

SELECTIVE CARBON-CARBON BOND FORMING REACTIONS VIA S-ALLYL DITHIOCARBAMATES.

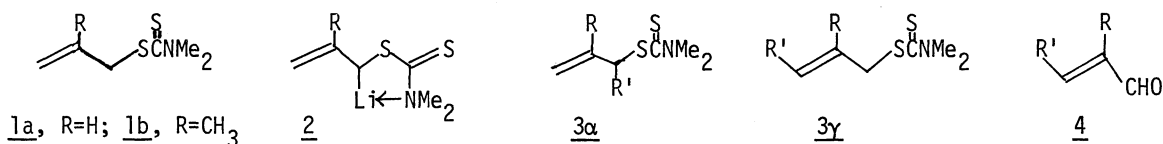
REDUCTIVE DESULFURIZATION OF ALLYLIC DITHIOCARBAMATES¹⁾

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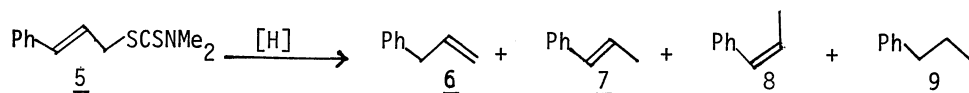
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A convenient method for the selective conversion of alkyl halides (R'X) to the olefins, R'CH=C(R)CH₃, was established by α alkylation of the lithium salts of allylic dithiocarbamates (CH₂=C(R)CH₂SCSMe₂; R=H or Me) followed by reductive desulfurization of the α -coupled products with the specific Raney Ni. Dependence of regioselectivity in the reductive fission of the dithiocarbamate group upon both substrate and reducing agent is described in some details.

The regioselective C-C bond formation via sulfur-stabilized allylic carbanions has received considerable current interest. Recently two independent studies^{2,3)} on alkylations of the anions derived from S-allyl dithiocarbamates (1) have shown the intriguing results: (i) the lithium salts of 1 were alkylated exclusively at the α -position due to intramolecular chelation⁴⁾ as depicted in formula 2; (ii) the α -alkylated products (3 α) were readily rearranged to 3 γ via a stereoselective [3,3]-sigmatropic process. On the basis of the two processes, we have further developed the synthetic sequence for the elaboration of 3 γ to (E)- α,β -unsaturated aldehydes (4).³⁾



We now wish to report the results of our study on the reductive desulfurization of these alkylated products, 3 α and 3 γ . This elaboration is of synthetic interest because this eventually provides a method for the conversion of an alkyl halide (R'X) to olefins, R'CH₂C(R)=CH₂ or R'CH=C(R)CH₃. In general, the reductive desulfurization of allylic sulfur compounds affords varying amounts of the products resulting from migration of the double bond, the degree of the migration being both substrate and reducing agent dependent.^{4a,b)} In order to find the best reagent for selective desulfurization, we first chose S-cinnamyl dithiocarbamate (5) as a test substrate since the double bond appears to migrate very easily. The results of reductive desulfurization of 5 with various types of reducing agents are collected in Table 1.

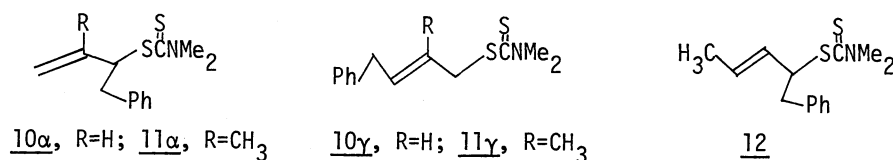
Table 1. Reductive Desulfurization of 5

Run	Reducing agent (mole ratio)	Solvent	Temp.	Time hr	Product ratio ^a			
					<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>
1	LiAlH ₄ -CuCl ₂ (4:2) ^b	THF	R.T.	2	5	: 2		---
2	∕ (∕)	THF	Rf1.	2	3	:	1	---
3	NaBH ₄ -NiCl ₂ (3:1) ^c	EtOH	Rf1.	7	4	:	1	---
4	Raney Ni (W-2 or W-4)	EtOH	Rf1.	2	---	---	---	~100%
5	Deact. Raney Ni (W-2) ^d	Acetone	Rf1.	2	---	~100%	---	---

^a Based on a combination of NMR and VPC. The overall yields were more than 80%. ^b Ref 4a.

^c Ref 5. ^d Raney Ni (W-2) was deactivated by refluxing in acetone for 1 hr just prior to use.

