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Selectivity in Cycloadditions. 5. Cycloadditions of Nitrile Oxides to Furan. Competing Mechanisms and Regiochemistry[1]

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Generation of benzonitrile oxide (BNO) in a large excess of furan gave a 91% yield of two regioisomeric monocycloadducts **1** and **2** in a 97:3 ratio and a 1% yield of the 1,3-addition product, **3**. The primary products can react further with BNO giving cycloaddition and fragmentation products, whose structures were established through spectroscopic evidence and chemical transformations. The cycloaddition with 2-methylfuran and cycloadditions of mesitonitrile oxide and *p*-nitro- and *m*-nitrobenzonitrile oxides to furan are also reported. Frontier orbital considerations allowed elucidation of the regiochemistry of the cycloadditions. A competing pathway stabilized by secondary orbital interactions is suggested for the formation of the 1,3-addition product.

In previous papers of this series we have evaluated the influence of polar and steric effects[3] as well as of π-conjugation[4] on nitrile oxide[5] cycloadditions. Although π-conjugation was remarkably effective in directing the regioselectivity of cyclopentadiene cycloadditions, nevertheless the two possible [4 + 2] cycloadducts of the dipole could be isolated. The results support the frontier orbital treatment of 1,3-dipolar cycloadditions,[6] which has recently led to a satisfactory understanding of regioselectivity and periselectivity phenomena.

Since the five-membered ring heteroaromatics, such as furan, thiophene, and pyrrole, have, in spite of their aromaticity, frontier orbital energies and shapes similar to those of cyclopentadiene[7]—which may be viewed as a cyclic diene aromatically stabilized through hyperconjugation[8]—it seemed to us interesting to extend our study to their dipolarophilic activities. A vast amount of material is available concerning the reactivity of heteroaromatics in substitution reactions[9] or in cycloadditions where the heteroaromatics enter as $_{\pi}4_{s}$ components,[10] but the study of their dipolarophilic activities has been relatively scanty to date. A second aim of the studies was based on the well-known propensity of heteroaromatics toward substitution rather than addition reactions. If diradical or zwitterionic intermediates with a finite lifetime are ever involved in cycloaddition reactions, they would be expected to convert easily, perhaps quantitatively, to the substitution products because of the gain of aromaticity.

We have already given an account of the reactions of furan with nitrile oxides[11] and nitrile imines.[12] In this paper we report a more detailed study of the cycloaddition of nitrile oxides to furan, with particular attention directed at the regiochemistry of the reaction and to the detection of the substitution products.

Results

Furan is very slightly reactive toward nitrile oxides. Only the in situ preparation of benzonitrile oxide (BNO) in furan as solvent permitted isolation of a complex mixture of cycloadducts along with considerable amounts of diphenylfuroxan, the dimer of BNO, as well as 3,5-diphenyl-1,2,4-oxadiazole.

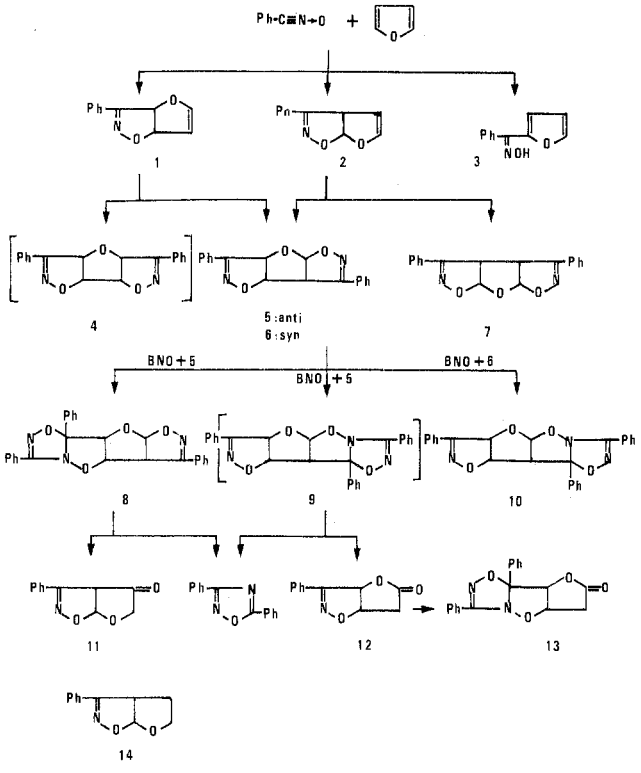
Because of the low reactivity of furan the primary monoadducts **1** and **2**, which have a reactive enol ether moiety,[6b,d] compete efficiently for BNO, even when furan is used as solvent. BNO also adds sluggishly on the C=N isoxazoline bonds of the bis adducts.

Chromatographic and fractional crystallization procedures led to isolation and characterization of not less than ten compounds. These products will be examined separately, depending upon whether they are 1:1 mono adducts or are derived from 2 mol of BNO and 1 mol of furan (bis adducts) or are further addition or transformation products.

Mono Adducts. On performing the reaction with a very small concentration of BNO (10^{-2} M) in furan in order to suppress any further reactions of the primary products, we obtained a 91% yield of the two cycloadducts **1** and **2** in a 97:3 ratio, and a 1% yield of the oxime **3**, as determined by GLC. In the normal runs (see Experimental Section) column chromatography gave the mono adducts in yields of 9–12, 0.3, and 0.1–0.2%, respectively.

The structures were assigned on the basis of chemical and NMR evidence. Acidic hydrolysis of **1** gives the isoxazoline

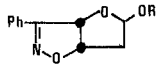
Scheme I



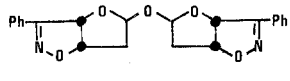
ring cleavage product, 2-benzoylfuran; **2** was selectively hydrogenated on the C=C bond to the known adduct of 2,3-dihydrofuran **14**,[13] whose structure has been unequivocally proven; **3** was found identical with a sample prepared according to the literature.[14] The NMR spectra of the cycloadducts (see Table I) are fully consistent with the assignments. The bridgehead protons of **1** and **2** adjacent to the C=C double bond couple with the olefinic protons. The values of these coupling constants are identical with those reported for 2,3-dihydrofuran itself.[15] It is worth noting the deshielding effect of the dihydrofuran oxygen on the adjacent bridgehead protons. These are shifted downfield by ca. 1 ppm from the range reported for 4- and 5-isoxazolinic protons.[16]

Cycloadducts decompose slowly in wet solvents, forming a mixture of products. This behavior, which complicates the separation and isolation procedures, has been studied in more detail in the case of mono adduct **1**. After standing for 1 week in chloroform, this compound gave five major products, which were isolated by column chromatography and characterized spectrally and through chemical transformations.

