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LITHIATED S-(2-METHOXYALLYL) N,N-DIMETHYLDITHIOCARBAMATE, A NEW, VERSATILE REAGENT FOR THE INTRODUCTION OF THE ACETONYL FUNCTIONAL GROUP INTO ORGANIC SUBSTRATES[1)]

Takeshi NAKAI*, Hiroyuki SHIONO, and Makoto OKAWARA
Research Laboratory of Resources Utilization,
Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

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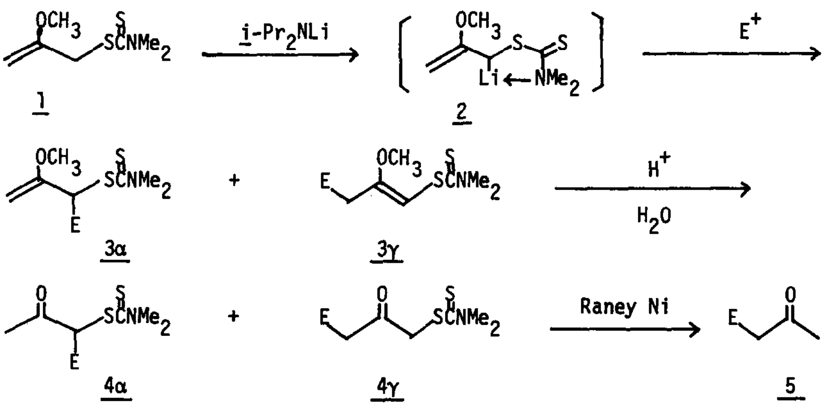
There has been considerable interest in the regioselective carbon-carbon bond formation of functionally activated allylic carbanions and their synthetic applications.[2)] In our continuing investigation of synthetic reactions via lithiated S-allyl dithiocarbamates,[3)] we have now demonstrated the synthetic potentiality of the title reagent (2) which provides a new synthetic procedure for the nucleophilic introduction of the acetonyl moiety into a wide variety of organic substrates via facile hydrolysis of the initially formed enol ethers followed by reductive desulfurization, as depicted in Scheme I. The complete scheme is therefore a three-step operation requiring no purification of intermediates. The procedure is operationally simpler and more versatile than the recently developed methods.[4)]

Scheme I



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* Correspondence concerning this work should be addressed to this author, Department of Chemical Engineering, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan.

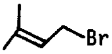
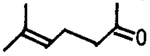
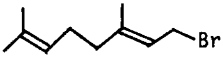
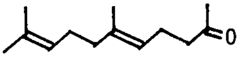
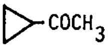
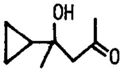
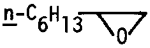
Treatment of S-(2-methoxyallyl) N,N-dimethyldithiocarbamate (1)[5)] with lithium diisopropylamide in tetrahydrofuran at -78° under nitrogen results in essentially quantitative formation of the lithium salt 2. We have found that 2 reacts immediately with alkyl halides (RX) exclusively at the α carbon atom to give the adduct 3α (E=R) in high yields (Table 1). The dramatic α regiospecificity is explained in terms of intramolecular chelation as depicted in formula 2.[2a,3)] The crude adduct 3α thus obtained can be converted by mild treatment (aqueous methanolic 0.02 N HCl, 25°) to the carbonyl compounds 4α which are further treated with the specifically deactivated Raney Ni (W-2)[6)] in refluxing acetone for 2 hr to afford the corresponding pure methyl ketones 5 in high yields (Table 1).

When the adduct 3α is subjected to the above desulfurization prior to hydrolysis, an isomeric mixture of the enol ethers, $RCH{=}C(OCH_3)CH_3$ and $RCH_2(OCH_3){=}CH_2$, is obtained in good yields (>85%); this permits the introduction of the masked acetonyl group into alkyl halides which should be more advantageous in some particular synthetic transformations.

The reagent 2 undergoes facile aldol reactions with carbonyl compounds (RR'C=O). We have observed the predominant formation of 3γ (E=C(OH)RR') over 3α as shown in Table 1, being in stark contrast to the α regiospecificity in the above alkylation reactions. Such substrate dependence of the site-reactivity of functionally activated allylic carbanions is now well precedented.[2b,7)] The crude adduct mixtures[8)] are further subjected to hydrolysis followed by desulfurization as described above to give the corresponding aldols 5 in high overall yields (Table 1). This route provides an attractive alternative to the recently developed directed aldol condensation methods.[4d,e,f)]

