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ON THE LEWIS ACID CATALYZED DIELS-ALDER REACTION OF FURAN. REGIO- AND STEREOSPECIFIC SYNTHESIS OF SUBSTITUTED CYCLOHEXENOLS AND CYCLOHEXADIENOLS.

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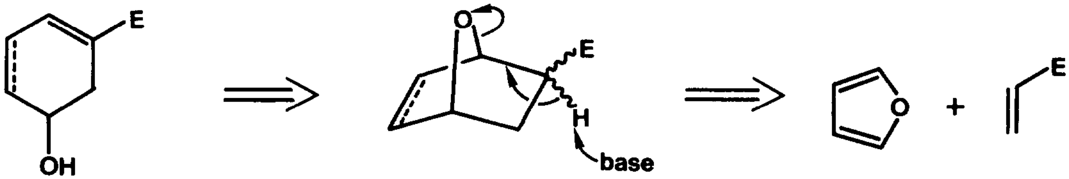
Summary : *The [4+2] cycloaddition between furan and some dienophiles can be greatly accelerated in the presence of a Lewis-Acid (i.e.ZnI_2). The 7-oxabicyclo [2.2.1] heptyl system readily undergoes a base promoted β-elimination of the heteroatom bridge leading to substituted cyclohexenols and cyclohexadienols.*

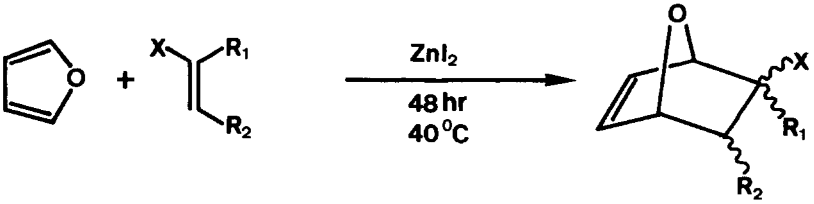
Short reaction sequences to variously substituted six membered rings are of continuing synthetic interest. The Diels-Alder reaction between 1- or 2- substituted dienes and electron deficient dienophiles gives rise to either ortho- or para- substituted cyclohexenes or cyclohexadienes (1,2). Therefore, it is important to find new methods for the synthesis of meta-substituted cyclohexyl systems.

For this purpose, we propose a scheme involving a base induced β-elimination of the heteroatom bridge of substituted 7-oxabicyclo [2.2.1] heptenes and heptanes (3). These latter were formed easily by a Lewis Acid catalyzed Diels-Alder reaction of furan.



The furan is a poor diene in Diels-Alder reactions and reacts only with very good dienophiles to form respectable yields of 7-oxabicyclo [2.2.1] heptene derivatives (4). Dauben and Krabbenhoft (5) have shown recently that the use of very high pressure can improve considerably the yields of the Diels-Alder reaction of furan.

We have found that the [4+2] cycloaddition between furan and some dienophiles can be greatly accelerated by the addition of a Lewis-Acid (i.e.ZnI_2) (6). In a typical experiment, a mixture containing furan (14 mmoles), the dienophile (10 mmoles) and dry Zinc Iodide (3 mmoles) is stirred in a closed system at 40°C for 48 hr; the reaction mixture is then diluted with AcOEt (100 ml), washed with a 0.1M aqueous solution of $Na_2S_2O_3$ (20 ml), dried and concentrated. A short filtration through silica gel affords the bicyclic derivatives. The results obtained are summarized in Table I (7) :

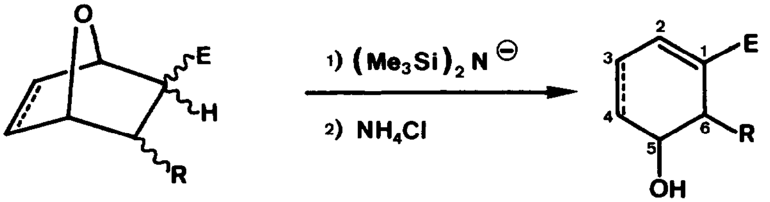


Entry	R_1	R_2	X	% yield	ratio endo:exo(vsX)	References (uncatalyzed reaction)
1	$COOCH_3$	H	H	55	1 : 2	(8)
2	CN	H	H	100	1 : 1	(9)
3	CN	H	Cl	60	1 : 1	(10)
4	$COOCH_3$	$COOCH_3$	H	55	1 : 1.5	(11)

Table I

Inspection of the data in Table I reveals that satisfactory yields of [4+2] adducts were obtained. Compared to the thermally induced processes, the use of ZnI_2 provides a substantial improvement in yield (12).

