with silver acetate–iodine, see R. C. Cambie, D. M. Gash, P. S. Rutledge, and P. D. Woodgate, *J. Chem. Soc., Perkin Trans. 1*, 1157 (1977). Note also the references cited in this article.
(11) G. M. Rubottom, unpublished results.
(12) For analogous use of fluoride ion, see G. M. Rubottom, J. M. Gruber, and G. M. Mong, *J. Org. Chem.*, **41**, 1673 (1976).
(13) R. H. Reuss and A. Hassner, *J. Org. Chem.*, **39**, 1785 (1974).
(14) (a) L. Blanco, P. Amice, and J. M. Conia, *Synthesis*, 194 (1976); (b) ref 13; (c) J. Strating, S. Reitters, and H. Wynberg, *Synthesis*, 211 (1971).
(15) S. Hunig and G. Wehner, *Synthesis*, 180 (1975).
(16) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
(17) P. L. Stotter and K. A. Hill, *J. Org. Chem.*, **38**, 2576 (1973).

## Synthesis of an 11-Deoxy-8-azaprostaglandin $E_1$ Intermediate

Achille Barco, Simonetta Benetti,* and Gian Piero Pollini

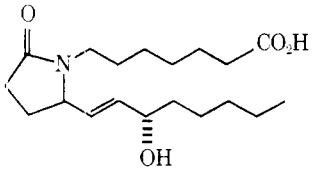
*Istituto Chimico, Ferrara 44100, Italy*

Pier Giovanni Baraldi, Daniele Simoni, and Chiara Beatrice Vicentini

*Istituto di Chimica Farmaceutica, Ferrara 44100, Italy*

*Received November 11, 1978*

In recent years considerable chemical and medicinal interest has been focused on prostaglandin analogues in which carbon atoms are replaced by heteroatoms.[1] Among the azaprostaglandin analogues, which contain one or more nitrogens at almost every position of the cyclopentane nucleus, the 11-deoxy-8-azaprostaglandin $E_1$ (**1**) is of special interest because of the attractive biological activities.



**1**

The synthesis of **1** from pyroglutamic acid via synthon **14** has recently been reported.[2,3] In connection with our recent studies in the field,[4] we report herein two alternative approaches to **14** employing the ω-carbinol lactam **4** and the isoxazole acid **9** respectively as starting materials.

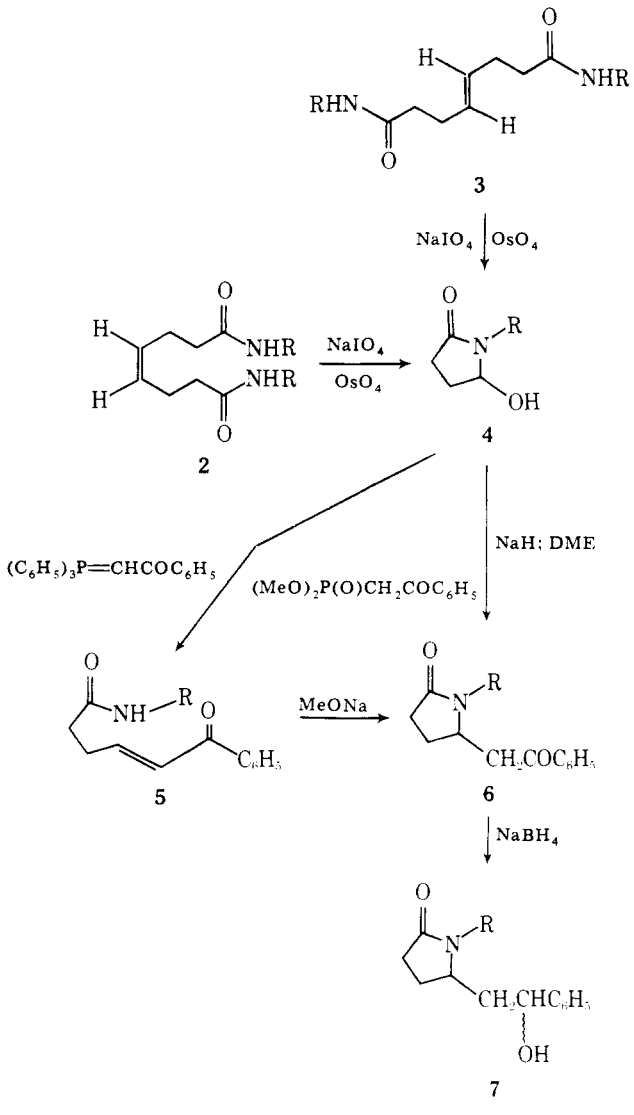
A synthetic approach to **7**, a precursor to the desired aldehyde **14**, could be realized by utilizing the 5-hydroxy-2-pyrrolidinone **4**, as outlined in Scheme I. Reaction of **2** or **3** with $OsO_4$ in the presence of $NaIO_4$[5] gave the hydroxy lactam **4** in 91% yield. Treatment of **4** with the sodium salt of dimethylphenacylphosphonate, by applying the recently developed elegant condensation of ω-carbinol lactams with Horner–Wittig reagents,[6] afforded a 68% yield of the keto lactam **6**. Alternatively, **6** could be obtained in 80% yield by reacting enone **5**, prepared by condensation of **4** with triphenylphenacylidenephosphorane, with NaOMe via an intramolecular Michael addition.

