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Short Research Article

The synthesis of ($^{13}C_6$)*N*-(3,4-dichlorophenyl)-2,2-dimethylpropanamide†

KENNETH W. M. LAWRIE*

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

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Introduction

Stable labelled isotopomers of compounds in drug development are routinely used as internal standards in LC/MS/MS assays. [$^{13}C_6$] *N*-(3,4-dichlorophenyl)-2,2-dimethylpropanamide **1** was required as an intermediate in the synthesis of such an isotopomer of a compound under development at GSK.

Results and discussion

Protection of [$^{13}C_6$]aniline as acetanilide moderates its reactivity and gives good control of regioselectivity of nitration. Nitration of [$^{13}C_6$]acetanilide with a mixture c. H_2SO_4 and $NaNO_3$ gives 4-nitro [$^{13}C_6$]acetanilide in 93% yield.[1] The 2-nitro isomer is not detected. Contrastingly use of the 'classic' HNO_3/H_2SO_4 nitration mixture gives around 20% of the 2-nitro isomer. The protecting group is readily removed by hydrolysis with NaOH, and the 4-nitro[$^{13}C_6$]aniline chlorinated cleanly and in high yield by reaction with NCS in acetonitrile at reflux.[2] Two sets of conditions were investigated for the diazotization/chlorination sequence; (i) 'classic' conditions; diazonium salt formation in aqueous HCl with $NaNO_2$ and decomposition with freshly prepared Cu(I)Cl and (ii) non-aqueous diazotization with isoamyl nitrite in acetonitrile and chlorination with Cu(II)Cl_2. The second set is significantly superior to the 'classic' method. The yield is higher (75–90% compared to 40–60%), a purer product results and commercially available Cu(II)Cl_2 can be used as opposed to Cu(I)Cl, which for good results needs to be freshly prepared. The nitro group is readily reduced by $SnCl_2$ in ethanol at reflux in quantitative yield. The title compound is formed by reaction with trimethylacetyl chloride in a two phase reaction (TBME/5M NaOH) in 93% yield.

Conclusions

A short, high yielding (overall 35–45%) and regiospecific synthesis of [$^{13}C_6$] *N*-(3,4-dichlorophenyl)-2,2-dimethylpropanamide **1** has been developed starting from the readily available [$^{13}C_6$]aniline. The non-aqueous diazotization protocol has been shown to be superior to traditional methods for the chlorination of [$^{13}C_6$]2-chloro-4-nitroaniline.

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*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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