SYNTHESIS OF ^{2}H, ^{13}C AND ^{15}N-ISOTOPOMERS OF ACETONITRILE AND THIOACETAMIDE

Uffe Anthoni and Per Halfdan Nielsen

Chemical Laboratory II, University of Copenhagen
The H. C. Ørsted Institute, DK-2100 Copenhagen, Denmark

SUMMARY

The syntheses of all the possible ^{2}H, ^{13}C, and ^{15}N singly and multiply labelled isotopomers of acetonitrile and thioacetamide are described. The pathway includes reaction between methyl iodide and potassium cyanide followed by treatment of the acetonitrile with diphenylphosphinodithioic acid to give thioacetamide, purified by sublimation in an overall yield of 55-60%.

Key Words: Acetonitrile, Thioacetamide, Carbon-13, Nitrogen-15, H-2, Synthesis.

INTRODUCTION

As part of continuing investigations into the vibrational spectra of thioacetamide, a detailed study of the infrared and Raman spectra has recently been undertaken.[1,2] Samples in the 50-100 mg scale of thioacetamide extensively marked with stable isotopes were required in order to facilitate the interpretation of the observed spectra. The details of the synthesis of these compounds are reported herein.

0362-4803/84/040375-06$01.00

Received November 22, 1983

DISCUSSION

Labelled acetonitrile has usually been produced by one of the methods outlined in Scheme 1. In the first route, acetic

$$(CH_3CO)_2O + {}^{15}NH_3 \xrightarrow{P_2O_5} CH_3C^{15}N \ (34\%)$$

$$(CD_3)_2SO_4 + KC^{15}N \longrightarrow CD_3C^{15}N \ (67\%)$$

$${}^{13}CH_3I + KCN/NaCN \longrightarrow {}^{13}CH_3CN \ (88\text{-}95\%)$$

Scheme 1. Synthesis of labelled acetonitrile

acid anhydride on treatment with $^{15}NH_3$ gives a mixture of acetamide and ammonium acetate, converted to acetonitrile on reaction with P_2O_5.[3] Due to the low cost of high-purity $^{15}NH_4Cl$ attempts were made to improve the yield, but were not met with success (maximum 47% yield). Another procedure reported [4] for simultaneous introduction of ^{2}H and ^{15}N makes use of deuterated dimethyl sulfate. It not only involves a substantial loss of deuterated material but is not convenient for generalisation due to the non-availability of other isotopical substitutes of dimethyl sulfate. In the third route, the conversion of $^{13}CH_3I$ to $^{13}CH_3CN$ is accomplished by treatment either with potassium cyanide in glycerol [5] or with sodium cyanide in dimethyl sulfoxide. [6] The former procedure adapted to small-scale preparations in our hands gave very satisfactory results (94-98%) and could easily be extended to other labelled acetonitriles.

Synthetic routes of labelled thioacetamide are illustrated in Scheme 2. Initially the direct reaction between hydrogen

$CH_3CN + H_2S \longrightarrow CH_3CSNH_2$ (66%)

$CH_3CN + (EtO)_2PS_2H \longrightarrow CH_3CSNH_2$ (24-39%)

$CH_3CN + Ph_2PS_2H \longrightarrow CH_3CSNH_2$ (yield not given)

Scheme 2. Synthesis of labelled thioacetamide

sulfide and acetonitrile [7] was extensively investigated. However, adaption of this method to microsynthetic conditions invariably resulted in yields of 25% or less. An alternative route involving the use of 0,0'-diethyl dithiophosphate as hydrogen sulfide donor was used by Walter et al.[8] in the small scale preparation of $^{13}CH_3CSNH_2$, $CH_3{}^{13}CSNH_2$ and $CH_3CS^{15}NH_2$. The main drawback of this method is the small and greatly varying yield. Recently [9] a closely related method for the preparation of thiamides using diphenylphosphinodithioic acid has been proposed instead. Unfortunately, though it is mentioned in the introduction of the paper that the method may be used for preparation of thioacetamide, it is completely absent in the experimental part and from the tables describing yield etc. Somewhat intrigued by this apparent contradiction, we undertook a study of the reaction between Ph_2PS_2H and acetonitrile under a variety of conditions.

We found that if the reaction was carried out in 2-propanol as proposed in the general experimental procedure a good yield of thioacetamide could not be secured. Work-up without aqueous extraction had the result that the contaminants were very difficult to remove. On the other hand it was observed, that the reaction carried out in toluene solution proceeded smoothly to

give directly the crude thioacetamide which was sublimated to a very pure product in 55-60% overall yield. This simple, one-step synthesis also has an added advantage in that it completely avoids the troublesome separation of by-products by chromatography.