The next step of the proposed scheme leading to a new synthesis of meta-substituted cyclohexenes and cyclohexadienes involves a base induced β-elimination of the heteroatom bridge of the substituted 7-oxabicyclo [2.2.1] heptyl system. At the outset of our study, it seems that only Kozikowski and Kuniak (13), using KH as a base, have reported a similar β-elimination for the synthesis of condensed heterocycles. The choice of the base for the carbanion formation, in our case, was critical (14). The best experimental conditions for the β-elimination are as follows : a solution of the 7-oxabicyclo [2.2.1] heptyl compound (4 mmoles in 5 ml THF) is added dropwise to a cold solution (-78°C) of lithium-bis (trimethylsilyl) amide generated from hexamethyldisilazane (4.4 mmoles in 30 ml THF) and n-Butyllithium at -78°C. The reaction mixture is then allowed to warm up (see Table II) and is hydrolyzed (saturated aqueous NH_4Cl solution). After extraction ($CHCl_3$), drying and concentration, the crude mixture is filtered through silica gel. The results obtained are summarized in Table II (15).



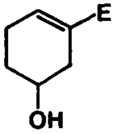
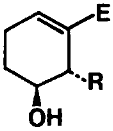
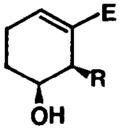
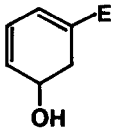
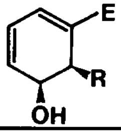
Entry*	E	R	Product	% yield	Reaction time and temperature of hydrolysis
5	$COOCH_3$ (endo and exo)	H	1 	85 %	1.5 hr, 0°C
6	$COOCH_3$ (endo)	$COOCH_3$ (endo)	2 	74 %	1.5 hr, 0°C
7	$COOCH_3$ (exo)	$COOCH_3$ (exo)	3 	79 %	1 hr, -20°C
8	$COOCH_3$ (endo and exo)	H	4 	85 %	1.5 hr, 0°C
9	$COOCH_3$ (exo)	$COOCH_3$ (exo)	5 	51 %	45 mn, -40°C

Table II

**In entries 5, 6 and 7, we used the saturated bicyclic derivatives obtained by hydrogenation of the corresponding unsaturated compounds. The bicyclo [2.2.1] heptene derivatives were used for entries 8 and 9.*

As is evident from Table II, the bicyclic derivatives readily undergo β-elimination with high stereoselectivity (16). Remarkably, this method provides a smooth formation of conjugated and substituted cyclohexadienols (18).

Since a large number of variously substituted furans are available, this method can provide a multitude of substituted six-membered rings. Applications using the pathway described above for the synthesis of various natural products are currently under investigation.

The author wish to thank Mrs S. Rinaudo for technical assistance and Mr. H. STRUB for the recording and assignment of ^{1}H-nmr spectra.

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2) *S. DANISHEFSKY, M.P. PRISBYLLA, S. HINER, J. Amer. Chem. Soc., 100, 2918, (1978).*

3) *For the use of 7-oxabicyclo [2.2.1] heptanes and heptenes in organic synthesis, see : T. MUKAIYAMA, N. IWASAWA, T. TSUJI, K. NARASAKA, Chem. Lett., 1175, (1979) and references cited therein.*

4) *R.M. ACHESON, "An Introduction to the Chemistry of Heterocyclic Compounds", Interscience, New York, 1960.*

5) *W.G. DAUBEN, H.O. KRABBENHOFT, J. Amer. Chem. Soc., 98, 1992, (1976).*

6) *Anhydrous $MgBr_2$ catalyzes also the reaction, but better yields were obtained with ZnI_2. In fact, the use of stronger Lewis acids such as $AlCl_3$ produces an addition-elimination reaction leading to 2-substituted furans (see ref. 2).*

7) *In addition to product, only starting materials were present at the conclusion of the reaction. Satisfactory analytical and spectral data were obtained for each product. Acrolein and methylvinylketone do not afford the corresponding adducts but produce only polymeric material.*

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10) *R.R. SCHMIDT, C. BEITZKE, A.K. FORREST, J. Chem. Soc., Chem. Commun., 909, (1982).*

11) *T.A. EGGELTE, H. de KONING, H.O.HUISMAN, Tetrahedron, 29, 2491, (1973).*

12) *By comparison, a month or more is required to obtain 20% of 2-carbomethoxy-7-oxabicyclo [2.2.1] hept-5-ene (entry 1) from furan and methyl acrylate. Likewise the cycloadduct from furan and acrylonitrile is produced in 39% yield after 5 weeks (entry 2). A yield of 11% of cycloadduct was observed during the reaction of furan and α-chloroacrylonitrile (entry 3).*

13) *A.P. KOZIKOWSKI, M.P. KUNIAK, J.Org. Chem., 43, 2083, (1978).*

14) *The use of KH or alcoolates at 50°C produce only retro Diels-Alder reactions. Lithium diisopropylamide gave low yields of desired compounds.*

15) *All new compounds have been characterized by ^{1}H NMR, U.V.,I.R. spectroscopy and mass spectrometry. The yields given refer to isolated products.*

16) *The cis stereochemistry of compound 5 was demonstrated by Diels-Alder reaction with N-phenyl-1,2,4-triazoline-3,5-dione (17). Partial hydrogenation of 5 (C_3-C_4 double bond) (Lindlar catalyst) provides specifically 3.*

17) *R.W. ASHWORTH, G.A. BERCHTOLD, Tetrahedron Letters, 339, (1977).*

18) *Compounds 4 and 5 dehydrate easily in $CHCl_3$ solution to form respectively methylbenzoate and dimethylphtalate.*

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