The most striking feature of the data is the dramatic selectivity observed with the specifically deactivated Raney Ni. Then 3 α and 3 γ derived from 1 as described above were desulfurized with LiAlH₄-CuCl₂ and the specific Raney Ni. Allylic compounds studied here are 10 α , 10 γ , 11 α , 11 γ , and 12 which were prepared from 1 in good yields (>85%) as follows.^{2,3)}



The α -benzyl compounds, 10 α and 11 α , were prepared by alkylating the anions derived from 1a and 1b with benzyl bromide, respectively. Thermal rearrangement (reflux in benzene, 3 hr) of 10 α and 11 α gave 10 γ and 11 γ , respectively.⁶⁾ The α,γ -dialkyl compound 12 was prepared via a similar benzylation of 2-butenyl dithiocarbamate which was obtained by methylation of 2a followed by the rearrangement. The results of desulfurization of these products are summarized in Table 2.

The results in Tables 1 and 2 show the following interesting features. (i) Modes of reductive desulfurization with LiAlH₄-CuCl₂ and the Raney Ni are definitely different; the former tends to afford favorably α -olefins whereas the latter selectively gives the thermodynamically more stable products, internal olefins. (ii) Reductions of 3 α and 3 γ with the Raney Ni gave the same product ratio.⁷⁾ (iii) Use of this desulfurization in the reaction sequence shown below eventually provides a versatile method for the selective linking of two different alkyl groups (R^1 and R^2) by the CH=C(R)CH₂ bridge (see Runs 12 and 13).

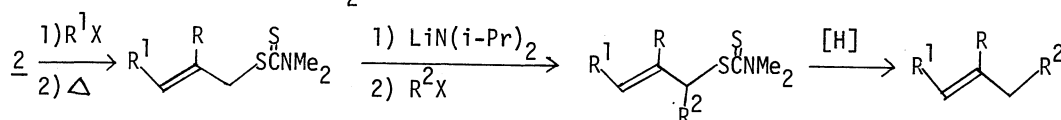




Table 2. Reductive Desulfurization of Alkylated Dithiocarbamates

Run	Substrate	Method ^a	Yield ^b	Product ratio ^b	
					
6	<u>10α</u>	L	99%	9	1
7		R	98%	1	4
8	<u>10γ</u>	R	100%	1	4
9	<u>11α</u>	L	37%	~100%	---
10		R	92%	1	6
11	<u>11γ</u>	R	91%	1	6
12	<u>12</u>	L	30%	~100%	---
13	<u>12</u>	R	70%	3	5

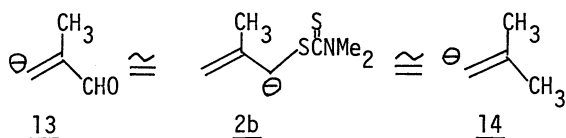
^a L: LiAlH₄-CuCl₂(4:2) under the same conditions as in the case of Run 2 in Table 1.

R: The specific Raney Ni under the same conditions as in the case of Run 5 in Table 1.

^b Based on a combination of NMR and VPC methods.

^c Contaminated with a small amount of the cis-isomer.

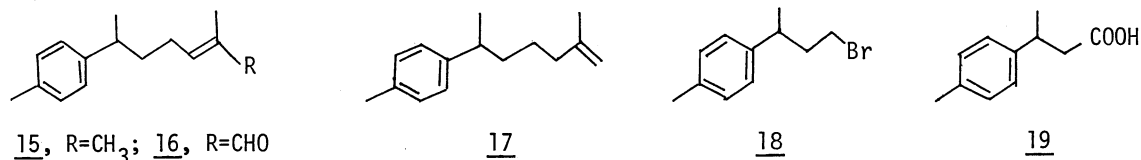
The synthetic value of employing the specific Raney Ni in desulfurization of the alkylated products derived from 1b lies in the selective formation of the olefins containing the isopropylidene group. In contrast to the synthetic equivalency between the anion 2b and the formylvinyl anion 13 previously reported from our laboratory,³⁾ this operation establishes the equivalency between 2b and the β,β -dimethylvinyl anion 14. Therefore, synthetic application of the present



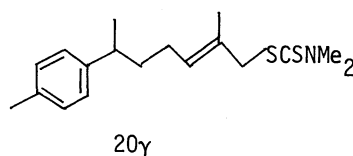
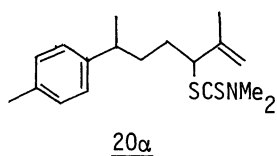
reaction sequence is of particular interest because both the isopropylidene group and (E)- β -alkylsubstituted methacroleins are commonly

occurring structural features found in naturally occurring products.

