The Conversion of 2-(Methylthio)ethanol into 1-Chloro-2-(methylthio)-ethane: A ^{13}C-Labelling Study with the Aid of ^{13}C Nuclear Magnetic Resonance Spectroscopy

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The synthesis of 2-(methylthio)[1-^{13}C]ethanol from [1-^{13}C]acetic acid is described. This labelled alcohol and ^{13}C n.m.r. spectroscopy were used to evaluate the propensity for rearrangement of four methods for effecting the conversion ROH $\longrightarrow$ RCl[R_3P(R = Ph, Pr^i, or n-C_8H_{17})–CCl_4; CCl_3CN–HCl; MsCl–collidine–LiCl; TsCl–py,-Cl^-]. In every case the product observed at all stages of the reaction was a 1 : 1 mixture of 1-chloro-2-(methylthio)[1-^{13}C]ethane and 1-chloro-2-(methylthio)[2-^{13}C]ethane. It is proposed that activation of the hydroxy-group of 2-(methylthio)[1-^{13}C]ethanol is followed by internal displacement by the methylthio-group giving the 1-methylthiiranium ion, which is captured by chloride.

A SYNTHESIS of '*rac*-[3-^{14}C]methionine' from $^{14}CO_2$ was published in 1974,[1] one step of which was the conversion of 2-(methylthio)[1-^{14}C]ethanol (1a) into '1-chloro-2-(methylthio)[1-^{14}C]ethane' (2a) by trioctylphosphine–CCl_4. An additional product from this reaction could be 1-chloro-2-(methylthio)[2-^{14}C]ethane (3a), produced *via* the 1-methylthiiranium ion (4) as shown in Figure 1. To test this possibility we have synthesised 2-(methylthio)-[1-^{13}C]ethanol (1b) and have examined by ^{13}C n.m.r. spectroscopy its conversion into 1-chloro-2-(methylthio)-[1-^{13}C]ethane (2b) effected by reagents of the type R_3P–CCl_4 (R = phenyl, isopropyl, and octyl). We have found that for each phosphine the product is a 1 : 1 mixture of 1-chloro-2-(methylthio)[1-^{13}C]ethane (2b) and 1-chloro-2-(methylthio)[2-^{13}C]ethane (3b).

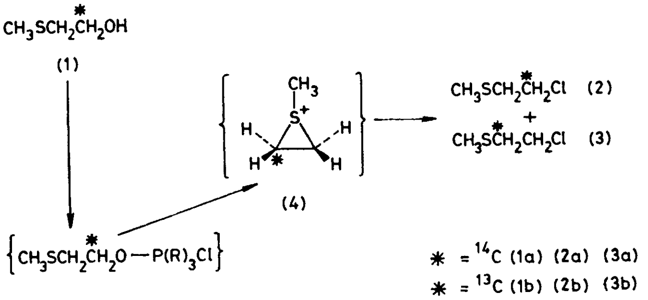

FIGURE 1 The result of the intermediacy of the 1-methylthiiranium ion in the conversion ROH→RCl effected by R_3P–CCl_4

It would be useful to be able to convert an alcohol such as 2-(methylthio)ethanol into the corresponding chloride *without* neighbouring group participation, and so we have examined three other methods which perform the conversion ROH $\longrightarrow$ RCl, purportedly with direct S_N2 displacement. The methods chosen operate under very mild conditions, therefore minimising the possible thermal interconversion of 1-chloro-2-(methylthio)[1-^{13}C]ethane (2b) with its [2-^{13}C]isomer (3b), *via* the 1-methylthiiranium ion. Thiiranium ions are established intermediates in many solvolytic and pyrolytic reactions of compounds of the type $RSCH_2CH_2X$, departure of leaving group X being assisted by sulphur.[2-4] However, with a sufficiently reactive nucleophile under favourable S_N2 conditions direct displacement of halide from β-halogenoalkyl sulphides can be observed (*e.g.* $MeSCH_2CH_2Cl + I^-$ in acetone[5]). The addition of sulphenyl halides to alkenes proceeds *via* thiiranium-like intermediates.[6]

A preliminary communication on part of this work has been published.[7]

Synthesis of 2-(*Methylthio*)[1-^{13}C]*ethanol* (1b).—Using a literature procedure for ^{14}C-labelled material,[8] [1-^{13}C]-acetic acid (90 atom % ^{13}C) was converted into ethyl [1-^{13}C]bromoacetate (90 atom % ^{13}C). This material was diluted to either 11.4 atom % or 20 atom % ^{13}C by the addition of unlabelled ethyl bromoacetate. Reaction of ethyl [1-^{13}C]bromoacetate with lithium methanethiolate (phase-transfer catalysis) gave ethyl [1-^{13}C]-methylthioacetate in good yield. This material was pure by ^1H n.m.r. spectroscopy and was directly reduced by lithium aluminium hydride in ether to 2-(methylthio)-[1-^{13}C]ethanol. An unlabelled sample of 2-(methylthio)-ethanol for comparison was prepared by a different route.[9] The $\{^1H\}^{13}C$ n.m.r. spectrum of 2-(methylthio)-[1-^{13}C]ethanol in $CDCl_3$ shows three singlets at δ 14.2 (CH_3S), 35.6 (SCH_2), and 59.4 (CH_2CH_2OH) p.p.m., the signal from the enriched carbon being enhanced *ca.* 10- or 20-fold above natural abundance, depending on the isotopic content.

