



1,2-Benzisothiazole-3-one-1,1-dioxide (saccharin) has been widely incorporated into a variety of biologically active compounds. The saccharin moiety has been identified as an important molecular component in various classes of 5-HT1a antagonists,[7] human leukocyte elastase inhibitors,[8] analgesics,[9] human mast cell tryptase inhibitors,[10] α1a and α1c adrenergic receptor antagonists,[11] aldehyde dehydrogenase inhibitors,[12] and bactericides.[13] To our knowledge, only one method has been reported in the literature for the transformation of *N*-alkyl-*o*-methyl-arenesulfonamides to *N*-alkyl saccharin derivatives.[14] However, this method is limited to *N*-methyl derivatives with electron-withdrawing aryl ring substituents and the yields are fairly low. During our recent study of chromium catalyzed periodic acid oxidations,[5–7,15] we found that *N*-alkyl-*o*-methyl-arenesulfonamides could be efficiently oxidized to saccharin and saccharin *N*-alkyl derivatives with H_5IO_6–CrO_3 in acetonitrile. Herein we report this novel and efficient method for the preparation of various saccharin skeletons.

2. Results

2.1. Direct oxidation of *N*-alkyl-*o*-toluenesulfonamides to saccharin derivatives

The results of oxidation of *N*-alkyl-*o*-methyl-toluenesulfonamides **1** to afford saccharin derivatives **2** are summarized in Table 1. The oxidation of *o*-toluenesulfonamide (**1a**) was incomplete with only 4 equiv of H_5IO_6 either at rt or 85 °C (Table 1, entries 1–3). At least 6 equiv of H_5IO_6 and 10 mol % of CrO_3 were required for complete reaction at 85 °C (Table 1, entry 5). The oxidation was also completed in 1 h by refluxing **1a** with 8 equiv of H_5IO_6 and 5% of CrO_3 in acetonitrile (Table 1, entry 7). Similar results were obtained at rt with 8 equiv of H_5IO_6 but longer reaction time (16 h) or higher catalyst loading (10 mol %) was required.

A competitive oxidation of the α-C–H of the *N*-alkyl group was observed in the oxidation of several *N*-alkyl-*o*-toluenesulfonamides. Oxidation of *N*-methyl-*o*-toluenesulfonamide

Keywords: Saccharin; Sulfonamides; Periodic acid; Chromium trioxide; Oxidation; Oxidative cyclization
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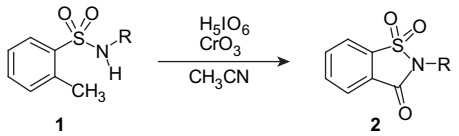
Table 1. Direct oxidation of *N*-alkyl-*o*-toluenesulfonamides to saccharin derivatives



Entry	1	R	2	H_5IO_6 (equiv)	CrO_3 (mol %)	Temperature (°C)	Time (h)	Yield (%)[a]
1	**1a**	H	**2a**	4	10	22	16	32
2	**1a**	H	**2a**	4	20	22	16	48
3	**1a**	H	**2a**	4	20	85	1	60
4	**1a**	H	**2a**	6	5	85	1	68
5	**1a**	H	**2a**	6	10	85	1	75
6	**1a**	H	**2a**	8	5	22	16	75
7	**1a**	H	**2a**	8	5	85	1	75
8	**1b**	Me	**2b**	8	5	22	8	35[b]
9	**1c**	Et	**2c**	8	5	22	8	12
10	**1d**	*i*-Pr	**2d**	8	5	22	8	20
11	**1e**	c-Pr	**2e**	8	5	22	16	46
12	**1f**	CF_3CH_2	**2f**	8	5	85	1	94
13	**1f**	CF_3CH_2	**2f**	8	10	22	8	94
14	**1g**	*t*-Bu	**2g**	6	5	22	16	76
15	**1g**	*t*-Bu	**2g**	6	5	22	16	84[c]
16	**1g**	*t*-Bu	**2g**	8	5	22	16	80
17	**1g**	*t*-Bu	**2g**	8	5	22	10	86[d]
18	**1g**	*t*-Bu	**2g**	8	10	22	8	86
19	**1g**	*t*-Bu	**2g**	8	10	22	8	88[d]
20	**1h**	MeO		8	5	22	3	0[e]

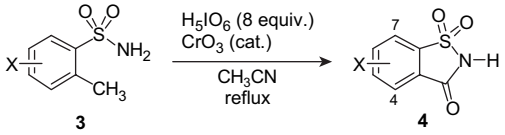
[a] Isolated yields.
[b] Saccharin was also obtained (20%).
[c] The reaction was performed in the presence of 6 equiv of Ac_2O.
[d] The reaction was performed in the presence of 8 equiv of Ac_2O.
[e] Intractable mixture.

(**1b**) (Table 1, entry 8) afforded *N*-methyl saccharin (**2b**) in 35% yield and saccharin (**2a**) was also obtained in 20% yield. Only a 12% yield of *N*-ethyl saccharin (**2c**) was obtained in oxidation of *N*-ethyl-*o*-toluenesulfonamide (**1c**, Table 1, entry 9). The competitive α-C–H oxidation was more significant in oxidation of *N*-isopropyl-*o*-toluenesulfonamide (**1d**) than that of *N*-cyclopropyl-*o*-toluenesulfonamide (**1e**) (Table 1, entries 10 and 11). However, the 2, 2, 2-trifluoroethyl group and *tert*-butyl group were tolerant of the oxidation conditions. Oxidation of *N*-2, 2, 2-trifluoroethyl-*o*-toluenesulfonamide (**1f**) afforded the corresponding saccharin derivative **2f** in 94% either at rt or at reflux (Table 1, entries 12 and 13). The oxidation of *N*-*tert*-butyl-*o*-toluenesulfonamide (**1g**) also gave high yields of the corresponding *N*-*tert*-butyl saccharin (**2g**) at rt (Table 1, entry 14). In addition, the yields of the **2g** were slightly improved when acetic anhydride was added to the reaction mixture to maintain anhydrous conditions (Table 1, entries 15, 17, and 19). Acetic anhydride was selected as a desiccant over molecular sieves or other inorganic reagents because of the heterogeneous character of the reaction mixture. Iodic acid (HIO_3) is formed as a by-product of the oxidation and precipitates from the reaction mixture. The addition of solid desiccant reagents was not desirable since adequate mixing could become difficult. To this end, optimal conditions were realized with 8 equiv of acetic anhydride to yield the *N*-*tert*-butyl saccharin (**2g**) in 88% yield. The presence of acetic anhydride also significantly shortened the reaction time (Table 1, entry 19). In addition, no acetylated products were identified. Attempts to oxidize the *N*-methoxy-*o*-toluenesulfonamide were unsuccessful and only an intractable mixture was obtained.

