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# Benzyl and t-Butyl Sulfoxides as Sulfenyl Halide Equivalents: A Convenient Preparation of Benzisothiazolones

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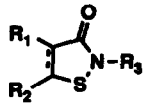
*Key Words:* isothiazolone; benzisothiazolone; cyclization; benzyl sulfoxide; t-butyl sulfoxide

***Abstract:*** *A new methodology is described for the synthesis of benzisothiazolones from benzylsulfinyl or t-butylsulfinyl substituted carboxamides that provides a mild alternative to conventional cyclization methods that employ halogens.*

Isothiazolones (1) and benzisothiazolones have attracted considerable interest as antibacterial and antifungal agents.[1] The isothiazolone ring is usually constructed by the cyclization of a suitably substituted sulfenyl halide (2), which is generally prepared from the corresponding disulfide or thiol by treatment with $Cl_2$, $Br_2$, $SO_2Cl_2$, or $SOCl_2$.[2] Alternatively, the isothiazolone may be prepared in one step by the treatment of a halosulfenyl acid chloride (3) with an amine.[3]

We have found the use of halogens or sulfenyl halides to be unduly harsh for general use in effecting ring closure. In addition, synthetic manipulations and the solubility of intermediates are considerably improved by protecting the sulfur atom. This avoids the presence of a reactive thiol group or the use of relatively insoluble disulfides in synthesis schemes. We therefore sought a means to oxidatively cyclize a suitably protected sulfide, without resorting to conventional deprotection sequences which afford the thiol.[4]

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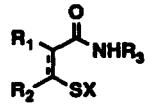


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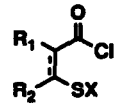


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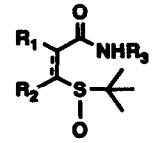


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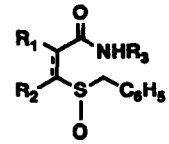
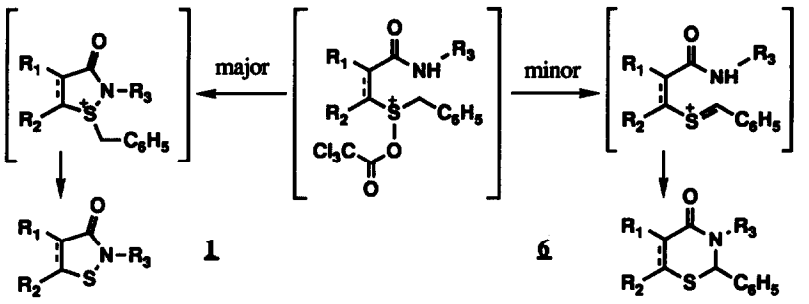



5

We reasoned that a t-butyl sulfoxide (4) should undergo thermal rearrangement with loss of isobutene to generate a sulfenic acid, which would cyclize with elimination of water to afford the desired isothiazolone. Indeed, this transformation occurred readily upon heating (see Table).[5] We then sought to extend this chemistry to other alkyl protecting groups for sulfur. Benzyl sulfoxides (5) did not cyclize to isothiazolones in useful yields upon heating. However, we found that exposure of the benzyl sulfoxide to trichloroacetic anhydride (TCAA) afforded the desired ring-closed product in good yield (see Table). Benzyl trichloroacetate could also

be isolated as a by-product.[6,7] Interestingly, the expected potential Pummerer rearrangement product (**6**) was isolated in only trace amounts (see Scheme 1).[8]

Scheme I

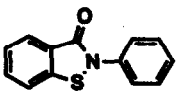
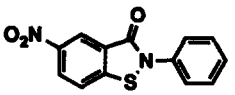
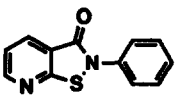
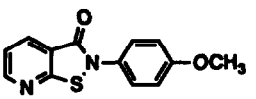
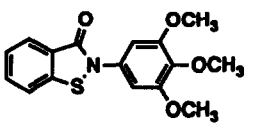
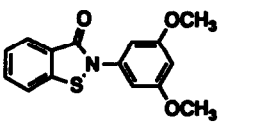
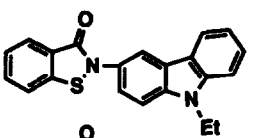
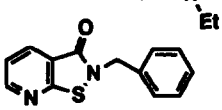
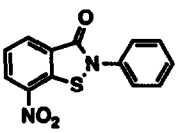