Studies of the Reaction between 2-(*Methylthio*)[1-^{13}C]-*ethanol and Carbon Tetrachloride*–R_3P (R = *Phenyl, Isopropyl, or Octyl*) *by* ^{13}C *N.m.r. Spectroscopy*.—During the synthesis of 'rac-[3-^{14}C]methionine',[1] 2-(methylthio)-[1-^{14}C]ethanol was converted into 1-chloro-2-(methylthio)ethane by trioctylphosphine–CCl_4 (12 h at room temperature). This reaction is probably complete in a much shorter time,[10] and so experiments in which reactions between alcohol (1b) and R_3P–CCl_4 were followed by ^{13}C n.m.r. spectroscopy were set up at low temperatures (−78 to −10 °C). If the product chloride were observed to be a mixture of C-1 and -2 labelled materials [(2b) + (3b)] this could be explained either as the result of the intermediacy of the 1-methylthiiranium ion (*cf.* Figure 1) or as the result of thermal rearrangement (again *via* the 1-methylthiiranium ion) of C-1 labelled product (2b) to its C-2 labelled isomer (3b). Recording the ^{13}C n.m.r. spectrum of 1-chloro-2-(methylthio)ethane as it is formed might enable these possibilities to be distinguished unless the rate of thermal rearrangement of (2b) to (3b) greatly exceeds its rate of formation from (1b).

The reaction between alcohol (1b) and tri-isopropyl- or trioctyl-phosphine–CCl_4 was much faster than its reaction with triphenylphosphine–CCl_4. For triphenylphosphine the reaction was followed by recording ^{13}C n.m.r. spectra at intervals, over a long period at room temperature. The initial spectrum consisted of a dominant peak at δ 59.4 p.p.m. from the labelled carbon of (1b). Subsequent spectra show the disappearance of this peak, and the appearance of two new peaks at δ 42.2 and 35.4 p.p.m., corresponding to the CH_2 groups of $MeSCH_2CH_2Cl$ (comparison with the spectrum of an unenriched sample [5]). The equal intensity of these two peaks [corresponding to the enriched methylene carbons in (2b) and (3b), respectively] throughout the reaction is consistent with the intermediacy of the 1-methylthiiranium ion in the formation of (2b)/(3b), rather than formation of C-1 labelled material (2b), followed by redistribution of label. The capture of the ^{13}C thiiranium ion by chloride may exhibit a small primary isotope effect favouring formation of (3b). The accuracy of the present analysis is not sufficient to measure this effect.

Owing to the sensitivity of the trialkylphosphines to atmospheric oxygen, all manipulations with them were carried out under an atmosphere of dry nitrogen. The reaction between tri-isopropylphosphine–CCl_4 and alcohol (1b) was violently exothermic at −5 °C and produced a 1 : 1 mixture of (2b) and (3b) by ^{13}C n.m.r. analysis. After mixing the reactants at −78 °C, and allowing the heterogeneous system obtained to become homogeneous by slowly warming up to −10 °C, a ^{13}C n.m.r. spectrum was recorded which showed a large peak at δ 59.4 p.p.m. from the enriched carbon in (1b), and a smaller doublet at δ 68 p.p.m. ($^2J_{PC}$ 9 Hz). Warming the solution to 30 °C and recording spectra at intervals resulted in the disappearance of the doublet at δ 68 p.p.m., and the slower disappearance of the singlet at δ 59.4 p.p.m., concomitant with the appearance of two new peaks at δ 42.2 and 35.5 p.p.m. (*cf.* Figure 2) corresponding to the enriched carbon atoms in (2b) and (3b), respectively. A similar experiment was performed with trioctylphosphine and gave an analogous result (*n.b.* appearance and disappearance of doublet, *J* 7 Hz, at δ 68 p.p.m.).

The doublets at δ 68 p.p.m. initially observed in the spectra could arise from the $^{13}CH_2$ grouping of a phosphorylated intermediate $R_3{}^+PO^{13}CH_2CH_2SMeCl^-$. The chemical shift and coupling constants are consistent with this assignment.[11] The intermediate $Me_3CCH_2OPPh_3Cl$ has been isolated from the reaction between neopentyl alcohol and $Ph_3P–CCl_4$ [12] (see below). The equal intensities of the two peaks from the enriched carbons in (2b) and (3b) throughout the reaction is consistent with the involvement of the 1-methylthiiranium ion in the conversion of alcohol (1b) into chlorides (2b)–(3b) by $R_3P–CCl_4$ reagents, leading to a *ca.* 1 : 1 mixture of 1-chloro-2-(methylthio)[1-^{13}C]ethane and 1-chloro-2-(methylthio)[2-^{13}C]ethane. This implies that the material designated ' *rac*-[3-^{14}C]methionine ',[1] obtained from ' 1-chloro-2-(methylthio)[1-^{14}C]ethane ' was actually a *ca.* 1 : 1 mixture of *rac*-[3-^{14}C]methionine and *rac*-[4-^{14}C]-methionine, obtained from a mixture of 1-chloro-2-(methylthio)[1-^{14}C]ethane (2a) and 1-chloro-2-(methylthio)[2-^{14}C]ethane (3a).

