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CATIONIC CYCLIZATIONS INITIATED BY ELECTROCYCLIC CLEAVAGE OF CYCLOPROPANES. SYNTHESIS OF LACTONES, TETRAHYDROPYRANS, AND TETRAHYDROFURANS

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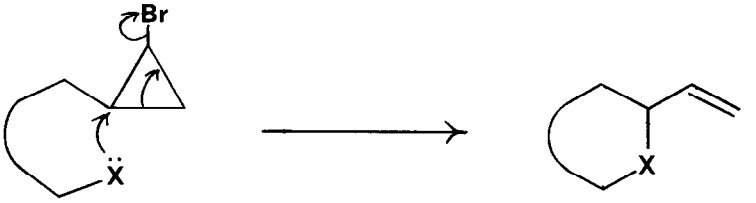
Summary: The electrocyclic opening of cyclopropane derivatives containing internal nucleophilic groups provides a new route to vinyl lactones, tetrahydropyrans, and tetrahydrofurans.

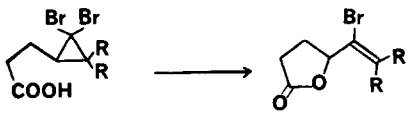
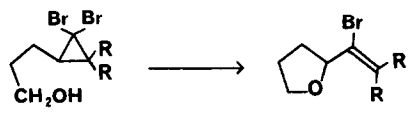
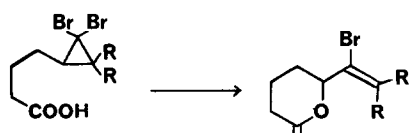
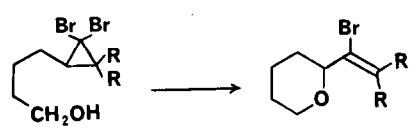
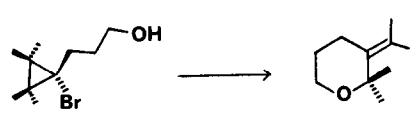
The "cation-π cyclization" constitutes an important method for the synthesis of alicyclic and heterocyclic compounds. This process involves the intramolecular reaction of a nucleophilic multiple bond with an electrophilic cationic center generated by reaction of Lewis or proton acids with suitable functional groups (the "initiator"). Initiators commonly employed in these cyclizations include alkenes, epoxides, and tertiary, allylic, and benzylic alcohols (and their sulfonate and phosphate esters).[1] More exotic initiators introduced recently include α-diazoketones,[2] α-acylimmonium ions,[3] ketene thioacetals,[4] and thionium ions derived from thioketals and vinyl sulfides.[5] The disrotatory electrocyclic cleavage of cyclopropane derivatives[6] provides a potentially useful new method for the initiation of cation-π cyclizations. In this communication we report that the electrocyclic opening



of bromocyclopropane derivatives containing internal nucleophilic hydroxyl and and carboxyl groups provides a new strategy for the synthesis of lactones, tetrahydropyrans, and tetrahydrofurans.[7]

Table I summarizes optimal conditions for effecting the electrocyclic cleavage-cationic cyclization of cyclopropanes 1-5.[8] The more substituted systems undergo the desired transformation simply upon warming to 40-50° in a nonnucleophilic polar solvent such as 2,2,2-trifluoroethanol. The rearrangement of less substituted cyclopropanes can be achieved under mild conditions with the assistance of silver(I) and mercury(II) salts. Substituted lactones, tetrahydropyrans, and tetrahydrofurans can be prepared in good yield in this manner. Vinyl lactones similar to 6 and 8 have recently been synthesized in the laboratories of Danishefsky and Trost, and serve as intermediates in

Table I. Synthesis of Lactones, Tetrahydrofurans, and Tetrahydropyrans by Electrocyclic Opening-Cyclization

