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THE FORMATION OF CYCLOPENTENONES AND 3(2H)-FURANONES FROM ACETYLENIC PRECURSORS

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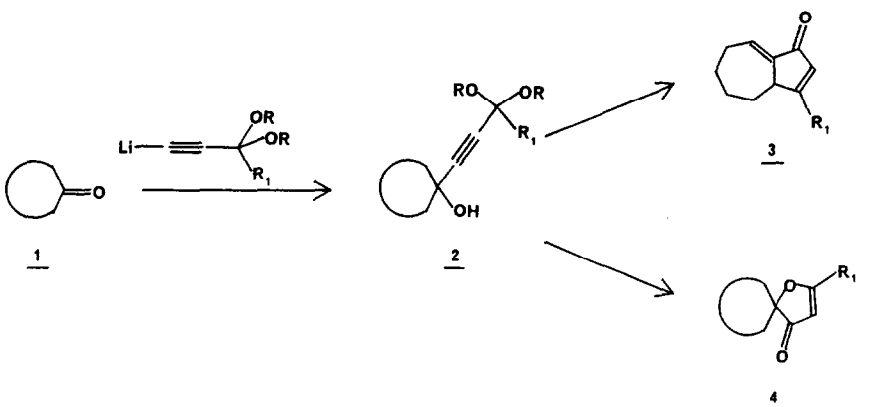
Summary: Acetylenic alcohols, obtained in high yield from condensations of 3,3-diethoxypropyne or 3,3-ethylenedioxybutyne with cyclic ketones, may be used as substrates for cyclopentenone annelation or spirofuranone synthesis.

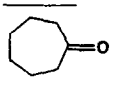
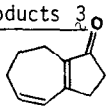
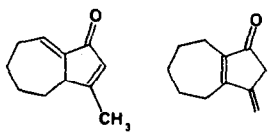
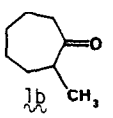
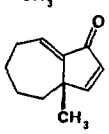
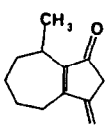
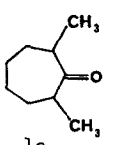
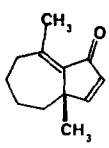
In recent years we have been investigating annelation methods utilizing the Nazarov cyclization for construction of terpenoid natural products.[2] In light of the enormous interest in the inhibition of neoplastic activity by many guianolides and pseudoguianolides[3] as well as the antitumor activity of terpenes containing the 3(2H)-furanone systems such as jatrophone,[4] geiparvarin,[5] the eramantholides,[6] and congener,[7] numerous synthetic efforts have been directed toward these substances.[8,9] Prompted by the recent communication of Hiyama and coworkers,[10] we wish to report our results concerning the condensation of lithium acetylides of 3,3-diethoxypropyne and 3,3-ethylenedioxybutyne with selected ketones which lead to construction of key structural features distinctive to each general group of these antineoplastic agents from a common synthetic intermediate.

Condensation of cyclic ketones 1 with three equivalents of the lithium acetylide (generated by addition of *n*-BuLi to the acetylene in THF at -10°C) selectively produces the desired acetylenic alcohols 2 in excellent yields (THF, 0°C, under N_2, 1 hr).[11] Although the condensation of ketones with dianions of simple propargylic alcohols achieves cyclopentenone annelation upon acid treatment,[12] the direct reaction of our adducts 2 in ethanolic sulfuric acid, or trifluoroacetic acid gave moderate yields of cyclopentenones 3 in some cases and formation of spirofuranones 4 in others



A reasonable mechanism for cyclopentenone annelation may involve (a) elimination of water, (b) hydration of the acetylene, (c) elimination of an alkoxy group forming a 1,4-pentadien-3-one, and (d) Nazarov cyclization followed by subsequent elimination reactions. Note that the presence of the ketal moiety in the starting acetylenes allows for direct introduction of an additional carbon double bond in the annelation products achieving the higher oxidation levels typical of many cytotoxic lactones of the guianolide and pseudoguianolide family. In a number of experiments where competing formation of spirofuranones 4 became a problem, it was effectively prevented by initial elimination of the acetylenic alcohols with methanesulfonyl chloride (1 equiv) and triethylamine (4 equivs) (CH_2Cl_2, 0°C, 30 min) prior to acid-mediated cyclization. Results are illustrated in Table I.[13] Where substitution of the starting ketone allows for regiosomers, the major hydroazulene product 3 is derived from formation of the more stable olefin in the initial acid-catalyzed dehydration. However, the positionally isomeric cyclopentenone annelation predominates after base-induced elimination to the less substituted olefin followed by cyclization (results obtained from ketone 1b are typical).