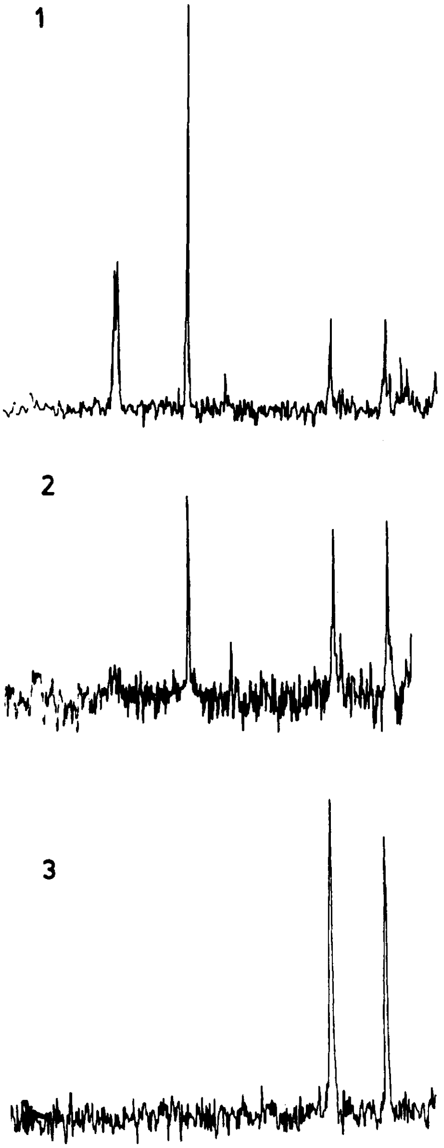

FIGURE 2 ^{13}C N.m.r. spectra recorded during the reaction of 2-(methylthio)[1-^{13}C]ethanol with $R_3P–CCl_4$ (R = isopropyl). Each spectrum was obtained from 200 scans (taking *ca.* 2 min 15 s to accumulate). Spectral accumulations began at the following times: 1, immediately the reaction became homogeneous at −10 °C, time = zero; 2, after 15 min at 30 °C; 3, after 17 h at 30 °C. The total width of each plot is *ca.* 50 p.p.m.

To confirm this, alcohol (1b) was converted into chlorides (2b)—(3b) which were subsequently condensed with the sodium salt of diethyl acetamidomalonate, both reactions being conducted under conditions similar to those of ref. 1. The ^{13}C n.m.r. spectrum of the ethyl 2-acetamido-2-ethoxycarbonyl-4-(methylthio)butanoate (5) thus obtained showed it to be a *ca.* 1 : 1 mixture of materials labelled at either C-3 or -4. Thus, *rac*-methionine obtained by the hydrolysis of this substance would be a *ca.* 1 : 1 mixture of [3-^{14}C]- and [4-^{13}C]-methionine.

The material designated as '*rac*-[3-^{14}C]methionine'[1] has since been re-examined by mass spectroscopy, and confirmed to be a 1 : 1 mixture of [3-^{14}C]- and [4-^{14}C]-methionine.[13]

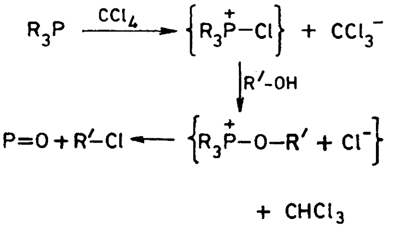

FIGURE 3 The overall mechanism of the conversion of ROH into RCl by R_3P–CCl_4

The Mechanism of the Reaction between Alcohols and Reagents of the Type R_3P–CCl_4.—The conversion of alcohols into alkyl chlorides by R_3P–CCl_4 was first reported in 1966[14] (R = phenyl) and was subsequently shown to proceed with inversion (for octan-2-ol; R = octyl).[10] The reaction is generally accepted[12,15] to proceed *via* a phosphorylated intermediate which collapses to phosphine oxide and alkyl chloride (Figure 3). There is some evidence[16] that compounds of the type $[R_3PCHCl_2]^+Cl^-$ and $[R_3PCH_2Cl]^+Cl^-$ rather than $CHCl_3$ are the end-products of this reaction, besides $R_3P{=}O$ and R′Cl. Detailed studies of the reaction R_3P–CCl_4 + R′OH ⟶ R′-Cl[17] showed, as well as a remarkable tendency for inversion, even in systems prone to rearrangement, that the reaction exhibited some characteristics distinctly different from normal S_N2 reactions. For example, the reaction of neopentyl alcohol with R_3P–CCl_4 results in a greater degree of inversion than the displacement of tosylate from neopentyl alcohol toluene-*p*-sulphonate by chloride. It was also observed that a large excess of external nucleophile (CN^-) is unable to compete with Cl^- for the phosphonium intermediate (R_3P^+-OR′) (*e.g.* in the reaction between 2-phenylethanol and R_3P–CCl_4), in contrast to the observation that this nucleophile is much more reactive than Cl^- in the displacement of OTs^- from the corresponding tosylate. One mechanism proposed to account for these observations[17b] involves the collapse of the phosphorylated intermediate *via* a tight ion pair. In this so-called four-centre mechanism, P–Cl bond cleavage precedes O–R′ bond cleavage, giving a tight ion pair, which collapses in an S_N2 manner.

