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A CONVENIENT PREPARATION OF *N*-BROMO-SACCHARIN, SOURCE OF ELECTROPHILIC BROMINE

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ABSTRACT. An extremely straightforward, high yield synthesis of a very reactive electrophilic brominating reagent *N*-bromosaccharin is described, allowing its preparation in multi-gram quantities and in high purity.

N-Bromo compounds have wide spread utility in organic synthesis, either through homolytic or heterolytic cleavage of the N-Br bond.[1] Attempts at regioselective functionalization of 7-hydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene led us to consider a hydroxyl-directed peri bromination using *N*-bromo reagents.[2] For this, the reaction with either *N*-bromoacetamide (NBA) or *N*-bromosuccinimide (NBS) in CH_2Cl_2, consistently resulted in low regioselectivity. Saccharin (**1**) has been reported to have complexing tendencies with phenols even in aqueous media.[3] This led us to consider the possibility that *N*-bromosaccharin (NBSac, **2**) might be a source of electrophilic bromine with different

complexation and thus reactivity characteristics compared to both NBA and NBS. *N*-Bromosaccharin has been documented to act as an oxidant,[4,5] while its utility in radical[6,7] and electrophilic[8-10] bromination has also been reported.

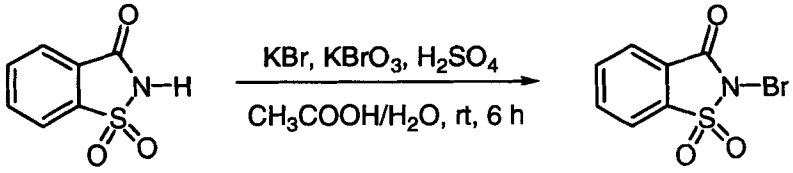
The difference in the reactivity of NBSac as compared to NBS has been first pointed out by Ziegler et al. in the bromination of cyclohexene. In this case, reaction with **2** resulted exclusively in the addition product *N*-(2-bromocyclohexyl)-saccharin, while only allylic bromination took place with NBS.[11] Subsequently, the greater electrophilic character of **2** was also reflected in the bromination of 2-methylnaphthalene, which under photolytic benzylic bromination conditions produced not only bromomethylnaphthalene but also substantial amounts of 1-bromo-2-methylnaphthalene by nuclear bromination.[7] However, exclusive benzylic bromination of 2-methylnaphthalene was observed with NBS under thermal conditions.[12] Srinivasan and Gnanapragasam have studied the bromination of substituted anisoles in 50% aqueous acetic acid and have postulated a carbocationic intermediate for the reaction.[8] In this study, the relative reactivities of *p*-nitroanisole with Br_2, NBS and **2** were reported to be 1.0, 1.7 and 18.2, respectively, indicating a higher reactivity of **2**.[8]

Given these results, in order to achieve our synthetic goals[2] convenient access to NBSac (**2**) was needed. Ziegler et al. reported the first synthesis of **2**, wherein the silver salt of saccharin (**1**) was reacted with bromine in CCl_4.[11] Although nearly quantitative conversion to **2** was observed, this was not separated from the silver bromide by-product prior to use in further reactions. Their synthetic attempts to convert alkali salts of saccharin to the *N*-bromo derivative with bromine in aqueous solution failed. Later literature reports describe the reaction of the sodium salt of saccharin with bromine in aqueous

solution leading to pure **2**. However the major drawback of these procedures was the low yield obtained (20%).[4,13] Based on this, Sánchez and Fumarola described a high yield preparation of **2**, by reacting the sodium salt of saccharin with bromine chloride generated *in situ*.[6] We therefore chose to follow their procedure, but we were unable to prepare pure **2** by this method. Although, the yields of **2** were indeed high, in our hands the *N*-bromosaccharin isolated was invariably contaminated with *N*-chlorosaccharin. This was reflected in the product composition, obtained from the halogenation of highly reactive polycyclic aromatic systems, such as substituted pyrene. For this reason we became interested in exploring other methods for its preparation, which would not only lead to good yields, but also exclude the potential formation of the *N*-chlorosaccharin. In order to avoid any possible complications, due to the ambident nucleophilicity of the saccharin salt, we chose saccharin (**1**) as the substrate.

Recently, the synthesis of a series of *N*-bromoimides and amides, using sodium bromate and hydrobromic acid or sodium bromide, was published by Fujisaki and coworkers.[14] However no functionalization of sulfonimides following this protocol has been reported to date. We disclose herein a convenient, high-yield preparation of **2**, also documenting the first *N*-bromosulfonimide preparation by this procedure. Under the reported conditions the reaction proceeds smoothly to provide **2** in 92% yield. The content of bromine was 30.5%, as determined by iodometric titration, which is the theoretical value of active bromine. Crystallization from a mixture of acetic acid and water affords a colourless crystalline product in 74% yield. Although the typical procedure described herein utilizes $KBr/KBrO_3$, the *N*-functionalization proceeds in a comparable manner with the $NaBr/NaBrO_3$ combination as well.

Scheme



Using N-bromosaccharin the peri-bromination of 7-hydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene proceeded smoothly to afford the desired bromo compound in high yield.[2] This indicates that NBSac does indeed have properties substantially different from NBS or NBA and could therefore have special applications.

EXPERIMENTAL

Reagents of commercial purity were used, with no further purification.

***N*-Bromosaccharin (2)**

To a mixture of saccharin (**1**, 14.64 g, 0.08 mol), $KBrO_3$ (6.68 g, 0.04 mol) and sulphuric acid (97%, 3.29 mL, 6.06 g, 0.06 mol) in aqueous acetic acid (70%, 56 mL), KBr (6.37 g, 0.054 mol) was added portionwise with stirring at room temperature. After addition, the reaction mixture was stirred at room temperature for 6 hours, the precipitate was filtered off, washed with water and dried to afford 19.18 g (92 %) of the crude colourless product. The crude product (18.74 g) was crystallized from acetic acid/water to yield 15.45 g (74%) of the pure product **2** which was thoroughly vacuum-dried over P_2O_5 at room temperature. Mp of the colourless crystalline **2** 177.5-181 °C (mp[4,13]: 171-173 °C; mp[6]: 170-172 °C). Thermogravimetric (TG) analysis showed slow

decomposition starting at 160 °C, while differential scanning calorimetry (DSC) curve indicated melting at 182.5 °C. HRMS: calcd. for $C_7H_4BrNO_3S$ 260.9095 (^{79}Br), found 260.9090. Anal. calcd. for $C_7H_4BrNO_3S$: C, 32.08; H, 1.54; N, 5.34, found: C, 31.82; H, 1.43; N, 5.24. Active bromine measured by iodometric titration: 30.5% (theoretical: 30.49%). IR (Nujol): ν_{max} = 1710 (CO); *asym.* 1352, *sym.* 1192 cm^{-1} (SO_2) [lit.[6] (KBr) 1730, 1350, 1145 cm^{-1}]. ^1H NMR (300 MHz, C_6D_6): 7.20 (1H, m); 6.87 (1H, m); 6.51 (2H, m).

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