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REACTION OF THE LITHIO DERIVATIVE OF METHYL METHYLTHIOMETHYL SULFOXIDE WITH α,β-UNSATURATED KETONES

Katsuyuki Ogura, Mitsuo Yamashita, and Gen-ichi Tsuchihashi
Sagami Chemical Research Center
Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan

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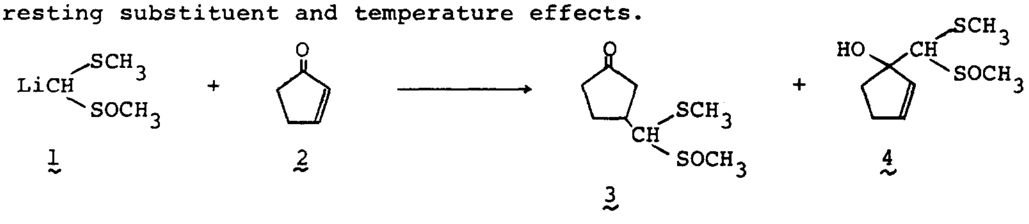
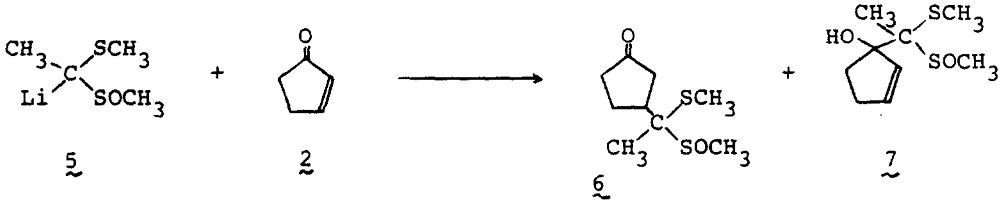
The Michael addition of acyl carbanion equivalents to α,β-unsaturated ketones (2-enones) is a particularly important reaction to construct synthetically useful 1,4-dicarbonyl compounds.[1] Although the sulfur-containing reagents such as the lithio derivatives of 1,3-dithiane and 2-substituted 1,3-dithianes are most commonly employed as the acyl carbanion equivalents,[2] the reaction of these reagents with 2-enones usually fails to yield 1,4-adducts, but results in the formation of 1,2-adducts.[3] We have found that the lithio derivative (1) of methyl methylthiomethyl sulfoxide reacts with 2-cyclopentenone (2) in a conjugate fashion to give predominantly a 1,4-adduct (3), which, to our best knowledge, is the first example of the 1,4-addition of a simple formyl carbanion equivalent (with lithium cation) to 2-enones.[4] Further, this 1,4-addition appeared to be a kinetically controlled reaction and showed very interesting substituent and temperature effects.



To a solution of 1 in tetrahydrofuran (THF)[5], was added 2-cyclopentenone (2) at -78° and the system was further stirred at the same temperature for 6 hr. After being quenched with acetic acid and ice-water, followed by the usual work-up, the resulting mixture was subjected to column chromatography on Florisil to afford a 1,4-adduct (3; 57% yield)[6] together with a 1,2-adduct

(4; 22% yield). The ratio of the products (3 : 4) was found to decrease slightly at a higher reaction temperature. Thus, the reaction at 0° for 3 hr gave 3 and 4 in 41% and 25% yields, respectively.



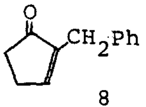
The same reaction of the lithio derivative (5)[7] of methyl 1-(methylthio)-ethyl sulfoxide with 2 at -78° afforded a 1,4-adduct (6) and a 1,2-adduct (7) in a ratio of 68 : 32 (total yield: 89%). Surprisingly, this ratio was reversed to 28 : 72 in the reaction carried out at 0° for 3 hr. However, when the reaction was performed at -78° for 3 hr and then at 0° for 3 hr, the ratio was found to be almost the same as that of the reaction at -78°.

These findings are quite different from those of recent studies on the reactions of 2-lithio-2-phenyl-1,3-dithiane and ester enolates with 2-enones, where 1,2-additions are preferential at -78° by kinetic processes, while 1,4-additions are predominant at 25° by thermodynamic processes.[3e,8] Therefore, it is very likely that the present 1,2- and 1,4-additions are kinetically controlled.

Table 1. The Reaction of 1 and 5 with 2-Enones in THF

carbanion	2-enone	reaction temperature	total yield	ratio of 1,4- and 1,2-adducts
1	2	-78°	79%	72 : 28
1	2	0°	66%	62 : 38
5	2	-78°	89%	68 : 32
5	2	-46°	94%	56 : 44
5	2	0°	68%	28 : 72
1	8	-78°	68%	29 : 71
1	9	-78°	73%	30 : 70
1	10	-78°	75%	9 : 91
1	11	-78°	85%	~0* : ~100

* The 1,4-adduct was not detected by an NMR analysis



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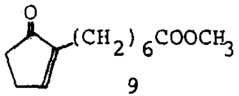

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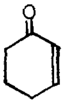

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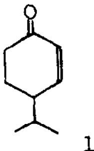

