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Furans in Synthesis.[1] The Preparation of Spiro-Cyclic Systems.

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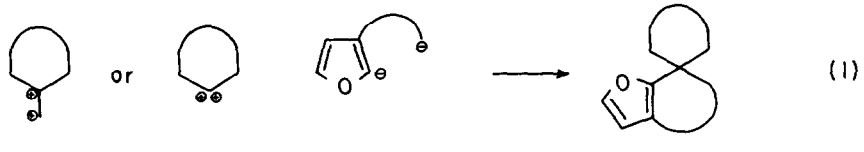
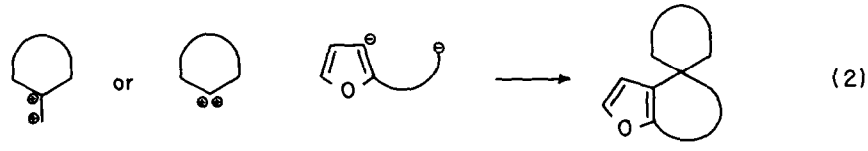
Summary: *Furan-terminated cationic cyclizations employing allylic alcohols, enones, and N-acyl iminium ions as initiators have been explored as routes to highly functionalized spiro[4,5]decanes, spiro[5,5]undecanes, spiro[4,6]undecanes, and spiro[5,6]dodecanes.*

The synthesis of complex natural products often requires the preparation of quaternary carbon atoms.[3] Although a large number of methods of broad utility exist for the construction of quaternary centers within fused- and bridged-ring systems[3], relatively few of these methods are applicable to the synthesis of spirocyclic structures.[4] Procedures which construct spiro-centers must do so with good-excellent regio- and stereochemical control; be mild enough to ensure the survival of synthetically useful functional groups; and must also provide sufficient "handles" so that the synthesis endeavor can be completed.

An inspection of a number of spirocycle-containing natural products such as acorenone B **1**[3b], α-chamigrene **2**[3b], histrionicotoxin **3**[5], pentalenic acid **4**[6a], and aflavinine **5**[6b,c] reveals spiro-systems of differing complexity. As part of a general program in furan chemistry[7], we have been examining furan-terminated cyclizations as a method for the construction of carbocyclic rings.[1,7b] Our interest in developing substituted furans as bis-nucleophilic synthons in annulative processes stemmed from the variety of useful functional groupings which might be realized from the relatively unreactive furyl nucleus.[7a,b] This communication describes our efforts to couple the hypothetical furyl dianions depicted in equations 1 and 2 with bis-electrophiles to form spirocyclic systems which differ with respect to the furan regiochemistry.



(1)



(2)

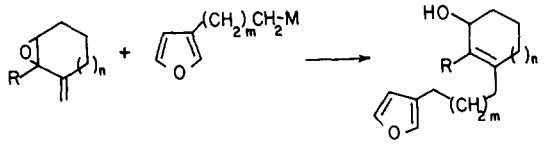
The potential bis-electrophiles studied are described in equations 3 and 4. Vinyl epoxides, prepared from cycloalkenones[8], and enol-ethers of 1,3-cycloalkanediones provide nearly identical intermediates when reacted with 2- or 3-substituted furyl organometallics (eqs. 3 and 4). The product allylic alcohols[8] and enones can be interconverted and/or serve as cyclization initiators to provide a variety of spirocycles. Imides, via intermediate carbinolamides[5h,i], will lead to spiro-lactams as is outlined in equation 4.

The synthesis of spiro[4,5]decane and spiro[5,5]undecane systems, using allylic alcohols as initiators, is described in equation 5. Grignard reagents prepared from furylmethyl-[1], 2-(3-furyl)ethyl-[1], and 3-(3-furyl)propyl[1] halides, respectively, were reacted in S_N2' fashion (CuCN)[8] with the corresponding vinyl epoxides derived from 2-methyl cyclopentenone and cyclohexenone to provide allylic alcohols **6a-e** in 59-82% yield. Exposure of alcohols **6a** and **6b** to the two-phase mixture of HCO_2H-cC_6H_{12}[1] gave spiro[4,5]decane **7a** (58%) and spiro[4,6]undecane **7b** (53%), respectively. Similarly, alcohols **6c-e** were treated with HCO_2H-cC_6H_{12} to afford the formate of **6c** (84%) and spiro[5,5]undecane **7d** (72%) and spiro[5,6]dodecane **7c** (58%).

