

THE PREPARATION AND ASSAY OF SPECIFICALLY [^{14}C]LABELLED BENZENE DERIVATIVES

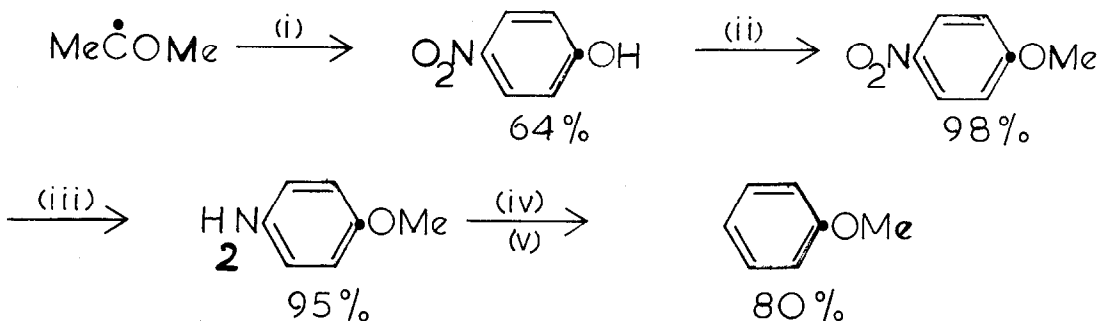
Neil J. Hales and Harry Heaney
Department of Chemistry, The University of Technology,
Loughborough, Leicestershire, LE11 3TU

(Received in UK 18 September 1975; accepted for publication 6 October 1975)

We recently required 1- ^{14}C anisole in connection with our study of rearrangement reactions of 1-methoxybenzobarrelenes.¹ The most frequently used methods for the preparation of benzene derivatives labelled with carbon isotopes at position-1 converge at 1-methylcyclohexene and proceed on through toluene, benzoic acid, aniline and phenol.² The wide variety of isotopically labelled compounds available in this way has been made use of in studies of metabolic pathways,³ organic reaction mechanisms,⁴ ^{13}C -n.m.r. spectroscopy,⁵ and mass spectrometry.⁶ Extensive, but variable, scrambling of the label has recently been reported during the dehydrogenation of 1-methyl-1- ^{13}C cyclohexene using a platinum on alumina catalyst.⁷ These latter authors suggest that it would be difficult to detect scrambling in ^{14}C labelled material due to the absence of suitable degradative methods.

We now describe degradation schemes for the detection and determination of this scrambling and report the application of the methods to the degradation of 1- ^{14}C anisole. We also describe an alternative preparation of 1- ^{14}C anisole which leaves no doubt about the location of the label and which is the shortest, most convenient and most efficient route thus far reported.

The condensation of sodium nitromalondialdehyde with 2- ^{14}C acetone has been used to prepare^{3b} 4- ^{14}C anisole but the intermediate 4-nitro-1- ^{14}C phenol has not previously been employed in the synthesis of 1-substituted-1- ^{14}C benzene derivatives. A large range of compounds is available by modification or nucleophilic displacement⁸ of the oxygen function followed by removal of the nitro-group. With the specific objective 1- ^{14}C anisole we carried out the transformations shown in Scheme 1 and obtained an overall isolated yield of anisole (starting with acetone) of 47.5%.

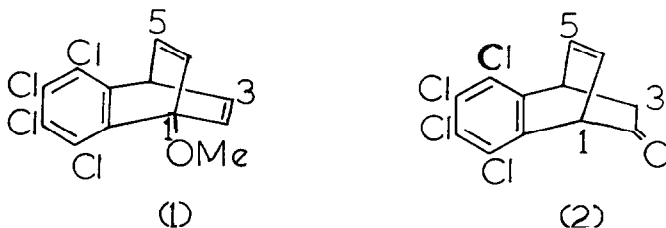


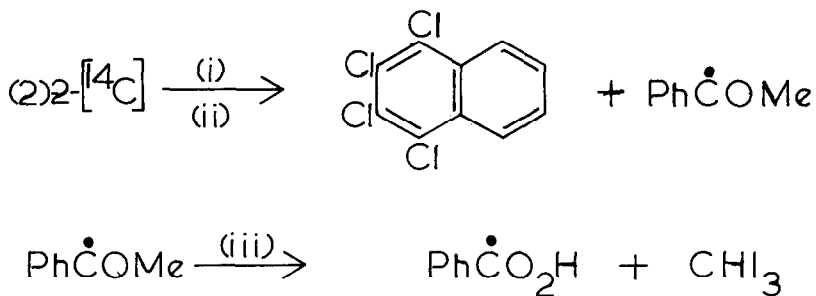
Scheme 1

Reagents: (i) aqueous sodium nitromalonialdehyde, (ii) methyl iodide on potassium salt in D.M.S.O., (iii) hydrazine hydrate - Pd/C in ethanol, (iv) sodium nitrite on solution in aqueous hydrochloric acid at 5°, (v) 30% aqueous hypophosphorous acid-pentane at 20°.

