Journal of Labelled Compounds and Radiopharmaceuticals
J. Labelled Cpd. Radiopharm. **44**, 169-172 (2001)

Preparation of $[^{13}C_6]$-ε-Caprolactam and $[^{13}C_6]$-Hexamethyleneimine

George J. Ellames and John M. Herbert*

Isotope Chemistry and Metabolite Synthesis Department, Sanofi-Synthélabo,
Willowburn Ave., Alnwick, Northumberland NE66 2JH, UK

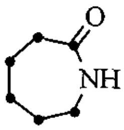
SUMMARY

An efficient route is described for the preparation of $[^{13}C_6]$-ε-caprolactam (**1b**), and thence to $[^{13}C_6]$-hexamethyleneimine (**2b**) hydrochloride. The sequence, from $[^{13}C_6]$-phenol, uses a rhodium-catalysed hydrogenation to generate labelled cyclohexanol, and thence cyclohexanone, whose oxime was subjected to a Beckmann rearrangement to give **1a**.

Key Words: $[^{13}C_6]$-Azepane; $[^{13}C_6]$-ε-Caprolactam; $[^{13}C_6]$-Cyclohexanone; $[^{13}C_6]$-Hexamethyleneimine Hydrochloride; Hydrogenation.

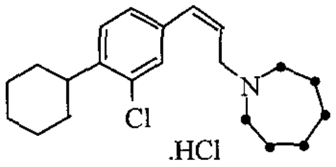
INTRODUCTION

ε-Caprolactam (**1a**) and hexamethyleneimine (azepane, **2a**) are important intermediates in number of commercially important synthetic processes.[1] The latter is also an important subunit in a variety of molecules of medicinal interest, including the sigma receptor ligand, SR31742A (**3a**).[2] Although the preparation of $[^{15}N]$-ε-caprolactam has been reported,[3] neither **1** nor **2** has been prepared in $[^{13}C]$-labelled form.



1a. unlabelled
1b. $[^{13}C_6]$

2a. unlabelled
2b. $[^{13}C_6]$



3a. unlabelled
3b. • indicates $[^{13}C_6]$

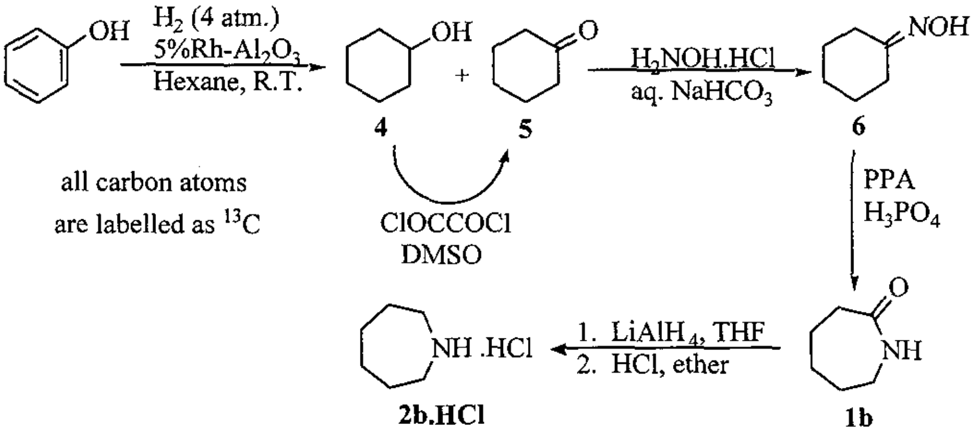
Received 30 October 2000
Accepted 7 November 2000

