



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at [http://www.nap.edu/catalog.php?record\\_id=12654](http://www.nap.edu/catalog.php?record_id=12654)). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

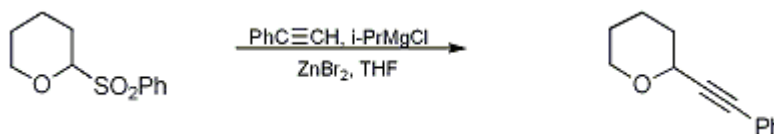
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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

*Organic Syntheses, Coll. Vol. 9, p.688 (1998); Vol. 70, p.157 (1992).*

## SUBSTITUTION REACTIONS OF 2-BENZENESULFONYL CYCLIC ETHERS: **TETRAHYDRO-2-(PHENYLETHYNYL)-2H- PYRAN**

### [2H-Pyran, tetrahydro-2-(phenylethenyl)-]



Submitted by Dearn S. Brown and Steven V. Ley<sup>1</sup>.

Checked by David J. Mathre and Ichiro Shinkai.

### 1. Procedure

An oven-dried, three-necked, 1-L, round-bottomed Morton flask equipped with a mechanical stirrer, gas bubbler outlet, 125-mL, pressure-equalizing addition funnel fitted with a rubber septum, and a nitrogen inlet (Note 1) is charged with 11.2 g (110 mmol) of phenylacetylene (Note 2) and 60 mL of dry tetrahydrofuran (THF) (Note 3). The addition funnel is charged with 60 mL of 2 M isopropylmagnesium chloride (Note 4) which is then added over a 5-min period (Note 5). The addition funnel is rinsed with 10 mL of dry THF and the solution is stirred at room temperature for 1 hr. The addition funnel is charged with 72 mL of 1 M anhydrous zinc bromide in THF (Note 6) which is then added to the light-grey solution over a 5-min period (Note 7). The addition funnel is rinsed with 10 mL of dry THF, and the mixture is stirred for a further 30 min at room temperature (Note 8). The addition funnel is charged with a solution of 22.6 g (100 mmol) of 2-(phenylsulfonyl)tetrahydro-2H-pyran (Note 2) dissolved in 100 mL of dry THF, which is then added over a 5-min period (Note 9). The resulting grey solution is stirred at room temperature for 18 hr and then quenched with 300 mL of 1 M hydrochloric acid (Note 10). The mixture is transferred to a single necked, 1-L, round-bottomed flask and concentrated under reduced pressure (40°C, 100 mm) to remove the THF. The residue is transferred to a 1-L separatory funnel and extracted with 300 mL of isopropyl acetate (i-PrOAc). The extract is sequentially washed with water (150 mL), 1 M aqueous dibasic potassium phosphate (3 × 150 mL), and brine (150 mL). The extract is dried over anhydrous sodium sulfate, filtered through a sintered glass funnel, washing the residue with more i-PrOAc, and then concentrated under reduced pressure (40°C, 10 mm) to give 19.6 g of crude product as a pale yellow liquid (Note 11). This is distilled under reduced pressure to afford 18.3 g (98%) of tetrahydro-2-(phenylethynyl)-2H-pyran as a colorless liquid, bp 110–115°C (0.01 mm) (Note 12).

### 2. Notes

1. A constant stream of anhydrous nitrogen (dried over molecular sieves) was maintained throughout the reaction.
2. All the chemicals used in this procedure were purchased from Aldrich Chemical Company, Inc., and were used without further purification unless otherwise stated.
3. Tetrahydrofuran was dried over 3Å molecular sieves (residual water content <20 µg/mL) and purged with nitrogen prior to use.
4. Isopropylmagnesium bromide can also be used in this type of experiment.
5. The reaction is exothermic, the internal temperature rising from 20°C to 44°C. *CAUTION: Do not run the reaction under more concentrated conditions, or on a larger scale without providing external cooling.*
6. Zinc bromide (100 g, 440 mmol) (98+%, (Note 2)) was dissolved in dry THF bringing the volume to 440 mL (exothermic heat of solution). The initial water content (1.2 mg/mL) was reduced to <50 µg/mL by drying the solution with 3Å molecular sieves (50 g) for 24 hr.
7. The reaction is exothermic, the internal temperature rising from 20°C to 34°C. See (Note 5).