Reduction of **6** with sodium borohydride in methanol at 0 °C gave **7** in 80% yield as an epimeric mixture of alcohols which was converted to **14** without purification as shown in Scheme II.

The second approach to aldehyde **14** deals with a reaction sequence previously used in the synthesis of 14-hydroxy-8-azaprostanoids.[4] The isoxazole ester **8**,[7] prepared in 70% yield by cycloaddition of the nitrile oxide, derived from methyl 4-nitrobutyrate in the presence of phosphorus oxychloride[8] instead of phenyl isocyanate and phenylacetylene, was quantitatively saponified to give the acid **9**.

The vinylogous amide **10**, readily formed by hydrogenolysis

**Scheme I**




**2** **3** **4** **5** **6** **7**

of **9**, underwent ring closure to the known[7] keto lactam **11** by treatment with ethyl chlorocarbonate in tetrahydrofuran at −10 °C. Exclusive N-alkylation of **11** with methyl 7-iodoheptanoate occurred smoothly to give **12** in 87% yield. Transformation of **12** into the alcohol **7** by catalytic hydrogenation at atmospheric pressure is quite critical and profoundly affected by the solvent and the catalyst used.

When the reduction was carried out in dioxane or methanol in the presence of $PtO_2$, **12** was recovered unchanged. However, the use of 10% Pd/C in dioxane afforded **7** in 79% along with minor quantites of over-reduced product. The latter, probably a 2-phenylethyl derivative, is the major product if methanol is substituted for dioxane as the solvent.

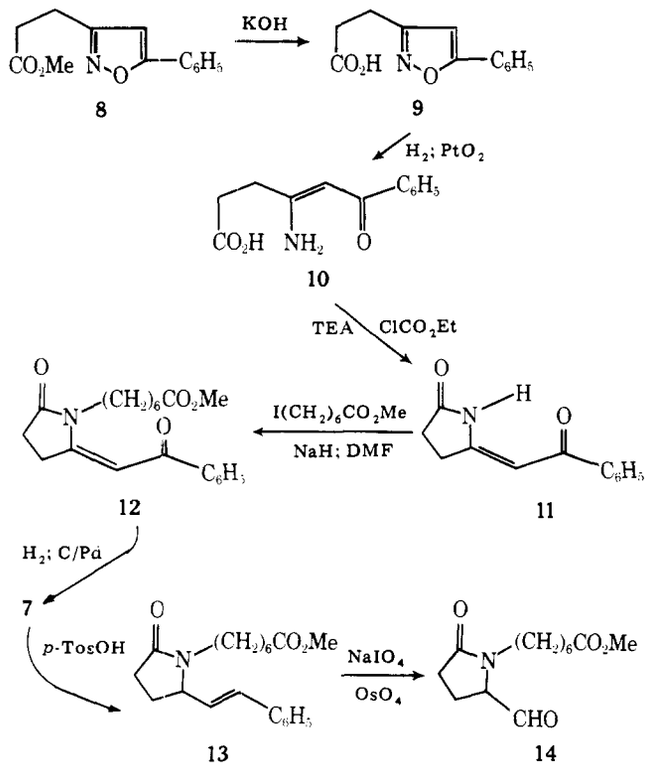
Dehydration of the alcohol **7** to the *trans*-styryl-derivative **13** proceeded without difficulty by heating **7** in toluene containing a trace amount *p*-toluensulfonic acid. When **13** was treated with Lemieux–Johnson reagent[5] in aqueous dioxane, double-bond cleavage occurred smoothly to give the known[2,3] aldehydo ester **14** in better than 70% yield, after chromatography. Since **14** has been transformed to 11-deoxy-8-azaprostaglandin $E_1$,[2,3] these sequences provide a convenient and new entry to **1** and related compounds.

