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CYCLOADDITION-REARRANGEMENT OF CYCLOHEXADIENOL ETHERS. A VERSATILE AND SELECTIVE SYNTHESIS OF CYCLOPENTENOID SYSTEMS

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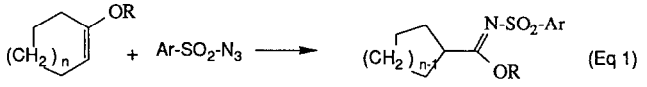
Summary: 1,4-Cyclohexadienol ethers prepared by the Birch reduction of alkyl aryl ethers react at ambient pressure and moderate temperatures with p-bromobenzenesulfonyl azide to yield cyclopentenecarboximidates. The cycloaddition-rearrangement is highly specific for the more electron rich of the two double bonds of the diene.

Arene sulfonyl azides react with the enol ethers of simple cyclic ketones to give ring contracted arenesulfonylimidate esters[1] (Eq 1). First described by Wohl[2] who used both methyl and trimethyl silyl enol ethers as substrates, the reaction has also been the subject of a study of reactions at high pressure[3]. The latter conditions were applied to the highly hindered tert-butyl dimethylsilyl enol ethers of several cyclic ketones, including cyclopentanone. One application of the reaction to a natural product synthesis model study has also been reported[4].



(Eq 1)

R = alkyl or trialkyl silyl

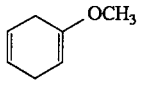
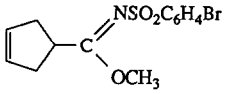
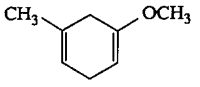
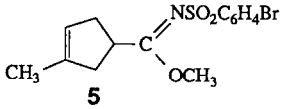
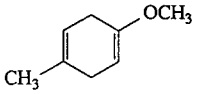
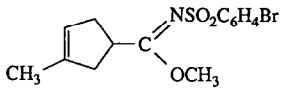
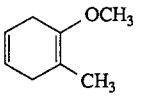
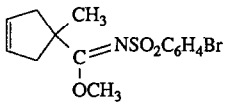
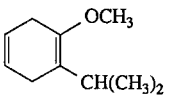
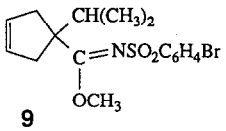
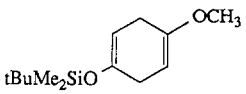
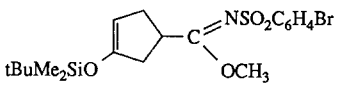
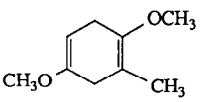
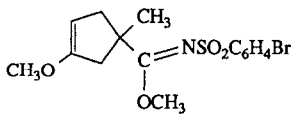
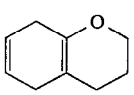
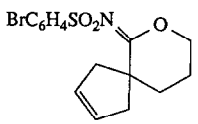
In each of these previous studies the substrate enol ethers were prepared from ketones either by enolization and subsequent trapping[2b,3,4] or by acid catalyzed elimination of methanol from dimethyl ketals[2a,4,5]. It was also pointed out by Wohl[1b], however, that silyl ethers are inherently more sluggish in their reactions than the methyl ethers[6].

We have have been interested in applying this ring contraction process to the synthesis of cyclopentanoid systems as well as exploiting the synthetic potentiality of the sulfonylimidate functional group. In this communication we report the results obtained with a special class of *alkyl* dienol ethers, ethers which are *not* obtainable from the trapping of ketone enolates. *As shown below these ethers not only yield highly useful cyclopentene derivatives but show significant chemo- , regio- , and stereoselectivity in their reactions with arenesulfonyl azides.*

In Table I are listed a series of non-conjugated cyclohexadiene methyl enol ethers, all of them produced by the Birch reduction[7] of anisole and substituted anisoles. None of these (or its silyl ether counterpart) is obtainable from a ketone precursor. All of them, however, undergo ring contraction at relatively mild temperatures and ambient pressure. Entries 1-4 are derived from anisole and the three isomeric cresol methyl ethers. All yield the corresponding ring-contracted cyclopentenecarboximidate products in good yield. Thus **1** affords **4** in 74% isolated yield, and **2** and **3** give **5** in yields of 80% and 89% respectively. None of the product derived from attack of the azide at the non-oxygenated double bond is observed.

