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HIGHLY REGIOSELECTIVE ADDITIONS OF CERTAIN 2-LITHIO-1,3-DITHIANES TO CONJUGATED KETONES

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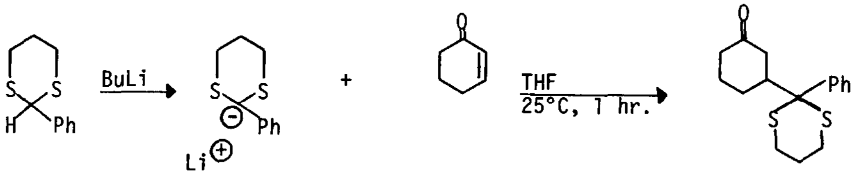
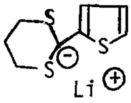
Since the late 1960's, considerable effort has been devoted towards the discovery of useful synthetic equivalents of the acyl anion[1]. Among the most widely used reagents are the metalated 1,3-dithiane derivatives[2]. The Michael addition of these acyl anion equivalents to α,β-unsaturated ketones is a reaction of particular synthetic utility, which has received significant attention and generally affords 1,2-addition products[2]. However, two recent publications have described the reactions of lithiated tris(phenylthio)[3]-, bis(methylthio)(silyl)-and bis-(methylthio)(stannyl)-methanes[4] with conjugated ketones to give 1,4-addition products exclusively. To date there is no information on the chemical reactivity of carbanions stabilized by adjacent bivalent sulfur atoms and an aromatic ring. We wish to report herein the successful utilization of these readily available carbanions in reactions with α,β-unsaturated ketones to afford predominantly either 1,2- or 1,4-addition products and demonstrate the effects of both solvent and temperature on these additions[5].

2-Lithio-2-phenyl-1,3-dithiane (2) was generated by the dropwise addition of *n*-butyllithium (19.2 mmol, 2.4 m in hexane) to a solution of 2-phenyl-1,3-dithiane (1)[6] (18.6 mmol) in dry tetrahydrofuran (THF) at -78°C under nitrogen. The addition of 2-cyclohexenone (3) (20.6 mmol) in THF at -78°C to this anion resulted in the immediate discharge of the intense yellow color. The reaction mixture was then warmed to 25°C, stirred for 1 hr. at this temperature, quenched and worked up to give the crystalline ketone 4 in 93% yield[7]: $C_{16}H_{20}OS_2$, M^+ 292, mp 124-125°, ir (KBr) 1709 cm^{-1} (CO), nmr ($CDCl_3$)δ 1.1-2.9 (m, 15 H), 7.2-7.6 (m, 3H, aryl), 7.7-8.1 (m, 2H, aryl). These data are consistent with the assignment of structure 4, a conjugate addition product.



1 2 3 4

The results of the reaction of 2, 2-lithio-2-thienyl-1,3-dithiane 5[8] and 2-lithio-2-α-naphthyl-1,3-dithiane 6[8] with a number of different electrophiles are shown in Table 1. All yields quoted are those of isolated products[9].



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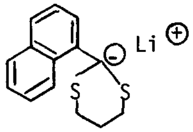

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Table 1

Anion	Substrate	Yield of 1,4-addition product (%)	Melting Point °C
2	2-cycloheptenone	86	94
2	2-cyclohexenone	93	125
2	2-methyl-2-cyclohexenone	93	112
2	2-cyclopentenone	81	129
2	3-methyl-2-cyclohexenone	89	110
2	3-methyl-2-cyclopentenone	68	76
5	2-cyclohexenone	90	125
5	Ph-CH=CH-CO-Ph	60	135
5	methylvinyl ketone	34	Liquid
6	2-cyclohexenone	96	107

As evident from Table 1, the reaction of 2, 5 and 6 with unsaturated ketones provides an efficient route to 3-substituted ketones. It is also noteworthy, that smooth nucleophilic addition was observed even with substrates prone to steric problems, e.g., 3-methyl-2-cyclohexenone[10].

However, if in the reaction of 2 with 3, the quenching process was carried out at -78°C 2 to 10 minutes after the addition of 3 and the reaction warmed to 25°C, a mixture of the ketone 4 (35%) and the allylic alcohol 7 (65%) was obtained. On the other hand, when dry hexane was added to the lithium anion reaction mixture to adjust the ratio of hexane to THF to 1.8:1 and 3 added in THF at -78°C, and quenched at that temperature, the result was the formation of the allylic alcohol 7 in 95% yield and the ketone 4 in 5% yield. The results of the reaction of 2 under the above conditions with several unsaturated ketones are listed in Table 2. It is evident *that this reaction is solvent and temperature dependent and leads predominantly to a* 1,2-addition product under these conditions.

