Tetrahedron Letters,Vol.27,No.46,pp 5583-5586,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A ONE-STEP PREPARATION OF (*E*)-4-MERCAPTO-2-BUTENOIC ESTERS AND NITRILES RELATIVE MICHAEL REACTIVITIES IN SIMPLE UNSATURATED SYSTEMS[1]

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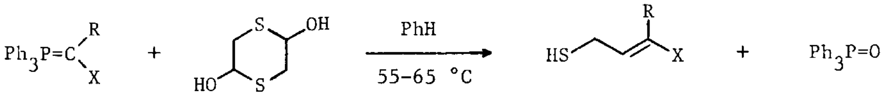
Abstract: A one-step procedure is described for the preparation of (*E*)-4-mercapto-2-butenoic esters and nitriles in 75-85% yield. The corresponding ketones could not be isolated due to dimerization of the initially-formed products by a double Michael reaction. The stability of these derivatives is related to their ability to serve as Michael acceptors.

Modern synthetic organic chemistry has an ever-increasing need for highly functionalized reagents. In this respect, the γ-functionalized α,β-unsaturated esters, nitriles and ketones constitute a family of compounds holding tremendous potential. We recently needed a series of such compounds, γ-substituted with $-NH_2$, -OH, and -SH, for our synthetic studies and found that the 4-mercapto derivatives were conspicuous in their absence from the literature. It was, therefore, necessary to develop a synthetic approach to these compounds and we report, here, a simple one-step synthesis of 4-mercapto-2-butenoic esters and nitriles.

In the planning stages, it was suspected that these molecules might be highly susceptible to self-condensation by a Michael reaction. Thus, a mild protocol, using essentially neutral conditions was sought. The successful route, formulated in eq. 1, involves reaction of triphenylphosphorane ylides, stabilized by electron withdrawing substitution at the ylide carbon, with the commercially available dimer of 2-mercaptoacetaldehyde (1,4-dithiane-2,5-diol) in benzene at 55-65 °C.

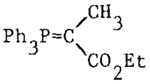
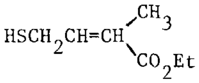
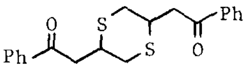
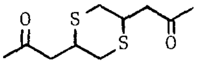


(1)

R = H, CH_3
X = ester, nitrile, ketone

The compounds prepared by reacting the stabilized triphenylphosphorane ylides with 2-mercaptoacetaldehyde are listed in Table 1. This appears to be the first report of

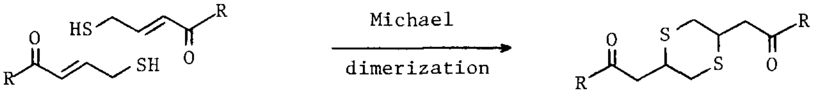
Table 1. Reaction of Stabilized Triphenylphosphorane Ylides with 1,4-Dithiane-2,5-diol.

Ylide	Time (h)	Product[a,b]	Yield (%)[c]
$Ph_3P=CHCO_2Bn$ (1)	2.0	$HSCH_2CH=CHCO_2Bn$ (7)	85
$Ph_3P=CHCO_2\underline{t}Bu$ (2)	2.5	$HSCH_2CH=CHCO_2\underline{t}Bu$ (8)	81
 $Ph_3P=C(CH_3)CO_2Et$ (3)	2.5	 $HSCH_2CH=CH(CH_3)CO_2Et$ (9)	83
$Ph_3P=CHCN$ (4)	6.0	$HSCH_2CH=CHCN$ (10)	78
$Ph_3P=CHCOPh$ (5)	2.5	 (11)	48
$Ph_3P=CHCOCH_3$ (6)	2.5	 (12)	45

[a] E isomers were obtained for all alkene products; [b] Dithiane products were isolated as mixtures of cis and trans isomers; [c] Isolated yields.