The product with the smallest R_f showed a hydroxyl ir band at 3445 cm^{-1} and a NMR spectrum consistent with a structure of hemiacetal **15a** and **15b**. The product epimerized very easily



R=H 15a anti
15b syn
R=Ac 16a anti
16b syn



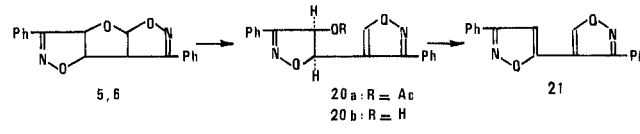
17 anti anti
18 anti syn
19 syn syn

in Me_2SO/D_2O and the process could be qualitatively followed by monitoring the appearance of the doublet of the epimer at 5.94 ppm, 0.03 ppm downfield of the doublet of the C-4 isoxazoline proton. Treatment of **15** with Ac_2O/Py yielded two isomeric acetyl derivatives, whose NMR spectra are in accordance with structure **16a/16b**. The chemical shifts at the acetoxy methyls (2.04 and 1.78 ppm) are significantly different in these two compounds. The syn structure **16b** is proposed for the higher melting isomer which has the upfield methyl. The position of this resonance may be attributed to shielding by the PhC=N group of the neighboring syn isoxazolinic ring.[17]

The other four products show neither hydroxyl nor carbonyl bands in the ir spectra, and have analytical and NMR data compatible with their formulation as acetals. Three pairs of diastereomers (**17–19**) are therefore feasible. Two of them (**17** and **19**) possess an element of symmetry, whereas the diastereomeric pair **18** lacks any symmetry. Therefore, the structures **18** are attributed to the two lower R_f products, whose NMR spectra (see Experimental Section) show ten distinct tetrahydrofuran protons. The other two products, probably the anti–anti couple **17**, each showed only five distinct protons in the NMR, but the spectral data do not allow one to choose between the symmetrical structures **17** and/or **19** with reasonable certainty.

Bis Adducts. The main product (10–16% yield calculated from BNO) in the normal runs was the bis adduct **5**, whose structure has already been demonstrated[11] through ring cleavage with BF_3/Ac_2O, hydrolysis of the acetate **20a**, and subsequent dehydration of the alcohol **20b** to the known 3,3′-diphenyl-4,5′-diisoxazole **21**[18] (see Scheme II).

Scheme II



Two other bis adducts have now been isolated and characterized. One of them (2.3% yield) led to the same ester obtained from **5** by treatment with BF_3/Ac_2O and was therefore assigned structure **6**, stereoisomeric with **5**. Both **4** and **5** were also obtained by regioselective cycloaddition of BNO to the mono adduct **1**. Inspection of NMR spectra confirmed the assigned structures and allowed elucidation of the stereochemistry. Coupling constants between the protons in positions 3 and 4 of the central tetrahydrofuran ring are 0.0 Hz for **5** and 8.7 Hz for **6**. Reference to the Karplus equation and to analogous values for bis adducts obtained from cyclopentadiene[4] unequivocally established the anti configuration for **5** and the syn structure **6** for the minor product.

The third bis adduct **7** was isolated in a very low yield (0.6%) and was independently obtained by cycloaddition of BNO to mono adduct **2**. Its symmetrical structure appears clearly from the NMR spectrum. The four isoxazoline protons occur as two coupled (J = 4.7 Hz) doublets at 6.21 and 4.37 ppm, respectively (2 H each). An anti stereochemistry is suggested by analogy to the stereospecific formation of the corresponding anti bis adduct on cyclopentadiene, where the stereochemistry could be safely deduced from the nonequivalence of the methylene protons.[4]

Tris Adducts and Derived Compounds. Two tris adducts (3 mol of BNO + 1 mol of furan) and two lactones were also isolated from the reaction mixture.

The NMR spectrum of the most abundant tris adduct (1.2% yield) showed the tetrahydrofuran protons as two pairs of doublets, with coupling constants of 2.8 and 5.7 Hz, respectively. These values are compatible with cis coupling constants for ring protons in isoxazolidine and isoxazoline, respectively, as previous examples in the cyclopentadiene series show.[4] A very low coupling (J = 0.5 Hz) between the hydrogens on the bond joining the two heterocyclic moieties indicates an anti configuration. Thermal breakdown of the compound yielded 3,5-diphenyl-1,2,4-oxadiazole and the ketone **11**, whose structure was deduced from spectral data and from the formation of the tosylhydrazone. An attempt to obtain the mono adduct **2** by alkaline degradation[19] of this latter derivative failed. From these spectral and chemical data, structure **8** was deduced for the tris adduct.

Table I. Chemical Shifts[a] (Coupling Constants[b]) of Cycloadducts[c]

Compd	4-H[d]	5-H[d]	Other
1	6.17 d (8.5)	5.93 o (8.5, 2.1, 1.0)	Vinyl 5.34 q (2.5, 2.1); 6.57 q (2.5, 1.0)
2	4.81 o (7.8, 2.7, 2.2)	6.70 d (7.8)	Vinyl 5.20 q (2.8, 2.7); 6:48 q (2.8, 2.2)
5[e]	6.04 d (6.5)	5.33 d (6.5)	
	5.08 d (6.0)	6.45 d (6.0)	
6[e]	6.46 bd (7.8)	5.80 q (7.8, 8.7)	
	4.72 q (8.7, 6.7)	6.58 bd (6.7)	
7	4.37 m (4.7)[f]	6.21 m (4.7)[f]	
8	4.39 bd (5.7)	6.43 d (5.7)	
	5.09 d (2.8)[g]	4.90 bd (2.8)[g]	
10	5.98 d (7.0)	5.00 t (7.0)	
	4.13 q (7.0, 4.0)[g]	6.17 d (4.0)[g]	
11	4.38 d (6.4)	6.73 d (6.4)	CH_2 4.15 s
12	6.04 d (7.3)	5.32 m	CH_2 2.98 m
13	5.23 d (3.5)[g]	4.74 m[g]	CH_2 2.68 m
15[e]	5.91 d (7.3)	5.22 m	CH_2 2.20 m, CHOR 5.53 m, OH 6.18 d (3.3)
16a	5.90 d (7.3)	5.42 m	CH_2 2.53 m, CHOAc 6.37 m, CH_3 2.04 s
16b	5.93 d (7.3)	5.28 m	CH_2 2.51 CHOAc 6.45 m, CH_3 1.78 s
20a	6.55 d (7.1)	5.50 bd (7.1)	CH 8.58 bs, CH_3 1.85 s
20b[e]	5.53 d (7.1)	5.37 bd (7.1)	CH 9.05 bs
22	5.98 m	5.98 m	Vinyl 5.39 m, 6.60 m
23	5.60 d (6.3)	4.97 d (6.3)	
	4.63 d (5.5)	6.35 d (5.5)	
24	6.33 (5.3 Hz)	3.98 d (5.3)	
25	6.11 d (8.3)	5.83 m	CH_3 1.82 t (1.1), =CH 5.00 m
26	5.84 d (6.7)	5.25 d (6.7)	CH_3 1.73 s
	4.31 s		

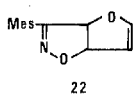
[a] Chemical shifts in parts per million (δ) from internal Me_4Si. Multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; sx, sextet; o, octet; m, multiplet; b, broad. Solvent: $CDCl_3$, unless otherwise stated. [b] In hertz. [c] Satisfactory combustion analytical data C, H, N (±0.4%) have been obtained for these compounds. Ed. [d] Numbering refers to the isoxazoline ring. [e] In Me_2SO-d_6. [f] $J + J'$. [g] Isoxazolidine ring protons.

