Journal of Labelled Compounds and Radiopharmaceuticals
*J Label Compd Radiopharm* 2007; **50**: 578–579.
Published online in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1284

JLCR

Short Research Article

# Carbon-14 labelling of 3-cyanoquinolines†

JOHN D. OLSZEWSKI[1,*], DAN M. BERGER[2] and MICHAEL K. MAY[1]

[1] Chemical Development—Radiosynthesis, Wyeth Research, 401 N. Middletown Road, Pearl River, New York 10965, USA
[2] Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Road, Pearl River, New York 10965, USA

*Received 20 June 2006; Revised 2 January 2007; Accepted 20 January 2007*

**Keywords:** carbon-14; cyanoquinoline; cyano-[$^{14}$C]-acetic acid; Buchwald; amidine; enaminone

## Introduction

Wyeth has recently reported the synthesis of 4-anilino-3-quinolinecarbonitrile analogues, including several compounds with amines at C7, that have been found to be inhibitors of MEK1.[1,2] The Radiosynthesis Group and Discovery Chemistry have developed a novel labelling approach to the 3-cyanoquinoline core structure that allows the flexibility to provide analogues.

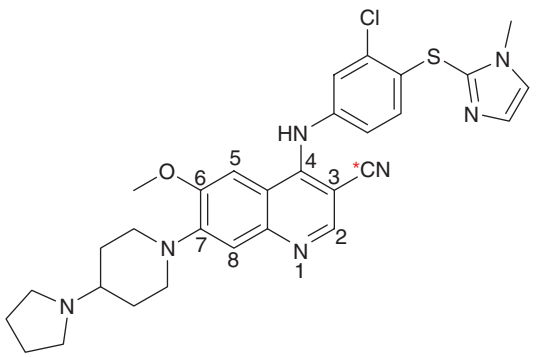


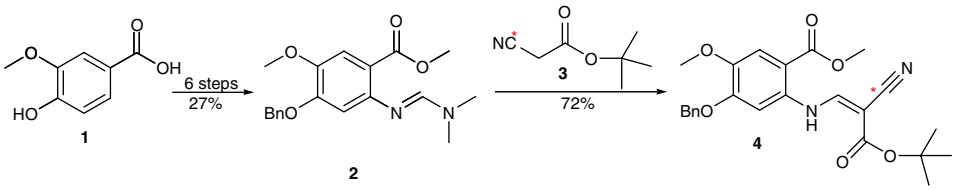

**Figure 1** [$^{14}$C]MKI-833.

The synthesis of [$^{14}$C]MKI-833 is an example of this approach (Figure 1).

Our strategy differs from prior work[3] and was developed as a result of experiences in preparing ring labelled $^{14}$C-cyanoquinoline compounds that were prone to decomposition. We decided to move the label outside the ring preparing a core structure useful for other analogues. [$^{14}$C]MKI-833 was envisioned to arise from a [$^{14}$C]cyanoquinoline, derived from an amidine and cyano-[$^{14}$C]acetic acid, aniline substitution at C4 and Buchwald coupling at C7.