Extension of the t-butyl sulfoxide route (Method A) and the benzyl sulfoxide route (Method B) to a variety of substrates revealed these methods to be generally useful for the synthesis of isothiazolones, and in particular for the preparation of compounds inaccessible by previous routes involving the use of halogens or sulfenyl halides. The mildness and selectivity of the present conditions are demonstrated by the variety of compounds generated in Table 1. For example, the di- and tri-methoxy compounds (Entries 5, 6) were both dichlorinated in the anilide ring upon exposure to $SO_2Cl_2$ before cyclization occurred. Attempts to prepare the carbazole derivative (Entry 7) by standard methods led to extensive decomposition. The N-benzyl compound (Entry 8) was partially halogenated at the $PhCH_2N$ methylene upon exposure to sulfuryl chloride or halogens.

A comparison of Methods A and B (Entries 1 and 3) shows that Method B generally affords *ca.* 10% - 15% higher yields than Method A. This is not unexpected, as the sulfenic acid intermediate formed in Method A can disproportionate before cyclizing.[9] The synthetic versatility of these methods is further enhanced by the ready availability of several convenient routes for the introduction of the required t-butyl sulfide or benzyl sulfide into the synthesis scheme. The t-butyl sulfide precursors may be conveniently prepared by (a) reaction of an organolithium species with di-t-butyl disulfide (Entry 1); (b) displacement of an activated halide by tBuSK (Entries 2, 3, 9); or (c) reaction of a thiol with isobutene. The benzyl sulfide precursors may likewise be prepared by (a) reaction of a thiol with benzyl chloride (Entries 4, 5, 6, 7); (b) displacement of halide by $KSCH_2Ph$ (Entry 8); or (c) reaction of an organolithium species with dibenzyl disulfide. In all cases, the sulfides were most conveniently oxidized to the sulfoxides by addition of 1 equivalent of m-CPBA[10] in $CH_2Cl_2$ to the sulfide in $CH_2Cl_2$ at 0°.[11] Representative experimental procedures for both cyclization methods are given below:

**Method A: Cyclization of t-Butyl Sulfoxides:** A solution of 2-(t-butylsulfinyl)benzanilide (0.602 g, 2.0 mmol) in $CH_2Cl_2$ (3 mL) was added dropwise over 10 min to a rapidly refluxing mixture of toluene (50 mL) and pyridine (1 mL) under an air cooled condenser. The mixture was heated for 40 minutes, then was cooled, concentrated, and the residue was recrystallized from 1-chlorobutane to give 0.341 g (75%) of 2-phenylbenzisothiazolone (Table entry 1), mp 140° - 142°.

**Table 1**

| Entry # | Structure | Method | Yield[a] | mp, °C[b] |
|---|---|---|---|---|
| 1 |  | A (B) | 75% (84%) | 140-142[c] |
| 2 |  | A | 70% | 221-223[d] |
| 3 |  | A (B) | 75% (91%) | 134-135[e] |
| 4 |  | B | 81% | 175-176[f] |
| 5 |  | B | 79% | 120-121 |
| 6 |  | B | 62% | 103-104 |
| 7 |  | B | 78% | 147-149 |
| 8 |  | B | 86% | 75-76[g] |
| 9 |  | C[h] | 75% | 152-153 |

Method A: t-butyl sulfoxide, 110°. Method B: benzyl sulfoxide, TCAA, 0° to 25°. [a] Yields are for purified (chromatographed or recrystallized) products. [b] Satisfactory $^1$H NMR, mass spectral data, and elemental analyses were obtained for all products. [c] lit. mp 143°. [d] lit. mp 228°. [e] lit. mp 135°. [f] lit. mp 175°. [g] lit. mp 75° [h] Prepared directly from the sulfide.[12]

**Method B: Cyclization of Benzyl Sulfoxides:** A suspension of N-(4-methoxyphenyl)-2-(benzylsulfinyl)nicotinamide (0.852 g, 2.3 mmol) in $CH_2Cl_2$ (50 mL) under $N_2$ was cooled to 0° and treated with TCAA (0.47 mL, 2.6 mmol). After gradually warming to 25° over 3.5 h, the reaction mixture was quenched with 2 M NaOH and extracted with $CHCl_3$. The organic extracts were dried ($Na_2SO_4$),

concentrated, and the residue was chromatographed on silica gel (3:7 EtOAc:hexanes) to afford 0.574 g (97%) of 2-(4-methoxyphenyl)-[5,4-b]-pyridoisothiazolone (Table entry 4), mp 175° - 176°.

