ORGANIC LETTERS

2000
Vol. 2, No. 18
2729−2731

A Two-Component Pericyclic Reaction for Synthesis of Substituted Benzofurans and Aryl–Quaternary Carbon Bonds[1]

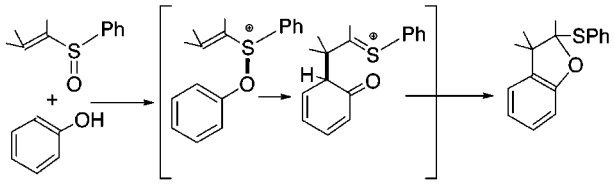
James B. Hendrickson* and Martin A Walker

Department of Chemistry, Brandeis University, Waltham, Massachusetts 02454-9110

jbh@jbh.chem.brandeis.edu

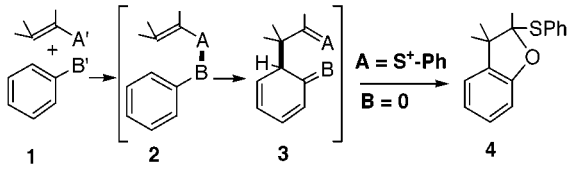
Received April 27, 2000

ABSTRACT



The reaction shown is presumed to be a new [3,3]-sigmatropic rearrangement involving an *O*-arylsulfoxonium species or related sulfurane. It allows a sulfoxide and a phenol to be joined and rearranged in one operation at or below room temperature, coupling an aromatic to a quaternary carbon and creating benzofurans or articulated dihydrobenzofurans in a number of examples.

In our organization of pericyclic reactions,[2] the 4X model, or [3,3]-sigmatropic rearrangement (**2** → **3**), is best known for the Claisen (A = C, B = O) rearrangement and the Fischer indole synthesis (A = B = N). We undertook a study of the family with A = S^+−Ph and B = O for two reasons. First, the S^+−O bond can be formed in situ from an activated sulfoxide, as in **1** → **2**, allowing the final product **4** to be created overall by a convergent joining of two much simpler starting materials (A′ + B′ in **1**). Second, the presence of a charged atom in the pericycle is considered to increase the reaction rate substantially.[3]



As with the Fischer indole synthesis, an important synthetic advantage is that the initial benzene ring substrate does *not* need to be *ortho*-disubstituted. The simplest application here is the synthesis of benzofurans[4] by elimination of thiophenol from **4**. However, when this elimination of thiophenol is blocked by formation of a quaternary carbon at the β-position of the dihydrobenzofuran product **4**, then the reaction serves the important but difficult synthetic objective of constructing the hindered bond between an aryl ring and a quaternary carbon.

The presumed overall mechanism is shown in Scheme 1. A formally similar rearrangement of a vinyl sulfoxonium intermediate but with no aryl component has been shown in the addition of sulfoxides to dichloroketene.[5] In either case, the reaction constitutes a net oxidation at the involved carbons via reduction at the sulfur.

The initial joining of the two components involves

(1) For further details, see: Walker, M. A. Ph.D. Dissertation, Brandeis University, Waltham, MA, 1999.

(2) Hendrickson, J. B. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 47−76; *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 852−860.

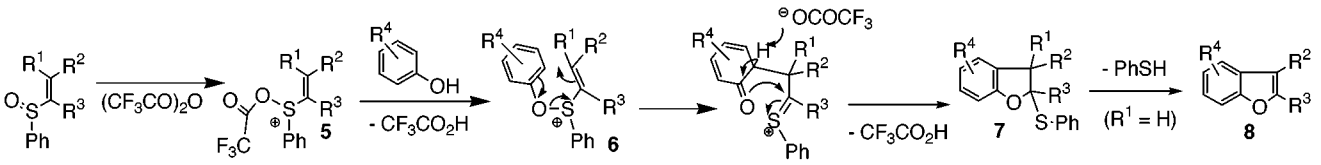
(3) For examples, see: Sundberg, R. J. *Indoles*, 54-5; Academic Press: London, 1996. Schiess, P.; Grieder, A. *Helv. Chim. Acta* **1974**, *57*, 2643. Beholz, L. G.; Stille, J. R.; *J. Org. Chem.* **1993**, *58*, 5095−5100.

(4) For other methods for the preparation of benzofurans, see: (a) Spagnolo, P.; *J. Chem. Soc., Perkin Trans. 1* **1972**, 556−559. (b) De Souza, N. J.; Nayak, P. V.; Secco, E. *J. Heterocycl. Chem.* **1966**, *3*, 42−45. (c) Burgstahler, A. W.; Worden, L. R. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 251−254.

