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Unexpected Nucleophilic Participation and Rearrangement of DBU in Reactions with Saccharin Derivatives

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ABSTRACT

DBU attacks saccharin derivatives with subsequent rearrangement to give rise to 3-[3'-(1''-azepin-2''-onyl)propylamino]-1,2-benzisothiazole-1,1-dioxide **2** after work-up.

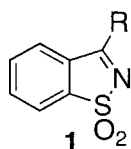
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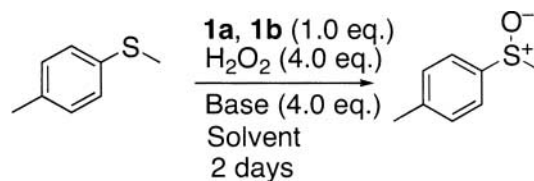
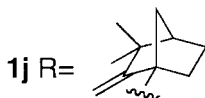


Key Words: DBU; Nucleophile.

In our earlier reports,^[1] it was shown that 3-substituted-1,2-benzisothiazole-1,1-dioxides **1** derived from saccharin are able to catalyze, in sub-stoichiometric amounts, the oxidation of sulfides to sulfoxides under basic reaction conditions, as are certain other sulfonylimines. The reactions are carried out by addition of hydrogen peroxide (30% w/v aqueous solution; 4.0 equiv.) to a stirred solution of base (4.0 equiv.), followed by the sulfonylimine (up to 1.0 equiv.) (Sch. 1).^[2] The imine mediators **1** were prepared according to a previously reported procedure.^[1,3] During oxidation of *p*-tolyl methyl sulfide using the mediators **1a** and **1b**, in which the 3-substituents are Cl and OEt respectively, yields of the sulfoxide are much lower than those observed when alkyl groups occupy the 3-position. Further, methyl *p*-tolyl sulfoxide was obtained in substantially lower yield when using DBU as the base in the oxidation reaction than when using aqueous potassium carbonate (see Table 1). It was observed that, in the DBU reactions, an additional product could be detected by TLC analysis. This was separated from the reaction mixture, crystallized, and the structure of



1a R=Cl; **1b** R=OEt; **1c** R=Me; **1d** R=Prⁱ; **1e** R=Buⁿ; **1f** R=Bu^s
1g R=Bu^t; **1h** R=Ph



Scheme 1.

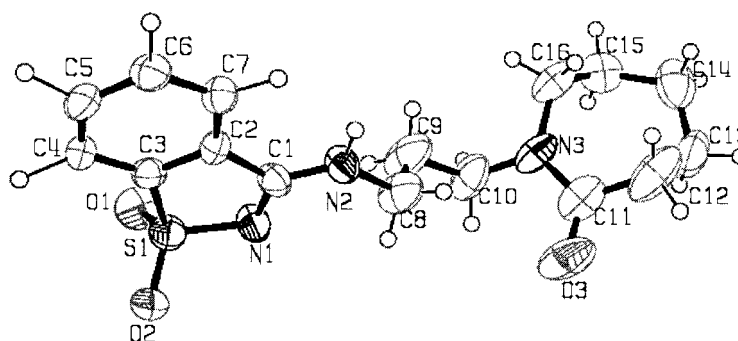


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Table 1. Oxidation of *p*-tolyl methyl sulfide catalysed by saccharin derivatives.

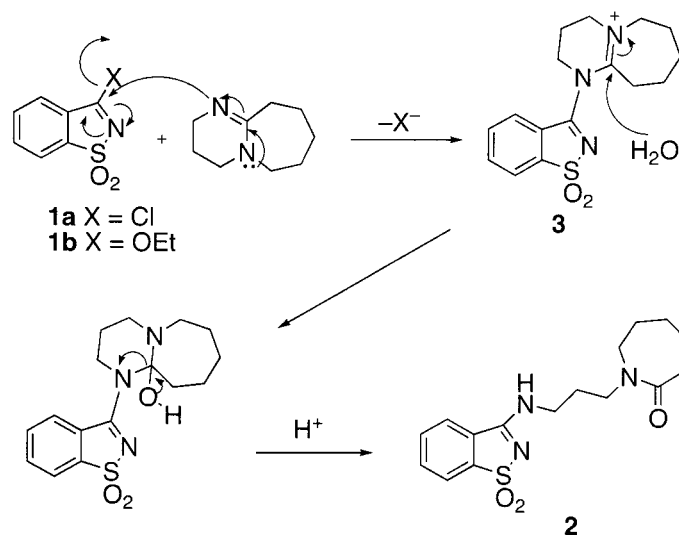
Mediator	Solvent	Base	Temp. (°C)	Reaction time	Yield of sulfoxide (%)	Yield of 2 (%)
1a	DCM	DBU	-25	2 days	11	12
1b	DCM	DBU	25	2 h		8
1b	DCM	DBU	25	2 days	13	25
1b	MeOH	K ₂ CO ₃	25	2 days	33	0
1g	DCM	DBU	25	2 h	100	0