The most abundant (1.0–1.1% yield) lactone was assigned structure **12** on the basis of spectral data (see Experimental Section) and of the hydrolytic cleavage, which yielded the known 3-phenyl-5-isoxazolylacetic acid.[20] Its reaction with BNO yielded the minor (~0.5% yield) lactone **13**, whose structure is fully consistent with spectral data. Furthermore, reaction of BNO with the bis adduct **5** yielded, along with the dimer of BNO and with some 3,5-diphenyl-1,2,4-oxadiazole, a mixture of **8**, **12**, and **13**. These latter lactones most likely originate from an unstable, nonisolated, tris adduct **9**.

The other tris adduct was isolated in 0.5% yield and was assigned structure **10**, since the same product was also obtained, along with lactone **13**, by reaction of the syn bis adduct **5** with an excess of BNO. The position of the chemical shifts of the four tetrahydrofuran ring protons as well as the lower value of the coupling constant for the isoxazolidine ring in comparison with that for the isoxazoline ring suggest the proposed structure, instead of the isomeric one, arising from an attack of BNO to the other isoxazoline ring.

Other Cycloadditions. In the reaction of furan with *p*- and *m*-nitrobenzonitrile oxides the major mono adducts could be isolated in fair yields and the regiochemistry was proven through acidic hydrolysis to the corresponding 2-nitrobenzoylfurans.[11] No attempt was made to characterize the minor products of these reactions.

Mesitonitrile oxide, a stable nitrile oxide which does not dimerize at room temperature, reacted with excess furan very slowly, but after 8 months mono adduct **22** (28%) and the bis adducts **23** (40%) and **24** (6%) were obtained. The NMR spectra show a strong resemblance to the corresponding BNO adducts.



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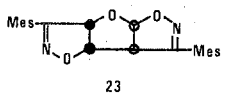

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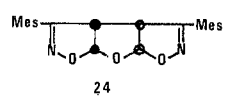

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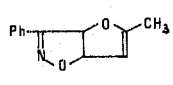

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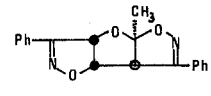
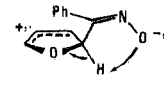


26

2-Methylfuran reacted with benzonitrile oxide to yield the mono adduct **25** as main product. Besides this minor amounts of the bis adduct **26** were isolated. Structural assignments were based on NMR spectroscopy.

Discussion

For the reaction of nitrile oxides with furan derivatives, three reaction patterns were a priori conceivable: (a) a [$_\pi 4_s$ + $_\pi 2_s$] cycloaddition of the dipole to one double bond of the ring; (b) a [$_\pi 4_s$ + $_\pi 2_s$] cycloaddition of furan to the nitrile oxide C≡N bond with possible subsequent dehydration to pyridine *N*-oxide derivative; (c) attack of the carbon atom of the nitrile oxide to the α position of furan to yield an oxime through a zwitterionic or diradical intermediate **27**.



27

Pattern b was unlikely, as previous results[4] demonstrated that conjugated dienes react as dipolarophiles rather than as dienes with nitrile oxides. As described above, the main products of the reaction with BNO were shown to be the mono cycloadducts **1** and **2** and their further addition or transformation products, consistent with the reaction pattern a. A 1% yield of the 2-benzoylfuran oxime **3**, path c, could also be detected. The cycloadducts **1** and **2** and the oxime **3** are primary products of the reaction, in the sense that they were shown to be stable and not to interconvert under the reaction conditions or during the isolation or analysis.

Taking into account the relative yields, the difference in free energy for the regioisomeric paths leading to the major cycloadduct **1** and to its regioisomer **2** could be evaluated at 2.1 kcal/mol, a value comparable to our more recent evaluations of 2.4 and 1.6 kcal/mol in the cycloadditions of BNO to cy-

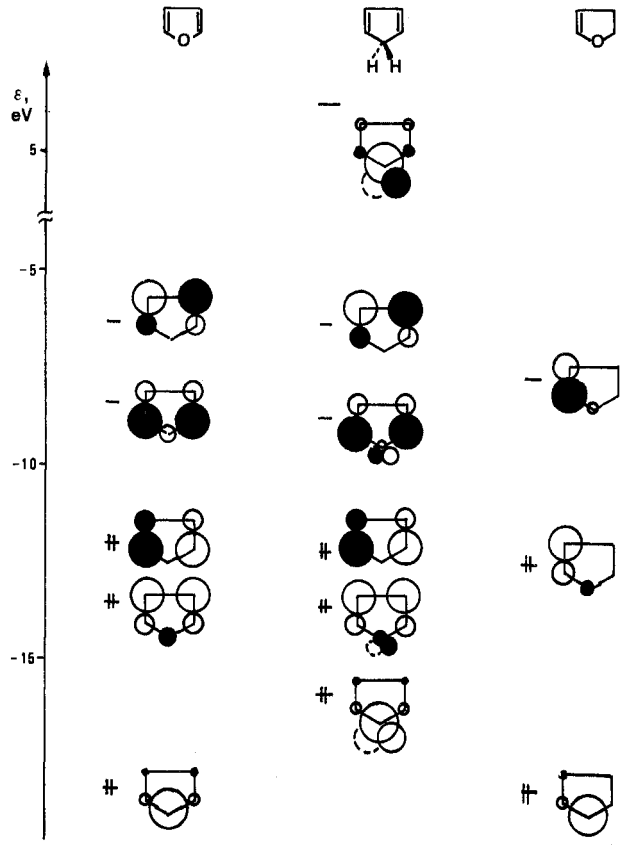


Figure 1. The π molecular orbitals of furan, cyclopentadiene, and 2,3-dihydrofuran. The radii of the circles represent the magnitudes of the atomic orbital coefficients at each center.