In contrast to the highly hindered tert-butyldimethylsilyl ethers which require high pressure[3] for the cycloaddition step *tetrasubstituted* methyl enol ethers are reactive at moderate temperatures and ambient pressure. Dihydro o-cresol methyl ether, **6** (Entry 4), in fact, reacts *faster* than the p- and m-isomers. Thus at 63°C the ortho compound has completely reacted after 20h[8] to yield **7**,

TABLE I

ENTRY	SUBSTRATE	PRODUCT	TEMP/ TIME	YIELD
1	 **1**	 **4**	62^0 / 72h	74%
2	 **2**	 **5**	75^0 / 48h	80%
3	 **3**	 **5**	62^0 / 48h	89%
4	 **6**	 **7**	63^0 / 20h	84%
5	 **8**	 **9**	65^0 / 30h	70%
6	 **10**	 **11**	70^0 / 70h	51%
7	 **12**	 **13**	68^0 / 20h	86%
8	 **14**	 **15**	82^0 / 20h	60%

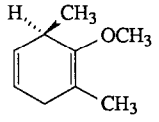
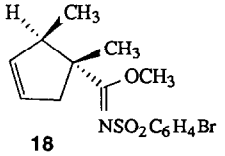
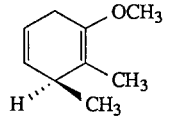
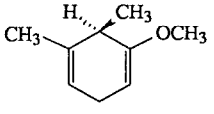
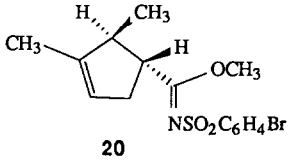
while complete reaction of the isomeric substances requires up to 48h. This enhanced reactivity[9]provides for remarkable selectivity with more complex substrates than the cresol derived dienes. For example, substitution of a larger group for methyl, e.g., isopropyl (substrate **8** leading to product **9**, Entry 5), retards the rate of cycloaddition-rearrangement but does not produce a decrease in selectivity. Again, no product resulting from attack at the isolated double bond is observed.

Taking advantage of the lower reactivity of silyl ethers compared to the alkyl ones we have also examined the behavior of the *bis* enol ether **10** (Entry 6). In accord with our observation of slow reactions with trisubstituted enol ether double bonds we find that extended reaction times are required for **10** to react, but it does so exclusively at the alkyl enol ether position to yield **11**. What is more striking, however, is the selectivity observed with *bis* methyl ether **12** (Entry 7). From **12** we obtain only **13** in an isolated yield of 86%. We observe none of the product from attack at the less substituted double bond.

We have also examined the case of a bicyclic enol ether. The only previous reports of reactions with cyclic enol ethers were concerned with dihydropyran itself[10,11]. in those cases the product resulted from the migration of a proton. As seen in Entry 8 alkyl migration occurs with a substituted dihydropyran, and in the case of **14** it yields spiroimidate **15**.

In addition to the chemo- and regioselective outlined above we have found, contrary to earlier evidence[4], the the addition-rearrangement is highly *stereoselective*. As shown in Table II enol ethers **16**, **17** both yield principally one diastereomer **18**, and **19** affords a single product only, **20**.

TABLE II

Substrate	Major Product	Yield	Diastereomeric Ratio
 **16**	 **18**	83%	15 : 1
 **17**	**18**	74%	6.5 : 1
 **19**	 **20**	81%	

Applications of these results to the synthesis of complex systems will be reported in forthcomimg publications.

