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Short Research Article

Use of simple stable labelled intermediates to produce complex isotopically labelled internal standards†

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Introduction

Stable isotopically labelled (SIL) compounds are of great value in the discovery process as they can confer greater sensitivity and robustness during the development of bioanalytical methods. Once thought of as a model for radioactive syntheses, SIL compounds are becoming increasingly important in their own right and, although structurally similar, can create many different synthetic challenges. Targets containing chlorine or sulphur atoms may require up to seven additional mass units to create sufficient mass differential from the parent. This can be difficult to achieve from the limited range of synthetic precursors available which offer little scope for the introduction of multiple isotopic labels. Consequently, compounds often have to be assembled from several different isotopic precursors or a common fragment to deliver the mass difference required.

Results and discussion

Common fragment synthesis

Where a chemical series is being explored, the identification and synthesis of an SIL common fragment can be particularly effective. The 2,3-dichlorobenzenesulphonyl chloride (Scheme 1) moiety was just such an example.

Trial reactions were initially undertaken to identify conditions that maximized the formation of the desired anion. Sulphonation followed by quenching with *N*-chlorosuccinimide afforded the sulphonyl chloride, which, using standard amide coupling with a range of amines, gave, the target sulphonamides.

Only the simplest [^{13}C]SIL aromatic building blocks are available and significant synthetic effort is required to elaborate these further to provide more useful intermediates as shown in Scheme 2.

Similarly, [$^{2}H_8$]toluene and [$^{2}H_8$]piperazine have been successfully utilized to provide several SIL compounds although care has to be taken to avoid isotopic exchange[1] as shown in Scheme 3.

Synthesis with multiple isotopes

Due to constraints of the compound it is sometimes not possible to use a single isotope source and it is necessary to use multiple isotopes. An example of which is shown in Scheme 4. The nature of the heterocyclic ring affords little opportunity for the introduction of the extra mass units required. However, by incorporating a nitrogen-15 isotope into ethyl [^{15}N]aminotrifluorocrotonate and subsequent ring closure gives the thiazalone intermediate. Reaction of [$^{2}H_5$]epichlorohydrin and [^{15}N]ammonia affords the labelled amino alcohol that is coupled to the thiazalone to afford the target compound with a total of seven mass units greater than the parent.

Another example of this strategy is described in Scheme 5. It was necessary to produce several SIL compounds in a short period of time in order to select a best candidate from the series.

The hydantoin fragment was common to the compounds that were under investigation. [$^{13}C_3$]Chloroacetone was prepared from [$^{13}C_3$]acetone with the monohalogenated product being obtained in good yield.[2] Alkylation followed by microwave-induced ring

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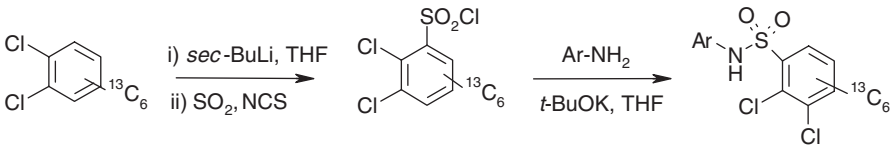
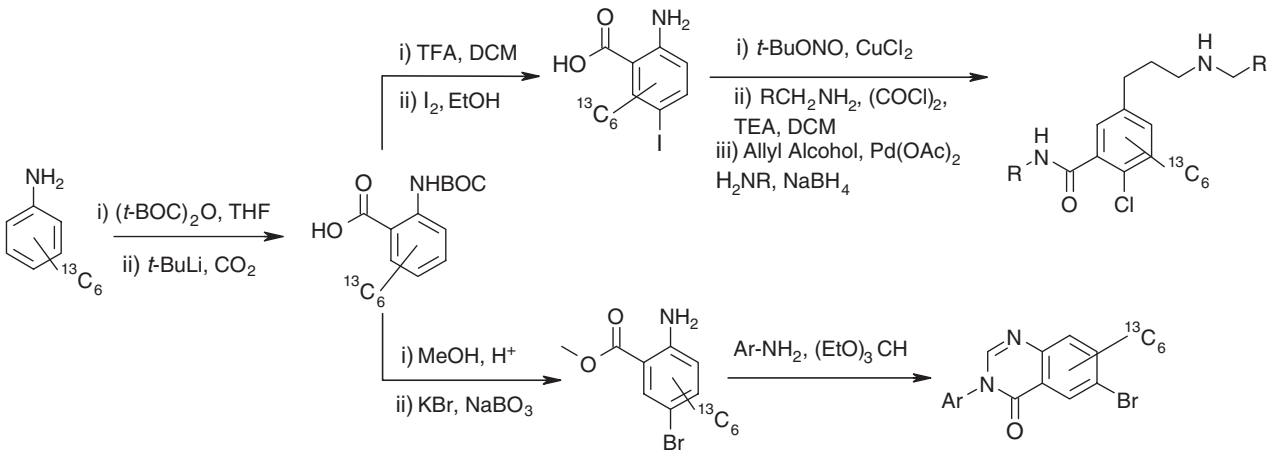
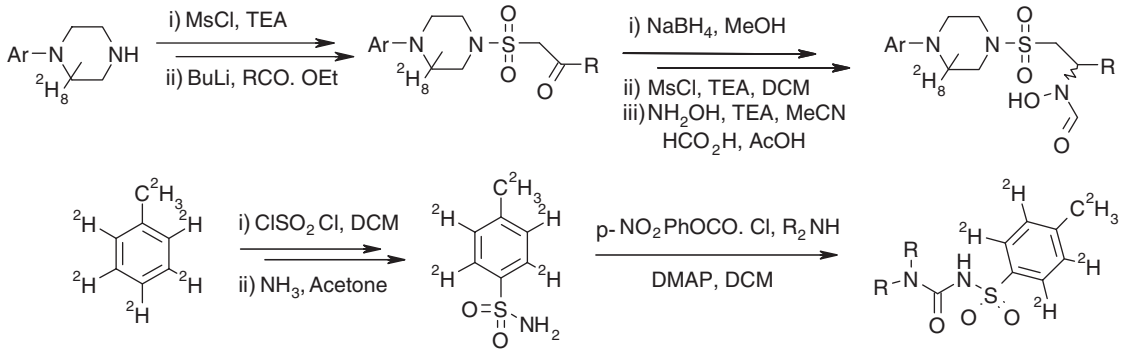