Aneja *et al.*[18] observed that treatment of 1,3-distearoylglycerol with Ph_3P–CCl_4 gave 2-chlorodeoxy-1,3-distearoylglycerol, in contrast to the reaction between the tosyl ester of 1-palmitoyl-3-stearoylglycerol and lithium chloride, which yielded primarily rearranged products (*via* a dioxolenium ion). They interpreted the lack of neighbouring group participation in the case of Ph_3P–CCl_4 to indicate a concerted $[\sigma_{2s} + \sigma_{2a}]$ process for the breakdown of the phosphorylated intermediate, without prior fission of the P–Cl bond.

However, the lack of neighbouring group participation may reflect the degree of cleavage of the O–R′ bond, rather than that of the P–Cl bond.[7] Our results, indicating neighbouring group participation in the reaction between 2-(methylthio)ethanol and R_3P–CCl_4 leading to the 1-methylthiiranium ion, require that fission of the O–C bond precedes attack of Cl^- on carbon. This excludes a concerted mechanism in this case.

Jones *et al.*[12] compared the rates of formation and decomposition of phosphorylated intermediates from reactions of primary, secondary, and neopentyl alcohols with Ph_3P–CCl_4. They observed the order of reactivity primary > secondary > neopentyl for both the rates of formation and decomposition of these intermediates. For neopentyl the intermediate was isolated, and its structure was elucidated as $Me_3CCH_2OPPh_3Cl$ by ^1H n.m.r. spectroscopy aided by ^{31}P decoupling experiments. For primary alcohols the rate of decomposition of the phosphorylated intermediate was found to be greater that its rate of formation. It was concluded that the mechanism of the conversion of alcohols into chlorides by R_3P–CCl_4, in best accord with available results, is an S_N2-type intramolecular displacement from a tight ion pair, as previously suggested.[17b]

In contrast, Cristol *et al.*[19] have shown that in the reaction of certain allylic alcohols with Ph_3P–CCl_4, products of rearrangement can arise. Reactions of a number of benzobicyclo-octadienyl and benzobicyclononatrienyl alcohols with Ph_3P–CCl_4 were shown to give products resulting from competing processes: direct displacement reactions, Wagner–Meerwein rearrangements, and allylic rearrangements (*i.e.* competing S_N1, S_N2, and other mechanisms). The reaction between 2-(methylthio)ethanol and R_3P–CCl_4 represents one extreme of the reaction spectrum proposed by Cristol *et al.*[19] The presence of a β-sulphur atom provides favourable neighbouring group participation leading to the 1-methylthiiranium ion. It is concluded that mechanisms of reactions between alcohols and R_3P–CCl_4 range from almost pure S_N2, through a situation where competing S_N1, S_N2, and other mechanisms co-exist, to an almost pure S_N1-type mechanism, depending on the structure of the substrate alcohol.

Studies of Other Reagents which Effect the Conversion ROH ⟶ RCl, *using* 2-(*Methylthio*)[1-^{13}C]*ethanol and* ^{13}C *N.m.r. Spectroscopy*.—(i) *Alkyl chlorides from the decomposition of imidate hydrohalides.* An alcohol (ROH) and a nitrile (R′CN) may be condensed in the presence of a hydrogen halide (HX) to give an imidate hydrohalide [R′C(=NH_2X)OR], often isolated as a crystalline solid.[20] On pyrolysis such salts yield the corresponding alkyl halide (RCl) and amide (R'CONH$_2$). If trichloroacetonitrile and an alcohol are condensed in the presence of anhydrous hydrogen chloride, the imidate hydrohalide produced decomposes rapidly at room temperature[21] to trichloroacetamide, and the corresponding alkyl chloride. This reaction has been used[22] to produce 6-halogeno-6-deoxysugars from the corresponding protected sugars in good yield, under mild conditions.

The mechanism of decomposition of solid imidate hydrohalides on pyrolysis is considered to be S_N2,[20] and so is that of the thermal decomposition of imidate hydrohalides in solution.[23] The former reaction has been shown to proceed with inversion in the case of the imidate hydrohalide derived from optically active butan-2-ol.[24] In studies on the decomposition of the imidate hydrohalides obtained from trichloroacetamide and alcohols, a mechanism involving formation of a tight ion pair, followed by collapse to products in an S_N2 manner, has been proposed.[21]

2-(Methylthio)[1-^{13}C]ethanol (1b), trichloroacetonitrile, and anhydrous hydrogen chloride were mixed in chloroform at −20 °C, and a ^{13}C n.m.r. spectrum recorded at once. This showed a predominant peak at δ 59.9 p.p.m., from (1b), and no change was observed over 45 min at 0 °C. At 25 °C the reaction proceeded slowly, with the disappearance of the peak at δ 59.9 p.p.m., and the appearance of two new peaks at δ 42.9 and 36.5 p.p.m. These peaks were of equal intensity at all stages of the reaction, and correspond to the enriched carbons in (2b) and (3b). These observations are consistent with the 1-methylthiiranium ion being an intermediate in the formation of chlorides (2b)—(3b) by the decomposition of 2-(methylthio)ethyl trichloromethylimidate. It is to be expected therefore that this reaction, previously held to be an exclusive S_N2 process, will exhibit a spectrum of mechanisms, as does the conversion of ROH into RCl by R$_3$P–CCl$_4$ reagents.[19]

