An Intramolecular 1,3-Dipolar Cycloaddition/Electrophilic Cyclization Sequence To Give Cyclic Ethers

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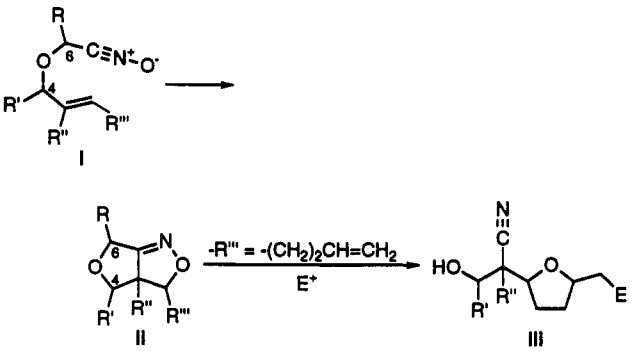
Summary: An intramolecular 1,3-dipolar cycloaddition/electrophilic cyclization sequence has been developed for the synthesis of cyclic ethers. This approach utilizes a diastereoselective nitrile oxide 1,3-dipolar cycloaddition to give furoisoxazoles, which undergo subsequent electrophilic cyclization to afford substituted tetrahydrofurans.

Cyclic ethers are important structural elements of polyether antibiotics[1] and have proven to be challenging synthetic targets.[2] In earlier work,[3] we described an approach to 2,5-disubstituted tetrahydrofurans utilizing an intermolecular 1,3-dipolar addition/electrophilic cyclization sequence. Herein we report the synthesis of 2,5-disubstituted tetrahydrofurans making use of an *intramolecular* 1,3-dipolar cycloaddition/electrophilic cyclization sequence as outlined in Scheme I. This method effectively converts dienols to cyclic ethers via furoisoxazoles.

As established in earlier studies, the intramolecular 1,3-dipolar cycloaddition of a nitrile oxide to a substituted double bond affords a furoisoxazole (**i** → **ii**) with excellent stereoselectivity.[4] The nitrile oxide moiety is prepared by dehydration of the corresponding nitroalkane.[5] This cycloaddition step sets two new stereocenters: (i) the geometry of the internal C=C bond provides stereochemical control at C_{3a} and C_3, and (ii) the C_4 stereocenter and, to a lesser extent, a stereocenter at C_6 dictate diastereofacial selectivity. By incorporating a 3-butenyl group at C_3 of this heterocycle, the stage is set for an electrophilic cyclization which results in concomitant unraveling of the furoisoxazole and cyclic ether formation. This transformation releases C_6, exposes latent hydroxyl and cyano functional groups, and sets a new stereocenter in the cyclic ether.

Scheme I



In initial studies, a C_6 phenyl group (**ii**; R = Ph) was employed in an attempt to stabilize the incipient positive charge that would develop at this center during the iodine monochloride-initiated electrophilic cyclization (**ii** → **iii**). This approach failed; instead, the ICl added across the C=C bond. We reasoned that an electron-donating group at the *para* position of the C_6 aryl ring would better stabilize the positive charge, and *p*-methoxy-β-nitrostyrene was thus selected as the starting nitroolefin. The requisite dienols were synthesized[6] from the corresponding enynols by reduction with lithium aluminum hydride[7] to give a *trans* internal double bond. The nitroethers **2**/**3** were formed by Michael addition[8] of the derived potassium alkoxides to *p*-methoxy-β-nitrostyrene (Scheme II). Subsequent phenyl isocyanate mediated dehydration[5] to the nitrile oxide with concomitant intramolecular 1,3-dipolar cycloaddition gave the targeted furoisoxazoles **4**/**5**. These furoisoxazoles were then cyclized by the action of ICl to give cyclic ethers **6**/**7**. Yields and diastereomeric ratios for the various compounds depicted in Scheme II (R′ = Ph, Me, H) are given in Table I.Racemic nitroethers **2a**/**3a** and **2b**/**3b** were formed in 1:1 diastereomeric ratios and, like racemic **2c**/**3c**, were used without separation in the dehydrative 1,3-dipolar cycloaddition. For the C_4 phenyl-substituted system, the reaction is 100% face-selective giving only furoisoxazoles **4a** and **4′a** in a 1:1 diastereomeric ratio. For the 4-methyl derivative, **4b**, **4′b**, and **5b** were obtained in a 39:45:16 diastereomeric ratio. Nitroether **2c** with no allylic substituent yielded furoisoxazoles **4c** and **4′c** in a 5.8:1 ratio. The relative stereochemistries of these furoisoxazoles were determined using 2-D NOESY correlation techniques with the pertinent data presented in Table II.

