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A Convenient Synthesis of 3,4-Dihydro-2,2-Dioxide 5-Hydroxy-2,1-Benzothiazine

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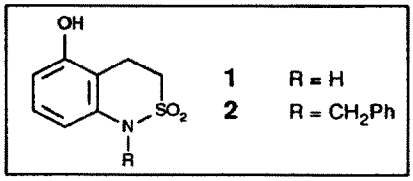
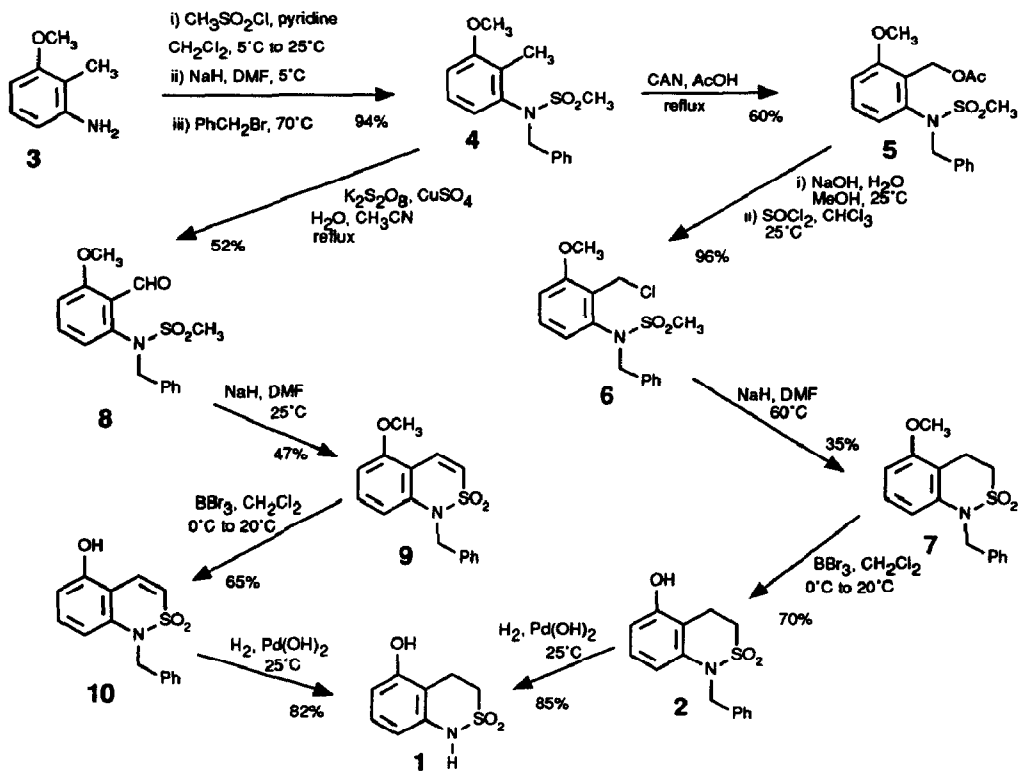
Abstract : *3-methoxy-2-methyl-aniline 3 is converted to the benzothiazine-dioxide 1 in a 7-steps procedure: the key transformation being the cyclization of an ortho-functionnalized N-benzyl sulfonanilide.*

As key intermediates on our research program, 3,4-dihydro-2,2-dioxide-5-hydroxy-2,1-benzothiazine **1** and its N-benzyl analogue **2** were required. These two compounds were previously described by the Suntory group[3], using the classic pathway already reported for the preparation of the corresponding unsubstituted derivatives[4], with the cyclization of an *ortho*-amino phenethyl-sulfonic acid as key-step. We disclose herein an alternative and shorter synthesis of the titled compounds which utilizes a cyclization of an *ortho*-(chloromethyl or carboxaldehyde) N-protected sulfonanilide. It is the first time, at our knowledge, that such strategy is employed for this kind of heterocycle.

Our synthetic approach involved the preparation of the N-benzyl-sulfonanilide **4**[5] obtained from the readily available 3-methoxy-2-methyl-aniline **3**[6] by reaction with methanesulfonyl chloride followed by alkylation with benzyl bromide in presence of sodium hydride. Surprisingly, attempts to brominate (NBS/Bz_2O_2) the benzylic position of **4** failed. This lack of reactivity could be explained by steric factors due to the bulky group located in *ortho*-position. Nevertheless, the methyl-group was successfully functionalized by oxidation with Cerium Ammonium Nitrate (CAN)[7] in acetic acid affording the acetate **5** which was quantitatively converted into the chloromethyl derivative **6**, via the corresponding alcohol. Alternatively, **4** was oxidized into the aldehyde **8**, using potassium peroxydisulfate according to the conditions of Carter and Wallace[8]. The cyclization steps of **6** and **8** were performed by deprotonation of the N-benzyl-sulfonanilide moiety using sodium hydride in DMF, giving the benzothiazine-dioxides **7** and **9**, respectively. The synthesis was achieved by cleaving the methyl ether in **7** or **9** with boron tribromide to provide the target compound **2**[9] or the dehydro-analogue **10**. Final hydrogenation (palladium hydroxide) of these two compounds lead to the debenzylated dihydro- benzothiazine-dioxide **1**[10] with a 12% overall-yield from 3-methoxy-2-methyl-aniline **3**.





References and Notes

1. Present address: 1 rue Jean Formigé, 75015 Paris, France.
2. Present address: 23 allée des Hautes Bruyères, 94230 Cachan, France.
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5. All yields are unoptimised and all new compounds provided spectral and analytical data consistent with their structures.
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9. Physical data for compound 2: m.p.:176°C (EtOH); ^{1}H-NMR ($CDCl_3$,200 MHz, ppm) δ 3.2 (t, 2H, J = 6 Hz), 3.5 (t, 2H, J = 6 Hz), 4.9 (s, 2H), 6.3 (d, 1H, J = 7.7 Hz), 6.6 (d, 1H, J = 7.2 Hz), 6.9 (dd, 1H, J = 7.3 Hz, 7.4 Hz), 7.4 (m, 5H), 9.9 (s, 1H); ^{13}C-NMR ($CDCl_3$, 200 MHz, ppm) 22.3, 44.3, 49.8, 109.0, 109.2, 110.3, 126.6, 127.1, 17.7, 128.4, 137.5, 141.3, 155.2.
10. Physical data for compound 1: m.p.:226°C (EtOH); ^{1}H-NMR (DMSO-d_6, 200MHz, ppm) δ 3.1 (t, 2H, J = 6 Hz), 3.4 (t, 2H, J = 6 Hz), 6.2 (d, 1H, J = 8 Hz), 6.6 (d, 1H, J = 9 Hz), 7.0 (m, 1H), 9.8 (s, 1H), 9.9 (, 1H); ^{13}C-NMR (DMSO-d_6, 200 MHz, ppm) 22.3, 44.4, 108.0, 108.3, 108.7, 127.7, 139.4, 155.4.

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