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Short Research Article

The syntheses of (^{14}C) and ($^{13}C_4$)pyromellitic acid†

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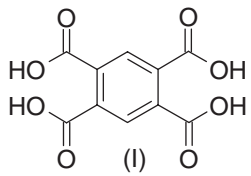
Introduction

In the drug development process appropriate salt selection can be critical. For a recent project a pyromellitic acid (1,2,4,5-benzene tetracarboxylic acid), **1,** salt proved optimal.



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We required carbon-14 and stable labelled versions of pyromellitic acid: the radio-isotopomer at 50–60 mCi/mmol for traditional ADME work and the stable label as an internal standard in a LC/MS/MS assay. In general an effective internal standard requires an increase of at least 3 a.m.u. over the test substance and a very high degree of isotopic incorporation (typically $<0.1\%$ unlabelled). We chose to fulfil these criteria by mass labelling each of the carboxyl groups with carbon-13.

Results and discussion

1,2,4,5-Tetracyanobenzene is readily saponified to pyromellitic acid. We therefore chose this as our initial target. We envisaged that a route common to both isotopomers could be developed by cyanation of tetrabromo or iodo benzene with either ^{13}CN or ^{14}CN. However, under a variety of conditions (CuCN, KCN/CuI, $Zn(CN)_2/Pd(Ph_3P)_4$) no useful product was isolated. An alternative related approach suggested itself at this point. Oxidation of aryl methyl groups to carboxylic acids is a well known and straightforward process[1]. We found that both 1,2,4,5-tetramethyl benzene and 2,4,5,-trimethylbenzoic acid could be oxidized by alkaline permanganate to pyromellitic acid in good yield (70–80%). This discovery proved crucial.

Cyanation of 2,4,5-trimethyl bromobenzene with Cu[^{14}C]CN in NMP at 175°C followed by saponification of the crude [^{14}C]nitrile (NaOH, EtOH, reflux) gave 2,4,5-trimethyl[*carboxyl*-^{14}C] benzoic acid in 84% yield from copper cyanide. Oxidation by slow addition of aliquots of 5% w/v $KMnO_4$ in water to a solution of the radiolabelled acid in 1.5M KOH at 90°C completed the synthesis. The crude product was triturated with ether/hexane and crystallized from hot water (60% yield, radiochemical purity >98%, specific activity 53 mCi/mmol).

Our initial plan was to prepare [$^{13}C_4$]tetramethylbenzene by exhaustive metalation and methylation of tetrabromobenzene and subsequent oxidation. We anticipated that a large excess of MeI would be required, but [^{13}C]MeI is inexpensive and readily available so this was not a major concern. Unfortunately, we were unable to drive the reaction to completion and isolated [*methyl*-$^{13}C_3$]2,4,5-trimethylbromobenzene as the major product. However, we had already demonstrated in the carbon-14 synthesis that this could be readily converted to pyromellitic acid by a cyanation, saponification and oxidation sequence. Simply substituting Cu[^{13}C]CN for Cu[^{14}C]CN gave the desired product with a chemical purity of >98% and no detectable unlabelled content by MS.

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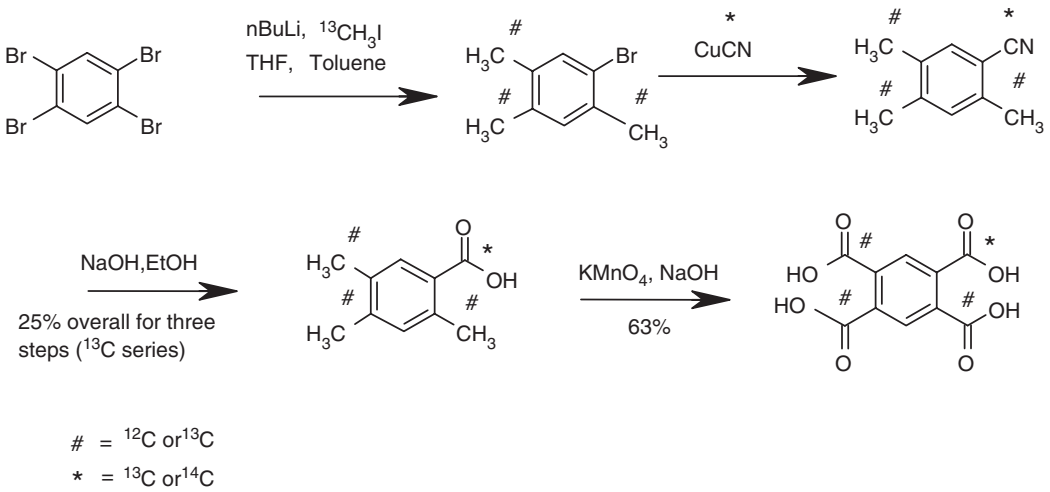

\# = ^{12}C or ^{13}C

* = ^{13}C or ^{14}C

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