A New Synthesis of Thiol Esters

Summary: New synthetic procedures for the direct preparation of thiol esters from carboxylic acids and thiols using diethyl phosphorocyanidate or diphenyl phosphorazidate are described.

Sir: In spite of its potential importance there is still no generalized method for the direct preparation of thiol esters from carboxylic acids and thiols.[1] We now wish to report this transformation, which involves treatment of a carboxylic acid and a thiol with diethyl phosphorocyanidate (DEPC)[2] or diphenyl phosphorazidate (DPPA)[3] in the presence of triethylamine in dimethylformamide solution.

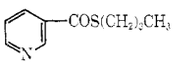
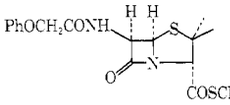
While optimum reaction conditions have yet to be established, the results summarized in Table I reveal that preparatively satisfactory yields can be obtained under exceptionally mild conditions. In general, DEPC was a superior condensing agent to DPPA. However, the latter was better in the formation of thiol esters of α-amino acid derivatives. The successful conversion of *N*-benzyloxycarbonyl-L-threonine to its ethyl thiol ester makes prominent the selective nature of the process, because its hydroxyl function was inert. Furthermore, a highly functionalized penicillin derivative easily afforded its thiol ester.

In a typical procedure, triethylamine (1.01 g, 10 mmol) was added to a mixture of pyridine-3-carboxylic acid (0.62 g, 5 mmol), DEPC (1.63 g, 10 mmol), and *n*-butanethiol (0.65 ml, 6 mmol) in dimethylformamide (5 ml) with stirring and ice cooling. The mixture was stirred at room temperature for 3 hr, diluted with benzene, and worked up with aqueous acid (5% citric acid) and saturated aqueous sodium bicarbonate. The evaporated residue was purified by a silica gel column chromatography with *n*-hexane and ethyl acetate (9:1) to give *S*-*n*-butyl 3-pyridinecarbothioate (0.85 g, 87%) as a colorless oil.

The quite interesting feature of the reaction is that the method can be efficiently applied to the thiol ester synthesis with little, if any, racemization. Benzoyl-L-leucine[2,3,4] was converted to its ethyl thiol ester with 93% optical purity, as compared with the optically pure thiol ester which was prepared from *tert*-butyloxycarbonyl-L-leucine[5] by

Table I
Preparation of Thiol Esters

$$RCO_2H + R'SH \xrightarrow[Et_3N \text{ in DMF at room temp, 3 hr}]{NCPO(OEt)_2 \text{ or } N_3PO(OPh)_2} RCOSR'^{a}$$

No.	Thiol ester[b]	Yield, %[c,d]	Mp or bp (mm), °C
1	$PhCH_2CH_2COSCH_2CH_3$	85 (75)	121 (5)
2	$PhCH_2CH_2COSCH(CH_3)_2$	70	121–123 (5)
3	$PhCH_2CH_2COS(CH_2)_3CH_3$	80 (71)	125–128 (5)
4	$PhCH_2CH_2COSPh$	75 (38)	49–51[e]
5	$CH_3(CH_2)_6COSCH_2CH_3$	74 (58)	90 (3)[f]
6	$(CH_3)_3CCOSCH_2Ph$	79	114 (4)
7	$PhCOS(CH_2)_3CH_3$	95	125 (5)[g]
8		87	95 (1)
9	$CH_3CHCHCOSCH_2CH_3$ (HO, $NHCO_2CH_2Ph$)	56 (61)	106–107[h]
10		Trace (51)[i]	Viscous oil
11	$(CH_3)_2CHCH_2CHCOSCH_2CH_3$ ($NHCO_2C(CH_3)_3$)	(82)	93–96[j]
12	$(CH_3)_2CHCH_2CHCOSCH_2CH_3$ ($NHCOPh$)	(83)[k]	118–119[l]