EXPERIMENTAL

Acetonitrile from acetic anhydride. The method described by Juchnovski et al.[3] was modified for the synthesis of $CH_3C^{15}N$ from $^{15}NH_4Cl$ and acetic anhydride. A reaction flask charged with potassium hydroxide pellets is equipped with a nitrogen inlet and addition funnel. A solution of ammonium chloride-^{15}N (1 g, 18.7 mmol) in water (2 ml) is added dropwise with nitrogen flushing. The outlet is connected to a trap containing vigorously (magnetically) stirred acetic anhydride (1 g, 9.8 mmol) and water (3 ml). As soon as the exit gases containing $^{15}NH_3$ are passed through the contents of the trap an exothermic reaction sets in which is allowed to proceed uninterrupted for 1 h. The reaction mixture is then taken to dryness, dried over P_2O_5 overnight, ground in a mortar with phosphorous pentoxide (4 g, 28 mmol) and distilled to give acetonitrile-^{15}N (364 mg, 47%).

Acetonitrile from methyl iodide and potassium cyanide. A suspension of freshly powdered potassium cyanide (456 mg, 7 mmol) in methyl iodide (994 mg, 7 mmol) and dried glycerol (0.4 ml) is placed in a five ml round-bottommed flask. It is closed with a tight glass stopper which should be well lubricated and secured with a clip because the pressure may rise during the reaction. The mixture is magnetically stirred at 40°C for 1 h and stirring

is continued at ambient temperature overnight. The trap is connected to a vacuum line and distilled at 30° directly into a receiver cooled in liquid nitrogen. It is important that the stirring be continued during the distillation and that this is allowed to proceed for at least 1 h in order to obtain a 94-98% yield of pure acetonitrile.

By this procedure CDH_2CN and CD_2HCN were prepared using CDH_2I (Roth, 96% D) and CD_2HI (Roth, 96% D). Similarly, $^{13}CH_3CN$, $CH_3{}^{13}CN$, $CH_3C^{15}N$, $^{13}CH_3{}^{13}CN$, $^{13}CH_3C^{15}N$, $CH_3{}^{13}C^{15}N$, and $^{13}CH_3{}^{13}C^{15}N$ have been obtained using $^{13}CH_3I$ (Stohler, 99% ^{13}C), $K^{13}CN$ (Prochem, 90% ^{13}C), $KC^{15}N$ (MSD, 99% ^{15}N) and $K^{13}C^{15}N$ (Prochem, 91,5% ^{13}C, 99.5% ^{15}N). With the additional use of $^{13}CD_3I$ (MSD, 90% ^{13}C, 98% D) and CD_3I (Aldrich 99% D) as starting materials, $^{13}CD_3CN$, $CD_3{}^{13}CN$, $CD_3C^{15}N$, $^{13}CD_3{}^{13}CN$, $^{13}CD_3C^{15}N$, and $CD_3{}^{13}C^{15}N$ were also prepared.

Thioacetamide from acetonitrile. Diphenylphosphinodithioic acid was prepared according to the instructions given by Higgins *et al.*[10] and recrystallized twice from 2-propanol before use. The pure acid (3.5 g, 14.0 mmol) was dissolved in dry toluene (3 ml) at 60° and the acetonitrile prepared above (6.6 - 6.7 mmol) added in one portion. The solution was left at room temperature overnight and the separated thioacetamide filtered off. Despite several attempts it was not possible to obtain an additional yield from the mother liquor. The thioacetamide was worked up using gradient sublimation to give a 55% yield of very pure fluorescence free compound and leaving a small amount of greasy residue in the sublimation tube. A small teflon container with impure thioacetamide is placed near the closed end of a horizontally orientated glass tube (inside diameter 23.2 mm). The other

end of the tube is connected to a dynamic vacuum at 5×10^{-2} torr. The sublimated crystals were collected on a removable teflon lining inside the glass tube. The gradient was $0.75^{\circ} \times cm^{-1}$, controlled at 45° at the high temperature end, kept in 3 - 5 h for 50 - 100 mg portions. By this general procedure all the labelled acetonitrile compounds described above were converted into the corresponding thioacetamide derivatives in almost identical yield.

REFERENCES

1. Anthoni, U., Nielsen, P. H. and Nielsen, O. F. - J. Mol. Struct. Accepted for publication.
2. Anthoni, U., Christensen, D. H. and Nielsen, P. H. - J. Mol. Struct. Accepted for publication.
3. Juchnovski, I. N., Dimitrova, J. S., Binev, I. G. and Kaneti, J. - Tetrahedron 34: 779 (1978).
4. Bertagnolli, H., Chieux, P. and Zeidler, M. D. - Mol. Phys. 32: 1731 (1976).
5. Klinge, D. E. and van der Plas, H. C. - Rec. Trav. Chim. 95: 34 (1976).
6. Whaley, T. W., Daub, G. H., Kerr, V. N., Lyle, T. A. and Olson, E. S. - J. Labelled Compds. 16: 809 (1979).
7. Kindler, K. - Liebigs Ann. 431: 187 (1923).
8. Walter, W. and Kubersky, H. P. - Liebigs Ann. 694: 56 (1966).
9. Benner, S. A. - Tetrahedron Letters 22: 1851 (1981).
10. Higgins, W., Vogel, P. and Craig, W. - J. Am. Chem. Soc. 77: 1864 (1955).