### Experimental Section

Melting points are uncorrected. NMR spectra were recorded on a Hitachi Perkin-Elmer R24A instrument using $Me_4Si$ as an internal

0022-3263/79/1944-1734$01.00/0 

**Scheme II**




standard; IR spectra were run on a IR Perkin-Elmer Model 257. Anhydrous sodium sulfate was used for all drying operations.

**7-Aminoheptanoic Acid Hydrochloride.** This compound was prepared from commercial oenantholactam (Fluka) in almost quantitative yield by a procedure similar to that used in the preparation of the 6-aminocaproic acid.[9] The corresponding methyl ester was obtained as reported.[10]

**Preparation of the Amides 2 and 3.** These compounds were prepared from the corresponding acid[11,12] and methyl 7-aminoheptanoate by standard procedure and have the following characteristics:

**(*Z*)-*N*,*N*′-Bis(6-carbomethoxyhexenyl)-3-hexenedicarboxamide (2)** obtained in 80% yield as a solid: mp 127 °C ($C_2H_5OH$–water 1:1); NMR ($CDCl_3$) δ 1.1–2 (m, 8 H), 2.07–2.53 (m, 6 H), 3–3.43 (m, 2 H), 3.67 (s, 3 H), 5.47 (t, 1 H, $J$ = 2 Hz), and 6.77 (s, br, 1 H); IR ($CHCl_3$) 3450, 1725, 1655, 1520, and 970 $cm^{-1}$. Anal. Calcd for $C_{24}H_{42}N_2O_6$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.49; H, 9.42; N, 6.30.

**(*E*)-*N*,*N*′-Bis(6-carbomethoxyhexenyl)-3-hexenedicarboxamide (3)** obtained in 85% yield as a solid: mp 102 °C ($CHCl_3$–$Et_2O$ 1:1); NMR ($CDCl_3$) δ 1.13–1.9 (m, 8 H), 2.1–2.6 (m, 6 H), 2.97–3.4 (m, 2 H), 3.6 (s, 3 H), 5.4 (t, 1 H, $J$ = 4 Hz), and 6.3 (s, 1 H); IR ($CHCl_3$) 3330, 1720, 1650, 1520, and 750 $cm^{-1}$. Anal. Calcd for $C_{24}H_{42}N_2O_6$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.54; H, 9.20; N, 6.33.

**Methyl 7-(2-Hydroxy-5-oxo-1-pyrrolidinyl)heptanoate (4).** To a stirred solution of the amides **2** or **3** (1.95 g, 4.29 mmol) in dioxane (40 mL) and water (13 mL) was added a small crystal (0.001 g) of $OsO_4$. When the solution turned brownish (ca. 10 min), sodium metaperiodate (2.06 g, 9.2 mmol) was added at 25–26 °C. The reaction mixture was stirred for 3 h at room temperature, the precipitated solid was filtered, and the filtrate was evaporated in vacuo (1 mm Hg). The residue was dissolved in $CHCl_3$ (50 mL), dried, and evaporated in vacuo to leave 1.9 g (91%) of **4**: pale yellow oil; NMR ($CDCl_3$) δ 3.67 (s, 3 H), 5.23 (m, 1 H), and 5.77 (s, br, 1 H); IR ($CHCl_3$) 3300, 1735, and 1680 $cm^{-1}$. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.32; H, 8.65; N, 5.90.