2.2. Oxidation of various substituted *o*-toluenesulfonamides to saccharin skeletons

To date a number of methods have been reported for the construction of the saccharin ring system.[16–21] However, currently available methods either employ sophisticated reagents or give only moderate yields of saccharin derivatives. A practical and general method for the preparation of saccharin-based compounds is still desirable. The direct oxidation of *o*-methyl arenesulfonamides is the simplest and most straightforward method for the preparation of saccharin skeletons. However, most of the reported oxidations are generally conducted in aqueous acidic or basic solutions affording the product in fairly low yields (40–50%).[16] Some oxidations even use excess CrO_3 as the oxidant but these conditions can lead to the environmental problem of waste metal disposal. Based on our initial results from the direct oxidation of *N*-alkyl-*o*-toluenesulfonamides (Table 1), we developed a practical and general method for the preparation of *N*-unsubstituted saccharin derivatives. As summarized in Table 2, various substituted *o*-toluenesulfonamides **3** were easily oxidized to the corresponding substituted saccharin derivatives **4** by refluxing with 8 equiv of H_5IO_6 and a catalytic amount of CrO_3 in acetonitrile. Higher catalyst loading (10 mol %) of CrO_3 was required for complete oxidation of substrates with strong electron-withdrawing groups. It is noteworthy that *p*-xylenesulfonamide (**3i**) was efficiently oxidized to the 6-CO_2H saccharin derivative **4i** with 10 equiv of H_5IO_6 and 10 mol % of CrO_3 (Table 2, entry 9).

Table 2. Oxidation of substituted *o*-toluenesulfonamides to saccharin skeletons



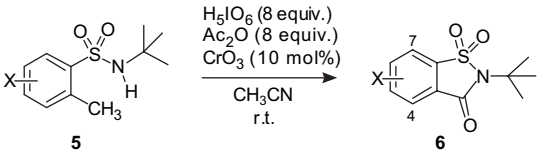
Entry	3	4	Saccharin X	CrO_3 (mol %)	Time (h)	Yield (%)[a]
1	**3a**	**4a**	6-Cl	5.0	1	76
2	**3b**	**4b**	5-Cl	5.0	1	76
3	**3c**	**4c**	4-Cl	5.0	1	74
4	**3d**	**4d**	7-Cl	5.0	1	75
5	**3e**	**4e**	6-Br	5.0	1	76
6	**3f**	**4f**	5-Br	5.0	1	76
7	**3g**	**4g**	6-F	5.0	1.5	74
8	**3h**	**4h**	5-F	5.0	1.5	74
9	**3i**	**4i**	6-CO_2H	10.0	2	75[b]
10	**3j**	**4j**	6-SO_2Me	10.0	2	70
11	**3k**	**4k**	6-$SONH_2$	10.0	3	68
12	**3l**	**4l**	6-NO_2	10.0	3	65

[a] Isolated yield.
[b] Starting material was *p*-xylenesulfonamide and H_5IO_6 (10 equiv).

2.3. Oxidation of *N*-*tert*-butyl-*o*-methyl arenesulfonamides to saccharin derivatives

From the study of *N*-alkyl substituted toluenesulfonamides described above, it was evident the *N*-*tert*-butyl group could be utilized as a protecting group in this system for the preparation of N-protected saccharin derivatives. As summarized

Table 3. Oxidation of *N-tert*-butyl-*o*-methyl arenesulfonamides to saccharin derivatives



5 **6**

Entry	5	6	Saccharin X	Time (h)	Yield (%)[a]
1	**5a**	**6a**	6-*t*-Bu	5	90
2	**5b**	**6b**	6-Cl	8	88
3	**5c**	**6c**	5-Cl	10	86
4	**5d**	**6d**	4-Cl	14	88[b](64)[c]
5	**5e**	**6e**	7-Cl	10	92[b](65)[c]
6	**5f**	**6f**	6-Br	8	90
7	**5g**	**6g**	5-Br	10	88
8	**5h**	**6h**	6-F	10	86
9	**5i**	**6i**	5-F	10	86
10	**5j**	**6j**	6-$MeSO_2$	14	80
11	**5k**	**6k**	6-SO_2NHt-Bu	16	76
12	**5l**	**6l**	6-NO_2	20	72
13	**5m**	**6m**	5-NO_2	20	72
14	**5n**	**6n**	7-NO_2	20	88[b](62)[c]
15	**5o**	**6o**	5-Cl-6-Me	4	42

[a] Isolated yield.
[b] Crude yield, >90% purity by ^{1}H NMR.
[c] The product was inseparable by chromatography, the yield was determined after recrystallization from ethanol.

in Table 3, a variety of *N-tert*-butyl-*o*-methyl arenesulfonamides (**5**) were smoothly oxidized to the corresponding N-protected saccharin derivatives (**6**) in good to excellent yields by using 8 equiv of H_5IO_6 and 10 mol % of CrO_3 in the presence of acetic anhydride at rt. The oxidation of *N-tert*-butyl-5-*tert*-butyl-*o*-toluenesulfonamides furnished the corresponding *N-tert*-butyl-6-*tert*-butyl saccharin **6a** in 90% yield (Table 3, entry 1). Longer reaction times were required for substrates with halogen or electron-withdrawing substituents.

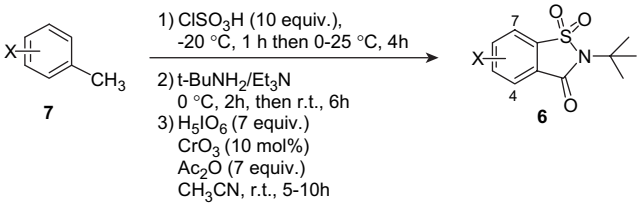
3. Discussion

For benzylic oxidation of substituted toluenes to benzoic acids, Yamazaki reported that only 3.5 equiv of H_5IO_6 was necessary for complete oxidation but 20 mol % CrO_3 was required for a complete oxidation of toluene derivatives with electron-withdrawing groups. Our investigation found that for the oxidation of *o*-toluenesulfonamides lower catalyst loading of only 5–10 mol % could be achieved with 8 equiv of H_5IO_6 in acetonitrile at reflux (Table 2). In addition, the oxidation reaction was significantly accelerated after addition of acetic anhydride. The oxidation of α-C–H of the *N*-alkyl group was identified as a competitive side reaction in oxidation of *N*-alkyl-*o*-methyl-arenesulfonamides, thus limiting the scope of utility of the process. The reactivity of N–α-CH bonds in this side reaction decreased in the following order: secondary>tertiary>primary. Only 12% of *N*-ethyl saccharin was obtained in oxidation of *N*-ethyl-*o*-toluenesulfonamide. For *N*-2, 2, 2-trifluoroethyl and *N-tert*-butyl substituted *o*-toluenesulfonamide, the α-C–H of *N*-alkyl group was not oxidized and high yields of products were obtained.

