

SYNTHESIS OF KETENE S,S-ACETALS FROM THIOAMIDES

T. Harada, Y. Tamaru, and Z. Yoshida*

Department of Synthetic Chemistry, Kyoto University,
Yoshida, Kyoto 606, Japan

Summary: A new method converting thioamides to ketene S,S-acetals, which exhibits wide compatibility with olefin, ketone, ester and amide groups, has been described.

Thioamides have proved to be synthetically very potential by the total synthesis of Vitamin B₁₂ (construction of corrin molecule) by Woodward and Eschenmoser¹ and indole alkaloids by Takano et al.² Recently we have developed some useful reactions making use of the characteristics of thioamides;³ the highly stereoselective coupling reaction of thioamides to give d,1-1,4-dithioamides⁴ and the Michael addition reaction of wide variety of organometallics to α,β -unsaturated thioamides.⁵

Although in these reactions thioamides have played an important role as the latent amines,^{4,6} enamines,⁷ ketene S,N-acetals,⁸ amides,⁹ etc., almost no report has appeared concerning on the conversion of thioamides to the ordinary carbonyl compounds, such as ketones,¹⁰ aldehydes, and esters.¹¹ Here we wish to report the very simple and versatile transformation of thioamides to ketene S,S-acetals and 1,3-dithianes, one of the most familiar synthons and protecting groups¹² of ketones and aldehydes.

S-methyl onium salt of thioamide, isolated by the filtration of the reaction mixture of thioamide and 2 \sim 3 equiv. of methyl iodide in ether, was allowed to react with 1,3-propanedithiol in the presence of K₂CO₃ in refluxing dichloromethane or tert-butanol under nitrogen (procedure A). The reaction was also successfully performed without isolation of onium salt. The onium salt generated in situ was subjected directly to the reaction according to the above-mentioned procedure (procedure B). The reaction is very clean and fast, and attained the completion within 1h. Single distillation (by Kugelrohr) provided spectroscopically and chromatographically homogeneous ketene S,S-acetal in good yield¹³ (Scheme 1).

In Table I are summarized the results with various kinds of thioamides. Apparently from this Table, the present reaction is general for N,N-dialkylthioamides possessing at least one hydrogen atom α to thiocarbonyl group. Among the methods reported,¹⁴ the reaction type of the present method is

Table 1. Synthesis of Ketene S,S-acetals from Thioamides

Entry	Reactant	Procedure ^a	Solvent	Product	Yield (%) ^b
1	$\text{PhCH}_2\text{CH}_2\overset{+\text{SMe}}{\parallel}\text{CNMe}_2 \text{ I}^-$	A	t-BuOH	$\text{PhCH}_2\text{CH}=\text{C} \begin{matrix} \text{S} \\ \diagup \quad \diagdown \\ \text{S} \end{matrix} \text{ c}$	73
2	$\text{PhCH}_2\overset{+\text{SMe}}{\parallel}\text{C}-\text{N} \begin{matrix} \diagup \quad \diagdown \\ \diagup \quad \diagdown \end{matrix} \text{ I}^-$	A	t-BuOH	$\text{PhCH}=\text{C} \begin{matrix} \text{S} \\ \diagup \quad \diagdown \\ \text{S} \end{matrix} \text{ e}$	80
3	$\text{Me}_2\text{CHC} \begin{matrix} \diagup \quad \diagdown \\ \diagup \quad \diagdown \end{matrix} \overset{+\text{SMe}}{\parallel} \text{ I}^-$	A	t-BuOH	$\text{Me}_2\text{C}=\text{C} \begin{matrix} \text{S} \\ \diagup \quad \diagdown \\ \text{S} \end{matrix} \text{ e}$	79
4	$\text{CH}_2=\text{CH}(\text{CH}_2)_8 \overset{\text{S}}{\parallel}\text{CNMe}_2$	B	CH ₂ Cl ₂	$\text{CH}_2=\text{CH}(\text{CH}_2)_7\text{CH}=\text{C} \begin{matrix} \text{S} \\ \diagup \quad \diagdown \\ \text{S} \end{matrix} \text{ d}$	97
5	$\text{CH}_3(\text{CH}_2)_4 \overset{\text{Me}^+\text{SMe}}{\parallel}\text{CH}-\text{CNMe}_2 \text{ I}^-$	A	t-BuOH	$\text{CH}_3(\text{CH}_2)_4 \overset{\text{Me}}{\text{C}}=\text{C} \begin{matrix} \text{S} \\ \diagup \quad \diagdown \\ \text{S} \end{matrix} \text{ d}$	73
6	$\text{PhCH} \begin{matrix} \diagup \quad \diagdown \\ \diagup \quad \diagdown \end{matrix} \overset{+\text{SMe}}{\parallel}\text{CNMe}_2 \text{ I}^-$	A	CH ₂ Cl ₂	$\text{PhCHCH}=\text{C} \begin{matrix} \text{S} \\ \diagup \quad \diagdown \\ \text{S} \end{matrix} \text{ c}$	70
7	$\text{t-BuOC} \begin{matrix} \text{O} \\ \parallel \end{matrix} \text{CH}_2 \overset{\text{Me}}{\text{C}} \begin{matrix} \diagup \quad \diagdown \\ \diagup \quad \diagdown \end{matrix} \overset{\text{S}}{\parallel}\text{CNMe}_2$	B	CH ₂ Cl ₂	$\text{t-BuOC} \begin{matrix} \text{O} \\ \parallel \end{matrix} \text{CH}_2 \overset{\text{Me}}{\text{C}} \text{CH}=\text{C} \begin{matrix} \text{S} \\ \diagup \quad \diagdown \\ \text{S} \end{matrix}$	91
8	$\text{t-BuC} \begin{matrix} \text{O} \\ \parallel \end{matrix} \text{CH}_2 \overset{\text{Me}}{\text{C}} \begin{matrix} \diagup \quad \diagdown \\ \diagup \quad \diagdown \end{matrix} \overset{\text{S}}{\parallel}\text{CNMe}_2$	B	CH ₂ Cl ₂	$\text{t-BuC} \begin{matrix} \text{O} \\ \parallel \end{matrix} \text{CH}_2 \overset{\text{Me}}{\text{C}} \text{CH}=\text{C} \begin{matrix} \text{S} \\ \diagup \quad \diagdown \\ \text{S} \end{matrix} \text{ c}$	83
9	$\text{Me}_2\text{NC} \begin{matrix} \text{O} \\ \parallel \end{matrix} \text{CH}_2 \overset{\text{Ph}}{\text{C}} \begin{matrix} \diagup \quad \diagdown \\ \diagup \quad \diagdown \end{matrix} \overset{+\text{SMe}}{\parallel}\text{CNMe}_2 \text{ I}^-$	A	CH ₂ Cl ₂	$\text{Me}_2\text{NC} \begin{matrix} \text{O} \\ \parallel \end{matrix} \text{CH}_2 \overset{\text{Ph}}{\text{C}} \text{CH}=\text{C} \begin{matrix} \text{S} \\ \diagup \quad \diagdown \\ \text{S} \end{matrix} \text{ c}$	79