2-mercaptoacetaldehyde, generated in this fashion under neutral conditions, for use as the carbonyl reacting partner in the Wittig reaction.[3] As earlier studies have shown,[4] the alkenes produced under these conditions generally had >98% selectivity for the E configuration. Even in the reaction of 1-ethoxycarbonylethylidene triphenylphosphorane (3), less than 5% of the Z isomer, or its cyclization product, was detected.

Based upon the present limited survey of ylides, the procedure appears to be useful only for the preparation of ester and nitrile derivatives. Reactions of benzoylmethylene and acetylmethylene triphenylphosphorane do not result in the formation of the expected γ-mercapto enones. Instead, compounds 13 and 14, corresponding to the dimers of 4-mercapto-1-phenyl-2-buten-1-one (11) and 5-mercapto-3-penten-2-one (12) are isolated. These products evidently result from self-condensation of the monomeric enones by a double Michael reaction as depicted in eq. 2.



(2)

11 R = Ph
12 R = CH_3

13 R = Ph
14 R = CH_3

The increased tendency of the 4-mercapto enones to dimerize by this process serves as a gauge of their relative reactivity as Michael acceptors compared to esters and nitriles. Examination of pK_a data for protons on carbons α to electron withdrawing groups[5] reveals that a carbon anion adjacent to a ketone moiety should be more stabilized than a carbanionic center in conjugation with an ester or a nitrile. Using this reasoning, it is possible to infer that in α,β-unsaturated systems bearing similar substitution, the relative reactivity for Michael acceptors should be ketone > ester $\cong$ nitrile. Further studies are underway to substantiate the generality of this proposal.

In summary, the present work reports a simple one-step route to γ-mercapto α,β-unsaturated systems. The stability of these derivatives is directly related to their propensity to undergo self-condensation by a Michael reaction and this has been used to estimate the relative reactivity of activated alkenes toward conjugate addition. Finally, the compounds reported will be important intermediates in a variety of synthetic applications.

Procedure.[6] A mixture of 25 mmol of the ylide and 12.5 mmol of 1,4-dithiane-2,5-diol in 250 mL of benzene was heated at 55-65 °C with stirring under nitrogen until all of the diol had reacted. This was evidenced by the dissolution of the suspended diol and the formation of a homogeneous solution (see Table 1 for approximate times). The reaction was cooled, then concentrated under vacuum using a rotary evaporator. Ether was added to the oily triphenylphosphine oxide which remained, the crystals were filtered and the filtrate was concentrated. Vacuum distillation of the resulting oil using a Kugelrohr apparatus afforded the final alkene products.[6] The dimeric products were best purified by flash chromatography of the initial concentrate on silica gel using 15-20% ether in hexane as the eluent.

References and Notes

1. This research was supported by the College of Arts and Sciences, Oklahoma State University and the OSU Center for Energy Research.

2. Undergraduate Research Participant, Summer 1986.

3. 2-Mercaptoacetaldehyde has been generated under basic conditions (Et_3N) and used for the preparation of 2,5-dihydrofurans, see (a) McIntosh, J. M.; Seiler, R. A. *J. Org. Chem.* **1978**, *43*, 4431; (b) Schmitthenner, H. F.; Weinreb, S. M. *J. Org. Chem.* **1980**, *45*, 3372.

4. House, H. O.; Rasmusson, G. H. *J. Org. Chem.* **1961**, *26*, 4278.

5. Self-consistent pK_a data on simple derivatives of ketones, esters and nitriles, measured in DMSO, can be found in (a) Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* 1975, **97**, 7006; Other pK_a scales also show ketones to be more acidic than esters and nitriles, see (b) House, H. O. "Modern Synthetic Reactions," 2nd Ed., Benjamin, Menlo Park, CA, 1972, p. 494.