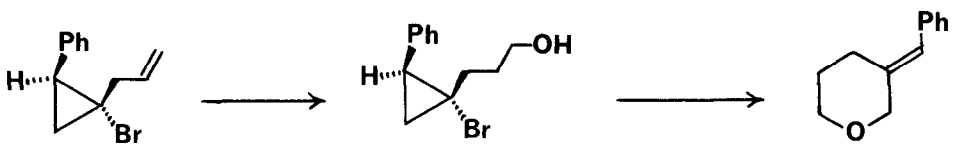
		Conditions[a]	% Yield[b]
 1a, R=H; 1b, R=CH_3 → 6a,b	R=H	$AgOCOCF_3$, TFA (25°, 6h)	83
		$AgOCOCF_3$, TFE (25°, 19h)	85
		$Hg(OAc)_2$, TFA (25°, 1h)	82
	$R=CH_3$	TFE (50°, 43h)	70
		$AgOCOCF_3$, TFA (25°, 0.5h)	94
		$AgOCOCF_3$, TFE (25°, 8.5h)	97
		$Hg(OAc)_2$, TFA (25°, 0.5h)	94
 2a, R=H; 2b, R=CH_3 → 7a,b	R=H	$AgClO_4$, TFE (25°, 22h)	63
	$R=CH_3$	TFE (40°, 43h)	72
		$AgOCOCF_3$, TFA (25°, 1h)	65
		$AgOCOCF_3$, TFE (25°, 8.5h)	73
		$Hg(OAc)_2$, TFA (25°, 1h)	48
 3a, R=H; 3b, R=CH_3 → 8a,b	R=H	$AgOCOCF_3$, TFA (25°, 8.5h)	63
		$AgOCOCF_3$, TFE (25°, 23.5h)	57
	$R=CH_3$	$Hg(OAc)_2$, TFE-CH_2Cl_2 (25°, 21.5h)	80
 4a, R=H; 4b, R=CH_3 → 9a,b	R=H	$AgClO_4$, CH_3CN (reflux, 16h)	61
	$R=CH_3$	$AgOCOCF_3$, $CHCl_2CO_2H$ (25°, 23h)	59
		$AgNO_3$, CH_3NO_2 (25°, 8d)	72
 5 → 10		AgOAc, TFE (25°, 0.5h)	63

[a]Reactions were carried out in the dark using 0.1 M solutions of cyclopropanes in the indicated solvents and employing 1.5 equiv of silver salts (5 equiv in the case of $AgNO_3$) and 1.0 equiv of mercury salts (2.0 equiv in the case of 3b→8b). [b]Isolated yields of purified products. Infrared, ^1H NMR, and mass spectral data were fully consistent with the assigned structures.

new synthetic approaches to functionalized cycloalkenes,[12] cyclopentanone and cycloheptenone derivatives,[13] and certain acyclic systems.[14]

The preparation of the tetrahydropyran 13 illustrates the application of this methodology to the stereoselective synthesis of *exocyclic* olefins. This strategy exploits the well-established[6] preference for the electrocyclic opening of cyclopropyl derivatives to proceed by the disrotatory mode which rotates the orbitals of the C_2-C_3 bond to the opposite side of the ring from the departing group.

A variety of methods are available for the stereoselective synthesis of the cyclopropanes required in this approach.[11,15-17] For example, reaction of 1,1-dibromo-2-phenylcyclopropane with n-butyllithium at -100° followed by addition of allyl bromide[11] produced the alkylated products in 80% yield as a 92:8 mixture of isomers. The major product 11 was easily separated by chromatography and converted to 12 in 79% yield by hydroboration. Exposure of this alcohol to 1.5 equiv of $AgClO_4$ in TFE (25°, 1.5h) then afforded the tetrahydropyran 13 in 74% yield; none of the isomeric olefin was detected in the crude reaction product.[18]



11 12 13

Further studies are underway to extend this methodology to the preparation of carbocyclic compounds and demonstrate its utility in the total synthesis of natural products.

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