a) For the details of procedures A and B, see text. The reaction mixture was refluxed for 40-60 min. in the indicated solvents after addition of K₂CO₃ and propanedithiol.

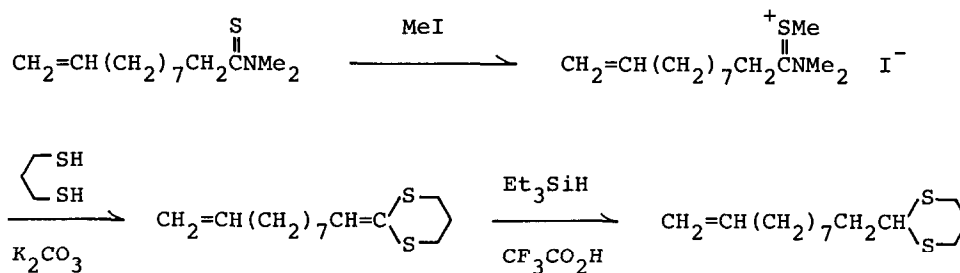
b) Yields refer to the isolated, spectroscopically (¹H NMR, IR, and mass) and chromatographically homogeneous materials.

c) Satisfactory analytical results have been obtained for these products.

d) For these compounds satisfactory analytical results have been obtained as dithianes.

e) Reference 14a.

Scheme I



similar to that reported by Corey et al.^{14e,f} In comparison with the latter, which is based on the activation of dithiol as an aluminium complex (bis-(diethylaluminium)-1,3-propanedithiol), the present method is based on the activation of carbonyl part. Consequently the present method shows wide compatibility especially with carbonyl groups such as ester, ketone, and amide (entries 7, 8, and 9 Table I). Also it seems worthwhile to note that (a) starting thioamides with a variety of structures are easily available according to the methods developed in these laboratories.^{3,4,5} (b) Manipulation is simple and reaction conditions are rather mild (weakly basic), which are illustrated by the synthesis of 2-(2-methyl-3-carbo-tert-butoxypropylidene)-1,3-dithiane (entry 7): *N,N*-dimethyl-3-methyl-4-carbo-tert-butoxythiobutanoamide (0.82 mmol), obtained by the conjugate addition of tert-butyl α -lithioacetate to *N,N*-dimethylthiocrotonamide,^{5b} was treated with 284 mg (1.2 equiv.) of CH_3I in 3 ml of CH_2Cl_2 under N_2 at ambient temp. for 1 day. Then anhydrous K_2CO_3 (68 mg, 1.2 equiv.) and 1,3-propanedithiol (90 μl , 1.1 equiv.) were added and refluxed with stirring for 1 h. After allowed to cool, the reaction mixture was treated with H_2O . Extraction with ether and drying over Na_2SO_4 , followed by evaporation of the solvents provided faintly yellow oil, which was distilled under reduced pressure to give 203 mg (91% yield) of colorless oil (170°C/0.01 mmHg, Kugelrohr): ^1H NMR (δ , in CCl_4); 1.06 (d, $J = 7.0$ Hz, 3 H), 1.43 (s, 9 H), 2.15 (m, 4 H), 2.85 (m, 4 H) 3.25 (m, 1 H), and 5.72 (d, $J = 9.0$ Hz, 1 H). IR (cm^{-1} , neat film); 1730(s), 1580(w), 1370(m), and 1160(s). Mass (m/e, relative intens.) 274(P^+ , 10), 118(53), 159(100), and 85(34).