Chromium(VI) oxide was found to be the most effective catalyst in this oxidative cyclization. Other chromium species such as chromium(III) acetylacetonate, chromium(III) acetate hydroxide or chromium(III) trichloride, while effective for the oxidation of sulfide to sulfones and alcohols and silyl ethers to carbonyl compounds, were inferior as catalysts for the α-C–H oxidation of the *N*-alkyl-*o*-methyl-arenesulfonamides.[7,15]

The *N-tert*-butyl group proved to be a suitable nitrogen-protecting group for the preparation of *N-tert*-butyl saccharin derivatives from *o*-methyl arenesulfonamides. It was found that the *tert*-butyl group could be more easily removed than protective groups (methyl or a *p*-methoxy benzyl) typically used for the preparation of saccharin derivatives.[22,23] In addition, the purification of the substituted saccharin derivatives either by column chromatography or by recrystallization from ethanol was greatly facilitated by the *N-tert*-butyl group. Based upon these results, it was of interest to develop a direct method for the preparation of substituted saccharin derivatives from substituted toluene derivatives that employ the *N-tert*-butyl group as a protecting group for the saccharin nitrogen atom. To this end, the required *N-tert*-butyl-*o*-methyl arenesulfonamides were easily prepared by chlorosulfonation of substituted toluene derivatives **7** with chlorosulfonic acid.[24] The resulting sulfonyl chlorides were treated with *tert*-butyl amine to furnish the *N-tert*-butyl-*o*-toluenesulfonamide derivatives. For toluene and some substituted toluene derivatives (F, Cl, Br, CF_3, *t*-Bu) a mixture of isomers was observed (NMR, TLC) derived from the chlorosulfonation step. The other regioisomers present in small amounts (10–20%) were very difficult to separate from the *N-tert*-butyl-*o*-toluenesulfonamide isomers either by distillation or column chromatography. However, typically the isomeric mixture of *N-tert*-butyl-toluenesulfonamides was carried forward without purification to the oxidation step. Upon H_5IO_6 –CrO_3 oxidation of the mixture, the *N-tert*-butyl-*o*-toluenesulfonamide isomer was converted into the desired saccharin derivative **6** while other *N-tert*-butyl-toluenesulfonamide regioisomers present in the mixture were converted into substituted benzoic acids. The acid derivatives could then be easily removed by washing with saturated sodium bicarbonate solution affording the clean *N-tert*-butyl protected saccharin derivatives in moderate to good yields. As summarized in Table 4, a series of 6- and 5-substituted saccharin

Table 4. Direct preparation of saccharin derivatives from substituted toluene derivatives



7 **6**

Entry	6	X	Yield (%)[a]	Entry	6	X	Yield (%)[a]
1	**2g**	H	45	6	**6g**	5-Br	52
2	**6a**	6-*t*-Bu	56	7	**6h**	6-F	79
3	**6b**	6-Cl	65	8	**6i**	5-F	66
4	**6c**	5-Cl	58	9	**6p**	6-CF_3	58
5	**6f**	6-Br	61	10	**6q**	5-CF_3	38

[a] Isolated yield.

skeletons were easily prepared by this direct method. This one-pot procedure was amenable to the preparation of a variety of substituted saccharin derivatives, some not readily available by other methods. In addition, to our knowledge, this is the first report of the preparation of trifluoromethyl substituted saccharin derivatives **6p** and **6q**.

The mechanism of this novel oxidative cyclization has not been clearly established. Based upon observation in this study and related studies, we believe that this oxidative cyclization is likely to occur through the mechanism illustrated in Scheme 1. Chromium oxo or peroxo species are believed to abstract a benzylic hydrogen atom from the *N*-alkyl-*o*-toluenesulfonamide **1** and form benzylic radical **A**. It is well known that Cr(VI) oxo and peroxo species can abstract activated hydrogen atoms from organic compounds to form alkylradical intermediates.[25] Although the initial catalyst is Cr(VI) other oxidation states of chromium [e.g., Cr(V) and Cr(IV)] may be involved in the oxidative cyclization. The presence of N-dealkylation by-products suggests the possibility of a N-centered radical intermediate formed by intramolecular hydrogen transfer to form radical **B**. The radical **B** could then be easily oxidized to carbonyl diradical **C** that could cyclize quickly to afford the saccharin skeleton **2**. Alternatively, **B** could undergo a second H atom abstraction to give an alkyl diradical species **D**. The intramolecular coupling of the N-centered radical and benzylic radical of **D** would then afford intermediate **E**. Once formed, intermediate **E** could be easily and quickly oxidized to the saccharin skeleton. This reaction pathway is supported by recent studies in our laboratories that have shown that *N*-alkylamides and *N*-alkylsulfonamides are easily oxidized by H_5IO_6–CrO_3 system to give high yields of imide derivatives.[5] In addition, it is not likely that the oxidative cyclization reaction takes place through the dehydration of a benzoic acid intermediate. We have found that 2-carboxy-*N*-alkyl benzenesulfonamides do not cyclize to generate the saccharin skeleton under acidic conditions (aqueous HCl). Therefore, it is believed that the excess H_5IO_6 used in this oxidation is necessary to force the reaction to completion but not for the dehydration. Moreover, benzoic acid intermediates were never observed during the oxidation of *N*-alkyl-*o*-methyl-arenesulfonamides.

4. Conclusion

In conclusion, we have developed a novel and practical method for the preparation of saccharin and saccharin derivatives from substituted toluene derivatives by oxidation with the H_5IO_6–CrO_3 system. This oxidative-cyclization procedure is superior to other methods in both yield and waste metal production for the construction of the saccharin ring system. In addition, this method is tolerant of a variety of functional groups and has allowed the facile preparation of substituted saccharin derivatives that were previously difficult to synthesize.