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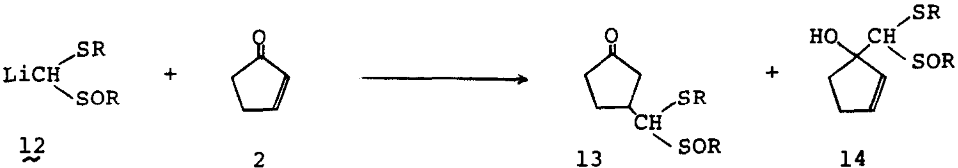
The introduction of the substituents at the 2-position of 2-cyclopentenone (2) was found to diminish the formation of 1,4-adducts. Thus, the reaction of 1 with 2-benzyl-2-cyclopentenone (8) and 2-(6-methoxycarbonyl-1-hexyl)-2-cyclopentenone (9) at -78° gave 1,4- and 1,2-adducts in ratios of 29 : 71 and 30 : 70, respectively. The structural change in 2-enones also altered the reaction path: The reaction of 1 with 2-cyclohexenone (10) afforded a 1,2-adduct in 68% yield together with a 1,4-adduct (7% yield). All these results are summarized in Table 1.



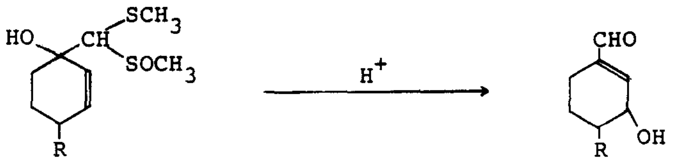
12 2 13 14

	13	14
R = isopropyl	14%	79%
R = p-tolyl	7%	79%

Another interesting feature of this reaction is the effect of R in the lithio derivative (12). When the reaction of 12 (R = isopropyl) and 12 (R = p-tolyl) with 2 was carried out at -78° in THF, 1,2-adducts (14) were formed predominantly, while the reaction of 1, which is identical with 12 (R = methyl), with 2 afforded the 1,4-adduct preferentially at -78°.

As shown above, the path leading to 1,2- or 1,4-adduct in the reaction of 1 with 2-enones can be controlled by structural modifications: changing R of 12 from methyl to bulky substituents such as isopropyl and p-tolyl leads the predominant 1,2-addition, while 5 favors the 1,4-addition at -78°; the use of 2-cyclohexenone (10) instead of 2 gives a 1,2-adduct as a major product; introduction of an alkyl group at the 2-position of 2 decreases the 1,4-addition. To account for these intriguing substituent effects, we are presently carrying out detailed mechanistic studies.

Not only the 1,4-additions for the synthesis of 1,4-dicarbonyl compounds but also the 1,2-additions are synthetically useful reactions. Thus, we have found a new way of converting the 1,2-adduct (15, R = H), derived from 1 and 2-cyclohexenone (10), into 3-formyl-2-cyclohexen-1-ol (16, R = H) in 82% yield by treatment with 1N sulfuric acid in diethyl ether at room temperature. By applying this method, a new terpene alcohol, 3-formyl-6-isopropyl-2-cyclohexen-1-ol (16, R = isopropyl) was synthesized from the 1,2-adduct (15, R = isopropyl), derived from 1 and 4-isopropyl-2-cyclohexenone (11), in 58% yield.



15 16

R = H

R = isopropyl

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1) R. A. Ellison, Synthesis, 397 (1973); T.-L. Ho, Synth. Commun., 4, 265 (1974).

2) For a review of the Michael addition of sulfur-stabilized carbanions, see B.-T. Gröbel and D. Seebach, Synthesis, 357 (1977).

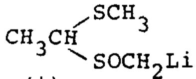
3) For the reports of successful 1,4-additions of sulfur-stabilized carbanions, see a) T. Mukaiyama, K. Narasaka, and M. Furusato, J. Amer. Chem. Soc., 94, 8641 (1972); b) J. L. Herrmann, J. E. Richman, and R. H. Schlessinger, Tetrahedron Lett., 3271 (1973); c) D. Seebach and R. Bürstinghaus, Angew. Chem. internat. Edit., 14, 57 (1975); d) A.-R. B. Manas and R. A. J. Smith, J. Chem. Soc. Chem. Commun., 216 (1975); e) P. C. Ostrowski and V. V. Kane, Tetrahedron Lett., 3549 (1977).

4) It was reported that the reaction of $[(PhS)_2CH]_2CuLi$ with methyl vinyl ketone gave 1,4- and 1,2-adducts in yields of 50% and 23%, respectively.[3a]

5) This was prepared by the reaction of methyl methylthiomethyl sulfoxide with n-butyllithium (n-hexane solution) in THF.

6) It was shown by an NMR analysis to consist of at least three diastereomers and was transformed by Na_2WO_4-catalyzed oxidation with hydrogen peroxide into a single disulfone (mp: 115-115.5°) in 96% yield.

7) This was prepared by addition of methyl 1-(methylthio)ethyl sulfoxide to the THF solution of lithium diethylamide (formed in situ from n-butyllithium and diethylamine) at -78°, followed by stirring the resulting solution at -10° for 30 min. By this procedure, the thermodynamically stable 5 can be obtained without contamination of an isomeric lithio derivative (i).


$CH_3CH(SCH_3)SOCH_2Li$

(i)

8) A. G. Schultz and Y. K. Yee, J. Org. Chem., 41, 4044 (1976).