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Short Research Article

Carbon-14 labelling of 3-cyanoquinolines†

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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.

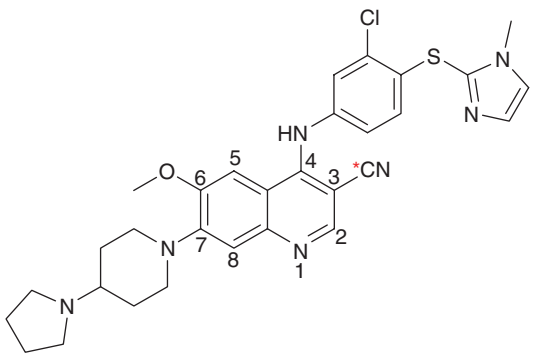


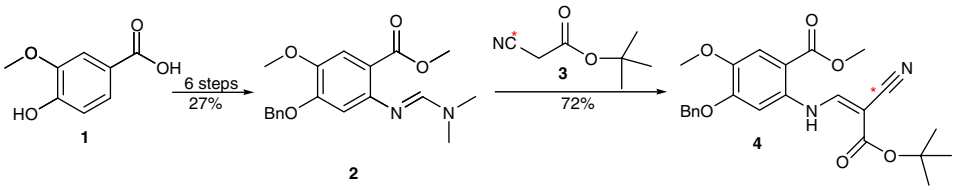
Figure 1 [^{14}C]MKI-833.

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

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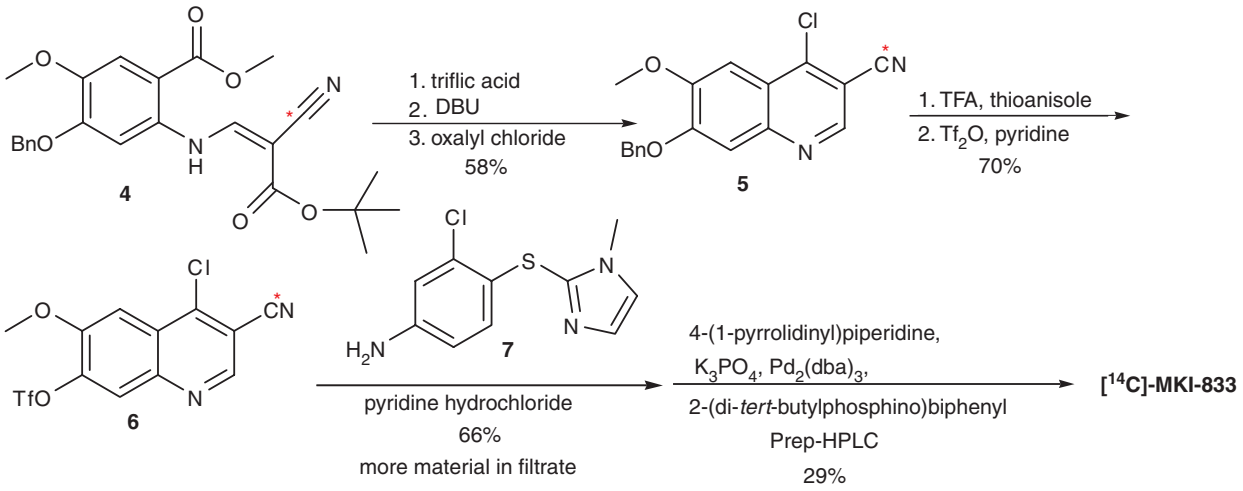

Scheme 2

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).

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