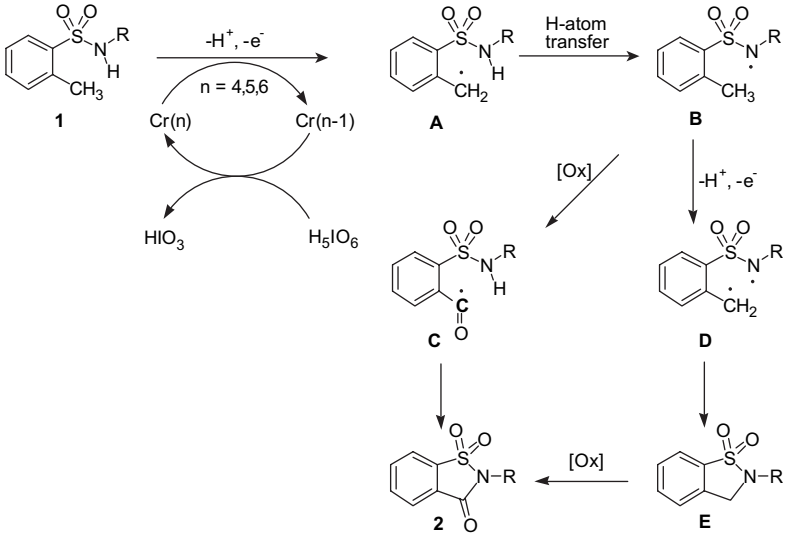
5. Experimental

5.1. General

All known compounds were identified by comparison of NMR spectral and physical data with the data reported in the literature and with the authentic samples when available. All new compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. NMR spectra were recorded on a Varian-400 MHz spectrometer at ambient temperature in $CDCl_3$/DMSO-d_6 with TMS as an internal standard. Infra red spectra were recorded with BOMEM Infrared Spectrometer, MB Series. Elemental analyses (C, H, N) were determined by Atlantic Microlabs, Inc., Norcross, GA. Melting points were recorded on a Hoover Mel-Temp apparatus and are uncorrected.

5.2. General procedure for the preparation of *N*-unsubstituted saccharin skeletons (2a and 4a–l)

A mixture of H_5IO_6 (18 g, 80 mmol), CrO_3 (50 mg, 0.5 mmol, 5 mol %) and *o*-methyl arenesulfonamide (10 mmol) in acetonitrile (100 mL) was heated to reflux until the oxidation was complete (monitored by TLC).



Scheme 1.

Isopropyl alcohol (10 mL) was added dropwise. After the addition was complete, the mixture was heated to reflux for an additional 10 min, cooled to rt, filtered and the solids were washed with acetone (2×60 mL). The filtrates were combined and concentrated under reduced pressure. The residue was triturated with 2 N H_2SO_4 solution (30 mL) and the crude product was collected by vacuum filtration. Most products were quite pure based on ^{1}H NMR and melting points. If necessary, further purification was performed by dissolving the crude product in satd Na_2CO_3 solution (40 mL). Any solids were filtered and the filtrate was extracted with EtOAc (40 mL). The aqueous layer was separated and acidified with concentrated HCl solution to pH 1. The resulting precipitate was collected by vacuum filtration to give pure products.

5.3. General procedure for the preparation of *N*-alkyl-*o*-methyl-arenesulfonamide derivatives

A solution of *o*-methylarenesulfonyl chloride (20 mmol) in CH_2Cl_2 (40 mL) was added dropwise to a solution of alkylamine (21 mmol) and triethylamine (21 mmol) in CH_2Cl_2 (80 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and then rt for 6 h. The mixture was washed, respectively, with 0.1 N HCl solution (50 mL) and satd $NaHCO_3$ solution (50 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded the *N*-alkyl-*o*-methyl-arenesulfonamides in sufficient purity for further use. If necessary, further purification by flash column chromatography (hexanes/EtOAc, 4:1) furnished the pure *N*-alkyl-*o*-methyl-arenesulfonamide derivatives.

5.3.1. *N*-Cyclopropyl-*o*-toluenesulfonamide (1e). Yellow oil. IR (liquid film) 3285, 3019, 1453, 1312, 1160, 1069, 881 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (s, 1H), 7.87 (d, J=7.6, 1H), 7.53 (t, J=7.6, 1H), 7.38–7.42 (m, 2H), 2.56 (s, 3H), 2.10–2.14 (m, 1H), 0.30–0.45 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 138.3, 136.5, 132.4, 132.3, 128.9, 126.1, 23.4, 19.7, 5.0. Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.87; H, 6.16; N, 6.63. Found: C, 57.06; H, 6.33; N, 6.62.

5.3.2. *N*-(2,2,2-Trifluoroethyl)-*o*-toluenesulfonamide (1f). Mp 78–80 °C. IR ($CHCl_3$) 3285, 3061, 1540, 1453, 1330, 1270, 1168 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.7 (t, J=6.8, 1H), 7.84 (d, J=8.0, 1H), 7.53 (t, J=7.2, 1H), 7.36–7.42 (m, 2H), 3.69–3.78 (m, 2H), 2.58 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 138.9, 136.5, 132.7, 132.5, 128.1, 126.3, 122.6, 43.4, 19.7. Anal. Calcd for $C_9H_{10}F_3NO_2S$: C, 42.68; H, 3.95; N, 5.53. Found: C, 42.75; H, 4.04; N, 5.49.

5.3.3. *N*-Methoxy-*o*-toluenesulfonamide (1h). Yellow oil. IR (liquid film) 3283, 3011, 1456, 1318, 1149, 1066, 883 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.5 (s, 1H), 7.85 (d, J=8.4, 1H), 7.58 (t, J=7.6, 1H), 7.48–7.37 (m 2H), 3.62 (s, 3H), 2.60 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 138.1, 135.6, 133.4, 132.5, 130.0, 126.3, 64.2, 20.1. Anal. Calcd for $C_8H_{11}NO_3S$: C, 47.76; H, 5.47; N, 6.96. Found: C, 47.48; H, 7.02; N, 6.74.

5.3.4. *N-tert*-Butyl-2-methyl-5-*tert*-butylbenzenesulfonamide (5a). Mp 140–142 °C. IR ($CHCl_3$) 3280, 2965, 2873, 1540, 1394, 1311, 1137, 1000 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, J=8.4, 1H), 7.35 (d, J=7.6, 1H), 7.36 (s, 1H), 2.57 (s, 3H), 1.26 (s, 9H), 1.08 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.3, 139.5, 136.4, 129.6, 128.6, 123.2, 53.6, 34.9, 31.2, 30.1, 20.3. Anal. Calcd for $C_{15}H_{25}NO_2S$: C, 63.60; H, 8.83; N, 4.94. Found: C, 63.56; H, 8.90; N, 4.86.