[a] The reactions using DEPC were performed as described for the typical example given in the text. When DPPA was a condensing agent, an equimolecular mixture of a carboxylic acid, DPPA, and triethylamine with a slight excess of a thiol was used, unless otherwise stated. [b] Characterized satisfactorily by spectral and elemental analysis. See paragraph at the end of paper regarding supplementary material. [c] Based on chromatographically purified materials, whose purities were checked by tlc and ir and nmr spectra. [d] Yields in parentheses were obtained using DPPA. [e] Lit. mp 49° [J. Gosselck, H. Barth, and L. Béress, *Justus Liebigs Ann. Chem.*, **671**, 1 (1964)]. [f] Lit. bp 94–96° (6 mm) [S. Okumura, M. Masumura, and T. Horie, *Yûki Gôsei Kagaku Kyokai Shi*, **17**, 415 (1954); *Chem. Abstr.*, **53**, 17957*i* (1959)]. [g] Lit. bp 160° (23 mm) [J. W. Kimball and E. E. Reid, *J. Amer. Chem. Soc.*, **38**, 2757 (1916)]. [h] $[\alpha]^{20}D$ −57.6° (*c* 2.1, $CHCl_3$). [i] Potassium salt of phenoxymethylpenicillin (kindly donated by Mr. M. Kuramoto of Toyo Jozo Co., Ltd.) was allowed to react with 7 equiv of ethanethiol and 2 equiv of DPPA without triethylamine. [j] $[\alpha]^{20}D$ −39.6° (*c* 2, $CHCl_3$). [k] The reaction was carried out at *ca.* −25 to −30° for 4 hr and then at 0° overnight. [l] Optically pure sample, $[\alpha]^{20}D$ +16.8° (*c* 3.2, Me_2CO).

successive treatment with ethanethiol and DPPA, hydrogen chloride, and benzoyl chloride.

Although this investigation is still in its preliminary stages, the data in Table I suggest that the procedures herein described provide a one-step method for preparing thiol esters containing reactive functions under mild reaction conditions.

Supplementary Material Available. Ir and nmr data for all compounds as well as microanalytical data for new compounds will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy of $2.00 for microfiche, referring to code number JOC-74-3302.

References and Notes

(1) T. C. Bruice, "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, New York and London, 1961, Chapter 35; T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanism," Vol. 1, W. A. Benjamin, New York and Amsterdam, 1966, Chapter 3.
(2) S. Yamada, Y. Kasai, and T. Shioiri, *Tetrahedron Lett.*, 1595 (1973).
(3) T. Shioiri, K. Ninomiya, and S. Yamada, *J. Amer. Chem. Soc.*, **94**, 6203 (1972); S. Yamada, K. Ninomiya, and T. Shioiri, *Tetrahedron Lett.*, 2343 (1973).
(4) *Cf.* M. W. Williams and G. T. Young, *J. Chem. Soc.*, 881 (1963).
(5) *Cf.* M. Bodanszky and M. A. Ondetti, "Peptide Synthesis," Interscience, New York, N. Y., Chapter VI.

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Cartilagineal. An Unusual Monoterpene Aldehyde from Marine Alga

Summary: A unique monoterpene aldehyde, $C_{10}H_{11}OCl_3$, has been isolated from the ether soluble extract of the red marine alga *Plocamium cartilagineum* (L.) Dixon and its structure has been determined from spectroscopic data.

Sir: Marine algae of divisions *Rhodophyta* and *Phaeophyta* have recently been found to elaborate antibiotics of a wide range of structural types.[1] The essential oils from certain brown alga have been shown to contain a number of C_{11} hydrocarbons some of which exhibit gamone activity.[2] Both red and brown algae have also been observed as possessing components with toxic activity,[3] while very little attention has been given to the isolation and identification of such compounds.