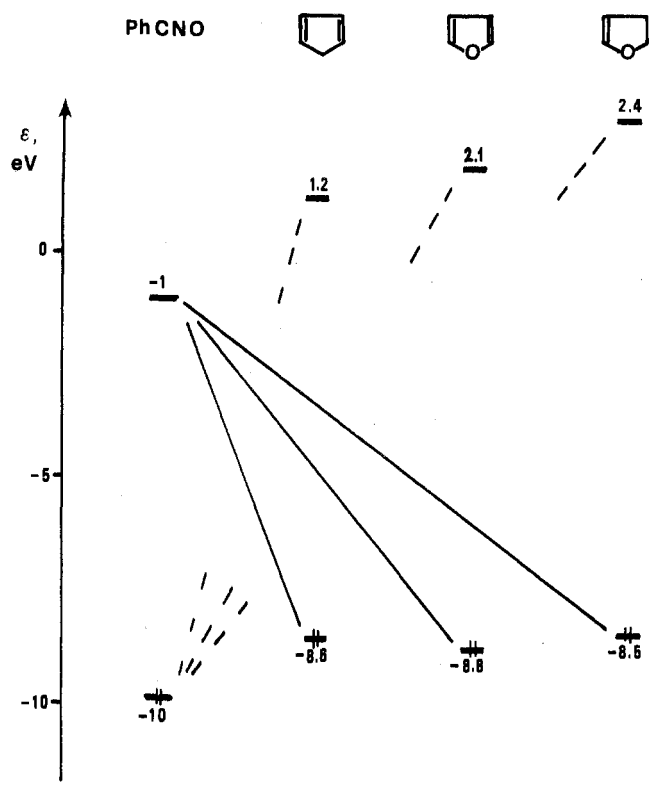


Figure 2. Interaction diagram of BNO with cyclopentadiene, furan, and 2,3-dihydrofuran.

clopentadiene and indene, respectively. The reactivity of furan is, however, reduced by a factor of 10^3 with respect to cyclopentadiene, as determined by competition experiments (see Experimental Section). A slightly lower, but comparable, regioselectivity for the reaction with mesitonitrile oxide is inferred by the isolation of bis adduct **24** in a 6% yield.

A frontier molecular orbital (FMO) treatment satisfactorily accounts for the regioselectivities observed for cyclopentadiene and furan on the one hand, and for the regiospecificity observed for the 2,3-dihydrofuran system present in the 1:1 adducts and for dihydrofuran itself[13] on the other. The shapes of the π MO's of these three dipolarophiles, as obtained from extended Hückel (EH)[21] calculations, are shown in Figure 1. The EH, CNDO/2, and MINDO/2 eigenvectors and eigenvalues for the FMO's are given in Table II. For cyclopentadiene and furan the HOMO and LUMO correspond essentially to the Ψ_2 and Ψ_3 π orbitals of butadiene. This is particularly true for the HOMO's, which have a node through the CH_2 group and oxygen, respectively. The HOMO of furan is inductively stabilized as shown by the lowest vertical IP of 8.88 eV[22] with respect to the value of 8.7 eV[7c,23] for cyclopentadiene. The LUMO of furan originates from the mixing of the Ψ_3 butadiene orbital with the p_z oxygen in an antibonding fashion, whereas in the case of cyclopentadiene, Ψ_3 mixes in the methylene π_{CH_2} and $\pi^*_{CH_2}$ orbitals out of phase and in phase, respectively. This causes nearly a cancellation of coefficient of p_z at the CH_2 group and a reinforcement of the hydrogen coefficients. As a result, the CH_2 orbital of π symmetry is mainly localized on the pair of hydrogens so that the overall shapes of the LUMO's of cyclopentadiene and furan are very similar. For dihydrofuran the shapes of the orbitals result from the influence of the oxygen donor in inducing mixing of the π and π^* orbitals of the vinyl group.[24] The IP of dihydrofuran can be estimated at 8.5 eV from the values reported for analogous enol ethers.[25]

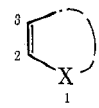
The IP and electron affinity (EA) of fulminic acid were estimated at 11 and 0.5 eV, respectively, and the empirical values of 10 and 1 eV were deduced for the π_{CNO} orbitals of BNO.[6b,c] The IP's of the dipolarophiles were discussed above and the EA's could be estimated from the $\pi \rightarrow \pi^*$ uv transitions[7b,25a] by considerations analogous to those reported.[6] The estimated orbital energies are displayed in Figure 2.

Thus the HOMO (dipolarophile)–LUMO (BNO) separation is here smaller than the other frontier orbital separation, the dipolarophiles behaving as donors and the nitrile oxides as acceptors. The nitrile oxides cycloadd in such a fashion that the electrophilic carbon terminus (largest LUMO coefficient) becomes bonded to the more nucleophilic carbon (largest HOMO coefficient). On the other hand the weaker interaction will favor bonding of the more nucleophilic oxygen of the dipole to the site of larger diene LUMO coefficient. This interaction favors the opposite regioselectivity with furan and cyclopentadiene. This mitigates somewhat the effect of the stronger interaction whereas with dihydrofuran a reinforcement of the regioselectivity occurs. The lesser regioselectivity of mesitonitrile oxide cycloadditions to furan as compared to the reactions of benzonitrile oxide may be due to the lower IP and EA of the former nitrile oxide. This will increase the nitrile oxide HOMO interaction somewhat at the expense of the LUMO interaction.

The FMO treatment does not explain the remarkably lower dipolarophilic reactivity of furan in comparison with cyclopentadiene, which must be attributed to the aromatic structure of the former dipolarophile.[6b] From the competition data the increase of the barrier leading to the major cycloadduct could be estimated at 4.0 kcal/mol. This value is compatible with an early transition state for the cycloaddition of nitrile oxides, as suggested by recent ab initio calculations.[26]

With 2-methylfuran only cycloaddition to the unsubstituted double bond, leading to **25**, was observed. The smaller reactivity of the substituted double bond can be ascribed to the destabilizing interaction between the methyl substituent and the nitrile oxide carbon. The shape of the HOMO of 2-meth-

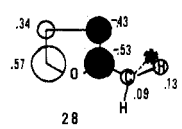
Table II. Eigenvectors and Eigenvalues of the Frontier Orbitals[a]



	HOMO				LUMO			
	C_1	C_2	C_3	E, eV	C_1	C_2	C_3	E, eV
EH[b]								
Cyclopentadiene	0.0	0.5545	0.3767	−12.271	−0.0472 (−0.2256)[c]	0.6447	−0.4359	−8.801
Furan	0.0	0.5655	0.3762	−12.059	−0.3605	0.6708	−0.4022	−8.401
Dihydrofuran	−0.2689	0.5815	0.6194	−12.561	−0.1918	0.8468	−0.8010	−7.708
CNDO/2[d]								
Cyclopentadiene	0.0	0.5746	0.4128	−12.457	0.1261 (−0.2952)[c]	0.5017	−0.3922	3.150
Furan	0.000	0.5866	0.3947	−12.187	−0.3596	0.5586	−0.3508	4.130
Dihydrofuran	−0.5412	0.4205	0.5147	−12.160	−0.1414	0.6805	−0.5979	4.919
MINDO/2[e]								
Cyclopentadiene	0.0	0.5685	0.4211	− 9.038	−0.0056 (−0.1851)[c]	0.5501	−0.4046	0.702
Furan	0.0	0.5756	0.4103	− 8.929	−0.3454	0.5687	−0.3413	0.936
Dihydrofuran	−0.5028	0.4555	0.5903	− 9.039	−0.1645	0.7182	−0.6479	1.259

[a] Experimental geometries were used for the calculations. Furan: B. Bak, D. Christensen, W. B. Dixon, L. Hansen-Nygaard, J. R. Andersen, and M. Schottlander, *J. Mol. Spectrosc.*, 9, 124 (1962). Cyclopentadiene: L. H. Scharpen and V. W. Laurie *J. Chem. Phys.*, 43, 2765 (1965). 2,3 Dihydrofuran: T. Ueda and T. Shimanouchi, *J. Chem. Phys.*, 47, 5018 (1967). [b] See ref 21. [c] Coefficient of the hydrogen of the CH_2 group above the molecular plane. The hydrogen under the molecular plane (not shown) as opposite sign. [d] J. A. Pople and J. L. Beveridge, "Approximate Molecular Orbital Theory", McGraw-Hill, New York, N. Y., 1970. [e] N. Bodor, M. J. S. Dewar, E. Haselbach, and A. Harget, *J. Am. Chem. Soc.*, 92, 3854 (1970).