RESULTS AND DISCUSSION

In order to complete the synthesis of [*azepane*-$^{13}C_6$]-SR31742A (**3b**) for use in human comparative bioavailability trials, it was necessary to develop a route to [$^{13}C_6$]-ε-caprolactam (**1b**), from which [$^{13}C_6$]-hexamethyleneimine (**2b**) could be prepared. Since labelling of SR31742 in either the benzene or cyclohexyl ring requires a lengthy synthesis, certain steps of which are difficult to control on a small scale,[2] the azepane ring was the most situable place in which to label the molecule. Azepane **2a** is available by reduction of ε-caprolactam,[4] which can be prepared in turn from phenol.[1]

The route to [$^{13}C_6$]-ε-caprolactam (**1b**) is outlined in Scheme 1. The catalytic hydrogenation of phenol tends to provide a mixture of cyclohexanone and cyclohexanol and, rather than attempt to form the ketone directly, the material was reduced completely, and then reoxidised. The choice of hydrogenation catalyst was influenced principally by a desire to minimise the pressure of hydrogen required. Hence, reduction of [$^{13}C_6$]-phenol over 5% rhodium on alumina gave [$^{13}C_6$]-cyclohexanol (**4**) containing a small amount of [$^{13}C_6$]-cyclohexanone (**5**). An additional advantage of the rhodium catalyst by comparison with Adams' catalyst or Raney nickel is that it is very much less pyrophoric than either.

The mixture of components **4** and **5** was subjected to a Swern oxidation[5] and the [$^{13}C_6$]-cyclohexanone obtained was converted into the corresponding oxime, **6**, using a modification of the published procedure.[6] Rather than attempting to isolate the volatile intermediates **4** and **5**, the first three steps were carried out without solvent removal, with only minimal characterisation (by GC/MS).



Scheme 1. Synthesis of [$^{13}C_6$]-ε-Caprolactam and [$^{13}C_6$]-Hexamethyleneimine

The Beckmann rearrangement of **6** was carried out using polyphosphoric acid, diluted with phosphoric acid in order to aid handle-ability.[7] This gave [$^{13}C_6$]-ε-caprolactam in essentially pure form; nevertheless, this material was purified by chromatography, in order to be sure that no trace of **6** remained which could, potentially, lead to impurities in **3b**. Finally, hydride reduction of **1b** using a modification of the literature method[4] gave **2b**, which was conveniently isolated and characterised as its hydrochloride salt. This was used in the subsequent formation of labelled SR31742A, **3b**.

EXPERIMENTAL

All nmr spectra were recorded using a Jeol GSX-270 instrument. Mass spectra were recorded using a VG Autospec magnetic sector instrument at the University of York. Reagents were obtained commercially and; in particular, [$^{13}C_6$]-phenol was obtained from Eurisotop.

[$^{13}C_6$]-Cyclohexanone Oxime (6). A suspension of 5% Rhodium on alumina (1.019 g) in hexane (100 ml) containing [$^{13}C_6$]-phenol (10.054 g, 0.010 mol) was stirred under hydrogen (30-60 psi) in a pressure reactor for 21 h, after which time hydrogen uptake was complete. The mixture was filtered through celite and the filter cake washed through with dichloromethane. *m/z* 106 ($M^{+\cdot}$), 88 ($M-H_2O$), 60 (100%). Swern oxidation using oxalyl chloride-DMSO[7] gave [$^{13}C_6$]-cyclohexanone as a solution in hexane-dichloromethane. *m/z* 104 ($M^{+\cdot}$), 58 (100%). This was added to a stirred solution of hydroxylamine hydrochloride (8.887 g, 0.125 mol) in water (150 ml). A solution of sodium hydrogencarbonate (31.096 g, 0.25 mole) in water (150 ml) was added and, after 15 min, the mixture was heated, over a period of 3h, to approximately 60°C. The mixture was allowed to cool overnight, and extracted with ethyl acetate (3 x 200 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give **6** (10.211 g, 86%) as a white solid, m.p. 86.6-87.8°C. $\delta_H(CDCl_3)$ 1.2-1.5 and 1.7-2.0 (6H, 2m), 2.22 (2H, dm), 2.53 (2H, dm); $\delta_C(CDCl_3)$ *ca.* 25 (3C, m), 32.0 (2C, dd), 161.0 (1C, t); *m/z* (EI) 119 (100%, $M^{+\cdot}$), 103, 87, 75; HRMS found: 119.1039 (calc. for $^{13}C_6H_{11}NO$ 119.1042).