(ii) *Conversion of* 2-(*methylthio*)*ethanol into* 1-*chloro*-2-(*methylthio*)*ethane by displacement of methanesulphonate and toluene*-p-*sulphonate*. The allylic alcohol 3-propylhex-2-en-1-ol has been reported to be converted (methanesulphonyl chloride–collidine–lithium chloride–DMF, 0 °C, 1.5 h) into the corresponding allylic chloride, without rearrangement.[25] We therefore studied the reaction between alcohol (1b) and methanesulphonyl chloride in DMF containing lithium chloride (1.1 mol. equiv.) and collidine. This produced 2-(methylthio)[1-^{13}C]ethyl mesylate at 0 °C. ^{13}C N.m.r. spectra recorded during this reaction showed the disappearance of the peak from labelled alcohol at δ 61.5 p.p.m., and the appearance of a single new peak at δ 70.8 p.p.m., from the enriched carbon atom of 2-(methylthio)[1-^{13}C]ethyl mesylate. Under these conditions, no conversion of 2-(methylthio)ethyl mesylate into chlorides (2b)—(3b) was observed.

Addition of a further 1.1 mol. equiv. of lithium chloride, and warming to 20 °C, resulted in the gradual conversion of the 2-(methylthio)[1-^{13}C]ethyl mesylate into a mixture of (2b) and (3b). ^{13}C N.m.r. spectra recorded during this reaction show the disappearance of the peak at δ 70.8 p.p.m., and the appearance of a single new peak at δ 43.5 p.p.m. (*ca.* half the intensity of that at δ 70.8 p.p.m.), corresponding to the enriched methylene carbon in (2b). After addition of benzene to the solution, the ^{13}C n.m.r. spectrum revealed a second peak, at δ 35.9 p.p.m., corresponding to the enriched carbon atom of (3b) which had previously been obscured by solvent peaks. Repeating the reaction in the presence of 3 mol. equiv. of lithium chloride at 10 °C gave an analogous result, *i.e.* quantitive formation of a single labelled mesylate occurs at 10 °C. Formation of chlorides (2b)—(3b) occurs on warming to 20 °C. The final product of this reaction was again a mixture of (2b) and (3b) as shown by ^{13}C n.m.r. spectra recorded after dilution with benzene.

The reaction between alcohol (1b) and toluene-*p*-sulphonyl chloride in pyridine at −20 °C produces 2-(methylthio)[1-^{13}C]ethyl tosylate in under 3 h. ^{13}C N.m.r. spectra recorded during the reaction show the disappearance of the peak from enriched alcohol at δ 60.1 p.p.m., and the appearance of a single new peak at δ 68.7 p.p.m., corresponding to the enriched carbon atom of 2-(methylthio)[1-^{13}C]ethyl tosylate. Over 72 h at −20 °C two additional peaks appear in the spectrum (accounting for *ca.* 10% of the overall intensity) at δ 43.2 and 36.3 p.p.m. These correspond to the enriched methylene carbons of (2b) and (3b) respectively, and are of about equal intensity. No peak from 2-(methylthio)-[2-^{13}C]ethyl tosylate was observed. These results are consistent with the formation of chlorides (2b)—(3b) from 2-(methylthio)[1-^{13}C]ethyl tosylate and pyridinium hydrochloride occurring *via* the 1-methylthiiranium ion. Addition of lithium chloride (2 mol. equiv.) to the above solution, and warming to 20 °C, resulted in conversion of more 2-(methylthio)[1-^{13}C]ethyl tosylate into (2b) and (3b) and some decomposition to other unidentified products. ^{13}C N.m.r. spectra recorded during the reaction show the peak at δ 68.7 p.p.m. decreasing in intensity, and the two peaks at δ 43.2 and 36.3 p.p.m. increasing in intensity, as well as the appearance of other peaks. The equal intensity of the two peaks due to chlorides (2b)–(3b) at all stages of this reaction is again consistent with the intermediacy of the 1-methylthiiranium ion.

It is concluded that none of the reagents investigated is suitable for the conversion of alcohol (1b) into chloride (2b) *without* neighbouring group participation.

At the beginning of this paper we referred to the possible thermal interconversion of (2b) and (3b) *via* (4). Our inability to prepare pure (2b) obviously does not allow the rate of this process to be compared with rates of conversions of (1b) into (2b)—(3b). However, the observations of the mesylate and tosylate of (1b) and their conversions into (2b)—(3b) without concomitant equilibration with the mesylate or tosylate of 2-(methylthio)[2-^{13}C]ethanol suggests that thermal equilibration of (2b) and (3b) is also slow relative to their formations under the reaction conditions described here.

EXPERIMENTAL

CAUTION: 1-chloro-2-(methylthio)ethane has vesicant properties (*cf.* ref. 5).

General.—Solvents were either AnalaR grade or redistilled laboratory reagent; solutions in organic solvents were dried with anhydrous magnesium sulphate; solvents were removed at *ca.* 20 °C with a rotary evaporator; glassware was dried by storing at 110 °C overnight and cooling under dry nitrogen; commercial triphenylphosphine was used without purification; commercial tri-isopropylphosphine was distilled under dry nitrogen just before use, to provide a material showing no ν(P=O) in its i.r. spectrum.