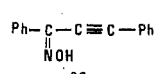
ylfuran, calculated by EH, is given below and results from the mixing of the π orbitals of furan caused by the asymmetric



28

methyl perturbation.[24] Steric effects (or the closed shell repulsion term of the complete perturbation treatment[27]) work in the same direction favoring **25.**

Oxime **3** was obtained in a 1% yield. The free-energy barrier leading to **3** can be calculated to lie 2.6 kcal/mol above the barrier leading to the predominant cycloadduct **1.** Phenylacetylene is also known to react with BNO to yield a mixture of 3,5-diphenylisoxazole and the acetylenic oxime **29** in a ratio



29

of 88:12.[28] For the phenylacetylene reaction, the influence of substituents and solvents and the absence of any significant isotope effect[29] support the occurrence of two independent pathways, a concerted cycloaddition and a competing two-step 1,3 addition through a rate-determining electrophilic attack of nitrile oxide on the π system of the aryl acetylene.[30]

A reasonable rationalization of the appearance of the oxime **3** in the reaction mixture of BNO with furan is based on the fact that the cycloaddition is slowed down owing to the loss of aromaticity. Thus the formation of oxime may merely indicate that the concerted pathway has been destabilized to such an extent that a stepwise mechanism, leading to cycloadduct or oxime, may now have a similar activation energy. On the other hand the appearance of oxime may indicate that the stepwise mechanism with furan has some special stabilizing features that are absent in other cases. The approach of the reagents with alignment which would lead directly to the intermediate **27,** from which oxime **3** may be formed, appears indeed to be well stabilized by secondary orbital interactions. The dominant HOMO (furan)–LUMO (BNO) interaction is considerably strengthened whereas an approximate cancellation of secondary orbital effects occurs in the less important LUMO (furan)–HOMO (BNO) interaction. An even better stabilization may be achieved in the case of phenylacetylene by both of the HOMO–LUMO secondary orbital interactions.[31] The relevant secondary interactions are indicated by the dashed lines in the two-plane transition state complexes of Figure 3. A considerable stabilization of the transition state for this alignment, and of the resulting intermediate, should result.

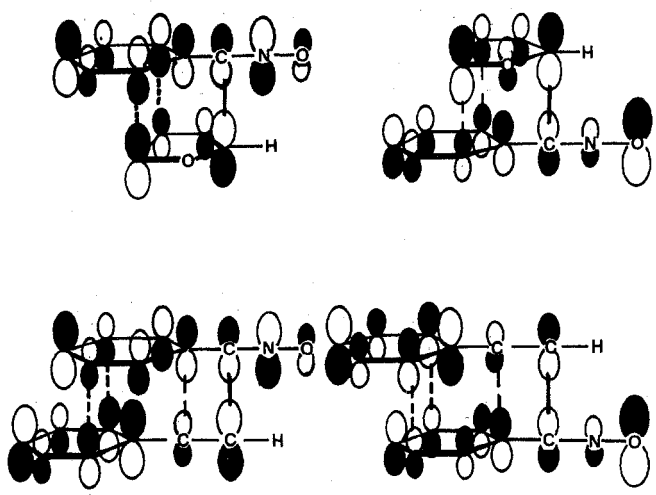


Figure 3. HOMO–LUMO interactions for two-planes transition state complexes. The HOMO and the LUMO of the reactants are represented in the lower and upper part of each complex, respectively. The lobes represent the magnitudes of the atomic orbital coefficient calculated by CNDO/2.

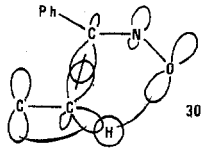
The lack of isotope effect and of rate dependence on the concentration of the base in the phenylacetylene reaction suggested that the proton transfer to form the oxime occurs in a subsequent fast intramolecular process. This is in line with the acid-strengthening effect of adjacent cationic moieties and the suitable location of the oxygen nucleophile for an intramolecular proton transfer. With furan, the additional gain of aromaticity may make this process even easier.

The cycloaddition leading to 3,5-diphenylisoxazole is slow, because of the two large HOMO–LUMO separations.[6b] Alkynes are well known to react slower than alkenes by a power of 10.[32] As a matter of fact, in both these cases where acyclic adducts were detected in the reaction mixtures, furan and phenylacetylene have reduced 1,3-dipolar reactivity toward BNO and also possess the better available geometry for maximal stabilizing interactions in the alignment for a two-step 1,3-addition reaction. Secondary orbital interactions allowed the rationalization of the exo–endo[33] and of the syn–anti[34] specificity in cycloadditions. They form the basis of the concept of steric attraction[35] and—under the heading of nonbonded interactions—were proven to be important contributors to the conformational[36] or configurational[37] preferences of normal molecules as well as of carbonium ions.[38] In the present case, they may be of importance in facilitating an otherwise noncompetitive reaction.

Alternatively viewed, two trajectories appear feasible for overcoming the hill to the products, and frontier molecular orbital theory helps in deciding upon the best ones. Trajectory considerations have been required for the interpretation of the chemistry of trimethylene[39] and tetramethylene[40] intermediates and were recently implicitly proposed for the loss of stereochemistry in the reaction of heterodienes with enol ethers.[41]

Conclusions

A common intermediate does not appear to be required to explain the competing reactions discussed in this paper. Moreover, we have retained the term intermediate in the discussion of the path leading to the oximes only for sake of simplicity. There are no stringent reasons requiring any discrete intermediate other than plausibility even in this case. The whole path leading to oxime could be indeed described as an energetically[42] concerted $[_{\pi}2_a + {}_{\pi}4_s + {}_{\sigma}2_s]$ allowed cycloaddition. As the reagents approach each other, stretching of the bonds and bending of the angles occur, and the allowed path is clearly recognizable in a rather advanced stage of the reaction as shown below.



30

As a consequence, in the energy profile of the reaction, the convenient energy minimum of the intermediate—which occurs after that of the transition state has been passed as discussed above—may disappear. Similar flat surfaces and the absence of energy minima have been described for trimethylene and tetramethylene diradicals.[39,40]

Only a detailed analysis of the surface, however, can give insights into the presence or absence of secondary minima on the cycloaddition and 1,3-addition pathways as well as into the availability of low-energy paths connecting them.

At the present, insights for prediction purposes and for devising further experimental tests seem to be attainable by a comparison of the factors affecting the cycloaddition with respect to those ways. Some useful generalizations will be reported elsewhere.

