

Short Research Article

The synthesis of ($^{13}\text{C}_6$)*N*-(3,4-dichlorophenyl)-2,2-dimethylpropanamide[†]

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Introduction

Stable labelled isotopomers of compounds in drug development are routinely used as internal standards in LC/MS/MS assays. [$^{13}\text{C}_6$] *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 [$^{13}\text{C}_6$]aniline as acetanilide moderates its reactivity and gives good control of regioselectivity of nitration. Nitration of [$^{13}\text{C}_6$]acetanilide with a mixture c. H_2SO_4 and NaNO_3 gives 4-nitro [$^{13}\text{C}_6$]acetanilide in 93% yield.¹ The 2-nitro isomer is not detected. Contrastingly use of the 'classic' $\text{HNO}_3/\text{H}_2\text{SO}_4$ nitration mixture gives around 20% of the 2-nitro isomer. The protecting group is readily removed by hydrolysis with NaOH, and the 4-nitro [$^{13}\text{C}_6$]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 $\text{Cu}(\text{I})\text{Cl}$ and (ii) non-aqueous diazotization with isoamyl nitrite in acetonitrile and chlorination with $\text{Cu}(\text{II})\text{Cl}_2$.

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 $\text{Cu}(\text{II})\text{Cl}_2$ can be used as opposed to $\text{Cu}(\text{I})\text{Cl}$, 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 [$^{13}\text{C}_6$] *N*-(3,4-dichlorophenyl)-2,2-dimethylpropanamide **1** has been developed starting from the readily available [$^{13}\text{C}_6$]aniline. The non-aqueous diazotization protocol has been shown to be superior to traditional methods for the chlorination of [$^{13}\text{C}_6$]2-chloro-4-nitroaniline.

REFERENCES

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