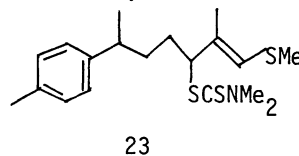
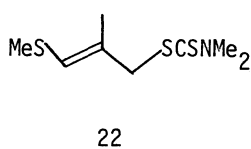
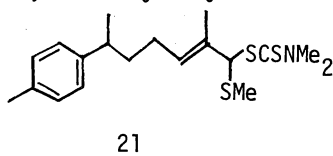
Finally, the present procedure for the introduction of the isopropylidene group and the synthetic method previously reported for the elaboration of 3 γ to α,β -unsaturated aldehydes were applied to the synthesis of a pair of the sesquiterpenes, α -curcumene (15)⁸⁾ and nuciferal (16).⁹⁾ The former occurs in nature along with its double bond isomer, iso- α -curcumene (17).⁸⁾ The bromide 18 required for the sequence was prepared by the standard methods from the known acid (19).¹⁰⁾



Lithiation of 1b followed by alkylation with 18 afforded the α -alkylated product (20 α) in 90% yield. The further rearrangement of 20 α gave 20 γ . Desulfurization of 20 α and 20 γ with the specific Raney Ni described above resulted in the quantitative formation of a mixture of 15 and 17, in the same ratio of 5 : 1, which approximated the composition of the natural mixtures.



On the other hand, the aldehyde 16 was prepared by the two methods. The first synthesis was initiated by further lithiation of 20 γ followed by quenching with dimethyl disulfide producing the sulfenylated product (21). Without purification, 21 was then hydrolyzed with mercuric chloride in an aqueous acetonitrile,^{3,11)} affording 16 in 45% of overall yield. Alternatively, lithiation of S- γ -methylthioallyl dithiocarbamate (22) derived from 1b¹²⁾ followed by alkylation with 18 provided, after hydrolysis of the crude product (23) with mercuric ion, 65% overall yield of 16.



References and Notes

- 1) Dithiocarbamates in Organic Synthesis. III. Part II: ref 3.
- 2) T.Hayashi, Tetrahedron Lett., 339 (1974).
- 3) T.Nakai, H.Shiono, and M.Okawara, *ibid.*, 3625 (1974).
- 4) For other examples of α alkylation due to intramolecular chelation in related allylic systems, see (a) T.Mukaiyama, K.Narasaka, K.Maekawa, and M.Furusato, Bull. Chem. Soc. Jap., 44, 2285 (1971); K.Narasaka, M.Hayashi, and T.Mukaiyama, Chem. Lett., 259 (1972); (b) K.Hirai, N.Matsuda, and Y.Kishida, Tetrahedron Lett., 4359 (1971); K.Hirai and Y.Kishida, *ibid.*, 2117, 2747 (1972); (c) D.A.Evans and G.C.Andrews, Accounts Chem. Res., 7, 147 (1974).
- 5) W.E.Truce and F.M.Ferry, J. Org. Chem., 30, 1316 (1965).
- 6) Rearrangements of 10 α and 11 α resulted in the formation of only E-isomer (10 γ) and a mixture (11 γ) of the E- and Z-isomer (E/Z = ca.9:1), respectively.
- 7) Control experiments indicated that the desulfurization process of 3 α was much faster than the rearrangement of 3 α into 3 γ under the reduction conditions.
- 8) C.H.Heathcock, "The Total Synthesis of Natural Products", Vol.2, Ed. by J.ApSimon, John Wiley and Sons, Inc., New York, N.Y. (1973), p.241-251.
- 9) T.Sakai, K.Nishimura, and Y.Hirose, Bull. Chem. Soc. Jap., 38, 381 (1965).
- 10) Prepared via the three steps starting with p-methylacetophenone and ethyl cyanoacetate according to the literature procedures: R.P.Gandhi, O.P.Vig, and S.M.Mukherji, Tetrahedron, 7, 736 (1959).
- 11) Cf. T.Nakai and M.Okawara, Chem. Lett., 731 (1974).
- 12) This compound (E, >90%) was readily obtained in 90% yield by quenching the anion derived from 1b with dimethyl disulfide via the spontaneous sigmatropic rearrangement.³⁾

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