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CYCLIC VINYL ETHER CARBANIONS I: SYNTHETIC EQUIVALENTS OF β-ACYLVINYL AND SUBSTITUTED ACYL ANIONS

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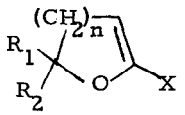
In connection with synthetic studies in the prostanoid field, we required a method permitting the preparation and use of carbanions derived from the cyclic vinyl ethers (1a-e).



X = H, Li

1a n = 1, R_1, R_2 = H
1b n = 2, R_1, R_2 = H
1c n = 2, R_1 = H, R_2 = OCH_3
1d n = 2, R_1 = alkyl, R_2 = OCH_3
1e n = 2 R_1, R_2 = OC_2H_5

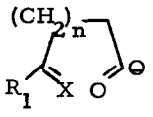
The preparation of carbanions derived from certain simple vinyl ethers has been described by Baldwin[2] and allyl ethers by Evans[3] and Still.[4] However, the feasibility of extension to the cyclic systems was not apparent. Isolated examples could be found in the literature,[5] but these procedures were unwieldy or provided the desired intermediates in relatively low yields. After our work was underway, one recent report of the preparation of the anion of dihydropyran appeared;[6] however, again the conversion was apparently low and not totally consistent with our observations.

We would like to report that our studies have resulted in the development of a convenient, general procedure for the preparation of carbanions (1a-e) which permits access to these intermediates in high yields. Initial attempts at deprotonation of (1b) (and 1a) with n-BuLi in ether or THF or sec-BuLi in THF were unpromising. We turned to t-BuLi and observed complete deprotonation could be achieved (monitored by NMR) with 1.1 eq of lithium reagent at -78 to 5°C (0.5 hr) provided that the concentration of THF was kept to a minimum.[7] Competition by THF for the alkyl lithium reagent was occurring; however, at least 0.5 equivalent of THF was essential to dissociate the aggregated lithium reagent to the reactive complex.[2,8]

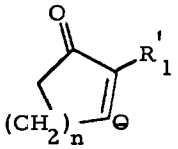
Unexpectedly, deprotonation of vinyl ethers (1c-e) requires somewhat more vigorous conditions (1.8-2.2 eq t-BuLi/eq of vinyl ether at 0°C for 1-2 hr), but good yields (~90%) of anion can be obtained.[9] Any excess lithium reagent is conveniently destroyed by addition of excess THF.[10]

As expected, the carbanions react readily with a variety of electrophiles in good to excellent yields. A representative series of examples is given in Table I. Particularly interesting is the selectivity for ketones and aldehydes over esters (case 1). Acylation is not readily accomplished due to rapid addition to the initially produced ketone. Some limitations are encountered in the reaction with alkyl halides. Primary bromides and secondary aliphatic halides are generally unreactive as well as more hindered alkylating agents.

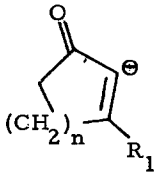
Perhaps the most interesting and useful aspect of these carbanions (1a-e) is the recognition that they constitute a useful series of protected substituted acyl anions (2a-e) and that anions (1c) and (1d) are, on further transformation (after reaction with an alkyl halide), functional equivalents of the α and β acyl vinyl carbanions (3) and (4).



(2) n = 1, 2
X = O; H, OH
R_1 = H, OC_2H_5, alkyl



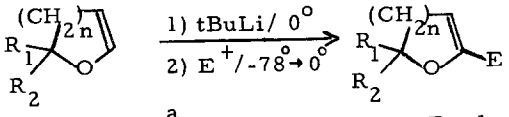
(3) n = 1, 2
R'_1 = H, alkyl

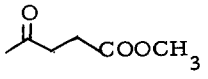
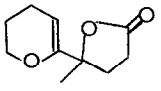
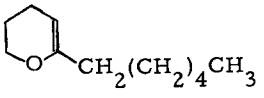
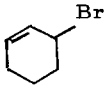
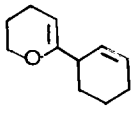
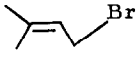
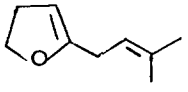
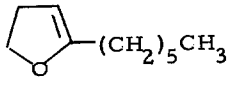


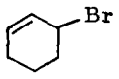
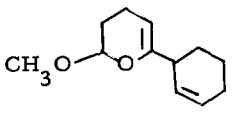
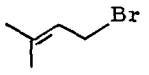
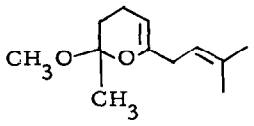
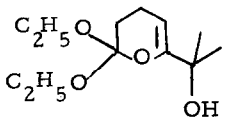
(4) n = 1, 2
R_1 = H, alkyl

Hydrolysis of the adducts can be achieved under extremely mild conditions; for example, (5) (cf Table I) affords (6) (bp 85-90°/0.05 mm) in 58% yield (7.5% HCl/THF (1:12), 25°, ~4 hr).