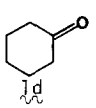
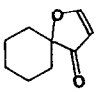
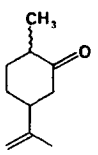
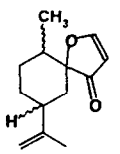
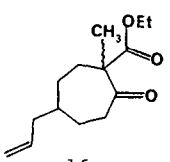
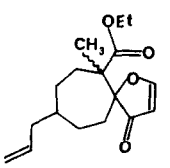
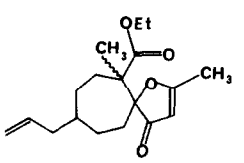
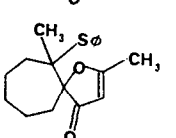
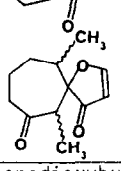
TABLE I

Ketone	Acetylene	Yield[a] of 2	Cyclization Products 3	Yield[b]
 1a	A	93%		25%
1a	B	96%		50% (54:46)[c]
 1b	A	78%		51%
1b	B	84%		23%
 1c	A	70%		73%[d]

A = 3,3-diethoxypropyne B = 3,3-ethylenedioxybutyne

(a) Isolated by bulb to bulb distillation
(b) Reactions were conducted by initial elimination (MsCl, Et_3N) followed by cyclization in 50% ethanolic sulfuric acid at 0°C (0.5-1 hr). Products were purified by preparative tlc on silica gel.
(c) Isomers were chromatographically separated on silica gel
(d) Preliminary elimination with methanesulfonyl chloride is unnecessary.

Recognizing the importance of the 3(2H)-furanone system, we also sought milder conditions for more selective formation of these products. This was accomplished in good yield by treatment of the acetylenic alcohols with boron trifluoride-etherate in absolute ethanol in the presence of catalytic amounts of mercuric oxide and trichloroacetic acid (0.1 equivalents of each). Reactions conducted on a 1 mmol scale were complete after stirring at room temperature for two hours. Several interesting examples are shown in Table II.[13]

TABLE II Ketone	Acetylene	Yield[a] of 2	Furanones 4	Yields
 1d	A	98%		68%
 1e	A	95%		88%
 1f	A	95%		69%
1f	B	95%		62%
1g	B	77%[b]		67%[c]
1h	A	30%		49%[d]

A = 3,3-diethoxypropyne B = 3,3-ethylenedioxybutyne

(a) Isolated by bulb to bulb distillation.
(b) Purified by column chromatography on silica gel.
(c) Cyclization was performed with 50% ethanolic sulfuric acid.
(d) Reaction was conducted using 1 *M* aqueous sulfuric acid in ethanol with a catalytic amount of mercuric sulfate (80°C, 1 hr). Isolation by Kugelrohr distillation.

No reaction was observed under these conditions without addition of mercuric oxide; however, omission of trichloroacetic acid, which apparently functions as a ready proton donor, cleanly gave transformation to the expected furanones in very good yields (75-85%). Unfortunately prolonged reaction times were often required (30-60 hours). We speculate a mercuric ion assistance for hydration of the triple bond with ethanol followed by solvolysis of the acetal moiety prompted by Lewis acid, and capture of a highly stabilized carbocation by the tertiary hydroxyl which results in closure of the five-membered ring. Aqueous workup affects facile hydrolysis of the vinyl ether and elimination to the α,β-unsaturated enone. Preparative tlc chromatography on silica gel or Kugelrohr distillation provided isolation of the products. It is noteworthy that considerable α-substitution in the starting ketones does not reduce the overall efficiency of this two-step spirofuranone synthesis.

Further efforts to utilize this methodology for natural product synthesis are underway.

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