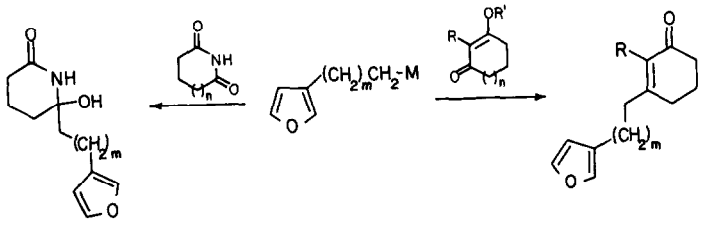
Alcohols **6** were oxidized (PCC) to yield enones **8** (eq. 6, 72-87%) which were separately dissolved in cC_6H_{12} and anhydrous HCO_2H was added. Of the five substrates examined, only enones **8a** and **8d**, leading to spiro[4,5]decane **9a** (72%) and spiro[5,5]undecane **9d** (66%), provided any cyclized products. Enones **8b,c** and **8e** were recovered unchanged. Compounds **8b,c** and **8e** also proved resistant to cyclization under a wide variety of other reaction conditions including Lewis acids and acylating agents (Ac_2O, $HClO_4$[10]; TFA, TFAA[11]). As is demonstrated in equation 7, the formation of a six-membered ring in an enone-initiated spirocyclization is not the only factor governing closure. Exposure of enone **10**, derived from the Grignard reagent prepared from 3-(2-furyl)-1-bromopropane and the isobutyl enol ether of 2-methyl-1,3-cyclohexane dione (85%), to a variety of Brønsted and Lewis acids as well as acylating agents[10,11] failed to promote the formation of the desired spiro[5,5]undecane. The relatively less favorable furan α- to β-cyclization[12] was observed upon treatment of the corresponding allylic alcohol ($NaBH_4$, $CeCl_3$[13]; 93%) with HCO_2H, cC_6H_{12} affording olefin **11** (68%). More highly functionalized relatives of **11** are being examined as precursors of aflavinine **5**.[6]

Having examined allylic alcohols and enones as initiators of furan-terminated spirocyclizations, we turned our attention to the versatile *N*-acyliminium ion[5h,i,14] as an initiating group for a furan-terminated spiro-closure. The reaction of glutarimide with CH_3MgI followed by the Grignard reagent prepared from 3-(2-furyl)-1-bromopropane provided carbinol amide **12**[5h] (eq. 8) which was immediately treated with HCO_2H, cC_6H_{12} giving spiro-piperidine **13** in 50% overall yield from glutarimide. Aza-spiro[5,5]undecane **13** is currently under study as a precursor of perhydrohistrionicotoxin[5] and histrionicotoxin **3**.[5]

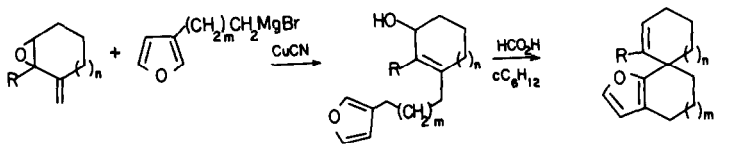
These results demonstrate the utility of furan-terminated cationic cyclizations for the synthesis of a wide variety of spirocyclic systems. Applications of this methodology to the preparation of spirocycle-containing terpenoids and alkaloids are under way and will be reported in due course.



(3)



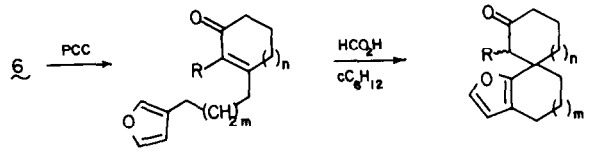
(4)



(5)

		R	m	n	Yield
6	a	Me	1	0	59%
	b	Me	2	0	63%
	c	H	0	1	82%
	d	H	1	1	58%
	e	H	2	1	62%

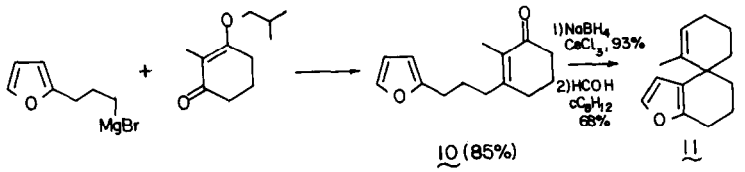
		R	m	n	Yield
7	a	Me	1	0	58%
	b	Me	2	0	53%
	c	H	0	1	formate 84%
	d	H	1	1	72%
	e	H	2	1	58%



(6)

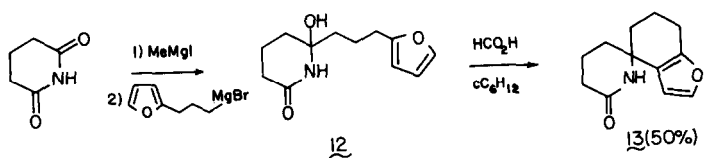
		R	m	n	Yield
8	a	Me	1	0	73%
	b	Me	2	0	72%
	c	H	0	1	87%
	d	H	1	1	83%
	e	H	2	1	84%

		R	m	n	Yield
9	a	Me	1	0	72%
	b	Me	2	0	NR
	c	H	0	1	NR
	d	H	1	1	66%
	e	H	2	1	NR



(7)

10 (85%)



(8)

12

13 (50%)

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