We were pleased to discover that these anisole-substituted furoisoxazoles underwent electrophilic cyclization as planned, unlike their phenyl-substituted counterparts. Clearly, the electron-donating methoxyl group in the C_6 aryl ring is necessary in order to promote cyclization to

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Scheme II

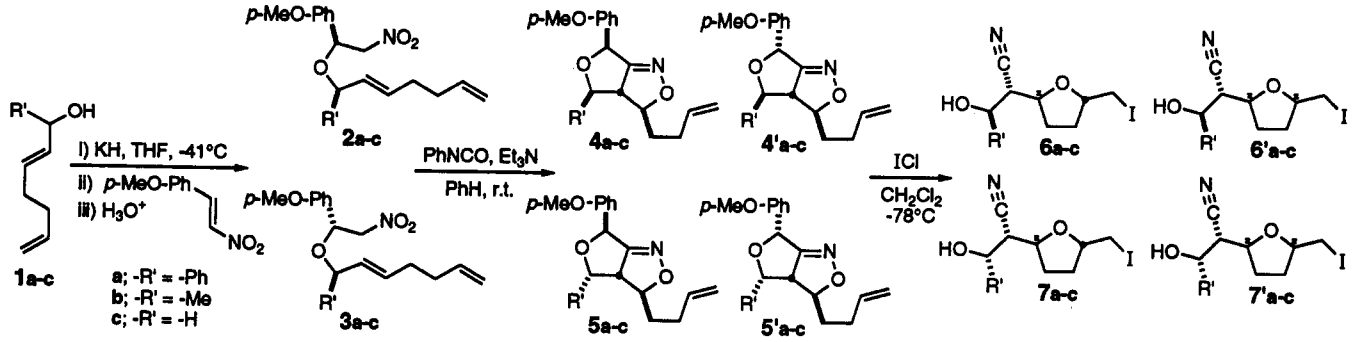

Table I. Yields and Stereoselectivities

	R'	yield (%)	2:3	yield (%)	4:4':5:5'	yield (%)	6:6':7:7'
a	Ph	70	1:1	76	1:1:–:–	86	4:1:–:–
b	Me	76	1:1	72	39:45:16:–	63	57:25:11:7
c	H	54		78	5.8:1:–:–	72	2.8:1:–:–

Table II. NOESY Correlation Results (+ ≡ Positive NOE Observed)

	4a	4'a	4b	4'b	5b	4'c
H-3 ⇔ H-4	+	+	+	+		
H-3a ⇔ H-6		+		+		+
H-4 ⇔ H-6	+		+			
H-3 ⇔ CH_3-4					+	
H-3a ⇔ CH_3-4			+	+		
H-6 ⇔ CH_3-4					+	

2,5-substituted tetrahydrofurans **6** and **7**. Furthermore, this reaction carries the $C_3/C_{3a}/C_4$ furoisoxazole stereocenters through to the propionitrile side chain of the cyclic ethers and unravels the furoisoxazole ring to reveal the hydroxy and cyano functionalities. The cyclization can afford the newly generated iodomethyl moiety either *cis* or *trans* to the propionitrile substituent: while there is some *trans* preference, selectivity is only moderate at ≈2–4:1. Thus, for the 4-phenyl systems (R' = Ph), only two cyclic ethers were expected (**6a** and **6'a**) since furoisoxazoles **4a** and **4'a** have identical relative stereochemistry in the incipent propionitrile. Indeed, no trace of tetrahydrofurans **7a** or **7'a** was detected, and the ratio of *trans*-**6a** to *cis*-**6'a** was 4:1. For the methyl-substituted furoisoxazoles, all four cyclic ethers were expected (**6b/6'b** from **4b/4'b** and **7b/7'b** from **5b**),[9] and the ratios of **6b/6'b** and **7b/7'b** were found to be 2.3:1 and 1.5:1, respectively. For the C_4-unsubstituted furoisoxazole, the ratio of **6c/6'c** was found to be 2.8:1. *Cis/trans* stereochemical assignments in the 2,5-disubstituted cyclic ethers were made by analogy with our earlier work in this area.[3]

We have described here a useful route to highly functionalized tetrahydrofuran derivatives by an intramolecular 1,3-dipolar cycloaddition/electrophilic cyclization sequence. Furoisoxazoles **ii** (R''' = $(CH_2)_2CH{=}CH_2$) are generally obtained with good diastereoselectivity and serve as masked 3-hydroxypropionitrile synthons in the process. We are currently developing a polymer-supported protocol to further improve this synthetic strategy, in a manner similar to our earlier studies of its intermolecular counterpart.[3a] Results of this approach, which employs an ether linkage to the C_6 aryl ring of the furoisoxazole, will be reported in due course.

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Supplementary Material Available: Full experimental details and ^1H and/or ^{13}C NMR spectra for **4a, 2b/3b, 5b, 4b, 4'b, 7b, 7'b, 6b, 4'c, 6c,** and **6'c** (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(9) With use of an HP 5930A, J &W Scientific DB-210 capillary GLC column at an initial oven temperature of 150 °C, a final oven temperature of 200 °C, an initial time of 5 min, and with a rate of 5 °C/min, the retention times were 13.48 min for **7'b**, 13.55 min for **7b**, 14.89 min for **6'b**, and 15.01 min for **6b**.