Experimental Section

All melting points are uncorrected. Ir spectra were taken on a Perkin-Elmer Model 257 spectrophotometer as Nujol mulls. NMR spectra were taken in $CDCl_3$ solution, with Me_4Si as internal standard, on a Perkin-Elmer R12 spectrometer (60 MHz). Gas chromatographic analyses were carried out on a glass column, 1% Carbowax 20M and 1% Apiezon L on Gas-Chrom P, with a column temperature of 175 °C on a Carlo Erba Fractovap instrument. Microanalyses were performed by Dr. L. Maggi Dacrema. Satisfactory analytical data (±0.4% for C, N, H) were obtained for all the compounds listed in Table I. Column chromatography and TLC were performed with silica gel H and GF_{254} (Merck), respectively, eluent cyclohexane–EtOAc (9:1 to 7:3) unless otherwise specified. The identification of samples from different experiments was secured by mixture melting points and superimposable ir spectra.

General Procedure for BNO Cycloadditions. To a stirred and ice-cooled solution of benzhydroximic acid chloride (155.5 mg, 1 mmol) and dipolarophile in anhydrous ether (25 ml), a stoichiometric amount of triethylamine (101.9 mg, 0.142 ml) in ether (5 ml) was added over a 30-min period. The mixture was stirred overnight at 0 °C and then kept for 2 days at 25 °C. The triethylamine hydrochloride was filtered off, and the filtrate was evaporated under reduced pressure, leaving a residue. In some cases, on dissolving the triethylamine hydrochloride in water (5 ml), insoluble products were obtained and were added to the residue. Separations were achieved by column chromatography. In all the reactions reported here, 3,4-diphenylfuroxan and 3,5-diphenyl-1,2,4-oxadiazole were eluted first, followed by the cycloaddition products.

Cycloaddition of BNO to Furan. A. To a stirred and ice-cooled solution of benzhydroximic acid chloride (5 g, 32 mmol) in freshly distilled furan (50 ml) a stoichiometric amount (32 mmol) of triethylamine was added over a 2-h period. After the mixture was kept overnight at 0 °C and 2 days at 25 °C, the mixture was diluted with anhydrous benzene (200 ml), the triethylamine hydrochloride was filtered off, and the filtrate was evaporated under reduced pressure, leaving a residue. Column chromatography gave 3,4-diphenylfuroxan (30%) and 3,5-diphenyl-1,2,4-oxadiazole (10%) along with the following products. (1) Mono adduct **1** (730 mg, 12.2%), which was purified by vacuum distillation [bp 170–180 °C (bath)(0.3 mm)]. Crystallization from petroleum ether gave an analytical sample, mp 45–46 °C. (2) Tris adduct **8** (56 mg, 1.2%). The analytical sample, recrystallized from EtOH, had mp 162–316 °C dec. (3) A mixture of mono adduct **2** (17 mg, 0.3%) and bis adduct **5** (738 mg, 15%). The last was separated from the more soluble **2** by crystallization from EtOH. Recrystallization from EtOH gave an analytical sample of **5**, mp 192 °C. From the mother liquors, **2** was isolated by vacuum distillation [bp 170–180 °C (bath)(0.3 mm)]. The analytical sample of **2**, recrystallized from petroleum ether, had mp 70 ° C. Separation could also be achieved using column chromatography, with benzene as eluent. With benzene, **2** is eluted faster than **5**. (4) Oxime **3** (10 mg, 0.2%), mp 149 °C from EtOH, was found to be identical with a sample prepared according to the literature.[14] (5) Bis adduct **7** (30 mg, 0.6%), analytical sample mp 172–173 °C from EtOH. (6) Tris adduct **10** (25 mg, 0.5%), analytical sample mp 161–162 °C dec from EtOH. (7) Lactone **13** (26 mg, 0.5%), analytical sample mp 152–153 °C dec from EtOH, $\nu_{C=O}$ 1782 cm^{-1}. (8) Bis adduct **6** (111 mg, 2.3%), analytical sample mp 227–228 °C from EtOH. (9) Lactone **12** (73 mg 1.1%), analytical sample mp 116–117 °C from EtOH, $\nu_{C=O}$ 1793 cm^{-1}. Similar yields were obtained in duplicate experiments. Eluting with benzene, then benzene/EtOAc, the order of elution of the products is the same, except that **2** is eluted together with **1**, and a better separation of **6** and **12** could be achieved.

B. To a stirred solution of benzhydroximic acid chloride (1 mmol) in furan (100 ml), at room temperature (25 °C), 2 equiv of triethylamine was added. After standing for 3 days, the triethylamine hydrochloride was filtered off and washed with anhydrous benzene. The filtrate was evaporated under reduced pressure, leaving an oily residue. The yields of **1** + **2** (91 ± 1% in a 97:3 ± 0.5% ratio) and **3** (1.0 ± 0.5%) were determined by GLC, by adding as an internal standard a known amount of the BNO adduct with cyclopentene. The area ratio was corrected by using response factors, determined on known mixtures of the adducts and the standard. The pure adducts **1–3** gave well-separated single peaks and are not interconverted under the gas chromatographic conditions. Samples of **1** and **3**, kept for 3 days under the same conditions of the cycloaddition reaction (in furan in the presence of NEt_3/NEt_3·HCl), did not reveal any appreciable interconversion.

The relative addition constants of furan, cyclopentene, and cyclopentadiene were evaluated by the competition method.[43]

Benzhydroximic acid chloride (1 mmol) and cyclopentene 2–2.5 mmol) in furan (50 ml) were reacted as above. By adding a standard, the yields of **1** and of the cyclopentene adduct were determined by GLC. After correction for **2** and **3**, a reactivity ratio of 460 ± 30 of cyclopentene and furan was calculated, as an average on three different reaction mixtures. Similarly, cyclopentadiene was found 2.02 times more reactive than cyclopentene in ether. This corresponds to a decrease of 0.93×10^3 in the reactivity of furan with respect to cyclopentadiene.

Cleavage of 1. A solution of **1** (1 mmol) in HOAc (3 ml) and 20% sulfuric acid (3 ml) was refluxed for 24 h. After cooling, the mixture was poured on ice (20 g) and extracted with ether. The extracts were washed with 10% NaOH, dried on Na_2SO_4, and distilled, giving a 72% yield of 2-benzolyfuran, bp 170 °C, identical (ir, NMR) with a sample prepared according to the literature.[44]

Hydrogenation of 2. **2** (0.2 mmol) and 10 mg of 10% Pd/C in 10 ml of 1:4 HOAc/AcOEt absorbed 1 equiv of hydrogen in 5 min. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure. Crystallization from petroleum ether afforded **14** (60%), mp 77 °C, identical with a sample prepared according to the literature.[13]