References and Notes

1. Apart from the reactions of vinyl ethers with arenesulfonyl azides the only other preparation of this functional group appears to be the one resulting from the interaction of triethyl orthoformate and benzene sulfonamide: Stetter, H.; Theisen, D. *Chem. Ber.* **1969,** *102*, 1641. For a review of azide cycloadditions see: Lwowski, W. in *1,3- Dipolar Cycloaddition Chemistry,* A. Padwa, Ed., J. Wiley and Sons, New York, **1984,** *Vol. 1.*
2. a)Wohl, R., *Tetrahedron Lett.* **1973**, 3111. b) Wohl, R. *Helv. Chim. Acta* **1973**, *56*, 1826.
3. Dauben, W.G., Bunce, R.A. *J. Org. Chem.* **1982**, *47*, 5042.
4. Dauben, W.G., Hart, D.J. *J. Org. Chem.* **1977**, *42*, 923.
5. Wohl, R. A. *Synthesis* **1974**, 38
6. The imidate silyl esters obtained from enol silyl ether substrates are also hydrolytically unstable and the products in these reactions were isolated as the transformed arene sulfonamide.[3,4]
7. Birch, A. J.; Smith, *H. Quart. Rev.* **1958**, *12*, 17.
8. The experimental procedure used for **6** is typical: A solution of 1-methoxy-2-methylcyclohexa-1,4-diene (300 mg, 2.41 mmol) and p-bromobenzenesulfonyl azide (633 mg, 2.41 mmol) in dry acetonitrile (10 ml) is heated for 20 hr at 63^{0}C (oil bath temperature) under nitrogen. (Disappearance of the azide is monitored by tlc.) Evaporation of the solvent at reduced pressure, flash column chromatography (25 g SiO_2, 9:1 hexane-EtOAc) and crystallization from hexane-EtOAc afforded the imidate ester (724 mg, 84%), mp 85-86^{0}C.

Spectral characteristics for representative products are, **11**: IR ($CHCl_3$) ν 1655, 1600, 1315, 1255, 1225, 1155, 1095 cm^{-1};^{1}H NMR($CDCl_3$) δ 7.80 and 7.63 (AB; J= 8.7 Hz; 4 x H_{Ar}) , 4.54 (dd, J= 4.0, 2.0 Hz; H-C=C) , 4.18 (tt, J= 8.5, 6.2 Hz; N=C-CH) , 3.73 (s, -OCH_3) , 2.73 (ddd, J= 14.8, 8.5, 1.4 Hz; SiO-C=C-CHa) , 2.62-2.54 (m, HC=C-CHbHb') , 2.48 (ddd, J= 14.8, 6.2, 2.3 Hz; SiO-C=C-CHa') , 0.9 (s, 9 x SiC-CH) , 0.14 (s, 6 x SiC-H).

15: IR($CHCl_3$) ν 1590, 1320, 1164 cm^{-1}; ^{1}H NMR δ 7.78 and 7.59 (AB; J= 8.9 Hz; 4 x H_{Ar}) , 5.56 (s, HC=CH) , 4.44 (t, J= 5.8 Hz; -OCH_2) , 3.02 and 2.36 (AB; J= 13.9 Hz; 4 x C=C-CH) , 1.98-1.90 (m, -OCH_2-CH_2) , 1.87-1.79 (m, -OCH_2CH_2-CH_2); **7:** IR ($CHCl_3$) ν 1628, 1600, 1320, 1156 cm^{-1}; ^{1}H NMR δ 7.84 and 7.62 (AB; J= 8.8 Hz, 4 x H_{Ar}) , 5.65 (s, 2 x H-C=C) , 3.68 (s, -OCH_3) , 3.07 and 2.52 (AB; J= 15 Hz, 4 x HC-C=C) , 1.47 (s, -C-CH_3) ; **13:** IR ($CHCl_3$) ν 1660, 1605, 1320, 1155 cm^{-1}; ^{1}H NMR δ 7.82 and 7.61 (AB; J= 9 Hz, 4 x H_{Ar}) , 4.35 (dd, J= 2.0, 1.9 Hz; H-C=C) , 3.67 (s, -OCH_3) , 3.58 (s, -OCH_3) , 3.17 (dd, J= 15.4, 1.8 Hz; MeO-C=C-CHa) , 3.04 (ddd, J= 14.8, 2.1, 2.0 Hz; HC=C-CHb) , 2.49 (ddd, J= 14.8, 1.9, 1.8 Hz; HC=C-CHb') , 2.37 (dd, J= 15.4, 2.1 Hz; MeO-C=C-CHa') , 1.52 (s, C-CH_3).

Satisfactory elemental analyses were obtained for all new compounds.

9. For a general discussion and review of the reactivity of olefins towards 1,3-dipoles see R. Huisgen in *1,3- Dipolar Cycloaddition Chemistry,* A. Padwa, Ed., J. Wiley and Sons, New York, **1984,** *Vol. 1.*
10. Rector, D.L., Harmon, R.E. *J. Org. Chem.* **1966,** *31*, 2837.
11. Franz, J.E., Dietrich, M.W., Henshall, A., Osuch, C., *J. Org. Chem.* **1966**, *31*, 2847.

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