5.3.5. *N-tert*-Butyl-2-methyl-5-chlorobenzenesulfonamide (5b). Mp 140–142 °C. IR ($CHCl_3$) 3285, 2969, 1540, 1467, 1320, 1142, 1009 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (s, 1H), 7.69 (s, 1H), 7.58 (d, J=8.4, 1H), 7.42 (d, J=8.4, 1H), 2.56 (s, 3H), 1.11 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 144.0, 135.8, 134.7, 132.2, 130.8, 127.9, 53.9, 30.1, 19.4. Anal. Calcd for $C_{11}H_{16}ClNO_2S$: C, 50.47; H, 6.12; N, 5.35. Found: C, 50.18; H, 6.21; N, 5.38.

5.3.6. *N-tert*-Butyl-2-methyl-4-chlorobenzenesulfonamide (5c). Mp 142–144 °C. IR ($CHCl_3$) 3294, 2965, 2878, 1559, 1464, 1312, 1151 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, J=8.8, 1H), 7.61 (s, 1H), 7.50 (s 1H), 7.44 (d, J=8.8, 1H), 2.59 (s, 3H), 1.11 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 140.9, 138.9, 136.5, 131.8, 130.2, 126.1, 53.4, 29.7, 19.5. Anal. Calcd for $C_{11}H_{16}ClNO_2S$: C, 50.47; H, 6.12; N, 5.35. Found: C, 50.49; H, 6.15; N, 5.25.

5.3.7. *N-tert*-Butyl-2-methyl-3-chlorobenzenesulfonamide (5d). Mp 146–148 °C. IR ($CHCl_3$) 3280, 2965, 1430, 1311, 1202, 1142, 1000 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J=8.4, 1H), 7.71 (s, 1H), 7.69 (d, J=8.8, 1H), 7.40 (t, J=8.0, 1H), 2.64 (s, 3H), 1.12 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 144.2, 135.6, 134.1, 132.8, 127.4, 127.3, 53.6, 29.7, 16.5. Anal. Calcd for $C_{11}H_{16}ClNO_2S$: C, 50.47; H, 6.12; N, 5.35. Found: C, 50.64; H, 6.19; N, 5.32.

5.3.8. *N-tert*-Butyl-2-methyl-6-chlorobenzenesulfonamide (5e). Mp 162–168 °C. IR ($CHCl_3$) 3308, 2969, 1536, 1449, 1320, 1151, 1005 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (s 1H), 7.47 (d, J=7.6, 1H), 7.42 (d, J=7.6, 1H), 7.34 (d, J=7.2, 1H), 2.63 (s, 3H), 1.11 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 140.3, 139.9, 132.8, 132.7, 132.6, 130.7, 54.0, 29.8, 23.6. Anal. Calcd for $C_{11}H_{16}ClNO_2S$: C, 50.47; H, 6.12; N, 5.35. Found: C, 50.47; H, 6.16; N, 5.29.

5.3.9. *N-tert*-Butyl-2-methyl-5-bromobenzenesulfonamide (5f). Mp 160–162 °C. IR ($CHCl_3$) 3276, 2974, 1540, 1472, 1316, 1137, 1009 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.71 (d, J=8.4, 1H), 7.70 (s, 1H), 7.36 (d, J=8.4, 1H), 2.55 (s, 3H), 1.12 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 144.2, 136.2, 135.1, 135.0, 130.7, 118.8, 53.9, 30.1, 19.5. Anal. Calcd for $C_{11}H_{16}BrNO_2S$: C, 43.13; H, 5.22; N, 4.57. Found: C, 43.20; H, 5.31; N, 4.56.

5.3.10. *N-tert*-Butyl-2-methyl-4-bromobenzenesulfonamide (5g). Mp 146–148 °C. IR ($CHCl_3$) 3285, 2969, 1540, 1316, 1151, 1009 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, J=8.4, 1H), 7.64 (s, 1H), 7.57–7.60 (m, 2H), 2.57 (s, 3H), 1.09 (s, 9H). ^{13}C NMR (75 MHz,

DMSO-d_6) δ 141.7, 139.5, 135.1, 130.6, 129.5, 125.9, 53.8, 30.0, 19.8. Anal. Calcd for $C_{11}H_{16}BrNO_2S$: C, 43.13; H, 5.22; N, 4.57. Found: C, 43.11; H, 5.27; N, 4.48.

5.3.11. *N*-*tert*-Butyl-2-methyl-5-fluorobenzenesulfonamide (5h). Mp 118–120 °C. IR ($CHCl_3$) 3299, 2976, 2868, 1490, 1316, 1229, 1142, 1005 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 7.67 (s, 1H), 7.60–7.63 (m, 1H), 7.42–7.45 (m, 1H), 7.33–7.39 (m, 1H), 2.56 (s, 3H), 1.12 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.9, 144.0, 134.8, 133.0, 119.4, 115.5, 53.9, 30.0, 19.2. Anal. Calcd for $C_{11}H_{16}FNO_2S$: C, 53.87; H, 6.53; N, 5.71. Found: C, 53.67; H, 6.60; N, 5.71.

5.3.12. *N*-*tert*-Butyl-2-methyl-4-fluorobenzenesulfonamide (5i). Mp 140–142 °C. IR ($CHCl_3$) 3294, 2978, 2878, 1582, 1476, 1311, 1147, 1005 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 7.90–7.93 (m, 1H), 7.53 (s, 1H), 7.25–7.28 (m, 1H), 7.17–7.21 (m, 1H), 2.59 (s, 3H), 1.09 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.7, 140.6, 138.8, 131.6, 119.3, 113.3, 53.7, 30.1, 20.1. Anal. Calcd for $C_{11}H_{16}FNO_2S$: C, 53.87; H, 6.53; N, 5.71. Found: C, 53.71; H, 6.63; N, 5.69.

5.3.13. *N*-*tert*-Butyl-2-methyl-5-methylsulfonylbenzenesulfonamide (5j). Mp 182–184 °C. IR ($CHCl_3$) 3285, 2976, 1545, 1316, 1147, 1005 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.04 (s, 1H), 7.82 (s, 1H), 7.69 (d, J=7.6, 1H), 3.26 (s, 3H), 2.69 (s, 3H), 1.12 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 143.3, 143.2, 139.3, 134.2, 130.8, 127.0, 54.2, 43.9, 30.1, 20.2. Anal. Calcd for $C_{12}H_{19}NO_4S_2$: C, 47.21; H, 6.22; N, 4.59. Found: C, 47.35; H, 6.22; N, 4.49.