**Methyl 7-[5-Oxo-2-(2-oxo-2-phenylethyl)-1-pyrrolidinyl]-heptanoate (6).** To a suspension of 57% sodium hydride in mineral oil (0.38 g, 8 mmol) and 10 mL of dry DME was added dropwise a solution of dimethyl phenacylphosphonate (1.71 g, 7.5 mmol) in 4 mL of DME under nitrogen. The mixture was stirred for 1 h at room temperature, then cooled to 0 °C, and a solution of **4** (1.8 g, 7.5 mmol) in 5 mL of DME was added. After 3 h at room temperature the reaction mixture was neutralized with glacial acetic acid. The solvent was concentrated in vacuo and the residue chromatographed on $Al_2O_3$. Elution with $Et_2O$ gave pure **6** (1.74 g, 68%) as an oil: NMR ($CDCl_3$) δ 3.6 (s, 3 H), 4.2 (m, 1 H), and 7.3–8.1 (m, 5 H); IR (film) 1735, 1680, and 1660 $cm^{-1}$. Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.76; H, 7.73; N, 3.88.

A mixture of **4** (1.3 g, 5.4 mmol) and triphenylphenacylidenephosphorane (2.04 g, 5.4 mmol) in $CHCl_3$ (20 mL) was stirred at room temperature for 12 h. After concentration in vacuo, the residue was chromatographed on $Al_2O_3$. Elution with $CHCl_3$–$Et_2O$ (1:1) afforded 1.1 g (60%) of **5**: mp 68–69 °C; NMR ($CDCl_3$) δ 3.17 (m, 2 H), 3.63 (s, 3 H), 7.17 (s, br, 1 H), and 8.23 (m, 7 H); IR (Nujol) 3300, 1735, 1670, 1640, 1625, and 1550 $cm^{-1}$. Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.72; H, 7.69; N, 4.18.

Treatment of **5** (1.1 g, 3.18 mmol) in MeOH (20 mL) with sodium methoxide (0.24 g, 4.35 mmol) at room temperature for 1 h, followed by neutralization with glacial acetic acid and evaporation of the solvent, gave a residue, which was chromatographed as above to give **6** (0.88 g, 80%).

**3-(2-Carboxyethyl)-5-phenylisoxaxole (9).** To a well-stirred mixture of phenylacetylene (10.2 g, 100 mmol), methyl 4-nitrobutyrate (14.7 g, 100 mmol), triethylamine (40 mL), and $CHCl_3$ (100 mL) was added dropwise at room temperature $POCl_3$ (17 g, 101.1 mmol) in 20 mL of $CHCl_3$. Stirring was continued overnight and then the mixture was poured into 100 mL of water. The $CHCl_3$ extracts were washed successively with 6 N aqueous hydrochloric acid and saturated brine and dried. The solvent was removed under reduced pressure to afford 16.2 g (70%) of **8**.[7]

The isoxazole **8** (10 g, 43.24 mmol) was refluxed for 3 h in a solution of water (20 mL) and MeOH (20 mL) containing KOH (6.5 g). Most of the solvent was removed in vacuo, 50 mL of water was added, and the resulting mixture was acidified with dilute HCl to give **9** (9.2 g, 98%) as a white solid: mp 159–160 °C (THF–hexane 1:4); NMR ($Me_2SO$-$d_6$) δ 2.5–3.1 (m, 4 H), 6.95 (s, 1 H), 7.5–8 (m, 5 H), and 12.0 (s, br, 1 H); IR ($CHCl_3$) 1690 and 1600 $cm^{-1}$. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.19; H, 4.95; N, 6.63.

**4-Amino-6-oxo-6-phenyl-4-hexenoic Acid (10).** The acid **9** (4 g, 18.4 mmol) in MeOH (20 mL) was reduced over $PtO_2$ at atmospheric pressure and room temperature. Removal of the catalyst and evaporation of the solvent provided **10**: mp 156 °C (*i*-PrOH); NMR (acetone-$d_6$) δ 2.66 (m, 4 H), 5.86 (s, 1 H), 6.56–8.2 (m, 7 H), and 10.16 (s, br, 1 H); IR (Nujol) 3390, 3260, 1720, 1620, and 1590 $cm^{-1}$. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.82; H, 5.79; N, 6.25.

