Communications to the Editor

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ELECTRONIC EFFECTS ON THE REGIOSELECTIVITY IN THE REACTIONS OF THIOALLYLIC ANIONS WITH CARBONYL COMPOUNDS

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In the reactions of lithium salts of allylic N,N-dimethyldithiocarbamates with *p*-substituted aromatic aldehydes and ketones, the α-selectivity increases as the substituent of the phenyl ring becomes more electron-attractive. The regioselectivity also depends upon the substitution pattern of the allylic moiety. The Hard and Soft Acid and Base (HSAB) approach was used to rationalize the results.

KEYWORDS——thioallylic anion; allylic dithiocarbamate; regioselectivity; HSAB approach; electronic effect

Thioallylic anions are very valuable synthetic intermediates for carbon-carbon bond formation. However, the regioselectivity of these ambident anions observed in the reactions with a variety of electrophiles are governed by so many complex factors that further investigation is needed before practicing synthetic chemists can make extensive use of these reagents.$^{1)}$ Recently, Murphy and Wattanasin demonstrated that in the reactions of anions of ketene dithioacetals with alkylating reagents, the ratios of α to γ-alkylation increases with the hardness of the leaving group of the alkylating reagents.$^{2)}$ In the present communication, we wish to describe the electronic factors of electrophiles controlling the regioselectivity, which have an important heuristic value for synthetic chemists.

It has been well documented that thioallylic anions react with alkyl halides at the α-position adjacent to sulfur, but with carbonyl compounds at the γ-position in a regioselective manner.$^{3)}$ However, in the course of study on the lithium salts of allyl N,N-dimethyldithiocarbamate (1) with carbonyl partners, we have found that the above generalizations are not always true. The facts prompted us to scrutinize these reactions.

The reactions of lithium salts of allylic dithiocarbamates (1) with carbonyl electrophiles were performed at -60°C as previously described.$^{3b)}$ In general, the reactions resulted in an isomeric mixture of products 3 and 4 (Chart 1).$^{4)}$ Their

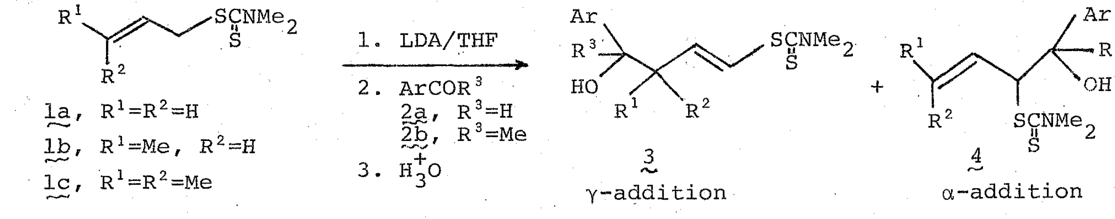


Chart 1

Table I. The Reactions of **1a**c) with *p*-Substituted Acetophenones

entry	substituent	yield (%)a)	α (%)b)	γ (%)b)
1	OMe	83	1.5 (-)	98.5 (-)
2	Me	97	1.6 (-)	98.4 (-)
3	H	98	1.8 (1.4)	98.2 (98.6)
4	F	98	3.2 (2.9)	96.8 (97.1)
5	Cl	96	13.0 (10.0)	87.0 (90.0)
6	CN	84	30.0 (28.0)	70.0 (72.0)

Table II. The Reactions of **1a**c) with *p*-Substituted Benzaldehyeds

entry	substituent	yield (%)a)	α (%)b)	γ (%)b)
7	NMe_2	83	- (5.0)	- (95.0)
8	OMe	95	20.0 (18.0)	80.0 (82.0)
9	H	88	22.0 (21.0)	78.0 (79.0)
10	F	83	30.0 (29.0)	70.0 (71.0)
11	Cl	94	35.0 (36.0)	65.0 (64.0)
12	Br	88	34.0 (36.0)	66.0 (64.0)
13	CN	72	60.0 (54.0)	40.0 (46.0)

Table III. The Reactions of **1b**c) with *p*-Substituted Benzaldehydes

entry	substituent	yield (%)a)	α (%)b)	γ (%)b)
14	NMe_2	87.0	3.8 (3.4)	96.2 (96.6)
15	OMe	90.0	8.6 (11.3)	91.4 (88.7)
16	H	79.0	19.2 (-)	80.0 (-)
17	Br	82.5	40.8 (41.9)	59.2 (58.1)
18	CN	70.1	79.0 (78.0)	21.0 (22.0)

Table IV. The Reactions of **1c**c) with *p*-Substituted Benzaldehydes

entry	substituent	yield (%)a)	α (%)b)	γ (%)b)
19	OMe	80.0	5.3 (7.4)	94.7 (92.6)
20	H	74.0	11.7 (-)	88.3 (-)
21	Cl	98.0	28.0 (28.4)	72.0 (71.6)
22	Br	76.2	29.6 (28.8)	70.4 (72.2)
23	CN	65.7	67.5 (66.6)	32.5 (33.4)

a) Isolated using a Merk lobar column with CH_2Cl_2:EtOAc (97:3) as solvent.

b) Determined by High Performance Liquid Chromatography (HPLC) analysis, using UV and RI detectors. The NMR method also gave almost the same values as the HPLC analysis. Parentheses show the values calculated from the isolated yields.

c) **1a**, **1b**, and **1c** are allyl, (E)-crotyl, and prenyl N,N-dimethyldithiocarbamates, respectively.

