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REGIOSELECTIVE 1-4 ADDITION OF ACYL ANION EQUIVALENTS TO α-ENONES

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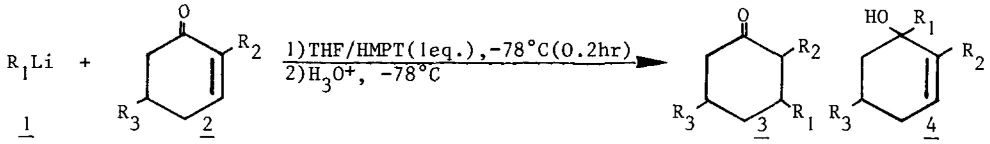
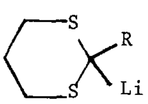
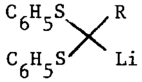
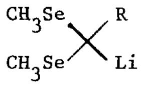
2-lithio-1,3-dithianes, bis(phenylthio)alkyllithiums and bis(methylseleno)alkyllithiums add 1-4 to α-enones if HMPT is present in the medium prior to the addition of enones. Most of the reactions occur under kinetic control.

Selective 1-4 addition of acyl anion equivalents[1-4] 1 to α-enones 2 is of actual synthetic interest. However, several organolithiums of this type in which the sp^3 carbanionic center does not bear extra stabilizing group generally react 1-2 in THF[3,4,5,7,8] or give a mixture of the two adducts[9] and some complicated methods have been proposed[10,11] to overcome this problem.

Our recent discovery[12] that polar solvents favor the 1-4 kinetic addition of some alkyllithiums led us to investigate the reaction of cyclohexenones with 1-lithio-1,3-dithianes[4,5], bis(phenylthio)alkyllithiums[6,7] and bis(methylseleno)alkyllithiums[13], in THF containing one equivalent of HMPT at -78°C. We interestingly found that they all add mainly 1-4 under these conditions [45-78% yield of pure product]. A small amount of the 1-2 adduct [1-8%] is also isolated. This can be minimized [<1%] if larger amount of HMPT is used but the overall yield of the reaction usually drops probably due to competitive metallation of the enone.



R_1Li	1		2			3 %	4 %	% 1-4 addition
			R_2	R_3				
	1a	R:H	H	H	a	70	6	92
	1b	R:CH_3	H	H	b	65	5	92
	1c	R:C_6H_{13}	H	H	c	60	7	90
	1b	R:CH_3	CH_3	$CH_3-\underset{\vert}{C}=CH_2$	d	65	5	92
	1d	R:H	H	H	e	65	5	92
	1e	R:CH_3	H	H	f	41	∿1	97
	1e	R:CH_3	CH_3	$CH_3-\underset{\vert}{C}=CH_2$	g	63	∿1	99
	1f	R:CH_3	H	H	h	78	∿1	99
			CH_3	$CH_3-\underset{\vert}{C}=CH_2$	i	66	5	92

On the other hand, in THF at -78°C, dithianyllithiums[5] 1a-c and 1-lithio-1,1-bis(methylseleno) ethane 1f react with cyclohexenone to give quite exclusively the 1-2 adducts which are not transformed to the 1-4 one's when HMPT is added [-78°C to 20°C, 1hr] prior to hydrolysis.

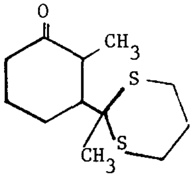
This secures that for 1a-c, 1f, both reactions described [THF-HMPT and THF] are under kinetic control.

However, in case of bis(phenylthio)alkyllithiums[7] 1d-e, substantial amount of the 1-4 adduct [3e/4e : 55/45; 3f/4f : 75/25] is formed in THF (-78°C) and whereas the 3e/4e ratio remains unchanged after further addition of HMPT to the medium [-78°C to 20°C, 1hr, prior hydrolysis] , substantial change occurs under similar conditions for the 3f/4f one [3f/4f : 93/7].

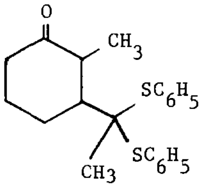
Furthermore, we have reacted 1-lithio-1,1-bis(methylseleno)ethane 1f with cyclohexenone in various solvents (-78°C, 2.5 hr) and observed appreciable change in the 3h/4h ratio [3h/4h (yield in isolated products) ether : 2/78; ether-HMPT (0.5 eq.) : 19/55; (1 eq.) : 60/4; ether-kryptofix 2.2.2. (1 eq.) : 43/17; THF : 16/43; THF-HMPT (1 eq.) : 72/1; DME : 54/7]

During the course of this study we successfully trapped the enolates formed in some 1-4 addition, by CH_3I[16] or D_2O (3b', 3f', 3i') and transformed the deuterated adduct 3i' to the corresponding diketone 5i' ($CuCl_2$, CuO, acetone 1% H_2O, 0.1 hr, 80% yield)[8,14].

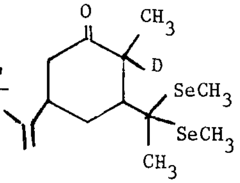
3b'



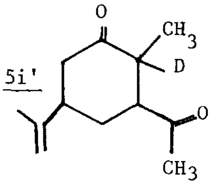
3f'



3i'



5i'



This work not only gives a simple reliable solution to the old, unsolved problem of the 1-4 addition of several acyl anion equivalents but also allows the foreseen, in connection with the results available from the literature[15], that when a specific organolithium is reacted with a specific enone, the 1-2 adduct formation should be exhalted when the reaction is performed in the less polar solvent, at the lowest temperature and for the shortest time whereas the 1-4 adduct should be favoured (kinetically or thermodynamically) when the reaction is performed in the more polar solvent, at the highest temperature and during the longest time possible. Work is in progress to propose more accurate previsions.

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16. Dr. Seyden-Penne (Thiais) informed us of successful trapping of some "1-4 addition derived enolates"- see also ref. 10

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