**5-(2-Oxo-2-phenylethylidene)-2-pyrrolidinone (11).** To an ice-cooled solution of **10** (3.94 g, 18 mmol) in anhydrous THF (40 mL) containing triethylamine (2.1 g, 20 mmol), ethyl chlorocarbonate (1.95 g, 18 mmol) in THF (10 mL) was added dropwise and stirring was continued for 2 h at 0 °C. The reaction mixture was allowed to warm at room temperature and stirring was continued for 3 h. The precipitated triethylamine hydrochloride was removed by filtration and the filtrate evaporated in vacuo leaving **11** (3.25 g, 90%), identical with that obtained by Stevens et al.[7]

**Methyl 7-[5-Oxo-2-(2-oxo-2-phenylethylidene)-1-pyrrolidinyl]heptanoate (12).** To a suspension of NaH (57% in mineral oil) (1.07 g, 22.3 mmol) in dry DMF (30 mL) was added dropwise a solution of **11** (4.22 g, 21 mmol) in 15 mL of DMF. The mixture was stirred for 1 h at room temperature. Methyl 7-iodoheptanoate (6 g, 23.25 mmol) was added all at once and the resulting reaction mixture was heated at 50 °C for 24 h. Most of the solvent was removed in vacuo and the residue diluted with 50 mL of water and extracted with $Et_2O$. Concentration of the combined organic extracts yielded 6.27 g (87%) of **12**: mp 60 °C ($Et_2O$–petroleum ether 1:1); NMR ($CDCl_3$) δ 1.1–2 (m, 8 H), 2–2.76 (m, 4 H), 3.2–3.66 (m, 4 H), 3.66 (s, 3 H), 6.33 (m, 1 H), and 7.26–8.1 (m, 5 H); IR ($CHCl_3$) 1725, 1650, 1600, and 1560 $cm^{-1}$. Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.33; N, 4.08. Found: C, 69.73; H, 7.45; N, 4.25.

**Methyl 7-[2-(2-Hydroxy-2-phenylethyl)-5-oxo-1-pyrrolidinyl]heptanoate (7). A. From 6.** A solution of **6** (1.73 g, 5 mmol) in MeOH (10 mL) was cooled to 0 °C with an ice bath. $NaBH_4$ (0.2 g, 5 mmol) was added in small portions over 1 h. The reaction mixture was poured in ice-water and extracted with $Et_2O$. Removal of the solvent left **7** (1.4 g, 80%) as an epimeric mixture, which was used without further purification.

**B. From 12.** A solution of **12** (2 g, 5.83 mmol) in dioxane (25 mL) was shaken with hydrogen at atmospheric pressure and room temperature until the absorption (about 2 mol of $H_2$) ceased. The reaction mixture was filtered through Celite and the filtrate concentrated yielding a residual oil (2 g) which was chromatographed on $Al_2O_3$. Elution with $CHCl_3$–$Et_2O$ 4:1) afforded **7** (1.6 g, 79%): NMR ($CDCl_3$) δ 3.6 (s, 3 H), 3.8 (s, br, 1 H), 4.66 (m, 1 H), and 7.3 (s, 5 H); IR (film) 3360, 1730, and 1660 $cm^{-1}$. Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.13; H,

8.41; N, 4.03. Found: C, 69.01; H, 8.37; N, 4.22.

**Methyl 7-(5-Oxo-2-styryl-1-pyrrolidinyl)heptanoate (13).** A solution of **7** (0.8 g, 2.3 mmol) in 20 mL of toluene containing a trace of *p*-toluensulfonic acid was refluxed for 8 h. The cooled reaction mixture was washed with water (40 mL), dried, and evaporated. The residue was chromatographed on $Al_2O_3$. Elution with ($Et_2O$–$CHCl_3$ 1:1) solution afforded 0.58 g (75%) of **13** as an oil: NMR ($CDCl_3$) $\delta$ 3.63 (s, 3 H), 4.17 (m, 1 H), 6.0 (dd, 1 H, $J$ = 16, 8 Hz), 6.6 (d, 1 H, $J$ = 16 Hz), and 7.34 (s, 5 H); IR (film) 1725, 1670, and 970 $cm^{-1}$. Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.95; H, 8.21; N, 4.25. Found: C, 73.21; H, 8.03; N, 4.42.

