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Short Research Article

Syntheses of Isotopically Labelled Xanthines†

KARL M. CABLE*
Isotope Chemistry, GlaxoSmithKline, Gunnels Wood Road, Stevenage SG1 2NY, UK

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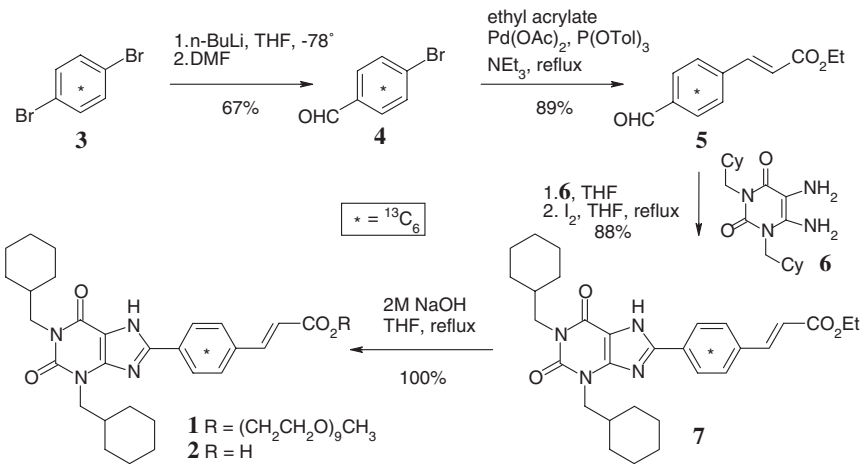
Introduction

Pegylated xanthine **1** is a potent inhibitor of endothelial cell adhesion molecule (ECAM) expression and was under development for the treatment of inflammatory disorders. Stable isotope labelled versions of **1** and the carboxylic acid metabolite **2** were required as internal standards for LC/MS assay of biological matrix. A carbon-14 labelled version of **1** at 50–60 mCi/mmol was required for ADME studies. Acid **2** can be prepared by the condensation of 4-formyl cinnamic acid with diaminouracil **6**. The resulting imine undergoes an oxidative cyclization on treatment with iodine.[1] Since unlabelled diaminouracil **6** was readily available, labelling of the cinnamate moiety in **2** was investigated.

Results and discussion

Stable isotope labelled compounds

For stable isotope labelled versions the chosen strategy employed [$^{13}C_6$]-1,4-dibromobenzene **3**, one of the few commercially available 1,4-disubstituted [$^{13}C_6$] benzene derivatives. Labelled acid **2** was obtained in 52% overall yield from [$^{13}C_6$]-1,4-dibromobenzene (Scheme 1). Sequential functionalization of the two brominated positions in **3** generated labelled 4-formyl cinnamate ester **5**. This linear synthesis involved the preparation of [$^{13}C_6$]acid metabolite **2** *en route* to labelled **1**. A portion of **2** was converted into pegylated [$^{13}C_6$]xanthine **1** in 62% overall yield.



Scheme 1

*Correspondence to: Karl M. Cable, Isotope Chemistry, GlaxoSmith-Kline, Gunnels Wood Road, Stevenage SG1 2NY, UK.
E-mail: karl.m.cable@gsk.com

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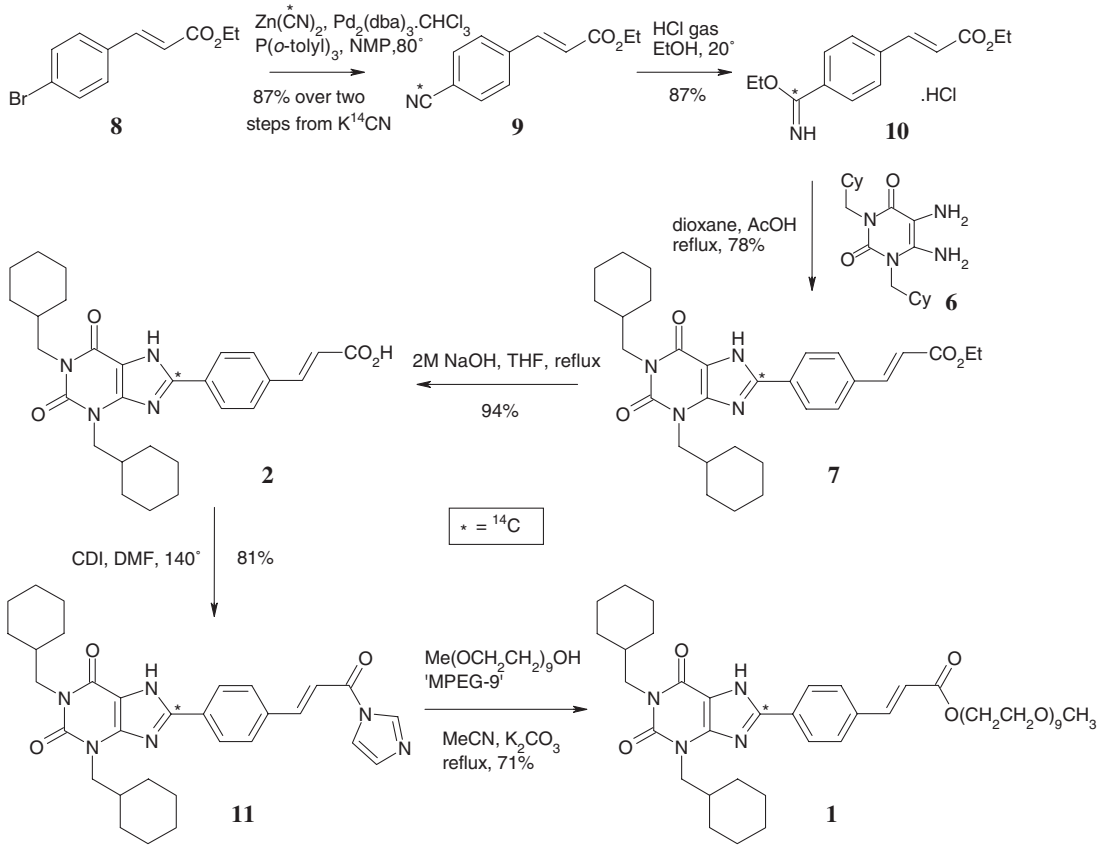

Scheme 2

Carbon-14 labelled compounds

Literature methods for the preparation of 8-aryl xanthines from diaminouracils often require two or more steps to construct the xanthine ring system.[2,3] It was envisaged that xanthine **1** could be constructed more efficiently using a single step process reported for the synthesis of benzimidazoles.[4] Carbon-14 labelled **1** was prepared in 32% overall yield from potassium [^{14}C]cyanide (Scheme 2).[5] Reaction of diaminouracil **6** with imino ether **10** gave [^{14}C]xanthine ester **7** directly.

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