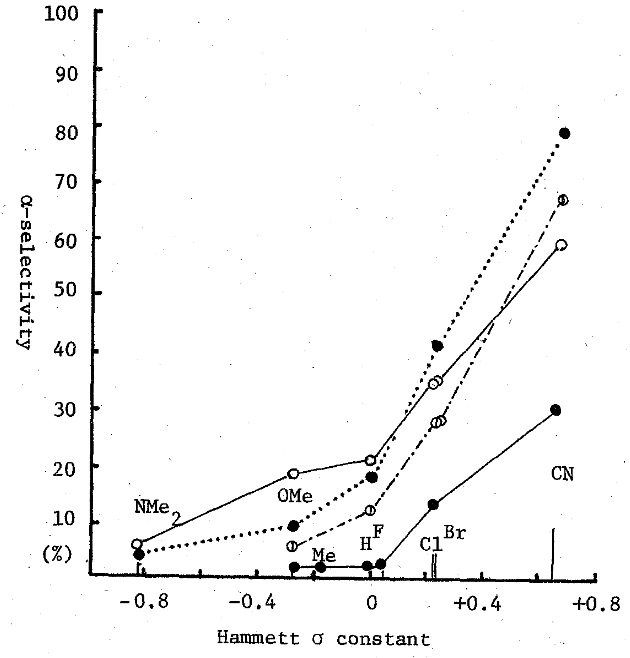
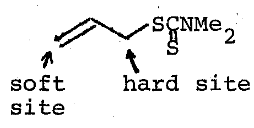


Fig. 1. The α-selectivity vs. Hammett σ
(—●—): Reactions of 1a with 2b
(—○—): Reactions of 1a with 2a
(····●····): Reactions of 1b with 2a
(--⦶--): Reactions of 1c with 2a

isomeric ratio (α/γ) were determined by HPLC analysis and compared with the values calculated from the isolated yields. The results are summarized in Tables 1-4. The agreement between the two methods is generally excellent. That the reactions are kinetically controlled was confirmed as follows. No isomerization of lithium salts of 3 to those of 4 and vice versa was detected even after they were allowed to stand at -60°C for 1 h. All of the products obtained were fully charcterized by combustion analysis and spectral methods. The NMR spectra of 3, which clearly showed a doublet of the C=CH-S unit near 6.50 ppm (J=15.7 Hz for the *trans* isomers and J=9.6 Hz for the *cis* isomers), were decisive in establishing their structures, and the characteristic vinyl signals or methyl signals attached to the γ-carbon served well in determining the structure 4.

The α-selectivity was plotted as the ordinate against the Hammett σ constant, as shown in Figure 1. It is reasonable to assume that the changes in electronic effects on the C=O function should be accompanied by at least minimal changes in steric factors for each series of the reactions, if the substituent is introduced at the *para*-position. Consequently, Figure 1 shows that increased electron withdrawal by the substituent on the C=O function increases the α-selectivity drastically. This also reveals that the α-carbon is the harder site of this ambident anion and the γ-terminus, the softer one. This conclusion is compatible with the one obtained by Murphy and Wattanasin.[2)] The reactions of anions 1 with harder C=O partners (benzaldehydes bearing the substituent with a positive σconstant) proceed with greater facility at the harder α-site to give the increased α/γ ratios, while the reactions with softer C=O partners (benzaldehydes bearing a negative σ constant) occur more effectively at the softer γ-terminus to afford the decreased α/γ ratios.



Comparison of the α-selectivity observed in the reactions of allyl, crotyl, and prenyl dithiocarbamates (1a, 1b, and 1c, respectively) with the *p*-substituted benzaldehydes also suggests that increased steric crowding of the γ-terminus of the allylic moiety should exert only a minor effect on the level of regioselectivity. Furthermore, it was observed that replacement of a hydrogen atom on the C=O function by a methyl group (conversion of aldehydes to ketones) decreased the α-selectivity substantially. The methyl group, when bonded to a carbon involved in a

π-system, is electron-releasing$^{5)}$ and therefore softens the ketonic carbon more than the aldehydic carbon. Accordingly, the reactions of **1a** with *p*-substituted acetophenones led to the decrease of the ratios, though in this case steric factors also might favor the formation of the γ-addition products.

In conclusion, although other parameters need consideration,$^{1)}$ it seems useful for qualitative prediction of regioselectivity to correlate first the hardness and softness of the allylic anions with those of electrophiles. In accord with the above conclusion, the reactions of **1a** with acety and benzoyl chlorides gave the α/γ ratios of 75:25 and 80:20, respectively.$^{6)}$ Furthermore, the reaction of **1a** with CO_2 afforded the α-addition product exclusively, whereas the reaction of **1a** with acetone yielded the γ-addition product with 97% γ-selectivity. However, it should be emphasized that the HSAB approach is concerned only with heuristic purposes, not directly with the mechanistic problems. Further studies on the regioselectivity toward other electrophiles containing a heteroatom and organic synthesis utilizing the differences in regioselectivity of thioallylic anions are being vigorously pursued.

REFERENCES AND NOTES

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4) When R^1=Me and R^2=H, the α- and γ-addition products led to the formation of diastereoisomers. However, this constitutes another area of study. For example, see reference 3b.

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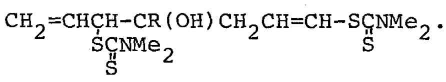
6) The reaction did not stop at the step of the formation of a ketone. The ketone, once formed, reacted further with another molecule of the anion to give the γ-addition product,



$\mathrm{CH_2{=}CH\underset{S\underset{\overset{\|}{S}}{C}NMe_2}{C}H{-}CR(OH)CH_2CH{=}CH{-}S\underset{\overset{\|}{S}}{C}NMe_2}$.

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