In summary, new methodology is presented that employs t-butyl sulfoxides or benzyl sulfoxides as precursors in a simple, mild, and high-yielding preparation of isothiazolones. Efforts to explore the extension of this methodology to other chalcogens and other ring systems are currently underway.

## REFERENCES AND NOTES


1. See, for example: US Patents 4,654,354 (31 Mar 1987); 4,548,942 (22 Oct 1985); 4,512,985 (23 Apr 1985); 3,965,107 (22 Jun 1976), 4,868,310 (19 Sep 1989).
2. US Patent 4,397,858 (9 Aug 1983). Monge, A.; Martinez-Merino, V. *J. Heterocyclic Chem.*, **1988**, *25*, 23. Schaper, W. *Synthesis*, **1985**, 861.
3. Baggeley, K. H.; English, P. D.; Jennings, J. A.; Morgan, B.; Nunn, B., Tyrrell, W. K. *J. Med. Chem.*, **1985**, *28*, 1661.
4. Cleavage of benzyl sulfides to sulfenyl chlorides by warming with $SO_2Cl_2$ or $Cl_2$ has been reported: Kharasch, N.; Langford, R. B. *J. Org. Chem.*, **1963**, *28*, 1903.
5. A related reaction with allyl sulfoxides has been reported: Hoffmann, R. W.; Goldmann, S. *Chem. Ber.*, **1978**, *111*, 2716.
6. Isothiazole formation has been noted in the Pummerer reaction: Murata, I.; Yamazaki, S.; Yamamoto, K.; Fukuzawa, Y. *J. Org. Chem.*, **1987**, *52*, 5239.
7. The cyclization of 2-(methylsulfinyl)benzenecarboxamides to benzisothiazolones has been reported to occur with $SOCl_2$: Uchida, Y.; Kozuka, S. *Chem. Commun.*, **1981**, 510. In the present study, the use of methyl sulfoxides with active acid derivatives frequently gave significant amounts of the methyl sulfide.[9] The cyclization of 3-alkylselenopropionamides to isoselenazolidin-3-ones with ozone *via* the intermediate selenoxide and selenenic acid have also been reported: Reich, H. J.; Jasperse, C. P. *J. Am. Chem. Soc.*, **1987**, *109*, 5549.
8. Approximately 5% of the Pummerer product can be isolated from a typical reaction mixture.
9. The t-butyl sulfoxide can be cyclized with trichloroacetic anhydride similarly to the benzyl sulfoxide. See also, Brichard, M. H.; Musick, M.; Janousek, Z.; Viehe, H. G. *Syn. Commun.*, **1990**, *20*, 2379. Treatment of the t-butyl and benzyl sulfoxides with other active acid derivatives, such as thionyl chloride, acetyl chloride, or isobutyryl chloride also results in cyclization to the benzisothiazolones in good yields; however, some reduction to the sulfide is occasionally noted in these cases (see Numata, T.; Oae, S. *Chem. Ind. (London)*, **1973**, 277). The benzyl sulfoxides will slowly cyclize by 2,3-sigmatropic rearrangement and elimination of *o*-cresol upon heating at 180°.
10. Peracid content was determined by iodometric titration before use.
11. The sulfoxides are conveniently crystallized from acetone.
12. The t-butyl sulfide was resistant to oxidation with m-CPBA. Cyclization was effected with 1 eq. $SO_2Cl_2$ in $CH_2Cl_2$ at -78°. A similar oxidative S-dealkylation has recently been reported: Chan, M.F.; Garst, M. E. *J. Chem. Soc., Chem. Commun.*, **1991**, 540.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