Benzene derivatives may be degraded as their tetrachlorobenzene cycloadducts. Although reactions of tetrachlorobenzene⁹ with arenes may appear to be esoteric a wide range of tetrachlorobenzobarrelene derivatives can be very conveniently prepared in high yield. The use of 2-carboxy-tetrachlorobenzenediazonium fluoroborate and pyridine as an efficient tetrachlorobenzene precursor¹⁰ is particularly useful for small scale reactions. The degradation of benzobarrelenes poses no major problems. Indeed, the fact that tetrachlorobenzene usually cycloadds to a monosubstituted benzene at both 1- and 4-, and 2- and 5- (or 3- and 6-) positions is advantageous for the degradation of C-labelled benzene derivatives.

The types of degradation available are exemplified for anisole and may be suitably modified for a range of benzene derivatives including for example toluene and N,N-dimethylaniline. The scope of the method is further enhanced by the use of the standard transformations utilised in the conversion of toluene to phenol. Thus the reaction of tetrachlorobenzene with 1-[¹⁴C]-anisole afforded the adducts (1) and (2) of which the compound (1) was the major product. The degradation of the ketone (2) was achieved in accordance with Scheme 2 in which the original carbon at position-1 of the anisole was isolated as benzoic acid. No radioactivity was detected in the other two fragments (1,2,3,4-tetrachloronaphthalene and iodoform).

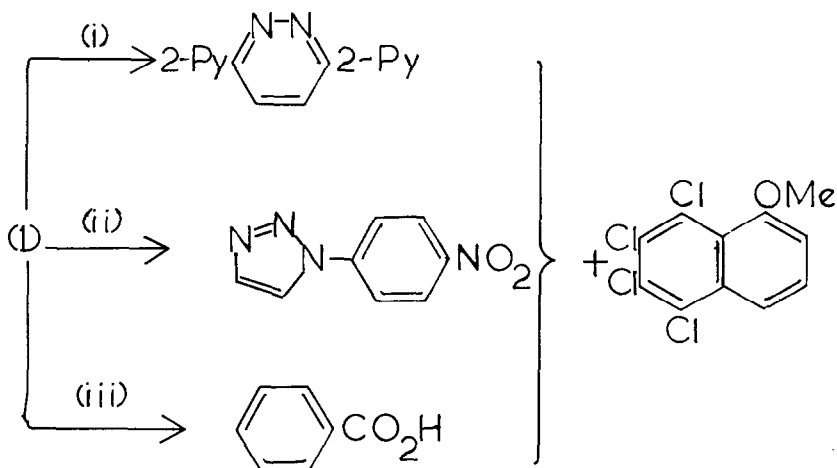




Scheme 2

Reagents: (i) phenyl magnesium bromide in ether at 20° , (ii) heat in boiling D.M.F. for 15 min., (iii) sodium hypiodite in aqueous dioxan.

Although we have not degraded the radio-labelled compound (1) we have shown that the degradation of cold (1) to remove the carbon atoms originally at positions 2- and 3- (≡ 5- and 6-) can be achieved in good yield using a number of cycloaddition-fragmentation processes as shown in Scheme 3.



Scheme 3

Reagents: (i) 3,6-di(2'-pyridyl)-s-tetrazine in boiling di-n-butyl ether, (ii) 4-nitrophenyl azide in boiling benzene, (iii) coumalic acid in acetic acid or p-xylene at 200° .

It would therefore be possible, using the method outlined above, to determine the activities of all of the ring carbon atoms in toluene and thus establish, using the previously standard routes, whether scrambling of the ring carbon atoms is a general phenomenon.

We thank the S.R.C. for the award of a research studentship (to N.J.H.) and Dr.S.V.Ley for interesting discussions.

References

1. N.J.Hales, H.Heaney and S.V.Ley, J.C.S. Perkin 1, 1974, 2702.
2. M. Fields, S. Rothchild and M.A. Leaffer, J. Amer. Chem. Soc., 1952, 74, 2435;
M. Fields, M.A. Leaffer, S. Rothchild and J. Rohan, ibid., 1952, 74, 5498.
A. Murray and D.L. Williams 'Organic Syntheses with Isotopes', Part I, Interscience, New York, 1958, p. 103.
3. (a) E.A. Williams, R.W. Meikle and C.T. Redemann, J. Agric. Food Chem., 1965, 13, 210;
(b) K. Kratzl and F.W. Vierhapper, Monatsh., 1971, 102, 224.
4. J.D. Roberts, H.E. Simmons, L.A. Carlsmith and C.W. Vaughan, J. Amer. Chem. Soc., 1953, 75, 3290;
R. Huisgen, F. Jacob and R. Grashey, Chem. Ber., 1959, 92, 2206.
5. A. Rieker, K. Scheffler and E. Mueller, Annalen, 1963, 670, 23.
6. A.V. Robertson and C. Djerassi, J. Amer. Chem. Soc., 1968, 90, 6992;
R.J. Dickenson and D. Williams, J. Chem. Soc. (B), 1971, 249.
7. J.L. Marshall, D.E. Mueller and A.M. Ihrig, Tetrahedron Letters, 1973, 3491.
8. J. Miller, 'Aromatic Nucleophilic Substitution', Elsevier, Amsterdam, 1968.
9. H. Heaney, Fortschr. Chem. Fortsch., 1970, 16, 35.
10. P.C. Buxton, N.J. Hales, B. Hankinson, H. Heaney, S.V. Ley and R.P. Sharma, J.C.S. Perkin 1, 1974, 2681.