**Figure 1.**

the compound determined by X-ray crystallography (Fig. 1).^a To our surprise, the structure proved to be **2**, containing both a saccharin residue and an *N*-aminopropyl caprolactam unit, presumably derived from DBU.

The formation of compound **2** can be explained by nucleophilic attack by one nitrogen atom of the 6-membered ring of DBU at the 3-position of *pseudo*-saccharin ethyl ether **1b** or *pseudo*-saccharyl chloride **1a**, displacing ethoxide ion or chloride ion respectively. Attack on the

^aMolecular formula C₁₆H₂₁N₃O₃S (M_r = 335.42), crystal size 0.200 × 0.200 × 0.450 mm³, monoclinic, space group P2₁/c, *a* = 8.463(7) Å, *b* = 16.475 (9) Å, *c* = 11.835 (7) Å, *V* = 1646 (2) Å³, *Z* = 4, *D* = 1.354 g cm⁻³, μ(MoKα) = 2.05 cm⁻¹, *F*₀₀₀ = 712.2997 Unique reflections collected on a Rigaku AFC6S sequential diffractometer, 2θ_{max} = 50.0°. The structure was solved by direct methods and H atoms were placed geometrically and allowed to ride on the relevant non-H atom. Refinement covered to give *R* = 0.061 and *R*_w = 0.069.



Scheme 2.

intermediate **3** by water, followed by opening of the bicyclic system, would afford compound **2** (Sch. 2). Consistent with this interpretation, compound **2** was not observed in the product mixture when alkyl saccharin derivatives **1c–1j** were used as mediators in the sulfoxidation reactions, 3-alkyl substituents not being good leaving groups. This reaction suggests that it would be wise to exercise caution when considering the use of DBU in reactions with electrophilic substrates, and particularly substrates containing good leaving groups.

EXPERIMENTAL SECTION

3-[3'-(1''-Azepin-2''-onyl)propylamino]-1,2-benzisothiazole-1,1-dioxide **2**

Hydrogen peroxide (30% w/v, 0.43 mL, 4 equiv.), was added to a stirred solution of DBU (576 mg, 3.78 mmol) in dichloromethane (10 mL) at room temperature, followed by 3-ethoxy-1,2-benzisothiazole-1,1-dioxide **1b** (200 mg, 0.946 mmol). Methyl *p*-tolyl sulfide (130 mg, 0.94 mmol) was added, and the reaction mixture was stirred at room temperature for 2 h, diluted with dichloromethane (30 mL), washed



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with brine (15 mL) and saturated aqueous sodium sulfite (20 mL), and dried over sodium sulfate. 3-[3'-(1''-Azepin-2''-onyl)propylamino]-1,2-benzisothiazole-1,1-dioxide **2** was isolated as a colourless solid by evaporation to dryness followed by flash column chromatography using ethyl acetate (25 mg, 8%), m.p. 212–213°C (from EtOH), (Found: C, 57.41; H, 6.35; N, 12.57. C₁₆H₂₁N₃O₃S requires C, 57.29; H, 6.31; N, 12.53%); $\nu_{\max}(\text{nujol})/\text{cm}^{-1}$ 1612, 1304 and 1152; $\delta_{\text{H}}(400 \text{ MHz}; \text{CDCl}_3)$ 1.50–1.94 (8H, m), 2.55 (2H, t, *J* 5.6), 3.4 (2H, t, *J* 7.4), 3.40–3.60 (4H, m), 7.50–7.70 (2H, m), 7.78–7.82 (2H, m), 8.74 (1H, s); $\delta_{\text{C}}(300 \text{ MHz}; \text{CDCl}_3)$ 23.8, 26.6, 28.5, 30.2, 37.4, 39.0, 45.4, 50.3, 122.0, 122.1, 128.8, 133.1, 133.4, 142.9, 160.0, 178.6; *m/z* (EI) 335.13036 (M⁺, 8%. C₁₆H₂₁N₃O₃S requires 335.13036), 140 (100) and 41 (44).

ACKNOWLEDGMENT

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