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# Use of 2,3-Dibromo-1-(phenylsulfonyl)-1-propene as a Reagent for the Synthesis of Annulated Furans

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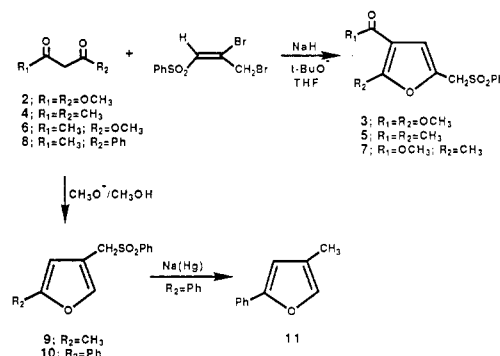
Received May 10, 1990

**Summary:** Treatment of 2,3-dibromo-1-(phenylsulfonyl)-1-propene with various  $\beta$ -dicarbonyl compounds in the presence of sodium methoxide affords 2,4-disubstituted and 2,3-fused bicyclic furans in high yield. Formation of the furan ring involves a sequence of addition-elimination, deacetylation, and  $S_N2$  displacement reactions.

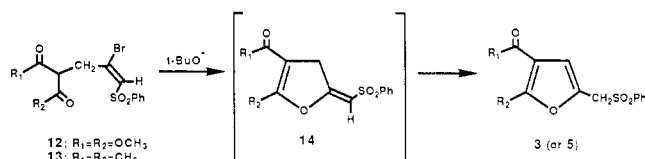
The development of procedures for efficiently constructing annulated furans continues to be of interest to synthetic chemists,<sup>1-8</sup> especially since various sesqui- and diterpenes contain the furan ring as a common structural unit.<sup>9-13</sup> We now report on the use of 2,3-dibromo-1-(phenylsulfonyl)propene (1) (DBP), which incorporates an aggregate of reactive electrophilic functional groups in a readily available, stable molecule.<sup>14</sup> In its chemical behavior, this reagent acts as a dielectrophile, permitting the facile formation of substituted furans of synthetic interest. In this paper we report the initial scope of the methodology and suggest its application as a means to synthesize a variety of annulated furans.

We envisioned using DBP in a route to furans by taking advantage of the ambident nature of ketones. By first alkylating a ketone enolate at the carbon atom with DBP, then effecting ring closure on the oxygen atom, furans could be formed. An example of the use of 1 as a dielectrophile is provided in its reaction with dimethyl malonate using NaH/*t*-BuOK in THF. The major product isolated in 77% yield was a crystalline solid whose structure was identified as furan 3. A similar transformation occurred with 2,4-pentanedione (4) or methyl acetoacetate (6), producing furans 5 and 7 in 80% and 87% yield, respectively.<sup>15</sup> Most interestingly, when the reactions of 4 (or 6) and 8 with DBP were carried out in methanol using sodium methoxide as the base, the 2,4-disubstituted furans 9 (85%) and 10 (82%) were obtained as the exclusive products. Desulfonylation of 10 with sodium amalgam

afforded a sample of the known 2-phenyl-4-methylfuran (11).<sup>16</sup>



By carrying out the reaction of the  $\beta$ -dicarbonyl compound with 1 for short periods of time, it was possible to isolate a series of intermediates and thus elucidate the source of this change in the regiochemical outcome. When the reaction was performed in THF using sodium hydride as the base, the resulting enolate anion selectively displaced the allylic bromide, giving rise to bromovinyl sulfone 12 (or 13) as an isolable species. This material was readily converted by reaction with potassium *tert*-butoxide to furan 3 (or 5) in high yield. This latter transformation



proceeds by a 5-*exo-trig* addition-elimination sequence, producing 14 as a transient species which rapidly isomerizes to the furan. When methanol was used as the solvent, the isomeric  $\beta$ -bromo sulfone 15 (or 16) is first formed (30 min) by an addition-elimination reaction of the enolate onto the activated  $\pi$ -bond of DBP.<sup>17</sup> The initially formed diketo compound is readily deacetylated upon further exposure (5 h) to sodium methoxide, giving rise to bromo sulfone 17 (or 18) in high yield. This compound readily affords furan 9 (or 10) by intramolecular displacement of bromide by the resulting enolate anion (i.e. 17  $\rightarrow$  19  $\rightarrow$  9). This protocol is not limited to the preparation of furans only. For example, treatment of an equimolar mixture of 2,4-pentanedione and DBP with 1 equiv of methanolic sodium methoxide followed by an excess of aqueous methylamine results in the clean formation of pyrrole 20 in high yield.

The methodology is also amenable to the synthesis of 2,3-fused bicyclic furans. Treatment of DBP with 1,3-cyclohexanedione in the presence of sodium methoxide

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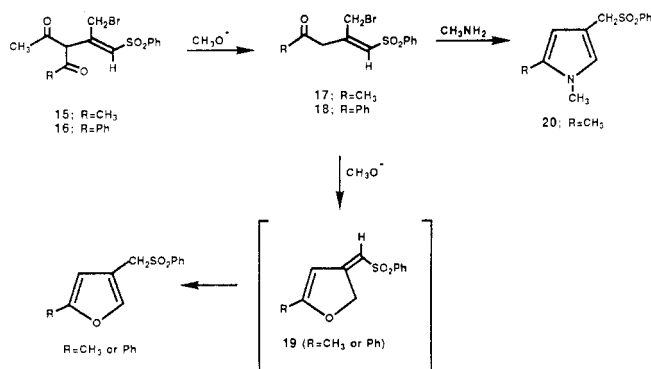
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(14) DBP is prepared by the addition of bromine to (phenylsulfonyl)allene in glacial acetic acid. It is a stable, crystalline solid, mp 62–63 °C. NOE experiments indicate that the bromo and sulfonyl groups are located trans to each other. For preparation of phenylsulfonyl allene see: Stirling, C. J. M. *J. Chem. Soc.* **1964**, 5856. Padwa, A.; Craig, S. P.; Chiacchio, U.; Kline, D. N. *J. Org. Chem.* **1988**, *53*, 2232.