5.3.14. *N*-*tert*-Butyl-2-methyl-5-(*N*-*tert*-butylaminosulfonyl)benzenesulfonamide (5k). Mp 224–226 °C. IR ($CHCl_3$) 3280, 2978, 2878, 1540, 1394, 1325, 1147, 995 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 7.92 (d, J=8.0, 1H), 7.76 (d, J=5.6, 1H), 7.58 (d, J=8.4, 1H), 2.65 (s, 3H), 1.109 (s, 9H), 1.107 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 142.6, 142.4, 140.6, 133.3, 129.5, 126.4, 53.6, 53.4, 29.79, 29.69, 19.70. Anal. Calcd for $C_{15}H_{26}N_2O_4S_2$: C, 49.72; H, 7.18; N, 7.73. Found: C, 49.71; H, 7.35; N, 7.68.

5.3.15. *N*-*tert*-Butyl-2-methyl-5-nitrobenzenesulfonamide (5l). Mp 127–129 °C. IR ($CHCl_3$) 3294, 2974, 1522, 1353, 1156, 995 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.34 (d, J=8.4, 1H), 7.92 (s, 1H), 7.71 (d, J=8.0, 1H), 2.73 (s, 3H), 1.13 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 145.4, 144.3, 143.1, 134.0, 126.3, 122.7, 53.7, 29.6, 19.7. Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.88; N, 10.29. Found: C, 48.66; H, 5.94; N, 10.22.

5.3.16. *N*-*tert*-Butyl-2-methyl-4-nitrobenzenesulfonamide (5m). Mp 157–159 °C. IR ($CHCl_3$) 3290, 2978, 2868, 1531, 1320, 1156, 1005 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 1H), 8.20 (d, J=8.8, 1H), 8.13 (d, J=8.8, 1H), 7.92 (s, 1H), 2.71 (s, 3H), 1.11 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 149.0, 147.5, 138.8, 129.8, 126.9, 121.3, 53.8, 29.7, 19.7. Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.88; N, 10.29. Found: C, 48.76; H, 5.89; N, 10.33.

5.3.17. *N*-*tert*-Butyl-2-methyl-6-nitrobenzenesulfonamide (5n). Mp 181–183 °C. IR ($CHCl_3$) 3290, 2976, 1545, 1330, 1156 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 1H), 7.68–7.62 (m, 3H), 2.68 (s, 3H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.0, 140.0, 135.2, 133.4, 132.9, 122.0, 54.6, 29.7, 20.6. Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.88; N, 10.29. Found: C, 48.77; H, 5.94; N, 10.35.

5.3.18. *N*-*tert*-Butyl-2, 5-dimethyl-4-chlorobenzenesulfonamide (5o). Mp 170–172 °C. IR ($CHCl_3$) 3294, 2974, 1545, 1316, 1142, 1005 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 7.82 (s, 1H), 7.54 (s, 1H), 7.46 (s, 1H), 2.53 (s, 3H), 2.34 (s, 3H), 1.1 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 141.1, 137.0, 136.3, 133.7, 132.6, 131.1, 53.7, 30.1, 19.4, 19.3. Anal. Calcd for $C_{12}H_{18}ClNO_2S$: C, 52.26; H, 6.53; N, 5.08. Found: C, 52.51; H, 6.63; N, 5.01.

5.4. General procedure for the preparation of *N*-alkyl saccharin derivatives

A mixture of H_5IO_6 (18 g, 80 mmol) in acetonitrile (140 mL) was stirred vigorously at rt for 1 h, then CrO_3 (100 mg, 1 mmol, 10 mol %) was added followed by acetic anhydride (8.2 g, 80 mmol). The resulting orange solution was cooled to 0 °C. The *N*-alkyl-*o*-methyl-arenesulfonamide (10 mmol) was then added in one portion. After stirring at 0 °C for 15 min, the reaction mixture was allowed to warm to rt and stirred until the oxidation was complete (monitored by TLC). The solvent was removed at rt under reduced pressure and the residue was extracted with EtOAc (2×80 mL). The combined organic portions were washed with satd $NaHCO_3$ solution (80 mL), satd $Na_2S_2O_3$ solution (60 mL), brine (60 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the crude product. Some of the crude saccharin derivatives were quite pure by ^1H NMR. If necessary, further purification by flash column chromatography (hexanes/EtOAc, 4:1) furnished the pure *N*-alkyl saccharin derivatives.

5.4.1. *N*-Cyclopropyl-1,2-benzisothiazole-3-one-1,1-dioxide (2e). Mp 144–146 °C. IR ($CHCl_3$) 3010, 1737, 1540, 1458, 1320,1183 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, J=7.2, 1H), 7.99–8.10 (m, 3H), 2.80–2.81 (m, 1H), 1.02–1.03 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.5, 136.6, 135.8, 135.1, 126.1, 124.9, 121.4, 20.2, 3.74. Anal. Calcd for $C_{10}H_9NO_3S$: C, 53.81; H, 4.04; N, 6.27. Found: C, 53.73; H, 4.07; N, 6.31.

5.4.2. *N*-(2,2,2-Trifluoroethyl)-1,2-benzisothiazole-3-one-1,1-dioxide (2f). Mp 132–134 °C. IR ($CHCl_3$) 3093, 3024, 1756, 1540, 1348, 1247, 1174 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, J=8.0, 1H), 8.19 (d, J=7.2, 1H), 8.13 (t, J=7.6, 1H), 8.06 (t, J=8.0, 1H), 4.62–4.69 (q, J=9.2, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.7, 136.7, 136.5, 135.6, 125.7, 125.60, 124.7, 121.9, 40.2. Anal. Calcd for $C_9H_6F_3NO_3S$: C, 40.75; H, 2.26; N, 5.28. Found: C, 40.68; H, 2.29; N, 5.18.

5.4.3. *N*-*tert*-Butyl-6-*tert*-butyl-1,2-benzisothiazole-3-one-1,1-dioxide (6a). Mp 120–122 °C. IR ($CHCl_3$) 2965, 2873, 1719, 1536, 1334, 1252, 1192 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J=7.6, 1H), 8.05 (d,

J=8.4, 1H), 7.97 (s, 1H), 1.69 (s, 9H), 1.35 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.7, 158.6, 134.4, 132.8, 126.3, 120.8, 120.5, 60.2, 35.4, 30.4, 27.2. Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 61.01; H, 7.12; N, 4.74. Found: C, 60.89; H, 7.20; N, 4.72.

