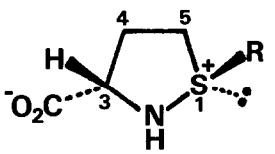
Tetrahedron Letters No. 31, pp 2937 - 2938. 0040-4039/79/0729-2937$02.00/0

PROTON EXCHANGE IN DEHYDROMETHIONINE; SYNTHESIS OF [C^2H_3]-L-METHIONINE

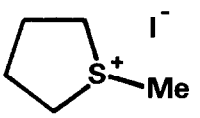
David C. Billington and Bernard T. Golding*
Department of Chemistry and Molecular Sciences,
University of Warwick, Coventry, CV4 7AL, U.K.

Summary: Methyl-labelled methionines can be easily prepared *via* dehydromethionine (1), which undergoes clean exchange at its methyl group with cat. MeONa/MeO^2H.



(1) R = Me

(2) R = $\bar{C}H_2$



(3)

Dehydromethionine (S-methylisothiazolidine-3-carboxylate, 1)[1,2], readily available from oxidising methionine (e.g. with I_2/MeOH)[1] and easily reduced to methionine by thiols[3], is an attractive intermediate for preparing specifically labelled methionines useful for biosynthetic studies[4,5]. In principle, 1 could undergo base-catalysed exchange at its methyl group and at its C-5 methylene group, with one of the diastereotopic hydrogen atoms at C-5 reacting faster than the other[6]. However, such processes may be slower than the conversion of 1 to methionine sulphoxide which occurs in aq. alkali[7].

Exposure of a 0.68 M solution of 1 in ^2H_2O to excess $^-O^2H$ caused a rapid production of methionine sulphoxide partially labelled in its methyl group. Competitive with base-catalysed exchange at the methyl group of 1 there is formation of methionine sulphoxide (which does not exchange under the reaction conditions) presumably *via* attack of $^-O^2H$ at the sulphonium centre of 1. With a deficiency of a base, 1 is converted to an amount of methionine sulphoxide exactly corresponding to the base used (NaO^2H). Further exchange of 1 and its degradation to sulphoxide then stops because all the base has been converted to the sodium salt of methionine sulphoxide.

Because the reaction of 1 with $^-O^2H$ leading to methionine sulphoxide requires eventual deprotonation of the attacking $^-O^2H$, we reasoned that an alkoxide ion in the corresponding alcohol (RO^2H) might effect selective exchange of 1 *via* ylid 2 without converting 1 to sulphoxide. Indeed, incubating 0.57 M 1 in MeO^2H containing 1.8 mol % MeONa caused exchange

at the methyl group of 1 ($\tau_{\frac{1}{2}} \lesssim 3$ min. at 310 K) without conversion to methionine sulphoxide. This process is much faster (*ca.* 30-fold) than exchange in 3 (with cat. MeONa/MeO^2H). Under these conditions (< 10 half-lives for methyl exchange) no detectable exchange occurs at the C-3 or C-5 protons of 1 (^1H NMR analysis). Bubbling H_2S through the methanolic solution of 1 after exchange, caused almost quantitative precipitation of labelled L-methionine. Therefore, exchange of 1 in MeO^2H followed by treatment with H_2S *in situ* provides a simple procedure for preparing methyl-labelled methionines from L-methionine:

(1R,3S)-Dehydromethionine (1) was prepared from L-methionine essentially as described for DL-methionine in Ref. 2. Purification of 1 was expedited by fast column chromatography[8] (Merck silica gel 60, 230-400 mesh, elution with methanol), followed by two recrystallisations (methanol/ether) and drying *in vacuo*. A solution of 1 (500 mg, 3.4×10^{-3} M) in MeO^2H (6 cm^3) containing 6.8×10^{-5} M MeONa was stored under nitrogen for 3 h/310 K. The solvent was removed under reduced pressure and replaced by fresh MeO^2H (6 cm^3) containing 6.8×10^{-5} M MeONa. After a further 3 h/310 K under N_2 the exchanged 1 was converted to methionine by bubbling H_2S for 1.5 min. After diluting with methanol to 10 cm^3 the precipitated methionine was filtered off, washed with methanol, then ether and dried: 497 mg (97%). TLC (Merck Kieselgel 5554 plate; '880' ammonia/ethanol, 23/77) showed a spot corresponding to methionine and a very faint spot (*ca.* 2%) corresponding to methionine sulphoxide. Recrystallisation of this material from aq. methanol gave a first crop (65%) and a second crop (14%) of L-methionine, each of which showed a single spot on TLC: $[\alpha_D]$20.9 (c 1.1 in N HCl) *cf.* 21.5 (c 1 in N HCl) for unlabelled L-methionine (BDH) used as starting-material ; ^1H NMR identical to unlabelled L-methionine except for the lack of a SMe peak; m.s. of N-trifluoroacetyl n-butyl ester showed m/e 227 (100%) 301 (0.6), 302 (0.6), 303 (9.6), 304 (47) (M^+ for $[C^2H_3]$-methionine) denoting a ^2H content of $\gtrsim$ 94% (confirmed by ^1H NMR). A similar procedure has been used to prepare $[^{13}C^2H_3]$-L-methionine from $[^{13}CH_3]$-L-methionine.

An attempt to exchange 1 at C-5 using 10 mol % MeONa in MeO^2H at 333 K caused decomposition of 1 to methionine and methionine sulphoxide.

References

1 T. F. Lavine, *J. Biol. Chem.*, 1943, 151, 283
2 R. S. Glass and J. R. Duchek, *J. Amer. Chem. Soc.*, 1976, 98, 965
3 D. O. Lambeth, *J. Amer. Chem. Soc.*, 1978, 100, 4808
4 Methyl-labelled methionines have been prepared by reacting the thiolate anion of homocysteine with an appropriately labelled iodomethane (see e.g. A. R. Battersby, E. McDonald, R. Holenstein, M. Ihara, F. Satoh, and D. C. Williams, *J.C.S. Perkin I*, 1977, 166)
5 Concerning applications of stereospecifically labelled amino-acids in biosynthetic studies see R. K. Hill (Ch. 5) and R. J. Parry (Ch. 10) in "Bioorganic Chemistry", Vol. II, ed. E. E. van Tamelen, Academic Press, New York, 1978
6 Concerning exchange of diastereotopic methylene hydrogens adjacent to a sulphonium centre, see G. Barbarella, P. Dembech, A. Garbesi, F. Bernardi, A. Bottoni and A. Fava, *J. Amer. Chem. Soc.*, 1978, 100, 200 and references cited therein
7 K-H. Gensch and T. Higuchi, *J. Pharm. Sci.*, 1967, 56, 177
8 W. Clark Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, 43, 2923

(Received in UK 14 May 1979)