## Results and discussion

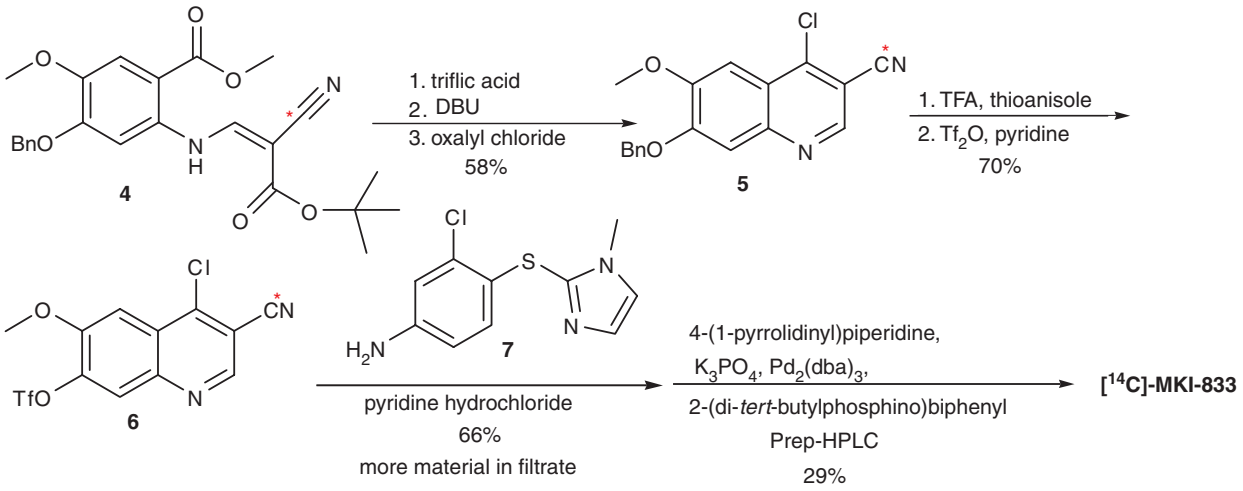
Preparation of amidine **2** used literature procedures with minor modifications.[4,5] Synthesis of *tert*-butyl cyano-[$^{14}$C]acetate **3** was accomplished from bromoacetic acid and [$^{14}$C]KCN[6] followed by esterification.[7] The amidine **2** was stirred with excess *tert*-butyl cyano-[$^{14}$C]-acetate in IPA at RT to give enaminone **4** which was filtered off. The enaminone **4** was cyclized to a cyanoquinoline in a one-pot procedure and followed by




**Scheme 1**

*Correspondence to: John D. Olszewski, Wyeth Research, Chemical Development—Radiosynthesis, 401 N. Middletown Road, Pearl River, New York 10965, USA. E-mail: olszewj@wyeth.com

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




**Scheme 2**

chlorination to **5**. At this point, the 4-chloro-3-cyano-[$^{14}$C]quinoline **5** could be converted into a variety of compounds by removal of the protecting groups and replacement of the chlorine. For [$^{14}$C]MKI-833, the benzyl group was removed followed by protection to give triflate **6**. Replacement of the chlorine with aniline **7** gave the penultimate compound. Preparation of [$^{14}$C]MKI-833 was accomplished via Buchwald coupling with 4-(1-pyrrolidinyl)piperidine. The optimized reaction conditions provided the product in modest yield. Typical Buchwald coupling solvents[8] could not be used due to solubility issues. Literature precedent conditions[9] and a reaction time of 20 h afforded higher yields of a cleaner product that was purified by HPLC and then used for ADME studies (Schemes 1 and 2).

## REFERENCES

1. Berger D, Dutia M, Powell D, Wu B, Wissner A, Boschelli DH, Floyd MB, Zhang N, Torres N, Levin J, Du X, Wojciehowicz D, Discafani C, Kohler C, Kim SC, Feldberg LR, Collins K, Mallon R. *Bioorg Med Chem Lett* 2003; **13**: 3031–3034.
2. Boschelli DH. *Curr Topics Med Chem* 2002; **2**: 1051–1063 and references therein.
3. Carr RM, Sutherland DR. *J Label Compd Radiopharm* 1994; **34**(10): 961–971.
4. Thurston DE, Varanasi SM, Langley DR, Jones GB. *Synthesis* 1990; **1**: 81–84.
5. Wang T, Lui AS, Cloudsdale IS. *Org Lett* 1999; **1**(11): 1835–1837.
6. Koltai E, Zolyomi G, Komaromy P, Banfi D, Szuts T, Takacs K. *J Label Compd Radiopharm* 1981; **18**(8): 1107–1113.
7. Shelkov R, Nahmany M, Melman A. *J Org Chem* 2002; **67**(25): 8975–8982.
8. Wolfe JP, Tomori H, Sadighi JP, Yin J, Buchwald SL. *J Org Chem* 2000; **65**(4): 1158–1174 and references therein.
9. Wu Y-J, Boissard CG, Greco C, Gribkoff VK, Harden DG, He H, L'Heureux A, Kang SH, Kinney CG, Knox RJ, Natale J, Newton AE, Lehtinen-Oboma S, Sinz MW, Sivarao DV, Starrett Jr. JE, Sun L-Q, Tertyshnikova S, Thompson MW, Weaver D, Wong HS, Zhang L, Dworetzky SI. *J Med Chem* 2003; **46**(15): 3197–3200.



DOI: 10.1002.jlcr