Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 513–514.
Published online in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1231

JLCR

Short Research Article

Synthesis of (^{14}C)*tert*-butyl acetylene†

KARLA G. CUEVAS-LICEA*, NATHAN X. YU, STEVEN J. STASKIEWICZ and CONRAD E. RAAB
Department of Drug Metabolism, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065, USA

Received 23 June 2006; Revised 13 December 2006; Accepted 14 December 2006

Keywords: CYP P-450; *tert*-butyl acetylene; Weinreb ketone synthesis

Introduction

The cytochromes P-450 (CYP) constitute a superfamily of heme-containing enzymes that are involved in the metabolism of a wide variety of endogenous and exogenous compounds.[1] Drug interactions involving P-450 are common, and generally result from either enzyme inhibition or induction. Understanding CYP enzyme interactions might allow prescribers the ability to better anticipate and manage each patient's response to a drug regimen.[2]

Recently, evidence has been found that *tert*-butyl acetylene (tBA) can act as mechanism-based inactivator of cytochrome P-450 enzymes.[3] We were therefore interested in conducting the synthesis of labeled tBA to perform enzyme inhibition studies and amino acid residue identification on the active site. The synthesis of [^{14}C]tBA has not been previously reported.

Results and discussion

Several possible syntheses have been published for tBA.[4] To date, the most efficient way of preparing tBA is by the method from Bartlett and Rosen.[5] We therefore decided to prepare [^{14}C]pinacolone by Weinreb ketone synthesis and then apply the method of Bartlett and Rosen for formation of [^{14}C]tBA.

Synthesis of the pivalamide **3** was easily accomplished by applying a previously published procedure by Tillyer[6] using Schotten-Baumann conditions. The [^{14}C]methyl Grignard was prepared using standard vacuum-transfer procedures. The formation of [^{14}C]-pinacolone **4** was accomplished in 28% yield, with 82% radiochemical purity.

The next step was initially carried out unsuccessfully using modified Negishi conditions.[7] The chlorination/dehydrochlorination step was therefore based on work

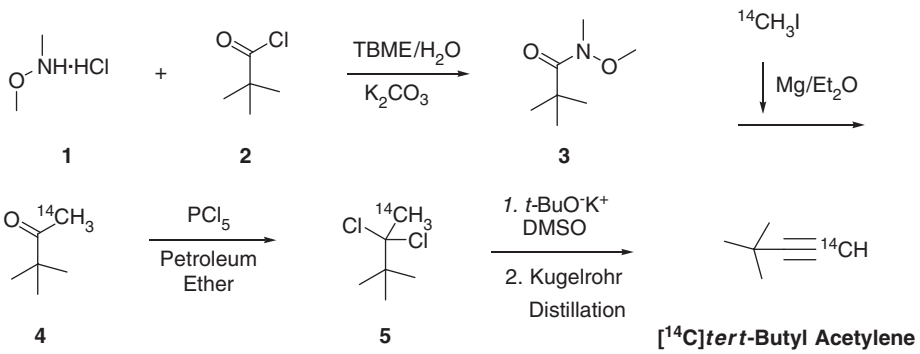

Figure 1 Synthesis of [^{14}C]tBA.

*Correspondence to: Karla G. Cuevas-Licea, Department of Drug Metabolism, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065, USA. E-mail: karla_cuevas_licea@merck.com

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

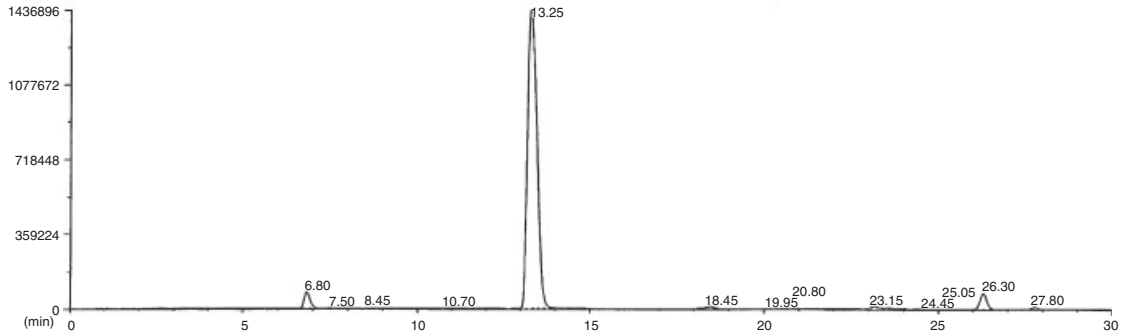

Figure 2 Radiochemical purity of [^{14}C]tBA.

by Bartlett and Rosen[5] and Kocienski[8] (Figure 1). The final product was obtained by Kugelrohr distillation in 25% isolated yield and 91% radiochemical purity (Figure 2). Identity was confirmed by comparison with unlabeled tBA on HPLC and GC-FID.

Conclusion

Modification of current literature procedures and the development of a modified distillation technique have allowed us to successfully synthesize and isolate [^{14}C]tBA, which will be used to develop P-450 enzyme inhibition studies.

REFERENCES

1. Gonzalez FJ. *Pharmacol Rev* 1998; **40**: 243–288.
2. Foye WO, Lemke TL, Williams DA. *Principles of Medicinal Chemistry*, (5th Ed). Lippincott Williams and Wilkins: Philadelphia.
3. Kent UM, Roberts-Kirchoff ES, Moon N, Dunham WR, Hollenberg PF. *Biochemistry* 2001; **40**: 7253–7261.
4. (a) Kazakov PV, Demina EI. *Russ Med Bull Int Ed* 2002; **51**: 2134-2135; (b) Collier WL, Macomber RS. *J Org Chem* 1972; **38**: 1367–1369; (c) Hargrove RJ, Stang PJ. *J Org Chem* 1973; **39**: 581–582.
5. Bartlett PD, Rosen LJ. *J Am Chem Soc* 1942; **64**: 543–546.
6. Tillyer R, Frey LF, Tschaen DM, Dolling UH. *Synlett* 1996; **3**: 225–226.
7. Negishi E, King AO, Klima WL. *J Org Chem* 1980; **45**: 2526–2528.
8. Kocienski PJ. *J Org Chem* 1974; **39**: 3285–3286.

DOI: 10.1002.jlcr