6. All reagents and solvents were used as received from commercial sources. The spectral data for new compounds is as follows:

   (**7**): bp 108-120 °C (0.025 mm Hg); IR (thin film) 2565, 1720, 1652, 739, 695 cm^{-1}; PMR ($CDCl_3$, 300 MHz) δ 7.38 (s, 5H), 7.10 (dt, 1H, J = 7,15 Hz), 6.00 (d, 1H, J = 15 Hz), 5.20 (s, 2H), 3.26 (t, 3H, J = 7 Hz), 1.50 (t, 1H, J = 7 Hz); CMR ($CDCl_3$, 75 MHz) 165.8, 146.4, 135.9 , 128.5, 128.2, 121.5, 66.2, 25.6 ppm; exact mass: 208.0556 (calcd for $C_{11}H_{12}O_2S$: 208.0558).

   (**8**): bp 90-100 °C (2 mm Hg); IR (thin film) 2565, 1720, 1658, 1395, 1372 cm^{-1}; PMR ($CDCl_3$, 300 MHz) δ 6.85 (dt, 1H, J = 7, 15 Hz), 5.76 (d, 1H, J = 15 Hz); 3.20 (t, 2H, J = 7 Hz), 1.49 (t, 1H, J = 7 Hz), 1.47 (s, 9H); CMR ($CDCl_3$, 75 MHz) 165.4, 144.5, 123.7, 80.5, 28.1, 25.6 ppm; exact mass: 174.0708 (calcd for $C_8H_{14}O_2S$: 174.0714).

   (**9**): bp 85-95 °C (3 mm Hg); IR (thin film) 2565, 1715, 1655, 1370 cm^{-1}; PMR ($CDCl_3$, 300 MHz) δ 6.85 (t, 1H, J = 7 Hz), 4.11 (q, 2H, J = 7 Hz), 3.27 (t, 2H, J = 7 Hz), 1.88 (s, 3H), 1.51 (t, 1H, J = 7 Hz), 1.30 (t, 3H, J = 7 Hz); CMR ($CDCl_3$, 75 MHz) 167.8, 138.8, 128.3, 60.7, 21.9, 14.2, 12.0 ppm; exact mass: 160.0565 (calcd for $C_7H_{12}O_2S$: 160.0558).

   (**10**): bp 32-35 °C (3 mm Hg); IR (thin film) 2570, 2238, 1638 cm^{-1}; PMR ($CDCl_3$, 60 MHz) δ 6.71 (dt, 1H, J = 7,17 Hz), 5.45 (d, 1H, J = 17 Hz), 3.20 (t, 2H, J = 7 Hz), 1.58 (t, 1H, J = 7 Hz); CMR ($CDCl_3$, 75 MHz) 152.5, 116.8, 100.5, 26.2 ppm; exact mass: 99.0142 (calcd for C_4H_5NS: 99.0143).

   (**13**): mp 115-117 °C; IR ($CHCl_3$) 1686, 1600, 1585, 1420, 755, 690 cm^{-1}; PMR ($CDCl_3$, 60 MHz) δ 7.78 (m, 4H), 7.28 (m, 6H), 3.32 (m, 6H), 2.92 (m, 4H); CMR ($CDCl_3$, 75 MHz) 196.9, 136.6, 133.4, 128.1, 42.8, 34.6, 33.1 ppm; exact mass: 356.0918 (calcd for $C_{20}H_{20}O_2S_2$: 356.0905).

   (**14**): mp 72-75 °C; IR ($CHCl_3$) 1718, 1415, 1365 cm^{-1}; PMR ($CDCl_3$, 300 MHz) δ 3.04 (m, 4H), 2.86 (m, 6H), 2.15 (s, 6H); CMR ($CDCl_3$, 25 MHz, all peaks doubled) 206.7, 35.5, 34.3, 34.2, 33.0, 30.6 ppm; exact mass: 232.0595 (calcd for $C_{10}H_{16}O_2S_2$: 232.0592).

(Received in USA 22 July 1986)