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Short Research Article

Isotopic labelling with chlorine-37†

ALAN H WADSWORTH, STEVE MONTGOMERY, KENNETH W. M. LAWRIE* and RICHARD M. CARR
GlaxoSmithKline, Isotope Chemistry, Medicines Research Centre Gunnels Wood Road Stevenage SG1 2NY, UK

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Introduction

Mometasone furoate[1] is a potent corticosteroid marketed by Schering and a stable isotope labelled version **1** with eight extra atomic mass units (amu) was required as an internal standard. Mass labelling of mometasone furoate with only deuterium and carbon-13 would be a significant challenge without manipulation of the steroid skeleton. The use of chlorine-37 as an isotopic labelling tool is rarely considered, since the sole commercial source of chlorine-37 label is sodium [^{37}Cl]chloride, available with 95% incorporation. However, its use in a synthesis of **1** was considered feasible, leaving only four amu to be incorporated into the furoic acid moiety, a straightforward task. A chlorine-37 isotopic abundance of not less than 75% was needed for sufficient sensitivity of the mass spectrometric assay.

Results and discussion

Furoic acid **3** was prepared by lithiation of furan **2** with *n*-butyllithium, followed by quenching with [^{13}C]carbon dioxide. The crude product was purified by sublimation to give furoic acid in 54% yield, and converted to the acid chloride in quantitative yield. In the published synthesis[1] of mometasone furoate, hydroxyketone **5** is converted into unlabelled chloroketone **7** by reaction with tosyl chloride and triethylamine in dichloromethane. This occurs *via* formation of the intermediate tosylate **6**, followed by subsequent displacement with *in situ* chloride ion. To incorporate a chlorine-37 label, this process requires separation of the two stages. Substitution of tosic anhydride for tosyl chloride allowed the clean conversion of alcohol **5** into tosylate **6**. Reaction of **6** with sodium [^{37}Cl]chloride (1.25 eq., ^{37}Cl/^{35}Cl = 95:5), partially solubilized in dimethylformamide with 18-crown-6, gave a quantitative yield of chloroketone 7. Conversion of **7** into **8** may potentially lead to dilution of the chlorine-37 labels with the unlabelled chlorine of furoyl chloride **4**. However, in a trial labelled reaction at 80% conversion (20 h) LC-MS showed a much greater dilution of the chlorine-37 label in unreacted **7** (^{37}Cl/^{35}Cl = 75:25) compared to product **8** (92:8). After **4** days, these ratios had changed to 60:40 and 90:10 respectively, indicating that isotopic dilution was not a significant problem in the more sterically hindered environment of the tertiary furoyl ester **8**.

Subsequently, a 60% molar excess of acylating agent **4** was found to give complete conversion to **8** in only 4 h with no significant dilution of the chlorine-37 label (92:8). The published method for the conversion of epoxide **8** into mometasone furoate requires a large excess of concentrated hydrochloric acid in chloroform. After much experimentation it was found that a mixture of sodium [^{37}Cl]chloride, concentrated sulphuric acid and a phase-transfer catalyst (tetrabutylammonium bisulphate) was an excellent alternative to concentrated hydrochloric acid. In this way, only four equivalents of sodium [^{37}Cl]chloride were required for

*Correspondence to: Kenneth W. M. Lawrie, GlaxoSmithkline, Isotope chemistry, Medicines Research centre Gunnels wood Road, Stevenage SG1 2NY, UK. E-mail: ken.w.lawrie@gsk.com
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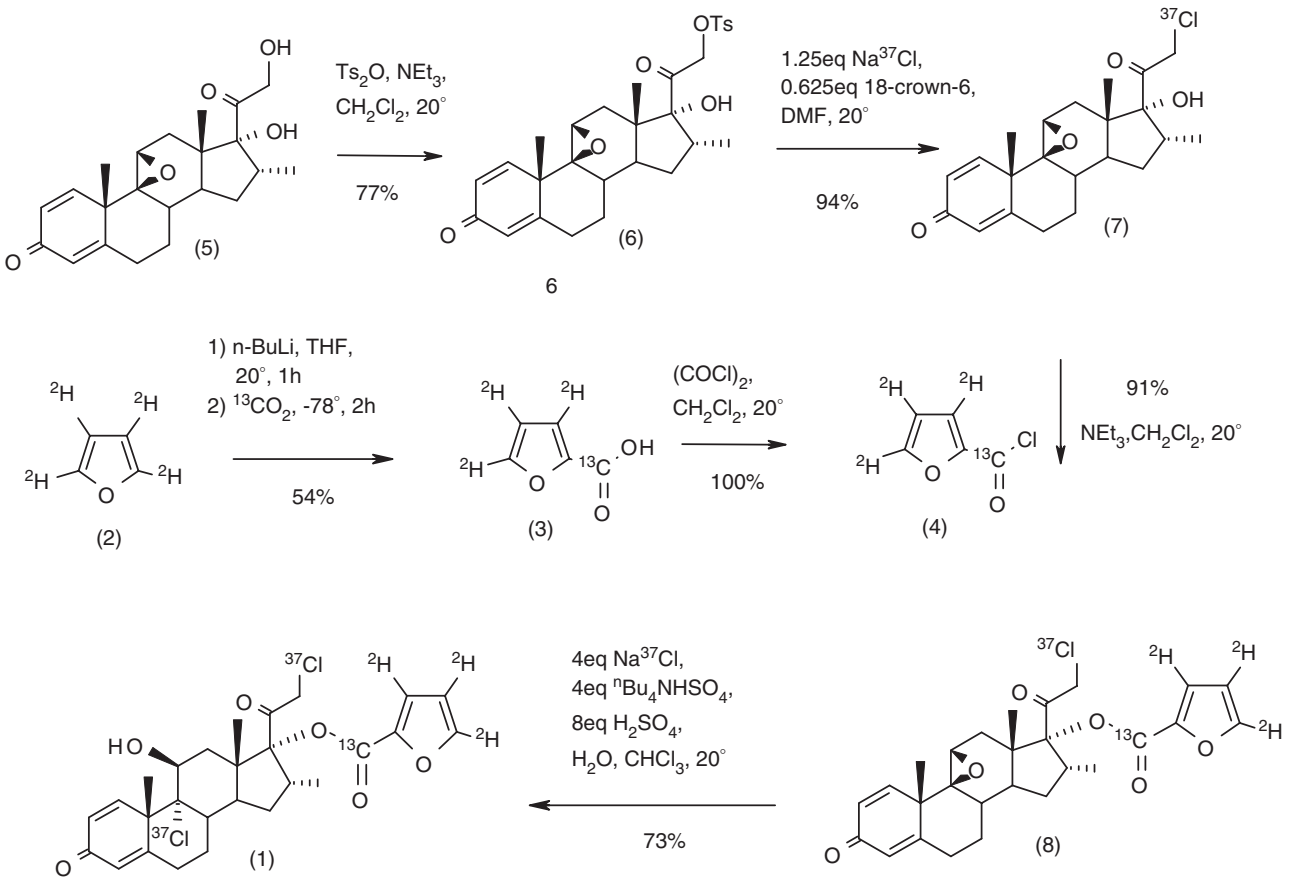

complete conversion of **8** into **1**. Isotopic dilution in the final product (**1**) was $^{37}Cl/^{35}Cl$ = 88:12, but more importantly there was no unlabelled compound detected.

REFERENCE

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