**Methyl 7-(2-Formyl-5-oxo-1-pyrrolidinyl)heptanoate (14).** Lemieux–Johnson oxidation of **13** (0.58 g, 1.76 mmol) was carried out as described above for **4**. Chromatography of the crude reaction mixture on silica gel and elution with $Et_2O$ and then with MeOH afforded 0.35 g (77%) of the aldehydo ester **14**. Spectroscopic properties of **14** are in full accord with the reported ones.[2,3]

**Registry No.**—**2**, 69257-84-7; **3**, 69257-85-8; **4**, 69257-86-9; **5**, 69257-87-0; **6**, 69257-88-1; **7** isomer 1, 69257-89-2; **7** isomer 2, 69257-90-5; **8**, 34718-84-8; **9**, 3919-86-6; **10**, 69257-91-6; **11**, 69257-92-7; **12**, 69257-93-8; **13**, 69257-94-9; **14**, 60289-35-2; 7-aminoheptanoic acid hydrochloride, 62643-56-5; (*E*)-4-octenedioic acid, 48059-97-8; (*Z*)-4-octenedioic acid, 38561-68-1; methyl 7-amino heptanoate, 39979-08-3; dimethyl phenacylphosephonate, 1015-28-7; triphenylphenacylidenephosphorane, 859-65-4; phenylacetylene, 536-74-3; methyl 4-nitrobutyrate, 13013-02-0; methyl 7-iodoheptanoate, 38315-25-2.

## References and Notes


(1) D. Orth and H. E. Radunz, *Top. Curr. Chem.*, **72**, 51 (1977).
(2) G. Bolliger and J. M. Muchowski, *Tetrahedron Lett.*, 2931 (1975).
(3) P. A. Zoretic, B. Branchaud, and N. D. Sinha, *J. Org. Chem.*, **42**, 3201 (1977); *Org. Prep. Proced. Int.*, **9**, 159 (1977).
(4) A. Barco, S. Benetti, G. P. Pollini, B. Veronesi, P. G. Baraldi, M. Guarneri, and C. B. Vicentini, *Synth. Commun.*, **8**, 219 (1978).
(5) R. Pappo, D. S Allen, Jr., R. V. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).
(6) J. J. J. de Boer and W. N. Speckamp, *Tetrahedron Lett.*, 4039 (1975).
(7) R. V. Stevens, C. G. Christensen, W. L. Edmonson, M. Kaplan, E. B. Reid, and M. P. Wentland, *J. Am. Chem. Soc.*, **93**, 6629 (1971).
(8) G. B. Bachman and L. E. Strom, *J. Org. Chem.*, **28**, 1150 (1963).
(9) J. C. Eck, "Organic Syntheses", Collect. Vol. II, Wiley, New York, 1943, p 28.
(10) G. Kupryszewski and T Sokolowska, *Acta Biochim. Pol.*, **4**, *85 (1957); Chem. Abstr.*, **53**, 19901i (1953).
(11) A. Barco, S. Benetti, G. P. Pollini, and R. Taddia, *Org. Prep. Proced. Int.*, **6**, 217 (1974).
(12) K. Sisido, K. Sei, and H. Nozaki, *J. Org. Chem.*, **27**, 2681 (1962).


---

# Use of Thionyl Chloride for Sulfurization of Active Methylene Compounds. Dechlorination of α-Chlorosulfenyl Chlorides


Kitaro Oka

*Tokyo College of Pharmacy, Horinouchi 1432-1, Hachioji, Tokyo 192-03, Japan*


*Received November 15, 1978*

During our investigation of the reaction of α-chlorosulfenyl chlorides with various nucleophiles,[1,2] we found that some of the starting materials give thiocarbonyl derivatives under the action of triphenylphosphine. In the literature[3] there was only one example of a preparation of a thioketone from α-chlorosulfenyl chloride by the action of the anion of dipivaloylmethane, and its synthetic scope had not been investigated. Another sequence starting from active methylene compounds has been reported[4,5] in which the base-catalyzed decomposition of Bunte salts in an aqueous system includes some undesirable competitive reactions.[5] In this paper we report the results from our study on the conversion of α-chlorosulfenyl chlorides to the corresponding thioketones by simple treatment with triphenylphosphine.