Hydration of 1. **1** (5 mmol) was dissolved in $CHCl_3$ (50 ml). On TLC the spot of **1** disappeared in 1 week. After evaporation of the $CHCl_3$, column chromatography yielded the following. (1) Colorless crystals (118 mg, 12%), mp 172–173 °C from EtOH. Anal. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.33; H, 5.14; N, 7.14. Found: C, 67.39; H, 5.29; N, 7.06. NMR: 2.46 m (4 H), 5.33 q (J = 7.3, 5.3 Hz, 2 H), 5.62 q (J = 4.7, 3.3 Hz, 2 H), 5.79 d (J = 7.3 Hz, 2 H), 7.2–8 m (10 H). (2) Colorless crystals (65 mg, .7%), mp 194–195 °C from EtOH. Anal. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.33; H, 5.14; N, 7.14. Found: C, 67.00; H, 5.18; N, 7.31. NMR: 2.43 m (4 H), 5.2–5.5 m (4 H), 5.90 d (J = 7.3 Hz, 2 H), 7.2–8 (10 H). (3) Colorless crystals (405 mg, 41%), mp 145–146 °C from EtOH. Anal. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.33; H, 5.14; N, 7.14. Found: C, 67.47; H, 5.38; N, 6.95. NMR: 1.6–2.1 m (3 H), 2.23–2.5 m (1 H), 5–5.35 m (3 H), 5.6–5.8 m (1 H), 5.66 d (J = 7.3 Hz, 1 H), 5.87 d (J = 7.3 Hz, 1 H), 7.30–7.9 m (10 H). (4) Colorless crystals (130 mg, 13%), mp 172–174 °C from EtOH. Anal. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.33; H, 5.14; N, 7.14. Found: C, 67.73; H, 5.31; N, 7.33. NMR: 2.2–2.5 m (4 H), 4.95–5.15 m (2 H), 5.20–5.35 m (2 H), 5.49 bd (J = 4.7 Hz, 1 H), 5.85 d (J = 7.3 Hz, 1 H), 7.3–8.5 m (10 H). (5) **15** (130 mg, 13%). Recrystallization from benzene gave an analytical sample, mp 126–127 °C, ν_{OH} 3445 cm^{-1}. **15** was acetylated with pyridine/Ac_2O, yielding the acetyl derivatives **16a** (46%) and **16b** (28%) which were separated by column chromatography, eluent benzene/AcOEt 9:1. Recrystallization from hexane gave the analytical samples of **16a**, mp 90–91 °C, $\nu_{C=O}$ 1743 cm^{-1}, and **16b**, mp 93–94 °C, $\nu_{C=O}$ 1743 cm^{-1}.

Cleavage of Bis Adducts 5 and 6. To a stirred suspension of 1 mmol of **5** in 10 ml of Ac_2O, 0.5 ml of boron trifluoride etherate was added. After 1 h, the clear solution was poured onto ice (50 g), stirred for 1 h, and extracted with ether. The extracts were washed successively with 5% $NaHCO_3$ and water and then were dried over Na_2SO_4 and evaporated. The residue was recrystallized from MeOH yielding 268 mg (77%) of ester **20a**. The analytical sample had mp 125 °C, $\nu_{C=O}$ 1760 cm^{-1}. Similarly **6** yielded **20a** in a 61% yield.

A solution of 5 mmol of **20a** in MeOH (30 ml) and concentrated HCl (8 ml) was refluxed for 4 h. After evaporation of the solvent, crystallization of the residue from MeOH afforded 1.0 g (63%) of **20b**, analytical sample mp 162.5–163 °C, ν_{OH} 3330 cm^{-1}. Acetylation of **20b** with Ac_2O (24 h at room temperature) gave back **20a** quantitatively.

A mixture of **20b** (2 mmol) and 2 g of finely powdered $KHSO_4$ was maintained for 4 h at 170 °C. The residue was washed with water and recrystallized from MeOH, yielding 350 mg (60%) of **21**, mp 99 °C, identical with an authentic specimen.[18]

Thermolysis of Tris Adduct 8. **8** (300 mg, 0.70 mmol) was kept at 170 °C for 5 min. Column chromatography yielded 122 mg (80%) of 3,5-diphenyl-1,2,4-oxadiazole and 99 mg (70%) of ketone **11**. Crystallization from hexane gave an analytical sample, mp 89–90 °C $\nu_{C=O}$ 1768 cm^{-1}. The tosylhydrazone of **11** was prepared in a 60%yield by refluxing 73 mg of **11** and an equimolecular amount of tosylhydrazine in 5 ml of MeOH for 15 min. Recrystallization from MeOH gave colorless needles, mp 205–206 °C. Anal. Calcd for $C_{18}H_{17}N_3SO_4$: C, 58.18; H, 4.62; N, 11.32. Found: C, 58.26; H, 4.71; N, 11.30.

Hydrolysis of Lactone 12. **12** (0.5 mmol) was refluxed with 50% H_2SO_4 for 2 h. After dilution with water (40 ml) the mixture was extracted with $CHCl_3$. The extracts were dried on Na_2SO_4 and evaporated, leaving 80 mg (80%) of 3-phenyl-5-isoxazolylacetic acid, mp 124–125 °C from C_6H_6, identical with a sample prepared according to the literature.[20]

Cycloaddition of BNO to Mono Adducts 1 and 2. **1** (500 mg, 2.65 mmol) and 8 mmol of BNO yielded the following products after column chromatography: (1) 35 mg (3%) of tris adduct **8**, (2) 315 mg (32%) of bis adduct **5**, (3) 25 mg (3%) of lactone **13**, (4) 25 mg (3%) of bis adduct **6**, (5) 20 mg (4%) of lactone **12**.

similarly from 75 mg (0.40 mmol) of **2** and 1.2 mmol of BNO, 60 mg (49%) of **7** was obtained.

Cycloaddition of BNO to Bis Adducts 5 and 6. **5** (3.06 g, 10 mmol) and 60 mmol of BNO in anhydrous benzene (200 ml) at room temperature yielded after column chromatography (1) 860 mg (20%) of trisadduct **8**, (2) 680 mg (21%) of lactone **13**, (3) 440 mg (21%) of lactone **12**. Under these conditions, 23% of bis adduct **5** was recovered unchanged.

Similarily, from 153 mg (0.5 mmol) of **6** and 3 mmol of BNO, 36 mg (15%) of tris adduct **10** and 19 mg (12%) of lactone **13** were obtained. Unchanged **6** (58 mg, 38%) was recovered.

Cycloaddition of BNO to Lactone 12. From 0.5 mmol of **12** and 3 mmol of BNO, 100 mg (62%) of lactone **13** and 20 mg (20%) of unchanged **12** were recovered by column chromatography.