The thus obtained ketene *S,S*-acetals were reduced to the corresponding 1,3-dithianes according to the method reported by Carey et al.;¹⁵ 2-(2'-heptyl)-1,3-dithiane (in 98% yield from 2-(1'-methylpentylidene)-1,3-dithiane), 2-(8'-decenyl)-1,3-dithiane (85% yield from 2-(8'-decenylidene)-1,3-dithiane (Scheme I)).

Acknowledgement: We are grateful for the partial financial support from the Ministry of Education, the Japanese Government (Grant-in-Aid for Scientific Research, No. 365306).

References and Notes

1. (a) R. B. Woodward, *Pure Appl. Chem.*, 17, 519 (1968); 25, 283 (1971); 33, 145 (1973); (b) A. Eschenmoser, *Q. Rev.*, 24, 366 (1970).
2. S. Takano, M. Hirama, T. Araki, and K. Ogasawara, *J. Am. Chem. Soc.*, 98, 7087 (1976).
3. For the α - and γ -allylations of α, β -unsaturated thioamides, see Y. Tamaru, T. Harada, and Z. Yoshida, *Tetrahedron Lett.*, 2167 (1978).
4. Y. Tamaru, T. Harada, and Z. Yoshida, *J. Am. Chem. Soc.*, 100, 1923 (1978).
5. (a) Y. Tamaru, T. Harada, H. Iwamoto, and Z. Yoshida, *J. Am. Chem. Soc.*, 100, 5221 (1978); (b) Y. Tamaru, T. Harada, and Z. Yoshida, *ibid.*, 101, 1316 (1979).
6. G. R. Pettit and E. E. van Tamelen, *Org. React.*, 12, 385 (1962).
7. (a) M. Roth, P. Dubs, E. Gotshi, and A. Eschenmoser, *Helv. Chim. Acta*, 54, 710 (1971); (b) G. C. Gerrans, A. S. Howard, and B. S. Orlek, *Tetrahedron Lett.*, 4171 (1975); (c) A. Gossauer, R. -P. Hinze, and H. Zilch, *Angew. Chem.*, 89, 429 (1977).
8. R. Gompper and W. Elser, "Organic Syntheses", *Collect. Vol. V*, Wiley, New York, N.Y., 1973, p. 780.
9. Amides by a basic hydrolysis of S-alkyl onium salts.
10. T. Fukuyama, L. V. Dunkerton, M. Aratani, and Y. Kishi, *J. Org. Chem.*, 40, 2011 (1975).
11. Synthesis of esters from thioamides will be reported soon.
12. B. -Th. Gröbel and D. Seebach, *Synthesis*, 357 (1977).
13. In some cases, the formation of the appreciable amounts of 2-alkyl substituted 2-methylthio-1,3-dithianes was detected by TLC or ^1H NMR. But during distillation ($\sim 150^\circ$ under reduced pressure), facile elimination of methyl mercaptane was caused to give ketene S,S-acetal as a single distillate.
14. The synthetic methods of ketene S,S-acetals may be classified into the following three modes from a point of view of types of reactions: Wittig type double bond formation; (a) D. Seebach, M. Kolb, and B. -Th. Gröbel, *Chem. Ber.*, 106, 2277 (1973); (b) B. T. Groebel and D. Seebach, *ibid.*, 110, 852 (1977) and references cited therein. Transformation from dithioesters or their derivatives; (c) B. Cazes and S. Julia, *Tetrahedron Lett.*, 4065, (1978); (d) F. E. Ziegler and C. M. Chan, *J. Org. Chem.*, 43, 3065 (1978) and references cited therein. Dithioacetalization of carbonyl compounds; (e) E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, 95, 5829 (1973); (f) E. J. Corey and A. P. Kozikowski, *Tetrahedron Lett.*, 925 (1975).
15. F. A. Carey and A. S. Court, *J. Org. Chem.*, 37, 1926 (1972).

(Received in Japan 11 June 1979)