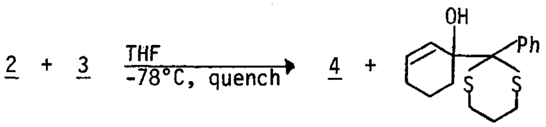

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Table 2

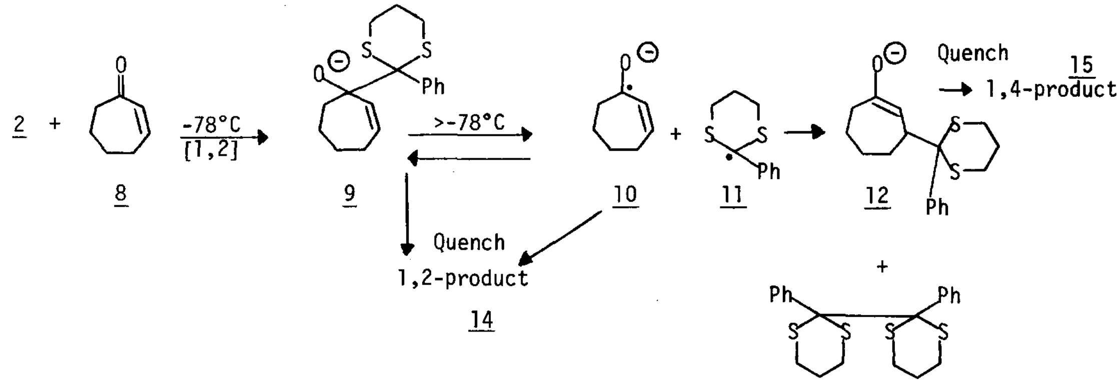
Product distribution as a function of solvent in the reaction of 2 with unsaturated ketones

	THF, -78°C reaction quench		Hexane/THF (1.8:1) -78°C reaction quench	
Substrate	% 1,2-addition	% 1,4-addition	% 1,2-addition	% 1,4-addition
2-cyclohexenone	65	35	95	5
2-cyclopentenone	50	50	94	6
2-cycloheptenone	90	10 [a]	100	- [a]
2-methyl-2-cyclohexenone	5	95	67	33

[a] Isolated yields, all other yields were determined by NMR analysis.

Our results clearly indicate that kinetic addition leads to a 1,2-product, while 1,4-addition is a thermodynamic process. Two possible pathways to explain these results are outlined below.

A



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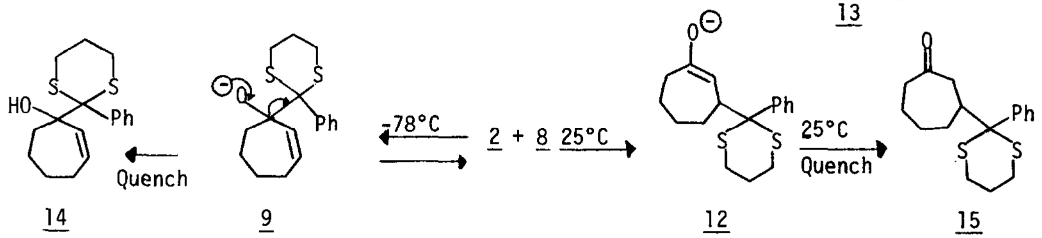

In an attempt to differentiate between A[11] and B, 14 was treated at -78°C with *n*-butyllithium, and the reaction allowed to warm to 24°C and stirred for 1 hour. This resulted in the isolation of 15 in 84% yield[12], without the formation of any dimeric product 13, strongly supporting pathway B.

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References and Footnotes

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6. D. Seebach, B.W. Erickson and G. Singh, J. Org. Chem., 31, 4303 (1966).
7. Normal workup involves extraction of the reaction mixture with ether, evaporation of the organic layer and chromatography of the crude product on SilicAR CC-7 (Mallinckrodt). A small amount of the starting dithiane is eluted first followed by the desired product.
8. 2-Lithio-2-thienyl-1,3-dithiane (5) and 2-lithio-2-α-naphthyl-1,3-dithiane (6) were prepared by the addition of *n*-butyllithium to 2-thienyl-1,3-dithiane and 2-α-naphthyl-1,3-dithiane in THF. These aromatic dithianes are readily prepared from the corresponding aromatic aldehyde and propane-1,3-dithiol following the procedure in reference 6.
9. Satisfactory elemental analyses were obtained for all new compounds and spectral data were consistent with the assigned structures.
10. A yield of less than 5% of 1,4-addition product was obtained when lithiated-tris-(phenylthio)-methane was reacted with 3-methyl-2-cyclohexenone, see reference 3.
11. Pathway A cannot be completely ruled out at present until further experiments such as chemically induced dynamic nuclear polarization (CIDNP) are carried out. We thank Professor J.E. Baldwin (MIT) for making us aware of this pathway.
12. We thank Mr. D.L. Doyle for repeating and confirming this result.