(5) Marino, J. P.; Neisser, M, *J. Am. Chem. Soc.* **1981**, *103*, 7687−7689. Posner, G. H.; Asirvatham, E.; Ali, S. F. *J. Chem. Soc., Chem. Commun.* **1985**, 542−543.

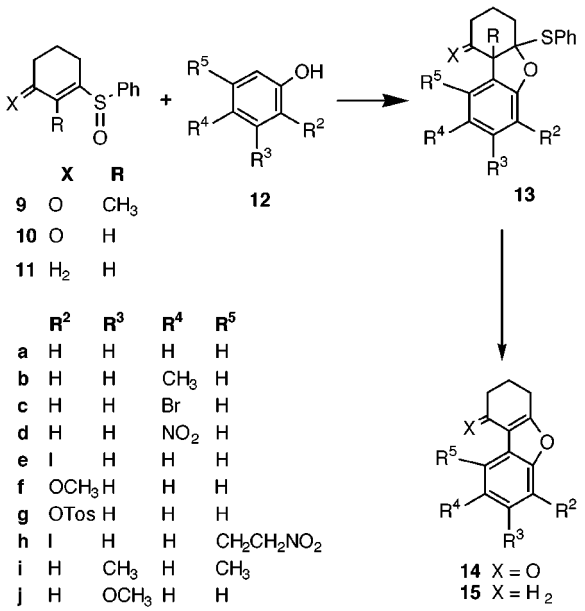
10.1021/ol000113n CCC: $19.00
Published on Web 08/08/2000

Scheme 1. Proposed Mechanism for Benzofuran Formation



activation of a vinyl sulfoxide by trifluoroacetic anhydride[6] to form **5** at −40° C, as in the ortho-thioalkylation of phenols.[7] The addition of the phenol presumably forms a sulfoxonium intermediate, **6**, probably in equilibrium with the related neutral or *O*-protonated trifluoroacetoxysulfurane. The intermediate then reacts cleanly and rapidly at −40 °C to give the dihydrobenzofuran **7**. Product **7** usually aromatizes spontaneously to the benzofuran **8** in cases with R^1 = H. When the reaction is complete, the acids are neutralized by quenching with triethylamine and the products isolated by chromatography.

The original strategy was aimed at the synthesis of morphinans, and so the first and major studies were carried out at reduced temperature on various phenols **12** with the sulfoxide **9**, to form the model dihydrobenzofurans **13**, as



exemplified in Table 1. The sulfoxides **9**−**11** were readily prepared from the corresponding ketones via their enol thioethers,[8] oxidized with MCPBA at low temperatures.[9]

In the series with sulfoxide **9**, we commonly found that, while the benzofuran was the only product formed, significant quantities of the two starting materials remained after the workup. Hence, a number of variations were pursued[1] in a search for conditions that would force the reaction to go to completion. The reaction may indeed be conveniently carried out briefly at room temperature, but even at this temperature the reaction did not go to completion.

In experiments using **9** with **12b** (*p*-cresol), **13b** was formed essentially quantitatively except for unreacted starting materials, and these were easily separated by chromatography. Racemization at sulfur apparently intervenes, since racemic **13b** was formed from nonracemic sulfoxide **9.** Extended reaction times at any temperature caused decomposition of the product **13b** as shown in Scheme 2. Trifluoroacetylation of the phenol only occurs *after* quenching with base, and no other byproducts were observed by NMR or TLC, at −40 °C or at room temperature. Nucleophilic attack by the phenol at the β-position of the sulfoxide was not observed.

Attempts to drive the reaction to completion using excesses of reagents failed, with excesses of *p*-cresol simply promoting the decomposition of **13b** as outlined above. A number of

Table 1. Reaction of Sulfoxides and Phenols

entry	sulfoxide	phenol	product	method[a]	% yield[b]
1	**9**	**12b**	**13b**	B	55 (100)
2	**9**	**12b**	**13b**	C	55 (100)
3	**9**	**12c**	**13c**	B	52 (100)
4	**9**	**12d**	**13d**	B	0
5	**9**	**12e**	**13e**	B	35 (62)
6	**9**	**12g**	**13g**	A	41
7	**9**	**12h**	**13h**	A	21
8	**10**	**12a**	**14a**	B	22 (63)
9	**10**	**12c**	**14c**	B	33 (68)
10	**10**	**12e**	**14e**	B	21 (36)
11	**10**	**12j**	**14j**	B	31
12	**11**	**12c**	**15c**	B	19
13	**11**	**12e**	**15e**	B	37
14	**11**	**12i**	**15i**	B	34
15	**18**	**12a**	**19a**	A	39
16	**18**	**12b**	**19b**	C	22
17	**18**	**12e**	**19e**	A	40