5.4.4. *N-tert*-Butyl-6-chloro-1,2-benzisothiazole-3-one-1,1-dioxide (6b). Mp 162–164 °C. IR ($CHCl_3$) 3079, 2974, 1714, 1540, 1330, 1266, 1151 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.02 (s, 2H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.6, 140.5, 138.3, 135.2, 126.3, 124.7, 121.1, 60.6, 27.2. Anal. Calcd for $C_{11}H_{12}ClNO_3S$: C, 48.26; H, 4.38; N, 5.11. Found: C, 48.25; H, 4.40; N, 5.06.

5.4.5. *N-tert*-Butyl-5-chloro-1,2-benzisothiazole-3-one-1,1-dioxide (6c). Mp 141–143 °C. IR ($CHCl_3$) 3088, 2987, 1714, 1540, 1417, 1330, 1174 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, J=9.2, 1H), 8.08 (d, J=7.2, 1H), 8.07 (s, 1H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.2, 139.9, 135.5, 135.4, 128.2, 124.5, 122.6, 60.7, 27.1. Anal. Calcd for $C_{11}H_{12}ClNO_3S$: C, 48.26; H, 4.38; N, 5.11. Found: C, 48.16; H, 4.38; N, 5.09.

5.4.6. *N-tert*-Butyl-4-chloro-1,2-benzisothiazole-3-one-1,1-dioxide (6d). Mp 162–164 °C. IR ($CHCl_3$) 3079, 2974, 1719, 1458, 1330, 1151 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (dd, J=6.0, 2.4, 1H), 7.95–8.00 (m, 2H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.2, 139.2, 136.7, 136.6, 131.5, 122.0, 119.7, 60.7, 27.1. Anal. Calcd for $C_{11}H_{12}ClNO_3S$: C, 48.26; H, 4.38; N, 5.11. Found: C, 48.12; H, 4.42; N, 5.10.

5.4.7. *N-tert*-Butyl-7-chloro-1,2-benzisothiazole-3-one-1,1-dioxide (6e). Mp 72–74 °C. IR ($CHCl_3$) 2987, 1728, 1545, 1453, 1343, 1158 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J=8.8, 1H), 7.9–8.0 (m, 2H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.2, 136.7, 135.9, 133.9, 128.8, 126.2, 123.4, 60.9, 27.1. Anal. Calcd for $C_{11}H_{12}ClNO_3S$: C, 48.26; H, 4.38; N, 5.11. Found: C, 48.31; H, 4.31; N, 5.00.

5.4.8. *N-tert*-Butyl-6-bromo-1,2-benzisothiazole-3-one-1,1-dioxide (6f). Mp 168–170 °C. IR ($CHCl_3$) 3083, 2965, 1714, 1540, 1334, 1151 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.16 (dd, J=8.4, J=1.6, 1H), 7.94 (d, J=7.6, 1H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.8, 138.3, 138.0, 129.2, 126.3, 125.3, 123.7, 60.6, 27.1. Anal. Calcd for $C_{11}H_{12}BrNO_3S$: C, 41.50; H, 3.77; N, 4.40. Found: C, 41.57; H, 3.84; N, 4.38.

5.4.9. *N-tert*-Butyl-5-bromo-1,2-benzisothiazole-3-one-1,1-dioxide (6g). Mp 146–148 °C. IR ($CHCl_3$) 3092, 2992, 1714, 1540, 1417, 1330, 1256, 1169 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16–8.24 (m, 3H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.2, 138.3, 135.7, 128.6, 128.1, 127.3, 122.6, 60.7, 27.1. Anal. Calcd for $C_{11}H_{12}BrNO_3S$: C, 41.50; H, 3.77; N, 4.40. Found: C, 41.33; H, 3.73; N, 4.33.

5.4.10. *N-tert*-Butyl-6-fluoro-1,2-benzisothiazole-3-one-1,1-dioxide (6h). Mp 134–136 °C. IR ($CHCl_3$) 3070, 2978, 1728, 1600, 1485, 1330, 12656, 1151 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (dd, J=7.2, J=2.0, 1H), 8.1 (dd, J=8.4, J=4.4, 1H), 7.82 (dt, J=8.8, J=2.0, 1H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.6, 139.1, 127.7, 122.7, 122.51, 109.1, 60.6, 27.2. Anal. Calcd for $C_{11}H_{12}FNO_3S$: C, 51.36; H, 4.67; N, 5.44. Found: C, 51.27; H, 4.74; N, 5.59.

5.4.11. *N-tert*-Butyl-5-fluoro-1,2-benzisothiazole-3-one-1,1-dioxide (6i). Mp 88–90 °C. IR ($CHCl_3$) 3102, 2983, 1724, 1472, 1279, 1174 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31–8.35 (m, 1H), 7.80–7.91 (m, 2H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.3, 133.05, 129.49, 123.9, 123.2, 122.9, 112.1, 60.7, 27.1. Anal. Calcd for $C_{11}H_{12}FNO_3S$: C, 51.36; H, 4.67; N, 5.44. Found: C, 51.53; H, 4.71; N, 5.36.

5.4.12. *N-tert*-Butyl-6-methylsulfonyl-1,2-benzisothiazole-3-one-1,1-dioxide (6j). Mp 194–196 °C. IR ($CHCl_3$) 3102, 2992, 2919, 1714, 1545, 1339, 1183 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.45 (d, J=7.6, 1H), 8.28 (d, J=8.4, 1H), 3.45 (s, 3H), 1.71 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.2, 147.0, 137.4, 133.3, 130.0, 126.1, 120.0, 61.0, 42.6, 27.1. Anal. Calcd for $C_{12}H_{15}NO_5S_2$: C, 45.42; H, 4.73; N, 4.41. Found: C, 45.42; H, 4.77; N, 4.27.

5.4.13. *N-tert*-Butyl-6-(*N-tert*-butylaminosulfonyl)-1,2-benzisothiazole-3-one-1,1-dioxide (6k). Mp 166–168 °C. IR ($CHCl_3$) 3285, 2978, 1728, 1545, 1398, 1339, 1151 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.35 (d, J=8.4, 1H), 8.23 (d, J=7.6, 1H), 7.99 (s, 1H), 1.70 (s, 9H), 1.13 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.3, 150.7, 137.4, 132.4, 128.6, 126.1, 118.4, 60.9, 54.0, 29.6, 27.1. Anal. Calcd for $C_{15}H_{22}N_2O_5S_2$: C, 48.12; H, 5.88; N, 7.48. Found: C, 48.33; H, 6.20; N, 7.36.