Cycloaddition of *p*- and *m*-Nitrobenzonitrile Oxide to Furan. *p*-Nitrobenzhydroximic acid chloride (25 mmol) in 100 ml of furan yielded, after the usual workup, 3.5 g (60%) of mono adduct as pale yellow crystals, mp 145–145 °C from MeOH. Anal. Calcd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.47; N, 12.07. Found: C, 56.78; H, 3.53; N, 11.99. Cleavage of 3 mmol of the adduct by refluxing with 1:1 HOAc/H_2SO_4 (20%) for 24 h yielded 400 mg (61%) of 2-*p*-nitrobenzoylfuran, pale yellow crystals, mp 184 °C from MeOH, $\nu_{C=O}$ 1640 cm^{-1}. Anal. Calcd for $C_{11}H_7NO_4$: C, 60.83; H, 3.25; N, 6.45. Found: C, 60.73; H, 3.49; N, 6.64. A solution of 2-*p*-nitrobenzoylfuran (2 g) in EtOH (150 ml) absorbed 3 equiv of hydrogen in 1 h in the presence of 10% Pd/C (0.2 g). After filtration of the catalyst and evaporation of the solvent, the crude 2-*p*-aminobenzoylfuran (1.7 g) was dissolved in 5% HCl (25 ml), $NaNO_2$ (0.67 g) was added, and the mixture was refluxed for 2 h. Extraction with ether gave 0.6 g (34%) of 2-*p*-hydroxybenzoylfuran, mp 163–164 °C from water, identicl with a sample prepared according to the literature.[45]

Similarily, 25 mmol of *m*-nitrobenzhydroximic acid chloride yielded 2.0 g (34%) of mono adduct, pale yellow crystals, mp 113 °C from MeOH. Anal. Calcd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.47; N, 12.07. Found: C, 56.69; H, 3.53; N, 12.03. Hydrolysis as above yielded 2-*m*-nitrobenzoylfuran, pale yellow crystals, mp 124.5 °C from MeOH, $\nu_{C=O}$ 1640 cm^{-1}. Anal. Calcd for $C_{11}H_7NO_4$: C, 60.83; H, 3.25; N, 6.45. Found: C, 60.99; H, 3.36; N, 6.82.

Cycloaddition of Mesitonitrile Oxide with Furan. A solution of 4 g (24.8 mmol) of mesitonitrile oxide in 70 ml of furan was kept at room temperature for 8 months. Bis adduct **23** (1.15 g) crystallized out. Recrystallization from EtOH gave an analytical sample, mp 257–258 °C. The filtrate was evaporated. Crystallization from ethanol yielded a mixture of 0.8 g of **23** (combined yield 40%) and 0.29 g (6%) of bis adduct **24**, which was separated by column chromatography, with benzene as eluent. An analytical sample of **24** was obtained by crystallization from EtOH and had mp 264–266 °C dec. The mother liquors were evaporated and distilled, yielding 1.6 (28%) of mono adduct **22**, bp 160–180 °C (bath) (0.1 mm), analytical sample mp 91 °C from petroleum ether.

Cycloaddition of BNO to 2-Methylfuran. Benzhydroximic acid chloride (5 g, 32 mmol) in 50 ml of 2-methylfuran yielded 1.77 g ((28%) of **25** and 0.17 g (3%) of bis adduct **26**. The analytical sample of **25** and **26** had mp 70 °C (from petroleum ether) and 213 °C (from EtOH), respectively.

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Registry No.—**1**, 59728-61-9; **2**, 59728-62-0; **5**, 59752-62-4; **6**, 59752-63-5; **7**, 59728-63-1; **8**, 59728-64-2; **10**, 59728-65-3; **11**, 59728-66-4; 11 tosylhydrazone, 59728-67-5; **12**, 59728-68-6; **13**, 59728-69-7; **15a**, 58728-70-0; **15b**, 59752-64-6; **16a**, 59728-71-1; **16b**, 59752-65-7; **17** isomer A, 59728-72-2; **17** isomer B, 59752-66-8; **18** isomer A, 59752-67-9; **18** isomer B, 59752-68-0; **19** isomer A, 59752-69-1; **19** isomer B, 59752-70-4; **20a**, 59728-73-3; **20b**, 59728-74-4; **22**, 59728-75-5; **23**, 59728-76-6; **24**, 59728-77-7; **25**, 59728-78-8; **26**, 59728-79-9; benzhydroximic acid chloride, 698-16-8; BNO, 873-67-6; furan, 110-00-9; *p*-nitrobenzhydroximic acid chloride, 1011-84-3; monoadduct A, 59728-80-2; 2-*p*-nitrobenzoylfuran, 21494-08-6; *m*-nitrobenzhydroximic acid chloride, 33512-94-6; monoadduct B, 59728-81-3; 2-*m*-nitrobenzoylfuran, 59728-82-4; mesitonitrile oxide, 59728-83-5; 2-methylfuran, 534-22-5.

References and Notes

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Reactions of 3-Methylbenzyne with 2-Substituted Furans.[1] Steric Effects

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3-Methylbenzyne generated from two pairs of isomeric precursors, namely, 2-amino-3-methylbenzoic acid (1)–2-amino-6-methylbenzoic acid (2) and 2-fluoro-3-methylbromobenzene (3)–6-fluoro-2-methylbromobenzene (4), has been reacted with 2-methylfuran (5), 2-*tert*-butylfuran (6), 2-(1,3-dioxolan-2-yl)furan (7), and 2-carbomethoxyfuran (8). The proportions of isomeric adducts produced were the same (±2%) for each furan and are expressed as ratio of less hindered isomer (1,5-naphthalene derivative) to more hindered isomer (1,8-naphthalene derivative) as follows: for **5**, 58/42; **6**, 64/36; **7**, 61/39; **8**, 57/43. Thus the addition of an unsymmetrical benzyne to a furan seems very slightly affected by steric or polar effects. The results are interpreted as evidence supporting a true benzyne intermediate.

Benzyne reacts readily with furans to form 1,4-dihydro-1,4-epoxynaphthalenes which are of great synthetic interest because of their ready conversion to other types of compounds.[3,4] In order to increase the synthetic utility and understanding of this type of reaction, we have studied the reactions of 3-methylbenzyne prepared from two isomeric pairs of precursors with 2-substituted furans.

Although a fair amount of work has been done on the relative reactivities in Diels–Alder type reactions of benzynes (prepared from different precursors) with pairs of other reactants,[5,6] little is known about steric effects.[7] Conflicting steric results have been reported in the reaction of 3,5-di-*tert*-butylfuran[8] (in which the predominant adduct proved to be the more hindered 1,3,6,8-tetra-*tert*-butyl-1,4-dihydro-1,4-epoxynaphthalene) and with 2-benzyl-5-*tert*-butylfuran[9] (in which the ratio of the less hindered isomer to the more hindered isomer was 14/11).

In the work reported herein we have determined the products formed when two pairs of isomeric compounds, 2-amino-3-methylbenzoic acid (**1**)–2-amino-6-methylbenzoic acid (**2**) and 2-fluoro-3-methylbromobenzene (**3**)–6-fluoro-2-methylbromobenzene (**4**), were treated to produce 3-methylbenzyne in the presence of 2-methylfuran (**5**), 2-*tert*-butylfuran (**6**), 2-(1,3-dioxolan-2-yl)furan (**7**), and 2-carbomethoxyfuran (**8**), to yield the isomeric adduct pairs (**9a, 9b**), (**10a, 10b**), (**11a, 11b**), and (**12a, 12b**). The results are summarized in Table I.

Examination of the results in Table I reveals that the ratio of products obtained from isomeric 3-methylbenzyne precursors is the same, within experimental error, for each of the