[$^{13}C_6$]-ε-Caprolactam (1b). A mixture of [$^{13}C_6$]-cyclohexanone oxime (10.184 g, 86 mmol), polyphosphoric acid (23 g) and 85% phosphoric acid (48 g) was heated for 18-24h at 50-55°C, then cooled to room temperature, diluted with water and neutralised to approximately pH 7 by addition of 2M aqueous sodium hydroxide. The mixture was extracted with dichloromethane (4 x 400 ml), and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography of the residue on silica gel in ethyl acetate gave **1b** (8.693 g, 85%) as a white solid, m.p. 65-66°C. $\delta_H(CDCl_3)$ 1.2-1.5 and 1.7-2.0 (6H, 2m), 2.22 (2H,

dm), 2.53 (2H, dm); $\delta_C(CDCl_3)$ 23.1 (t), 29.5 (t), 30.6 (t), 36.55 (dd), 42.85 (d), 179.25 (d); *m/z* 119 ($M^{+\cdot}$), 89, 59, 58 (100%); HRMS found: 119.1041 (calc. for $^{13}C_6H_{11}NO$ 119.1042).

*[$^{13}C_6$]-Hexahydroazepine Hydrochloride (**2b**).* Lithium aluminium hydride in tetrahydrofuran (1M; 73 ml, 73 mmol) was added to a stirred solution of **1b** (8.693 g, 73 mmole) in anhydrous tetrahydrofuran (145 ml) under nitrogen. The mixture was stirred for 18 h. Water (5.25 ml) was added slowly, and the mixture was stirred for 1 h, then dried ($MgSO_4$) and filtered. Ethereal hydrogen chloride (1M; 80 ml) was added to the filtrate, and the suspension obtained was filtered to give [$^{13}C_6$]-hexahydroazepine hydrochloride (8.433 g, 82 %) as a white solid, m.p. 232.5-233°C. Found: *C 51.0, H 10.1,* N 9.85, Cl 25.1. $C_{11}{}^{13}CH_{10}ClN$ requires: C 50.9, H 10.0, N 9.9, Cl 25.05%. $\delta_H(CD_3OD)$ 1.72 (4H, dm), 1.89 (4H, dm), 3.23 (4H, dt); $\delta_C(CD_3OD)$ 26.2 (m), 27.6 (m), 47.3 (d) ; *m/z* (EI) 105 ($M^{+\cdot}$), 74 (100%), 59; HRMS found: 105.1249 (calc. for $^{13}C_6H_{13}N$ 105.1249).

ACKNOWLEDGEMENTS

The authors wish to thank Dr. S.J. Byard for NMR spectra and Dr. T. Dransfield (University of York) for high resolution mass spectra.

REFERENCES

1. Tedder, J.M., Nechvatal, A., and Jubb, A.H. - "Basic Organic Chemistry, Part 5: Industrial Products" (Wiley, Chichester, 1975), p. 187
2. Sanofi s.a., European Patent 0461986 (1996).
3. Powell, D.G., and Mathias, L.J. - J. Am. Chem. Soc., 112: 669 (1990).
4. Schill, G., Priester, C.U., Windhövel, U.F., and Fritz, H. - Tetrahedron, 43: 3765 (1987).
5. Mancuso, A.J., and Swern, D., - Synthesis, 165 (1981).
6. Bousquet, E.W. - Organic Syntheses Collective Vol. II: 313 (1943).
7. Pearson, D.E., and Stone, R.M. - J. Am. Chem. Soc., 83: 1715 (1961).