TABLE I



Case	Vinyl Ether	Substrate[a]	Product	Yield[b,c]
1	(1b)			68%
2	(1b)	$CH_3(CH_2)_4CH_2I$		54%
3	(1b)			60%
4	(1a)			67%
5	(1a)	$CH_3(CH_2)_4CH_2I$		64%

Case	Vinyl Ether	Substrate[a]	Product	Yield[b,c]
6	(1c)			52%
7	(1d)			57%[d]
8	(1e)	CH_3COCH_3		53%

a) The stoichiometry for ketones and aldehydes was 1.0 mol anion and 1.0 mol carbonyl compound. For alkyl halides, 1.2 mol/mol of anion was utilized. All reactions were conducted at -78° C (0°C for halides) and HMPA was added to the reaction mixture in the case of alkyl halides (1 mol/mol of anion).

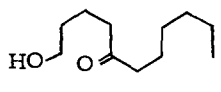
b) Yields refer to distilled or chromatographically purified materials.

c) All new compounds exhibited satisfactory spectral characteristics and analytical data (high resolution mass spectrum or combustion analysis).

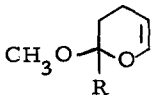
d) Yield based on recovered starting material, conversion was ~75%.

Similar conditions appear applicable for most cases in Table I.

Further transformation of the intermediate δ-keto-aldehydes and δ diketones derived from alkylation of anions (1c) and (1d) leads to α- and/or β-substituted enones where regiospecific aldol/dehydration is feasible. For example, (7a) can be converted to (8) (46%), but (7b) affords a mixture of (9) and (10) (1:1.5) (68%) or (10) (85%) depending on cyclization

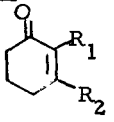


(6)



(7a) R = H

(7b) R = CH_3

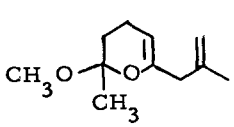


(8) $R_1 = nC_5H_{11}$; R_2 = H

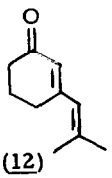
(9) R_1 = n = C_5H_{11}; $R_2 = CH_3$

(10) R_1 = H; $R_2 = nC_6H_{13}$

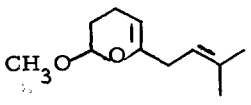
conditions.[11] Furthermore (11), available from methallylbromide (80%), gave enone (12) upon hydrolysis (7.5% HCl/dioxane/Δ) and cyclization (pyrrolidine/HOAc (~70%), a facile entry to β-vinyl enones. The difficultly accessible α-vinyl enones are also available; for example,



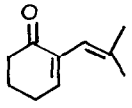
(11)



(12)



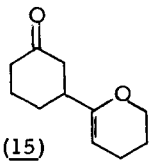
(13)



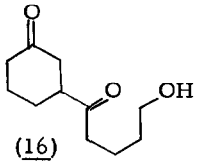
(14)

(13), prepared as described above (80%), was cyclized in one step to (14) (7.5% HCl/THF (1:12) /40-45° C,~4 hr) in 95% yield.[12] In some less substituted cases, double bond migration cannot be prevented during hydrolysis.

We have briefly explored the preparation of mixed and homogeneous cuprates from anion (1b). Addition of mixed reagent with 1-pentyne (1.2 mol) to 2-cyclohexenone afforded the unstable ketone (15) (91%) which was readily hydrolyzed to (16) under mild conditions (10% $H_2O/Et_2O/SiO_2/25°$ C).[12]



(15)



(16)

We are currently investigating the scope of the above-described carbanion chemistry particularly extensions to 1,2-dehydrosugars in the furanose and pyranose series. Suitably protected dehydrosugars could serve as readily available synthons for prostanoid synthesis as well as in other applications.

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7. NMR experiments could monitor the progress of metallation which was incomplete in THF.
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   b) F. A. Settle, M. Hagerty and J. F. Eastham, J. Am. Chem. Soc., 86, 2076 (1964).
9. Ethers (1c-e) were 2-4 times slower to metallate under comparable conditions.
10. Undesirable side products and non-homogeneous systems could be avoided by dilution with THF to 0.1-1.0 M in anions which were stable in THF once formed.
11. S. Danishefsky and A. Zimmer, J. Org. Chem., 41, 4059 (1976).
12. New compounds had satisfactory spectral data: (6) NMR ($CDCl_3$): 0.95 (t, 3H), 1.4 (m, 8H), 1.65 (m, 5H), 2.4 (m, 4H), 3.65 (m, 2H); (12) 1.9 (d, 6H), 2.15 (m, 2H), 2.5 (m, 4H), 6.02 (s(Br), 1H), 6.95 (t, 1H); (14) 1.1-2.8 (m, 13H), 4.0 (t, 2H), 5.2 (t, 1H).