^{13}C N.m.r. spectra were recorded with a Bruker WH90 spectrometer at 22.63 MHz, equipped with a variable-temperature accessory. All spectra were run with decoupling from proton nuclei.

Ethyl [1-^{13}C]*Bromoacetate* (90 *atom* % ^{13}C).—Bromine (7.5 cm^3, 23.4 g, 0.146 mol) was added dropwise with stirring to an ice-cold suspension of purified red phosphorus (0.335 g, 0.0114 mol) in [1-^{13}C]acetic acid (2 g, 0.033 mol; 90 atom % ^{13}C). The mixture was boiled under reflux for 5 h, with the exclusion of atmospheric moisture, and then cooled to 0 °C. Anhydrous ethanol (6 cm^3, 4.68 g, 0.1 mol) was added, and the mixture was warmed to 20 °C over 20 min. After dilution with water (20 cm^3) the solution was extracted with ether (3 × 40 cm^3). The combined organic extracts (containing ethyl [1-^{13}C]bromoacetate, Br_2, and HBr) were quickly washed with small portions of saturated aqueous sodium carbonate (total 150 cm^3) until the washings were just alkaline, 5% aqueous sodium thiosulphate, until the organic phase was just colourless, and finally with 50% aqueous potassium bromide. Drying and evaporation under reduced pressure gave ethyl [1-^{13}C]bromoacetate (5.1 g, 92%; 90 atom % ^{13}C), as a liquid, δ_H 1.3 (3 H, t), 3.8 [2 H, d, *J* (^{13}C-^{1}H) 6 Hz], and 4.18 [2 H, 2 × q, *J* (^{13}C-^{1}H) 4 Hz] p.p.m. This material was diluted to either 11.4 atom % or 20 atom % by addition of unlabelled ethyl bromoacetate.

Ethyl [1-^{13}C]*Methylthioacetate* (20 *atom* % ^{13}C).—To an ice-cold solution of lithium methylthiolate (10.8 g, 0.2 mol) * in water (100 cm^3) was added a solution of ethyl [1-^{13}C]bromoacetate (22.6 g, 0.134 mol; 20 atom % ^{13}C) and benzyltri-n-butylammonium bromide (1.28 g, 0.0041 mol; 3 mol %) in dichloromethane (125 cm^3). The mixture was vigorously stirred at room temperature for 2 h, when analysis of the organic layer by ^{1}H n.m.r. showed no residual Br*C*H_2 at δ 3.8 p.p.m. The layers were separated, and the aqueous phase extracted with dichloromethane (2 × 25 cm^3). The combined organic phases were dried, and evaporated at reduced pressure, the bulk of the solvent (*ca.* 80%) being removed at 25 mmHg and 25 °C. The remaining solvent was distilled off at atmospheric pressure to avoid loss of volatile product. The residue (15.81 g) contained phase transfer catalyst (1.28 g), which was removed by dissolving the product in ether and filtering off the insoluble catalyst. Evaporation of the filtrate gave ethyl [1-^{13}C]methylthioacetate (14.53 g, 81%; 20 atom % ^{13}C), δ_H 1.3 (3 H, t), 2.2 (3 H, s), 3.2 (2 H, s), and 4.2 (2 H, q). ^{13}C Satellites arising from signals at δ 3.2 and 2.2 (each *ca.* 10% intensity of main peak), *J*(^{13}C-^{1}H) 8 and 54 Hz, respectively, were present. This material was used directly in the next preparation.

2-(*Methylthio*)[1-^{13}C]*ethanol* (20 atom % ^{13}C).—Lithium aluminium hydride (3.3 g, 0.086 mol) was added to anhydrous ether (100 cm^3) and the suspension was boiled under reflux for 1.5 h, under dry nitrogen. A solution of ethyl [1-^{13}C]methylthioacetate (14.5 g, 0.108 mol; 20 atom % ^{13}C) in anhydrous ether (50 cm^3) was added dropwise over 20 min, and the mixture was boiled under reflux for a further 20 h. The excess of lithium aluminium hydride was destroyed by the *careful* addition of water (3.3 cm^3) followed by 15% aqueous sodium hydroxide (3.3 cm^3) and finally a further portion of water (10 cm^3). The precipitated solids were filtered off under suction, and washed well with ether (4 × 20 cm^3). The combined organic filtrates were dried and evaporated under reduced pressure, to provide a pale yellow oil. Fractional distillation gave 2-(methylthio)[1-^{13}C]ethanol (20 atom % ^{13}C) as a liquid (7.47 g, 75%), b.p. 70—71 °C at 20 mmHg, pure by g.l.c. (20% D.E.G.S., 150 °C, N_2 at 20 cm^3 min^{-1}) (R_t identical to that of authentic material produced by another route [9]), δ_H 2.12 (3 H, s), 2.7 (2 H, t), 3.12 (1 H, s), and 3.74 (2 H, t). ^{13}C satellites arising from the signal at δ 3.74 (each *ca.* 10% of the main peak), *J*(^{13}C-^{1}H) 144.5 Hz, were present. δ_C ([$^2H_6$]C_6H_6; Me_4Si) 14.2 (–SCH_3), 35.6 (S–CH_2), and 59.4 (CH_2*C*H_2OH) p.p.m. The signal at δ 59.4 p.p.m. corresponding to the enriched carbon was *ca.* 20-fold enhanced over natural abundance.