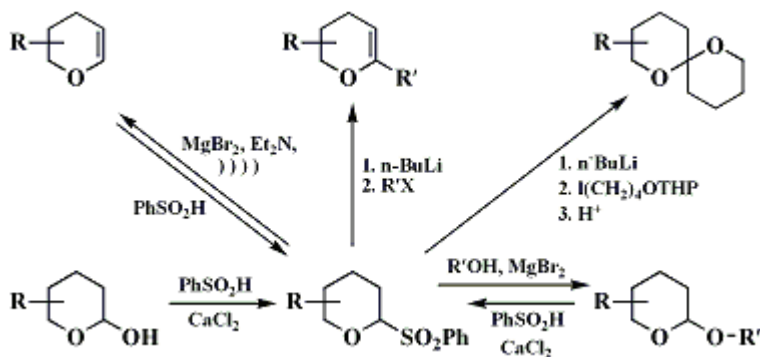
8. On addition of **zinc bromide** a fine white precipitate is sometimes formed (observed by checkers).
9. The reaction is exothermic, raising the internal temperature from 20°C to 32°C. See (Note 5).
10. The quench is exothermic during addition of the first ca. 25 mL of the aqueous **hydrochloric acid**, the internal temperature rising from 20°C to 30°C.
11. HPLC analysis is as follows: 94.1 wt% product, 2.4 wt% **phenylacetylene**, remainder i-PrOAc. HPLC conditions are as follows: [4.6 × 250 mm Zorbax RX; 40:60 H<sub>2</sub>O (0.01 M KH<sub>2</sub>PO<sub>4</sub>)/MeCN; 1.5 mL/min; UV 210 nm] **phenylsulfonic acid** (2.6 min), **2-(phenylsulfonyl)tetrahydro-2H-pyran** (4.7 min, decomposes in solution), **phenylacetylene** (6.1 min), **tetrahydro-2-(phenylethynyl)-2H-pyran** (9.2 min).
12. The physical properties are as follows: literature bp 149°C (8 mm);<sup>2</sup> HPLC analysis: >99 wt% product, <0.1% **phenylacetylene**; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.50–2.00 (m, 6 H, C3-H<sub>2</sub>, C4-H<sub>2</sub>, C5-H<sub>2</sub>), 3.53–3.66 (m, 1 H, C6-H), 4.00–4.13 (m, 1 H, C6-H), 4.52 (dd, 1 H, J = 2.8, 7.4, C2-H), 7.26–7.35 (m, 3 H, Ar-H), 7.41–7.51 (m, 2 H, Ar-H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 21.8 (t), 25.7 (t), 32.2 (t), 66.6 (t), 67.5 (d), 85.2 (s), 88.1 (s), 122.8 (s), 128.2 (d), 128.3 (d), 131.8 (d).

### Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

### 3. Discussion

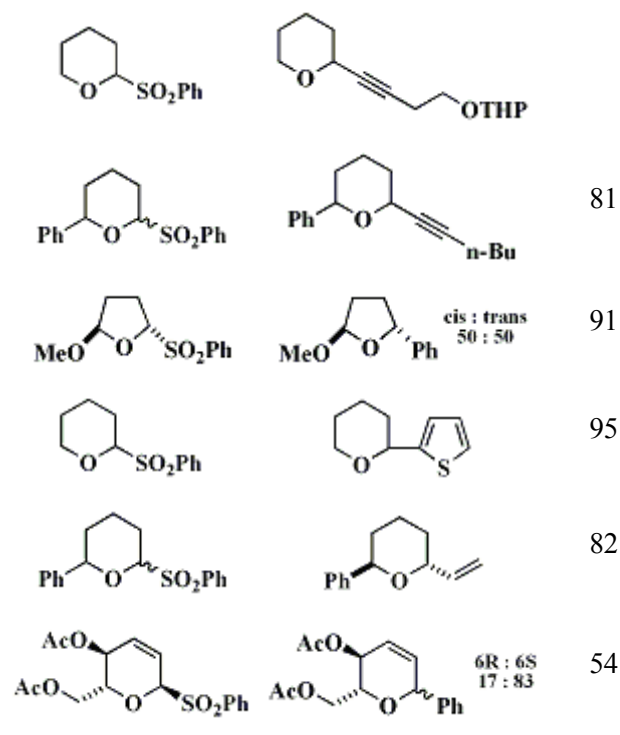
Methods for forming carbon-carbon bonds at the anomeric position of cyclic ethers are important processes in organic synthesis. We have shown how lactols and their derivatives can be readily converted into the corresponding 2-benzenesulfonyl cyclic ethers.<sup>3,4</sup> These versatile intermediates can then be transformed into the corresponding dihydropyrans,<sup>3</sup> 2-substituted dihydropyrans,<sup>4</sup> spiroacetals,<sup>4,5</sup> and tetrahydropyranyl ethers<sup>6</sup> (Scheme 1).



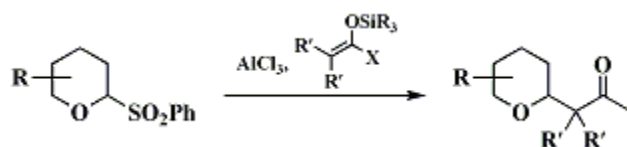
The procedure illustrated here is representative of a general and versatile method for the preparation of 2-substituted tetrahydrofurans and tetrahydropyrans from cyclic ether sulfones and the appropriate alkynyl, vinyl, or aryl Grignard reagent. From the examples shown in the Table and others previously reported,<sup>3,7</sup> a selectivity for the trans-product is observed with 6-substituted tetrahydropyrans irrespective of the initial geometry of the sulfone. This implies the presence of a common reaction intermediate such as an oxonium ion which is trapped by preferred axial bond formation at the 2-position. For 5-substituted tetrahydrofurans, significant trans-selectivity is only observed with large substituents.

TABLE  
SUBSTITUTION REACTIONS OF 2-  
BENZENESULFONYL CYCLIC ETHERS

Sulfone	Product(s)	Yield (%)
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The benzenesulfones also undergo nucleophilic displacement with silyl enol ethers and ketene silyl acetals in the presence of a Lewis acid such as aluminum trichloride (Scheme 2).<sup>8</sup>



## References and Notes

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## Appendix

### Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

brine

hydrochloric acid (7647-01-0)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

aluminum trichloride (3495-54-3)

Ketene (463-51-4)

Phenylacetylene (536-74-3)

isopropylmagnesium bromide (920-39-8)

isopropylmagnesium chloride (1068-55-9)

Tetrahydrofuran (109-99-9)

zinc bromide (7699-45-8)

isopropyl acetate (108-21-4)

phenylsulfinic acid (618-41-7)

silyl (13765-44-1)

Tetrahydro-2-(phenylethynyl)-2H-pyran (70141-82-1)

2H-Pyran, tetrahydro-2-(phenylethenyl)-

2-(phenylsulfonyl)tetrahydro-2H-pyran (96754-03-9)

potassium phosphate (7778-53-2)