^{13}C-Labelling Study of the Reaction between 2-(Methylthio)ethanol and Carbon Tetrachloride–Phosphines†

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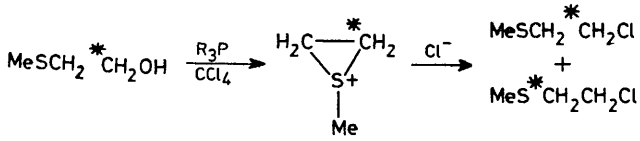
Summary The reaction between $MeSCH_2{}^{13}CH_2OH$ and CCl_4–R_3P (R = Ph, Pr^i, or n-C_8H_{17}) gives a 1 : 1 mixture of $MeSCH_2{}^{13}CH_2Cl$ and $MeS{}^{13}CH_2CH_2Cl$ *via* the 1-methylthiiranium ion.

METHIONINES specifically labelled at C-3 and/or C-4 are potentially useful for biosynthetic studies. The synthesis of a compound designated [3-^{14}C]methionine (*rac.*) *via* 1-chloro-2-(methylthio)ethane supposedly labelled with ^{14}C at C-1 has been reported.[1] This intermediate was prepared by the reaction of [1-^{14}C]-2-(methylthio)ethanol with CCl_4–(n-$C_8H_{17})_3P$ overnight at room temperature. We anticipated that an additional product from this reaction would be [2-^{14}C]-1-chloro-2-(methylthio)ethane *via* the 1-methylthiiranium ion[2] (*cf.* Scheme). Although most



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alcohols (*e.g.* octan-2-ol) react with CCl_4–Ph_3P[3] to give chloroalkanes of inverted stereochemistry, examples are known where internal attack on the organophosphorus intermediate is competitive with its capture by chloride ion.[4] We now describe a study of the reaction between [1-^{13}C]-2-(methylthio)-ethanol ($MeSCH_2{}^{13}CH_2OH$) and CCl_4–R_3P (R = Ph, Pr^i, or n-C_8H_{17}) which shows the product to be a 1 : 1 mixture of $MeSCH_2{}^{13}CH_2Cl$ and $MeS{}^{13}CH_2CH_2Cl$. Therefore, methionine prepared from '[1-^{14}C]-1-chloro-2-(methylthio)ethane' (see above) will be a 1 : 1 mixture of [3-^{14}C]- and [4-^{14}C]-methionine.‡

Using a procedure described[5] for ^{14}C-labelled acetic acid, [1-^{13}C]acetic acid (91% ^{13}C at C-1) was converted into ethyl [1-^{13}C]bromoacetate, which was diluted with unlabelled ethyl bromoacetate to a ^{13}C-content at C-1 of 11·4%. This material was converted (aq. LiSMe; catalytic $PhCH_2\overset{+}{N}Bu_3Br^-$) into ethyl [1-^{13}C]methylthioacetate (82%), which was reduced ($LiAlH_4$–ether) to $MeSCH_2{}^{13}CH_2OH$ (66%) [pure by g.l.c. (20% DEGS, 150 °C), R_t identical to that of unlabelled $MeSCH_2CH_2OH$ prepared by another method[6]]. The $\{^1H\}^{13}C$ n.m.r. spectrum (in $CDCl_3$) of this compound, shows signals at δ 14·2, 35·6, and 59·4 p.p.m. (relative to *C*DCl_3 at δ 76·9 p.p.m.). The signal at δ 59·4 p.p.m., corresponding to the enriched carbon, is *ca.* 10 times as intense as the other signals.

Solutions of redistilled Pr^i_3P (5·2 mmol) in [$^2H_6$]benzene§ (0·5 cm^3) and $MeSCH_2{}^{13}CH_2OH$ (2·2 mmol) in CCl_4 (5·2 mmol) were degassed by argon bubbling and transferred in a dry-box to an n.m.r. tube cooled to 195 K. The capped tube was warmed to 263 K in the probe of a Bruker WH-90 machine equipped with variable temperature accessory, whereupon the contents of the tube became a homogeneous solution. A spectrum was run immediately and then the solution was heated to 303 K. Further spectra were run

† No reprints are available.

‡ Dr. L. Pichat has confirmed our conclusion about the labelling pattern of his [^{14}C]methionine by mass spectrometry; personal communication.

§ Required for the lock signal. Although benzene was absent from the reaction mixture of ref. 1, the presence of this non-polar compound in our system is unlikely to alter the course of the reaction.

at intervals and show the disappearance of the signal at δ 59·5 p.p.m. ($MeSCH_2{}^{13}CH_2OH$) concomitant with the appearance of peaks at δ 35·5 and 42·2 p.p.m. The new peaks correspond to the methylene carbon atoms of $MeSCH_2CH_2Cl$, as shown by comparison with a spectrum of authentic unlabelled material.[7] The equal intensities of these peaks at all stages of the reaction are consistent with the 1-methylthiiranium ion (*cf.* Scheme) being an intermediate in the production of $MeSCH_2{}^{13}CH_2Cl$ and $MeS{}^{13}CH_2CH_2Cl$. Similar results were obtained from the reaction of $MeSCH_2{}^{13}CH_2OH$ with CCl_4–$(n\text{-}C_8H_{17})_3P$ or CCl_4–Ph_3P, the latter reaction being appreciably slower than that with CCl_4–Pr^i_3P.

Our results show that $MeSCH_2CH_2Cl$ prepared from $MeSCH_2CH_2OH$ by the CCl_4–R_3P method is not a suitable intermediate for preparing methionines specifically labelled at C-3 or C-4. However, for some purposes (*e.g.* monitoring microbiological production of ethylene from methionine[8]) a mixture of C-3 and C-4 labelled methionines is applicable and the synthesis of such a mixture *via* $MeSCH_2CH_2Cl$ is very quick.

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[7] W. R. Kinder and W. Windus, *Org. Synth., Coll. Vol. II*, 1943, 136. ^{13}C-labelled $MeSCH_2CH_2Cl$ from the reaction of $MeSCH_2{}^{13}CH_2OH$ with $(n\text{-}C_8H_{17})_3P$–CCl_4 according to ref. 1 was converted into ethyl 2-acetamido-2-ethoxycarbonyl-4-(methylthio)butanoate by the method of ref. 1. The $\{^1H\}$ ^{13}C n.m.r. spectrum of this product shows signals from C-3 and C-4 of equal but enhanced (*ca.* 5 times) intensity on comparison with authentic, unlabelled material prepared by the method of D. Goldsmith and M. Tishler, *J. Amer. Chem. Soc.*, 1946, **68**, 144.
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