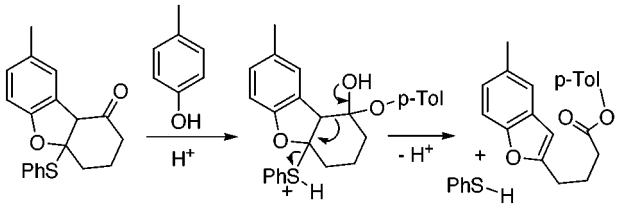
[a] Method A: reactants mixed at −78 °C and then warmed to 0 °C and quenched at −78 °C. Method B: reactants mixed at −40 °C ending with slow phenol addition (1.5 h), followed by 2 h stirring and quenching at −40 °C. Method C: reactants mixed at 25 °C and left only 5 min before quenching. [b] Yields after isolation by flash chromatography. Yields in parentheses allow for recovered starting materials.

(6) For other examples of the activation of alkenyl sulfoxides by TFAA, see: (a) Craig, D.; Daniels, K.; MacKenzie, A. R. *Tetrahedron Lett.* **1990**, *31*, 6441−6444. (b) Brichard, M.-H.; Janousek, Z.; Merenyi, R.; Viehe, H. G. *Tetrahedron Lett.* **1992**, *33*, 2511−4.

(7) (a) Burdon, M. G.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 4656−4658. (b) Pfitzner,.K. E.; Marino, J. P.; Olofson, R. A. *J. Am. Chem. Soc.* **1965**, *87*, 4658−4659. (c) Gassman, P. G.; Amick, D. R. *J. Am. Chem. Soc.* **1978**, *100*, 7611−7619. (d) Lee, T. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: London, 1991; Vol. 7, pp 292−309.

(8) Labiad, B.; Villemin, D. *Synthesis* **1989**, 143−4.

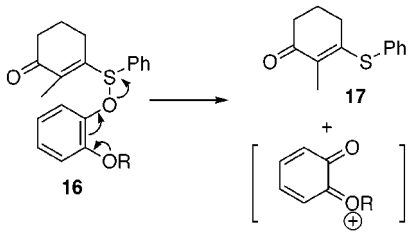
Scheme 2. Decomposition of Product **13b**



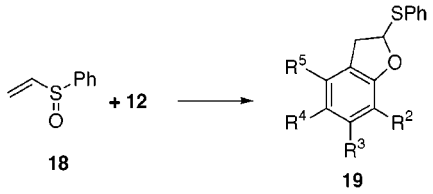
other common electrophilic activators (acetic, triflic, and methanesulfonic anhydrides, oxalyl chloride, trifluoroacetyl triflate, etc.) were either less successful or gave no product.

The reaction tolerates a variety of functional groups on the phenol component, including halogen (**12c**,**e**), *meta*-methoxy (**12j**), and exocyclic nitro (**12h**), but aryl nitro (**12d**) did not react. The methoxy example is capable of forming two isomeric products, but only the less crowded, **13j**, was formed in significant yield. The intermediate **13h** intended for morphinan synthesis was formed cleanly but in low yield, presumably also owing to crowding at the reaction site.

However, the effect of an *o*-methoxy (**12f**), needed for morphinans, was to deoxygenate the sulfoxide to the sulfide **17** as the only isolable product, presumably via an alternative collapse of the intermediate **16**. This deoxygenation of the



sulfoxide was not observed in any other case. The mechanism sketched on **16** is supported by the normal reaction of the *o*-tosyloxy phenol **12g** (**16**, R = Tos), in which the release of electrons is suppressed. Synthesis of simple benzofurans was examined in seven examples with sulfoxides **10**−**11** as shown in Table 1. In each case the intermediate sulfide (**7**) spontaneously lost thiophenol to aromatize to the benzofurans **14** and **15**. However, when the parent, commercially available sulfoxide **18** was used, the thiophenol did not eliminate spontaneously from **19**.



In conclusion, we have generated a new C−C construction reaction which should have broad utility, for it cleanly joins two readily available starting materials at low temperature to form a variety of substituted benzofurans or a hindered bond between a quaternary carbon and an aryl ring.

Acknowledgment. We are grateful to Prof. B. B. Snider for valuable discussions.

Supporting Information Available: Experimental procedures and spectral data for the preparation of the benzofurans and also for sulfoxides **9**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL000113N

(9) Trost, B. M.; Seoane, P.; Mignani, S.; Acemoglu, M. *J. Am. Chem. Soc.* **1989**, *111*, 7487−7500.