Improved Synthesis of 2,3-Dibromo-1-(phenylsulfonyl)-1-propene (DBP)

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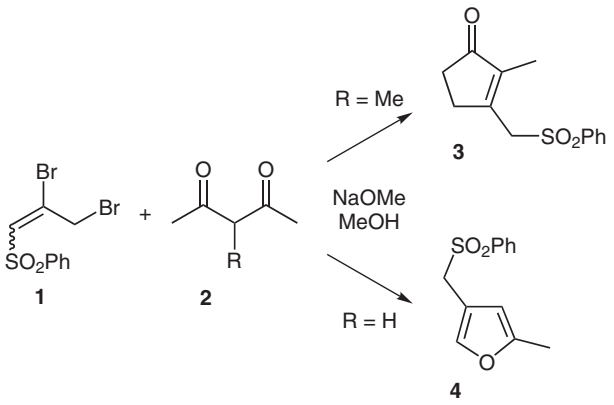
Abstract: A convenient preparation of 2,3-dibromo-1-(phenylsulfonyl)-1-propene (DBP, **1**) is available through the one-pot propargylation and oxidation of thiophenol to give the propargyl sulfone **11**, which is isomerized and brominated in another one-pot reaction. The new preparation is significantly more scalable, as well as more convenient and robust than the prior art.

Key words: sulfones, halogenation, alkynes, allenes, thiols

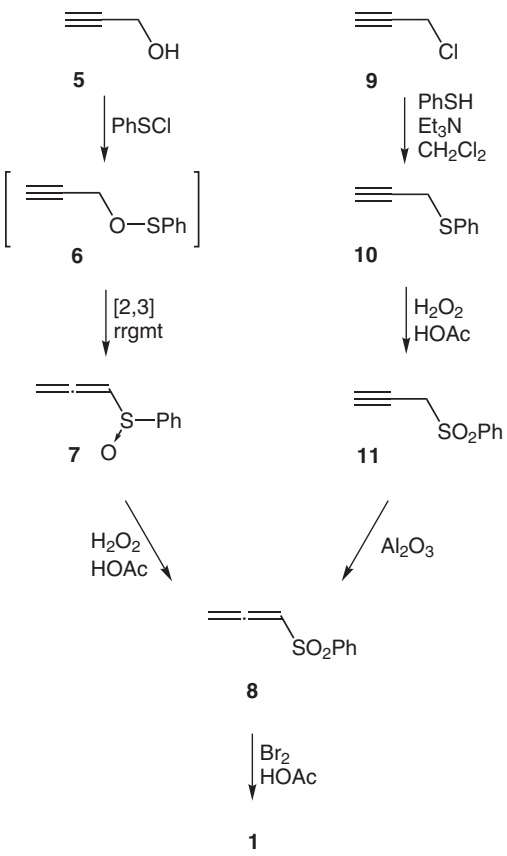
2,3-Dibromo-1-(phenylsulfonyl)-1-propene (DBP, **1**)[1] is a multifunctional three-carbon synthon which can be used to prepare cyclopentenones (**3**)[2,3] and furans (**4**)[2,4] from 1,3-dicarbonyl compounds (Scheme 1). Despite its versatile reactivity, DBP is a shelf-stable crystalline compound which can be stored indefinitely without any particular precautions.



Scheme 1 DBP (**1**) as a precursor to cyclopentenones and furans

DBP is prepared by the dibromination of phenylsulfonyl allene (**8**), an interesting shelf-stable sulfone reagent in its own right.[5] While there are several known methods to access **8**, including the reaction of an allenyl cobaloxime[6] or propargyl triphenylstannane[7] with phenylsulfonyl chloride, the two previously known methods most amenable to the large scale are shown in Scheme 2. As one option, propargyl alcohol (**5**) is treated with phenylsulfenyl chloride to give the thermally unstable thioperoxide **6** which undergoes spontaneous [2,3] rearrangement to the allenyl sulfoxide **7**; oxidation with hydrogen peroxide gives sulfone **8**.[1,8] The alternative classical synthesis proceeds via phenyl propargyl sulfide (**10**), which results from the S_N2 reaction of propargyl chloride (**9**) with thiophenol in the presence of triethylamine. The sulfide is typically oxidized in glacial acetic acid to the terminal alkynyl sulfone **11**, which in turn can be isomerized to the thermodynamically more stable allene **8** by percolation through an alumina column.[9] With **8** in hand, bromination in acetic acid provides DBP.