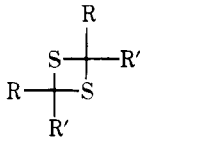
Attempts have been made to explain the highly exothermic reaction of simple sulfenyl chlorides with phosphites or

RR′CClSCl

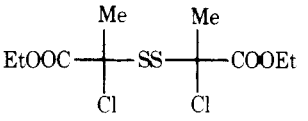
**1a**, R,R′ = COOEt
**b**, R = PhCO; R′ = Ph
**c**, R = Ph; R′ = COCl
**d**, R = Me; R′ = COCl
**e**, R = Ph; R′ = COOEt
**f**, R = Me; R′ = COOEt

RR′C=S

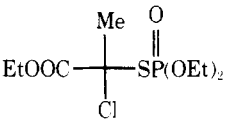
**2a**, R,R′ = COOEt
**b**, R = PhCO; R′ = Ph
**c**, R = Ph; R′ = COOEt



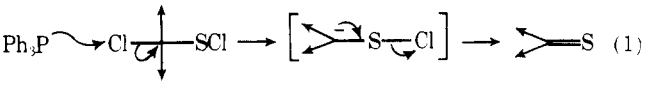
**3a**, R,R′ = COOEt
**b**, R = Ph; R′ = COOEt



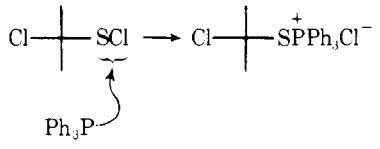
**4**



**5**



(1)



(2)

phosphines using "hard and soft acids and bases theory",[6] but the site of initial attack (S or Cl) has not been determined. In the present case, the problem seems to be more difficult owing to the substitution of another chlorine and strong π-electron acceptor(s) on the central carbon atom. The starting materials **1a** and **1b** were prepared from diethyl malonate and benzyl phenyl ketone, respectively, by treatment with thionyl chloride as described in our previous paper.[2] The sulfenyl chloride **1e** was synthesized from the corresponding acyl chloride **1c**[2,7] under the action of an equimolar amount of sodium ethoxide. This esterification was regiospecific as suggested by HSAB theory.[6] Chlorosulfenyl derivatives of monocarboxylic esters have not been reported so far. Compound **1e** showed two strong carbonyl-stretching bands at 1742 and 1715 $cm^{-1}$, as previously reported with other analogous derivatives of acyl chlorides[7] and ketones.[2] Two single peaks in the $^{13}C$ NMR spectrum at 166.5 and 83.8 ppm representing the carbonyl carbon and sulfur-substituted carbon, respectively, assured the purity of the material. The sulfenyl chloride **1f** was also prepared from the acyl chloride **1d**, which was derived from propionic acid. Since direct chlorosulfenylation of carboxylic esters, except diethyl malonate, failed, these esterifications of acyl chlorides provide a convenient synthetic method.

The sulfenyl chloride **1a** was treated with triphenylphosphine to give 1,3-dithietane **3a** in excellent yield. Intermediacy of the thioketone **2a** in this reaction was expected from the following results. When the sulfenyl chloride **1b** was treated similarly, the initial formation of monothiobenzil (**2b**) was detected by the appearance of 608-nm blue color.[5] Isolation of this material failed because of its facile polymerization to give a slightly green oil as the solvent was removed.[5] The sulfenyl chloride **1e** was also treated with triphenylphosphine to give thiobenzoyl formate **2c**, whose blue color completely disappeared during addition of the reagent. The product was assigned as the 1,3-dithietane **3b**.

We also applied the reaction to the aliphatic acid derivative **1f**. However, the formation of dichloro disulfide **4** occurred predominantly.[8] When triethyl phosphite was used as reagent,

0022-3263/79/1944-1736$01.00/0 