Trioctylphosphine.[26]—1-Bromo-octane (20 g, 18 cm^3, 0.104 mol) in anhydrous ether (25 cm^3) was added to magnesium turnings (2.58 g, 0.106 mol) and iodine (*ca.* 5 mg), under dry nitrogen, at a rate sufficient to maintain vigorous reaction. After boiling the solution under reflux for 15 min, and cooling to −5 °C, phosphorus trichloride (4.72 g, 3 cm^3, 0.034 mol) in anhydrous ether (10 cm^3) was added to the stirred solution over 30 min. Stirring was continued for a further 20 min and the mixture subsequently allowed to warm up to room temperature. After boiling under reflux for 96 h, and cooling to room temperature, water (15 cm^3) was added, followed by hydrochloric acid (24 cm^3 of a 2 mol dm^{-3} solution) and aqueous ammonia (29 cm^3 of a 2 mol dm^{-3} solution). The organic phase was separated, filtered through glass wool, and evaporated under reduced pressure to give a yellow oil (11.6 g, 90%). Kugelröhr distillation (210 °C, 0.1 mmHg) gave trioctylphosphine as a liquid, pure by i.r. spectroscopy (film), 2 900s, 1 650m, 1 460s, 1 370m, and 710m cm^{-1}. *N.b.* absence of P=O stretch at 1 138 cm^{-1}. Exposure of an i.r. film to the atmosphere gave rise to a broad band centred at 1 138 cm^{-1}.

^{13}C *N.m.r. Study of the Reaction between* R_3P†–CCl_4 (*where* R = *Phenyl, Isopropyl, or Octyl*) *and* 2-(*Methylthio*)-[1-^{13}C]*ethanol* (1b).—(a) A solution of redistilled tri-isopropylphosphine (0.83 g, 5.2 mmol) in [$^2H_6$]benzene (0.5 cm^3) in a 10 mm diameter n.m.r. tube was degassed by argon bubbling, and frozen by cooling to −78 °C. A degassed solution of 2-(methylthio)[1-^{13}C]ethanol (0.2 g, 2.2 mmol; 11.4 atom % ^{13}C) in CCl_4 (0.8 g, 5.2 mmol) was added, and the mixture maintained at −78 °C. The above operations were carried out in a dry-box under nitrogen. The capped n.m.r. tube was transferred to the pre-cooled (−10 °C) probe of the ^{13}C n.m.r. spectrometer. When the contents of the tube became a homogeneous solution (*ca.* 3 min), a spectrum was recorded at once (200

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* Prepared from lithium hydroxide monohydrate (8.4 g, 0.2 mol) and methanethiol (9.6 g, 0.2 mol).

† Both trioctyl- and tri-isopropyl-phosphine are subject to rapid atmospheric oxidation. All manipulations with these materials were carried out under a blanket of dry nitrogen, or in a dry-box under nitrogen.

scans, *ca.* 2 min 15 s). The mixture was then warmed to 30 °C and spectra recorded at intervals (each 200 scans, taking 2 min 15 s to accumulate) and the results are depicted in Figure 2 and discussed in the text. When no further reaction was evident, the sample was allowed to stand at room temperature for 17 h, and a t_∞ spectrum was recorded.

(b) The above experiment was repeated, using trioctylphosphine in place of tri-isopropylphosphine. After mixing at -78 °C the reactants were warmed to -13 °C and an initial ^{13}C n.m.r. spectrum recorded. The mixture was then warmed to 17 °C and spectra recorded at intervals. The results are discussed in the text, and were analogous to those of the tri-isopropylphosphine reaction.

(c) To a solution of 2-(methylthio)[1-^{13}C]ethanol (11.4 atom % ^{13}C; 0.2 g, 2.2 mmol) in [^{2}H$_6$]benzene (0.5 cm^3) was added a solution of triphenylphosphine (1.37 g, 5.2 mmol) in CCl$_4$ (2.4 g, 15.6 mmol). The mixture was incubated at room temperature in a 10 mm diameter n.m.r. tube and ^{13}C spectra recorded at intervals, over 7 days. The results are discussed in the text.