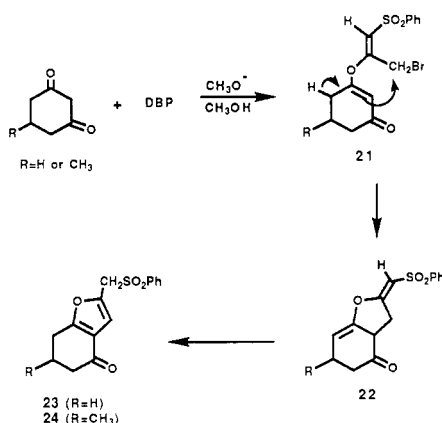
(15) Alkylation of simple ketones with DBP gave complex reaction mixtures.

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(17) The difference in product distribution as a function of the nature of the solvent is probably related to a number of factors. Nucleophilic substitution reactions carried out in aprotic solvents often occur more readily than comparable reactions in protic solvents since, in hydrogen-bonding solvents, the enolate anion is subject to strong solvation forces that lower its ground state energy. Also, hydrogen bonding of methanol onto the sulfonyl group might be expected to lower the LUMO of the  $\pi$ -bond and thereby enhance the conjugate addition pathway.



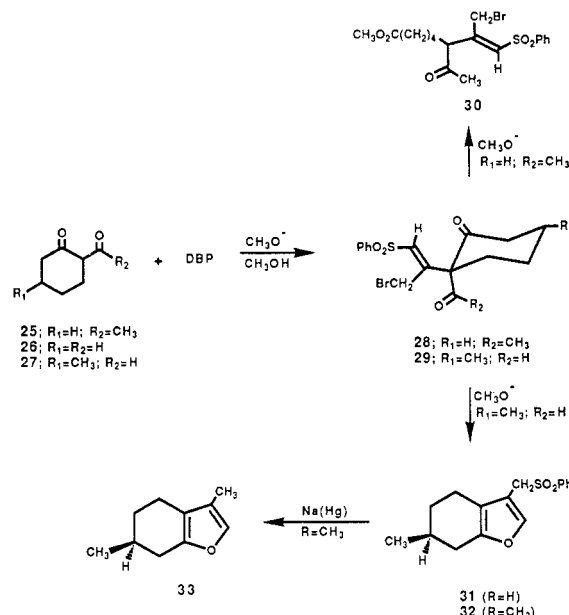
produced dihydrobenzofuranone **23** (R = H) in 85% yield. Note that in this case, the substitution pattern about the furan ring is different from that encountered with the acyclic dicarbonyl compounds. More than likely the initial step involves O-alkylation to give **21** as a transient species.<sup>18</sup> Further reaction of this material with base results in cyclization to **22**, which then undergoes a subsequent aromatization. A similar series of reactions was used to prepare furan **24**.



When 2-acetylcyclohexanone was used, employing sodium methoxide as the base, ring opening of the intermediate adduct **28** to give **30** takes precedence over deacetylation, presumably as a consequence of the stability of the anion formed. This circumstance can be avoided, however, by the use of a formyl group in place of the acetyl group to activate the cyclic ketone. Thus, DBP reacted with the sodium salt of 2-formylcyclohexanone (**26**) to give,

(18) 1,3-Cyclohexanediones preferentially alkylate on the O atom of the diketone enolate, see: Stetter, H. In *Newer Methods of Preparative Organic Chemistry*; Foerst, W., Ed.; Academic Press: New York, 1964, Vol II. Taylor, E. C.; Hanks, G. H.; McKillip, A. *J. Am. Chem. Soc.* **1968**, *90*, 2421. An alternate, but less likely, mechanism for the formation of **23** (or **24**) could involve S<sub>N</sub>2 displacement of the allylic bromide by the enolate carbon followed by cyclization and aromatization.

after treatment with potassium *tert*-butoxide, tetrahydrobenzofuran **31** in good yield. We sought to further demonstrate the utility of this approach as an entry into the vast number of 3-methyl furanoterpenoids<sup>13</sup> by employing DBP in the total synthesis of (*R*)-menthofuran (**33**).<sup>19</sup> The menthofuran precursor **32** was prepared in



the same fashion as **31**, using the commercially available (*R*)-3-methylcyclohexanone. Furan **32** was then treated with sodium amalgam to give (*R*)-menthofuran in 85% overall yield.

In conclusion, the DBP approach is a general method for the synthesis of C-2 and C-3 substituted furans. In addition to its ease of removal, the pendant sulfone at C-4 offers a convenient and versatile site for further elaboration (via alkylation<sup>20</sup> or Julia coupling<sup>21</sup>). This strategy toward furans clearly could be applied to more complex targets. We are currently investigating the scope and limitations of this protocol.

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**Supplementary Material Available:** Experimental procedures and spectroscopic data for new compounds (5 pages). Ordering information is given on any current masthead page.

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## Total Synthesis of Mycalamides A and B

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**Summary:** A total synthesis of mycalamides A (**1**) and B (**2**) was accomplished in an enantiomerically pure form, establishing unambiguously their absolute configuration.

Mycalamides A (**1**) and B (**2**) and onnamide A have recently been isolated from marine sponges.<sup>1,2</sup> Struc-

turally, they are strikingly similar to pederin (**3**), the vesicatory principle of staphylinid beetles *Paederus*.<sup>3</sup>

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