In connection with our interest in marine chemical products we have examined an abundant red alga, *Plocamium cartilagineum* (L.) Dixon (*Plocamium coccineum var. pacificum*),[4] native to the Pacific coast whose ether soluble components are toxic to goldfish. There are several unique monoterpenes in this fraction and we report below the characterization of an odoriferous polychlorinated aldehyde.

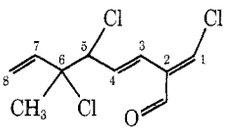
Hplc purification of the $CHCl_3$–CH_3OH (85:15) extract of the wet alga (2 Kg, dry weight) afforded an α,β-unsaturated aldehyde (0.01%) as a viscous liquid [ir 3070, 2950, 2860, 2740, 1690 cm^{-1}; uv λ_{max} 245 (ϵ 15,800, EtOH)] which could be distilled [Kugelrohr point, 130° (0.1 mm)] but decomposed upon prolonged standing in air. A molecular formula of $C_{10}H_{11}OCl_3$ was deduced from the mass spectra:

Table I
100-MHz Pmr Data for Cartilagineal (1)

Proton	δ, ppm[a]	Pattern[b]	J, Hz[c]	Spin decoupling
H_A	7.05	s		
H_B	9.04	d	2.0	irr at H_C, s
H_C	6.49	d of dd	15.3, 2.0, 1.0	irr at H_B, br d (J = 15.3) irr at H_E, sharp dd (J = 15.3, 2.0)
H_D	7.05	dd	15.3, 8.5	irr at H_C, d (J = 8.5) irr at H_E, d (J = 15.3)
H_E	4.47	br d	8.5	
H_F	6.06	dd	17.0, 10.5	
H_G	5.40	dd	17.0, 1.0	
H_H	5.26	dd	10.5, 1.0	
CH_3	1.71	s		

[a] Relative to internal TMS. [b] s, singlet; d, doublet; dd, doubled doublet; d of dd, doublet of doubled doublets. [c] J's are based on a first-order analysis and in some cases represent close, approximate values.

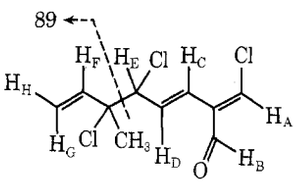
Table II
25.1-MHz Cmr Data for Cartilagineal (1)



Carbon	δ, ppm[a]	Multiple[b] pattern	J, Hz[c]
1	143.9	d	193
2	137.3	s	
3	122.5	d	158
4 or 7	134.0	d	170 or 168
5	69.5	d	155
6	71.5	s	
7 or 4	139.5	d	168 or 170
8	116.3	t	160
O=C	189.3	d	175
CH_3	24.6	q	128

[a] Relative to TMS. [b] H^1 coupled spectra obtained *via* the alternatively pulsed H^1 decoupling technique: O. Ganson and W. Shittenhelm, *J. Amer. Chem. Soc.*, **93**, 4294 (1971). [c] Error, ±1 Hz.

M^+ 252, 254, 256, 258; $M^+ - Cl$ 217, 219, 221; $M^+ - Cl - HCl$ 181, 183; $M^+ - 3Cl$ 147. The base peak $M^+ - C_6H_5OCl_2$, 89, 91 was accompanied by a less intense fragment $M^+ - C_4H_6Cl$ 163, 165, 167. These data along with magnetic resonance experiments (Tables I and II) enabled us to deduce structure **1**. In particular a 3-chloro-1-butenyl



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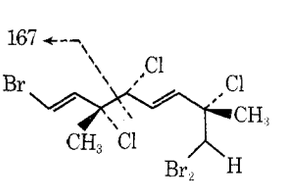

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substituent was required by the mass spectral fragmentation and pmr assignments of a tertiary methyl group and a clean vinylic ABX pattern (J = 17.0, 10.5, and 1.0 Hz) at δ 5.26, 5.40, and 6.06. On the other hand a somewhat unusual architecture was indicated for the enal function. The aldehyde proton (H_B) appeared as a sharp doublet, J = 2.0