Our ongoing research requires the frequent preparation of DBP on a multi-gram scale, and we have come to recognize several problems with the existing methodology, particularly for undergraduate laboratories. The propargyl alcohol route is burdened by the preparation of phenylsulfenyl chloride,[10] which is logistically involved and requires the handling of large amounts of sulfuryl chloride. Once formed, the air- and moisture-sensitive phenylsulfenyl chloride must be used immediately or yields and purity of the end product deteriorate sharply.



Scheme 2 Two conventional routes to DBP (**1**)

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As for the propargyl chloride route, the initial S_N2 reaction proceeds practically quantitatively without incident, although mechanical stirring is required on the preparative scale, due to the voluminous triethylammonium chloride that precipitates midway through the reaction. Also, even though the initial NMR spectrum of the phenyl propargyl sulfide (**10**) looks quite pure, the crude phenyl propargyl sulfide (**10**) must be distilled under vacuum for adequate yield in the subsequent oxidation, and mass recovery can vary widely at this step.

The oxidation itself provided some logistical challenges, particularly with respect to the narrow temperature window of 96–102 °C required during the peroxide addition. Higher temperatures lead to lower yields, and lower temperatures can result in a pause in oxidation that can resume violently after a considerable portion of the peroxide has been added. The authors have experienced the latter phenomenon on more than one occasion. Finally, the removal of all traces of the solvent acetic acid from the isolated crystalline product required storage for several days at 1 Torr. The subsequent isomerization encountered scalability issues with respect to the capacity (and cost) of the alumina column, and the bromination presented the same issue as the oxidation with respect to solvent handling and removal.

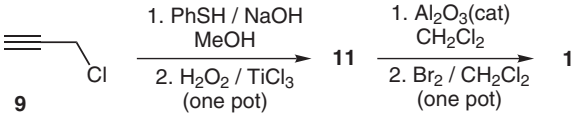
Studies were thus undertaken to improve the robustness and reduce the time cycle of this important preparation. Attempts to access phenyl propargyl sulfone (**11**) directly through the reaction of sodium benzenesulfinate with propargyl chloride – by analogy to previous work of Wildeman and Van Leusen[11] – did not provide **11** in high yields, presumably due to base-catalyzed isomerization and polymerization of the product.

After considerable optimization, however, an improved synthesis was indeed developed (Scheme 3), beginning with novel one-pot conditions for the alkylation and oxidation of thiophenol. First, the organic base was replaced with sodium hydroxide, and the less expensive and more environmentally friendly methanol was used as a solvent instead of dichloromethane. Care must be taken to ensure a stoichiometric amount of base is added, since excess hydroxide irreversibly displaces phenylsulfide to give propargyl alcohol, and thereby reduces the overall yield.

Using methanol as a solvent also allows for subsequent oxidation in the same pot. Here we took inspiration from the report of Watanabe and co-workers regarding the selective oxidation of sulfides to sulfoxides in methanolic hydrogen peroxide using titanium trichloride as a catalyst.[12] Since sulfoxides are obtained almost immediately at room temperature, we reasoned that the same catalyst might be applied to the low-temperature oxidation to sulfones (albeit with longer reaction times), thus circumventing the latency issues encountered under conventional methodology.

Thus, the crude methanolic solution of phenyl propargyl sulfide (**10**) was treated with excess hydrogen peroxide at room temperature in the presence of 2 mol% $TiCl_3$. Since the product sulfone (**11**) tends to undergo unwanted side reactions under strongly basic conditions, the excess hydroxide from the initial alkylation step was neutralized with hydrochloric acid prior to the oxidation as a precautionary measure. To our delight, these conditions led to a smooth and controllable exotherm throughout the course of the peroxide addition, after which the reaction mixture had typically warmed to about 45 °C on its own. Once the addition was complete, the solution was heated to reflux for one hour, diluted with water, and cooled to room temperature to precipitate phenyl propargyl sulfone (**11**) as colorless crystals in high purity and 81% isolated yield (over two steps).

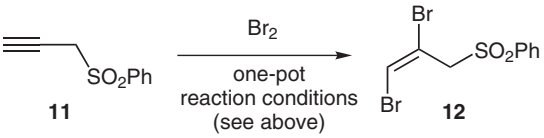
While the oxidation of aryl alkyl sulfides to prepare the corresponding sulfones is well documented,[13] the development of new catalytic methodology continues to be of current interest.[14] The present example demonstrates the considerable utility of applying Watanabe's conditions to sulfone synthesis. Attempts to oxidize **10** in methanol without catalyst led to low yields and complex product mixtures.