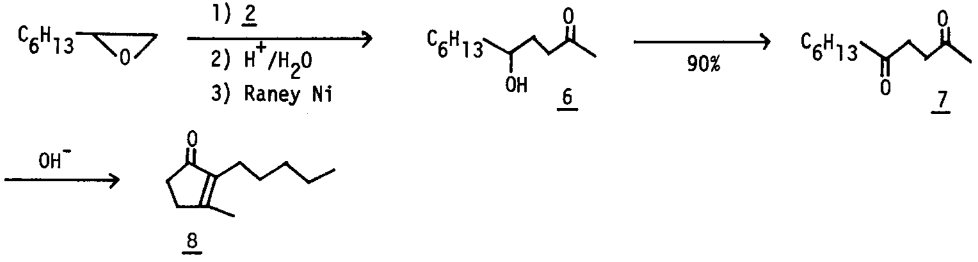
Finally, we have found that the reagent 2 is also reactive toward epoxides, thus providing a convenient route to 1,4-diketones, valuable intermediates for further elaboration to either furan or cyclopentenone systems.[9)] To demonstrate the efficiency of this synthetic scheme, we have carried out the synthesis of dihydrojasmone (8) as illustrated in Scheme II. Thus, treatment of 2 with the epoxide derived from 1-octene at -65° for 10 hr results in a 63% crude yield of the adduct mixture, 3α and 3γ ($E{=}CH_2CH(OH)C_6H_{13}$), in a ratio of 1 : 5. Hydrolysis of the crude adduct mixture followed by desulfurization as previously described affords 54% overall yield of γ-hydroxyketone 6. Jones oxidation of 6 followed by aldol condensation gives dihydrojasmone (8) which exhibited spectral properties in agreement with those of an authentic sample.[10)]

Table 1. Reactions of Reagent 2 with Electrophiles[a]

Electrophile, E^+	Yield, % ($3\alpha + 3\gamma$)	Ratio[b] $3\alpha : 3\gamma$	Methyl Ketone 5[c] (% yield isolated[d])
$\underline{n}$-$C_5H_{11}I$	97	> 98 : 2	$\underline{n}$-$C_6H_{13}COCH_3$ (68)[e]
$PhCH_2Br$	98	> 98 : 2	$Ph(CH_2)_2COCH_3$ (88, 81[e])
	99	> 98 : 2	 (82)[e]
	98	> 98 : 2	 (79)
PhCHO	98	17 : 83	$PhCH(OH)CH_2COCH_3$ (63)
CH_3COCH_3	96	20 : 80	$(CH_3)_2C(OH)CH_2COCH_3$ (87)
PhCOPh	97	20 : 80	$Ph_2C(OH)CH_2COCH_3$ (65)
	96	20 : 80	 (69)
	63	15 : 85	$\underline{n}$-$C_6H_{13}CH(OH)CH_2CH_2COCH_3$ (64)

[a] All reactions were run at -65°. [b] Determined by nmr of the adduct mixture (3α and 3γ) and/or the hydrolytic mixture (4α and 4γ). [c] Produced by hydrolysis of the adduct mixture followed by desulfurization. All products exhibited spectral and physical properties in accordance with the assigned structure or with the reported literature values. [d] Based upon the adduct mixture (3α and 3γ). No attempt to maximize yields has been made. [e] Yields of 5 produced by desulfurization followed by hydrolysis.

Scheme II



In summary, the reagent 2 is an efficient acetonyl synthon which permits readily access to a wide variety of ketones, aldols, and 1,4-diketones. Furthermore, the present examples point to the fundamental differences in the relative directive effects that are observed in the reactions of functionally activated allylic carbanions with electrophiles.

REFERENCES AND NOTES

1) Dithiocarbamates in Organic Synthesis. IV. Part III: ref 3b.

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3) (a) T.Nakai, H.Shiono, and M.Okawara, *Tetrahedron Lett.*, 3625 (1974);(b) T.Nakai, H.Shiono, and M.Okawara, *Chem. Lett.*, 249 (1975). See also (c) T.Hayashi, *Tetrahedron Lett.*, 339 (1974).

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5) Prepared by the reaction of sodium N,N-dimethyldithiocarbamate with 2-methoxyallyl bromide generated in situ from 1,3-dibromo-2-methoxypropane and sodium hydride [D.E.Horning, G.Kavadias, and J.M.Muchnowski, *Can. J. Chem.*, **48**, 975 (1970)]; **1**, 88% after chromatographic purification; nmr (CCl_4, TMS) δ 3.40 (s, NCH_3), 3.43 (s, OCH_3), 3.96 (s, $-CH_2-$), 4.02 and 4.22 (2d, J=3 Hz, $CH_2=$).

6) Raney Ni (W-2) [G.R.Pettit and E.E.van Tamelen, *Org. React.*, **12**, 356 (1962)] was deactivated by refluxing in acetone for 1 hr just prior to use. For the specific activity of the deactivated Raney Ni in the reductive desulfurization of allylic dithiocarbamates consult ref 3b.

7) R.Kowand and W.M.Rathke, *J. Amer. Chem. Soc.*, **95**, 2715 (1973); E.J.Corey and D.E.Cane, *J. Org. Chem.*, **34**, 3053 (1969); P.M.Atlani, J.F.Biellmann, S.Dube, and J.J.Vicebs,*Tetrahedron Lett.*, 2265 (1974); K.Kondo, K.Matsui, and A.Negishi, *Chem. Lett.*, 1371 (1974); H.Baba, T.Hayashi, and H.Midorikawa, the 31st Annual Meeting of the Chem. Soc. of Japan (Sendai), 1974, Abstract-I, pp 498.

8) We have found that direct reductive desulfurization of the adduct mixture fails to afford the corresponding enol ether mixture since the vinylic dithiocarbamates (**3γ**) do not undergo the reductive cleavage under these conditions.

9) For recent reviews, see R.A.Ellison, *Synthesis*, 397 (1973); T.-L. Ho, *Synth. Commun.*, **4**, 265 (1974).

10) T.Nakai, E.Wada, and M.Okawara, *Tetrahedron Lett.*, 1531 (1975).