

Short Research Article

Syntheses of Isotopically Labelled Xanthines[†]

KARL M. CABLE*

Isotope Chemistry, GlaxoSmithKline, Gunnels Wood Road, Stevenage SG1 2NY, UK

Received 3 July 2006; Revised 13 December 2006; Accepted 14 December 2006

Keywords: carbon-14; cyanation; palladium; xanthine; zinc cyanide

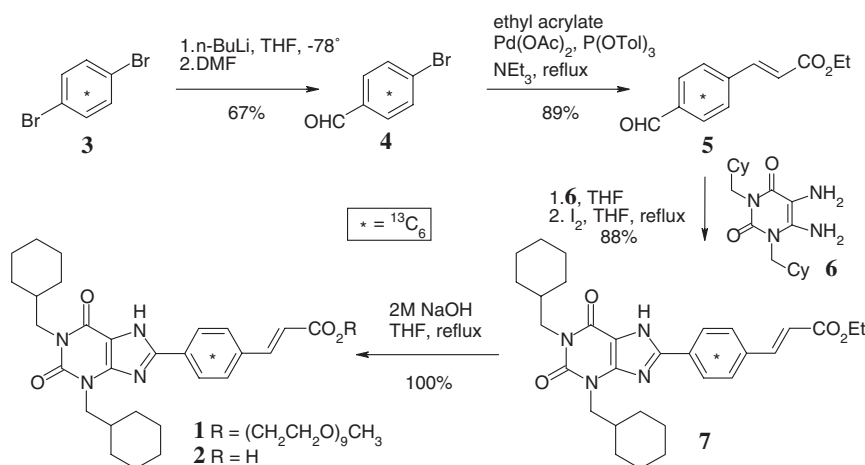
Introduction

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

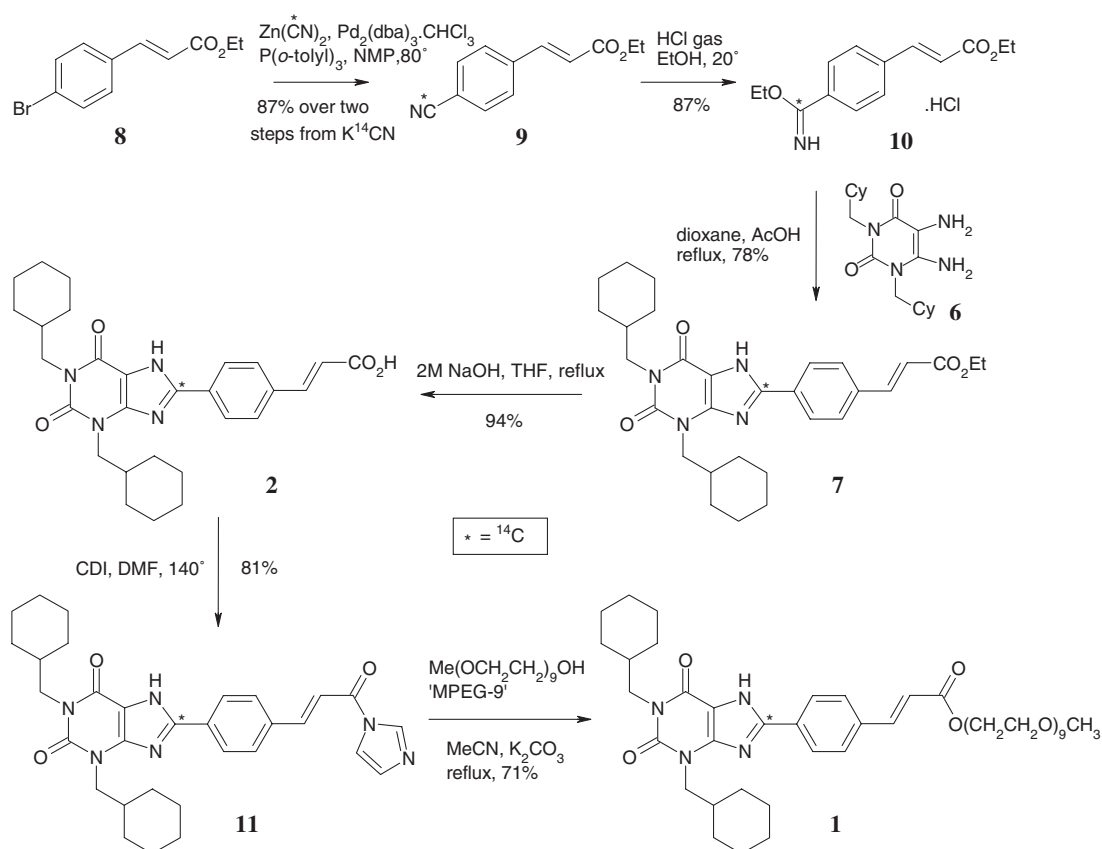
For stable isotope labelled versions the chosen strategy employed [¹³C₆]-1,4-dibromobenzene **3**, one of the few commercially available 1,4-disubstituted [¹³C₆] benzene derivatives. Labelled acid **2** was obtained in 52% overall yield from [¹³C₆]-1,4-dibromobenzene (Scheme 1). Sequential functionalization of the two brominated positions in **3** generated labelled 4-formyl cinnamate ester **5**. This linear synthesis involved the preparation of [¹³C₆]acid metabolite **2 en route** to labelled **1**. A portion of **2** was converted into pegylated [¹³C₆]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

[†]Proceedings of the Ninth International Symposium on the Synthesis and Applications of Isotopically Labelled Compounds, Edinburgh, 16–20 July 2006.



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.

REFERENCES

1. Perumattam J. *Synth Commun* 1989; **19**: 3367.
2. Daly JW, Padgett W, Shamim MT, Butts-Lamb P, Waters J. *J Med Chem* 1985; **28**: 487.
3. Peet NP, Lentz NL, Dudley MW, Ogden AL, McCarty DR, Racke MM. *J Med Chem* 1993; **36**: 4015.
4. De Selms RC. *J Org Chem* 1962; **27**: 2165.
5. Tschäen DM, Abramson L, Cai D, Desmond R, Dolling U-H, Frey L, Karady S, Shi Y-J, Verhoeven TR. *J Org Chem* 1995; **60**: 4324.