5.4.14. *N-tert*-Butyl-6-nitro-1,2-benzisothiazole-3-one-1,1-dioxide (6l). Mp 182–184 °C. IR ($CHCl_3$) 3111, 2996, 1733, 1545, 1334, 1270, 1188 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H), 8.68 (dd, J=8.4, 1H), 8.26 (d, J=8.0, 1H), 1.71 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.9, 151.7, 137.7, 130.6, 130.0, 126.4, 117.1, 61.2, 27.1. Anal. Calcd for $C_{11}H_{12}N_2O_5S$: C, 46.47; H, 4.23; N, 9.85. Found: C, 46.65; H, 4.26; N, 9.79.

5.4.15. *N-tert*-Butyl-5-nitro-1,2-benzisothiazole-3-one-1,1-dioxide (6m). Mp 151–153 °C. IR ($CHCl_3$) 3102, 2983, 1728, 1540, 1339, 1266, 1156 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (d, J=8.4, 1H), 8.58 (s, 1H), 8.52 (d, J=8.4, 1H), 1.71 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.6, 151.5, 140.7, 130.6, 128.0, 122.8, 119.7, 61.2, 27.1. Anal. Calcd for $C_{11}H_{12}N_2O_5S$: C, 46.47; H, 4.23; N, 9.85. Found: C, 46.59; H, 4.28; N, 9.87.

5.4.16. *N-tert*-Butyl-7-nitro-1,2-benzisothiazole-3-one-1,1-dioxide (6n). Mp 152–154 °C. IR ($CHCl_3$) 3102, 2992, 1719, 1545, 1348, 1197 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, J=8.4, 1H), 8.44 (d, J=7.6, 1H), 8.23 (t, J=8.0, 1H), 1.72 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.5, 141.1, 136.9, 130.7, 130.5, 130.3, 129.2, 61.2, 27.2. Anal. Calcd for $C_{11}H_{12}N_2O_5S$: C, 46.47; H, 4.23; N, 9.85. Found: C, 46.55; H, 4.25; N, 9.76.

5.4.17. *N-tert*-Butyl-5-chloro-6-methyl-1,2-benzisothiazole-3-one-1,1-dioxide (6o). Mp 205–207 °C. IR ($CHCl_3$) 3001, 2960, 1714, 1545, 1325, 1261, 1165 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 8.03 (s, 1H), 2.52 (s, 3H), 1.69 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.4, 144.7, 140.1, 135.4, 125.6, 124.6, 122.8, 60.6, 27.1, 20.2. Anal. Calcd for $C_{12}H_{14}ClNO_3S$: C, 50.08; H, 4.87; N, 4.87. Found: C, 50.06; H, 4.85; N, 4.86.

5.5. General procedure for direct preparation of saccharin skeletons from toluenes

Toluene or a substituted toluene derivative (20 mmol) was added portionwise over a period of 30 min to pre-cooled chlorosulfonic acid (0.2 mol) at −20 °C. After addition, the reaction mixture was stirred at −20 °C for 1 h, then gradually allowed warm to rt over 1 h and stirred at rt for additional 4 h. The mixture was poured onto ice (500 g), extracted with Et_2O or CH_2Cl_2 (120×2 mL). The extracts were combined and washed with satd $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was dissolved in dry CH_2Cl_2 (40 mL). The solution was then added dropwise to a solution of *tert*-butyl amine (21 mmol) and triethylamine (21 mmol) in CH_2Cl_2 (80 mL) at 0 °C. After addition, the reaction mixture was stirred at 0 °C for 2 h and then rt for 6 h, washed, respectively, with 0.1 N HCl solution and satd $NaHCO_3$ solution, dried over $MgSO_4$. Removal of the solvent afforded the isomers *N-tert*-butyl-*o*-methyl arenesulfonamides.

A mixture of H_5IO_6 (0.14 mol) in acetonitrile (200 mL) was stirred vigorously at rt for 1 h, then CrO_3 (200 mg, 2 mmol, 10 mol %) was added followed by acetic anhydride (0.14 mol). The resulting orange solution was cooled to 0 °C. To this solution was added the isomers of *N-tert*-butyl-*o*-methyl arenesulfonamides in one portion. After stirring at 0 °C for 30 min, the reaction mixture was allowed to warm to rt and stirred until the oxidation was complete (monitored by TLC). The solvent was removed at rt under reduced pressure and the residue was extracted with EtOAc (2×100 mL). The extracts were collected and washed, respectively, with satd $NaHCO_3$ solution (160 mL), satd $Na_2S_2O_3$ solution (120 mL) and brine, dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the crude product. Some of the crude saccharin derivatives were quite pure by ^1H NMR. If necessary, further purification by flash column chromatography (hexanes/EtOAc, 4:1) or recrystallization from ethanol furnished the pure *N-tert*-butyl saccharin derivatives.

5.5.1. *N-tert*-Butyl-6-trifluoromethyl-1,2-benzisothiazole-3-one-1,1-dioxide (6p). Mp 156–158 °C. IR ($CHCl_3$) 2982, 1732, 1419, 1252, 1152 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.34 (d, J=8.0, 1H), 8.23 (d, J=8.0, 1H), 1.71 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.3, 137.7, 135.1, 134.8, 132.1, 129.7, 125.9, 118.9, 60.9, 27.1. Anal. Calcd for $C_{12}H_{12}NF_3O_3S$: C, 46.90; H, 3.90; N, 4.56. Found: C, 46.82; H, 3.85; N, 4.53.

5.5.2. *N-tert*-Butyl-5-trifluoromethyl-1,2-benzisothiazole-3-one-1,1-dioxide (6q). Mp 132–134 °C. IR ($CHCl_3$) 2989, 1723, 1430, 1263, 1130 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J=8.4, 1H), 8.42 (d, J=8.4, 1H), 8.32 (s, 1H), 1.71 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.3, 140.1, 135.0, 134.7, 132.8, 127.7, 122.4, 121.9, 60.9, 27.1. Anal. Calcd for $C_{12}H_{12}NF_3O_3S$: C, 46.90; H, 3.90; N, 4.56. Found: C, 46.90; H, 3.87; N, 4.58.

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