Scheme 3 Optimized synthetic route to DBP (**1**)

Turning our attention to the allene isomerization, this step was modified to be more amenable to the large scale by removing the alumina column chromatography and instead stirring a chloroform solution of **11** with a catalytic amount of neutral alumina. After three hours, a 93:7 (allene/alkyne) equilibrium ratio had been reached, and the bromination could be carried out by the direct addition of bromine to the reaction vessel without prior purification or removal of the alumina.

The bromination itself was operationally straightforward: the bromine was added by syringe in one portion at room temperature, and the reaction was complete within two hours. Filtration and rotary evaporation provided an oil containing **1** in over 90% yield as a 5:1 (*E*/*Z*) mixture of diastereomers, along with ca. 5% of the regioisomeric by-product **12** arising from the bromination of residual phenyl propargyl sulfone (**11**) (Scheme 4). This contaminant was easily removed by silica gel chromatography to yield **1** in 88% yield (*E* and *Z* isomers).



Scheme 4 Bromination by-product from phenyl propargyl sulfone

It is interesting to note that the present method exhibits a modestly enhanced preference for the *E* isomer (5:1) com-

pared to the prior art (7:3).[1a] The origin of this improved stereoselectivity is unclear at this time, but remains a subject of further study in our laboratory.

In conclusion, we report a less expensive, more scalable, robust, and environmentally benign process for the preparation of propargyl sulfone **10**, allene **11**, and DBP (**1**) featuring a low-temperature oxidation of sulfides to sulfones. We are currently investigating the scope and limitations of this methodology.

Phenyl Propargyl Sulfone (11)

To a stirred solution of thiophenol (97%, 60.0 mL, 0.568 mol, 1.00 equiv) in MeOH (600 mL, ACS grade) under nitrogen is added dropwise over 5 min at 0 °C NaOH (10 N, 57.0 mL, 0.570 mol, 1.00 equiv), followed by propargyl chloride (98%, 43.2 mL, 0.584 mol, 1.03 equiv). The mixture is allowed to warm to r.t. and stir until TLC (25% EtOAc in hexane) indicates the disappearance of thiophenol (ca. 3–5 h), by which time NaCl has precipitated in the reaction mixture.

To this heterogeneous mixture is added HCl (37.2%, 1.2 mL, 17 mmol, 0.03 equiv), followed immediately by $TiCl_3$ (20%, 7.2 mL, 11 mmol, 0.02 equiv). An excess of H_2O_2 (33%, 232 mL, 2.27 mol, 4.00 equiv) is added over ca. 20 min, starting at r.t. and allowing the temperature to rise to about 65 °C, cooling with an ice bath as necessary. After the addition is complete, the mixture is heated to reflux until TLC (25% EtOAc in hexane) indicates the disappearance of the intermediate phenyl propargyl sulfide (about 1 h). While still hot, the mixture is diluted with H_2O (600 mL), then allowed to cool to r.t. and stand overnight, during which time white crystals of phenyl propargyl sulfone precipitate. The slurry is cooled to 0 °C to further facilitate crystallization, isolated on a Büchner funnel (Whatman No. 2 paper), washed with H_2O, and dried, to yield 93.8 g (92% of theory) of phenyl propargyl sulfone as a white crystalline solid with spectroscopic properties identical to those reported in the literature.[1a]

2,3-Dibromo-1-phenylsulfonyl-1-propene (DBP, 1)

In a 100 mL round-bottom flask equipped with magnetic stirring, phenyl propargyl sulfone (1.00 g, 5.55 mmol, 1.00 equiv) is dissolved in $CHCl_3$ (15 mL). The solution is treated with neutral alumina (1.00 g), Brockman activity I, and allowed to stir for 3 h at r.t. The solution of allene is then treated with Br_2 (0.33 mL, 1.02 g, 6.41 mmol, 1.15 equiv). The dark red solution is allowed to stir at r.t. for 2 h to give a light-orange or colorless reaction mixture. After TLC (20% EtOAc in hexane) had confirmed the total consumption of starting material, the alumina was removed by filtration, the organic layer was washed with a dilute solution of $Na_2S_2O_3$ to remove excess Br_2, dried over Na_2SO_4, and concentrated to give a light-yellow oil containing ca. 1.76 g (93%) of DBP (**1**) as a 5:1 mixture of diastereomers, and ca. 0.09 g (5%) of *E*-2,3-dibromo-1-(phenylsulfonyl)-2-propene (**12**). This crude oil was typically used without further purification. However, flash chromatography (silica gel, 25% EtOAc in hexane) cleanly separated the crude mixture into the following components:

***E*-2,3-Dibromo-1-(phenylsulfonyl)-1-propene (*E*-1)**:[1a] 1.38 g; R_f = 0.67; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.90 (s, 2 H), 6.76 (s, 1 H), 7.59–7.96 (m, 5 H).

***Z*-2,3-Dibromo-1-(phenylsulfonyl)-1-propene (*Z*-1)**:[1a] 0.29 g; R_f = 0.41; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.23 (s, 2 H), 6.89 (s, 1 H), 7.59–8.01 (m, 5 H).

***E*-2,3-Dibromo-1-(phenylsulfonyl)-2-propene (11)**: 0.07 g; R_f = 0.54; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.39 (s, 2 H), 6.75 (s, 1 H), 7.55–7.96 (m, 5 H).

References

(1) (a) Watterson, S. H.; Ni, Z.; Murphree, S. S.; Padwa, A. *Org. Synth.* **1997**, *74*, 115. (b) '2,3-Dibromo-1-(phenylsulfonyl)-propene': *Reagents for Organic Synthesis*, Vol. 16; Fieser, M., Ed.; John Wiley & Sons: New York, **1992**, 107.
(2) Padwa, A.; Ishida, M.; Muller, C. L.; Murphree, S. S. *J. Org. Chem.* **1992**, *57*, 1170.
(3) (a) Padwa, A.; Murphree, S. S.; Yeske, P. E. *J. Org. Chem.* **1990**, *55*, 4241. (b) Padwa, A.; Austin, D. J.; Ishida, M.; Muller, C. M.; Murphree, S. S.; Yeske, P. E. *J. Org. Chem.* **1992**, *57*, 1161.
(4) (a) Padwa, A.; Muller, C. L.; Rodriguez, A.; Watterson, S. H. *Tetrahedron* **1998**, *54*, 9651. (b) Murphree, S. S.; Muller, C. L.; Padwa, A. *Tetrahedron Lett.* **1990**, *31*, 6145.
(5) (a) Guildford, A. J.; Turner, R. W. *J. Chem. Soc., Chem. Commun.* **1983**, 466. (b) Denmark, S. E.; Harmata, M. A.; White, K. S. *J. Org. Chem.* **1987**, *52*, 4031. (c) Saito, S.; Hirayama, K.; Kabuto, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10776.
(6) Gupta, B. D.; Roy, S. *Tetrahedron Lett.* **1986**, *27*, 4905.
(7) Russell, G. A.; Herold, L. L. *J. Org. Chem.* **1985**, *50*, 1037.
(8) Horner, L.; Binder, V. *Liebigs Ann. Chem.* **1972**, *757*, 33.
(9) (a) Stirling, C. J. M. *J. Chem. Soc.* **1964**, 5863. (b) Pourcelot, G.; Cadiot, P. *Bull. Soc. Chim. Fr.* **1966**, *9*, 3024.
(10) Barrett, A. G. M.; Dhanak, D.; Graboski, G. G.; Taylor, S. *J. Org. Synth., Coll. Vol. VIII* **1993**, 550.
(11) Wildeman, J.; Van Leusen, A. M. *Synthesis* **1979**, 733.
(12) Watanabe, Y.; Numata, T.; Oae, S. *Synthesis* **1981**, 204.
(13) (a) Hollingworth, G. J. In *Comprehensive Organic Functional Group Transformations*, Vol. 2; Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W.; Pattenden, G., Eds.; Elsevier: Oxford, **1995**, 144-152, 154–156. (b) *The Synthesis of Sulphones, Sulphoxides, and Cyclic Sulphides*; Patai, S.; Rappoport, Z., Eds.; Wiley: New York, **1994**.
(14) (a) Sato, K.; Hyodo, M.; Aoki, M.; Zheng, X.-Q.; Noyori, R. *Tetrahedron* **2001**, 2469. (b) Alonso, D. A.; Nájera, C.; Varea, M. *Tetrahedron Lett.* **2002**, *43*, 3459.