Conversion of 2-(*Methylthio*)[1-^{13}C]*ethanol into Ethyl* 2-*Acetamido*-2-*ethoxycarbonyl*-4-(*methylthio*)*butanoate* (*by the Method of Ref.* 1).—To stirred 2-(methylthio)[1-^{13}C]ethanol (0.146 g, 1.58 mmol; 11.4 atom % ^{13}C), at 0 °C, a solution of trioctylphosphine (1.18 g, 3.19 mmol) in CCl$_4$ (0.488 g, 0.3 cm^3, 3.19 mmol) was added, over 2 min, under nitrogen. The reaction vessel was sealed, and the mixture stirred for 5 min at 0 °C, and then overnight at room temperature. Dimethylformamide (3 cm^3) was added, and the mixture distilled at 20 mmHg to give an oil (*ca.* 3 cm^3), b.p. 58—60 °C at 20 mmHg. This solution of 1-chloro-2-(methylthio)ethane (*ca.* 1.58 mmol) in dimethylformamide (*ca.* 3 cm^3) was added to a solution of the sodium salt of diethyl acetamidomalonate (0.762 g, 3.19 mmol) in anhydrous ethanol (3.8 cm^3), and the mixture was stirred for 20 h at 55 °C, with the exclusion of atmospheric moisture. The solution was filtered, the solid residue was washed with ethanol (2 × 5 cm^3), and the combined filtrates evaporated under reduced pressure to provide an orange oil. This was dissolved in dichloromethane, filtered through Celite, and evaporated under reduced pressure. Dimethylformamide was distilled off at 80 °C and 1 mmHg and the residue was purified by column chromatography on silica gel (80—200 mesh; 40 g), using dichloromethane–methanol (97 : 3) as eluant. Evaporation of fractions gave a product which was *ca.* 1 : 1 diethyl acetamidomalonate (A) and ethyl 2-acetamido-2-ethoxycarbonyl-4-(methylthio)-butanoate (B) by ^{13}C n.m.r. spectroscopy, δ_C 14.0 [CH_3–CH$_2$, (A) and (B)], 15.4 [CH_3S, (B)], 22.7 [CH_3CO, (A) and (B)], 28.4 [SCH_2CH$_2$, (B)], 31.9 [SCH$_2$$CH_2$, (B)], 56.6 [CH$_2$–*C*–N, (A) and (B)], 62.2 [CH_2–O, (A) and (B)], 167.4 [COO, (A) and (B)], and 170 [CONH, (A) and (B)] p.p.m. Each of the peaks corresponding to the methylene carbons of the MeSCH$_2$CH$_2$C grouping were enhanced about fivefold over natural abundance compared to the ^{13}C n.m.r. spectrum of a 1 : 1 mixture of unenriched (B) with (A).

^{13}C *N.m.r. Study of the Reaction between* 2-(*Methylthio*)-[1-^{13}C]*ethanol and Trichloroacetonitrile*–HCl.—Trichloroacetonitrile (0.17 g, 117 µl, 1.18 mmol) was added to a solution of 2-(methylthio)[1-^{13}C]ethanol (0.1 g, 1.09 mmol; 20 atom % ^{13}C) in dry deuteriochloroform (2 cm^3) at -20 °C (in a 10 mm diameter n.m.r. tube), and the resulting solution was saturated with dry HCl at -20 °C. These operations were carried out under dry nitrogen. The capped n.m.r. tube was then transferred to the pre-cooled (-10 °C) probe of the ^{13}C n.m.r. spectrometer. The solution was allowed to warm to 25 °C, and ^{13}C n.m.r. spectra were recorded at intervals. The results are discussed in the text.

The Conversion of the Mesyl and Tosyl Esters of 2-(*Methylthio*)[1-^{13}C]*ethanol into* 1-*Chloro*-2-(*methylthio*)*ethane*; *a* ^{13}C *N.m.r. Study*.—(i) *Toluene*-p-*sulphonyl ester*. To a solution of 2-(methylthio)[1-^{13}C]ethanol (0.1 g, 1.09 mmol; 20 atom % ^{13}C) in [^{2}H$_5$]pyridine (0.5 cm^3), contained in a 10 mm diameter n.m.r. tube and cooled to -20 °C, was added a solution of purified toluene-*p*-sulphonyl chloride (0.22 g, 1.16 mmol) in dry pyridine (0.5 cm^3). This was performed under dry nitrogen. The capped n.m.r. tube was transferred to the pre-cooled (-20 °C) probe of the ^{13}C n.m.r. spectrometer, and a spectrum recorded at once. Spectra were recorded at intervals, over 72 h, and the results are discussed in the text. Lithium chloride (0.09 g, 2.11 mmol) was added, and the mixture warmed to 20 °C to obtain a homogeneous solution. ^{13}C N.m.r. spectra were recorded at intervals and the results are discussed in the text.

(ii) *Methanesulphonyl ester* (cf. *ref.* 25). To a solution of 2-(methylthio)[1-^{13}C]ethanol (0.1 g, 1.09 mmol; 20 atom %), lithium chloride (0.05 g, 1.18 mmol), and collidine (0.145 g, 1.18 mmol) in dry dimethylformamide (1.5 cm^3) contained in a 10 mm n.m.r. tube and cooled to -30 °C, was added methanesulphonyl chloride (0.134 g, 91 µl, 1.18 mmol). These operations were carried out under dry nitrogen. The capped n.m.r. tube was transferred to the pre-cooled (-20 °C) probe of the ^{13}C n.m.r. spectrometer, and a spectrum was recorded at once. The mixture was then warmed to 0 °C and ^{13}C n.m.r. spectra were recorded at intervals. The results are discussed in the text. When no further reaction was evident, lithium chloride (0.05 g, 1.1 mmol) was added, and the solution was warmed to 20 °C. ^{13}C N.m.r. spectra were recorded at intervals, and the results are discussed in the text.

The above reaction was repeated in the presence of 3 mol. equiv. of lithium chloride and an analogous result was obtained, which is discussed in the text.

We thank the S.R.C. for a CASE award with B.O.C. Ltd., Prochem. The interest and encouragement of Dr. I. M. Lockart (Prochem) is gratefully acknowledged.

[1/911 *Received*, 8*th June*, 1981]

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