Scheme 1



Scheme 2



Scheme 3

closure afforded material that was readily converted to the sulphonyl chloride. Standard coupling with a range of amines gave several sulphonamide compounds from the series.

Conclusion

Stable isotopically labelled (SIL) compounds can be used as powerful tools in the development of robust, sensitive bioanalytical methods. The synthesis of SIL compounds can be resource intensive, costly and synthetically challenging due to the need to provide multiple labelled products. Ultimately, they can provide the analyst with methodology, which is reliable and requires little modification during the lifetime of the project thereby avoiding unwanted scrutiny from regulatory authorities.

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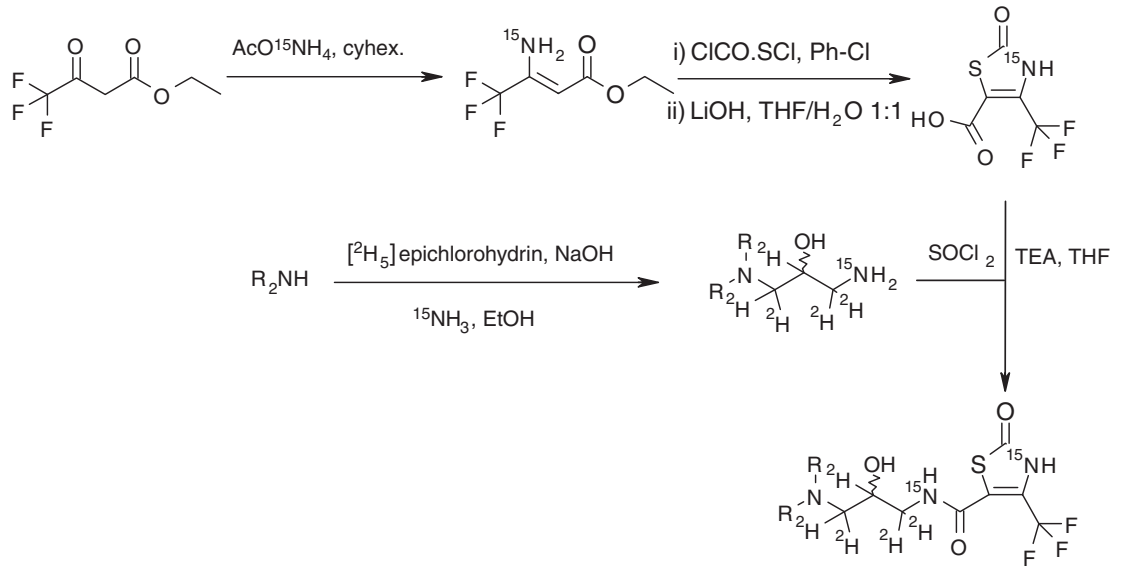
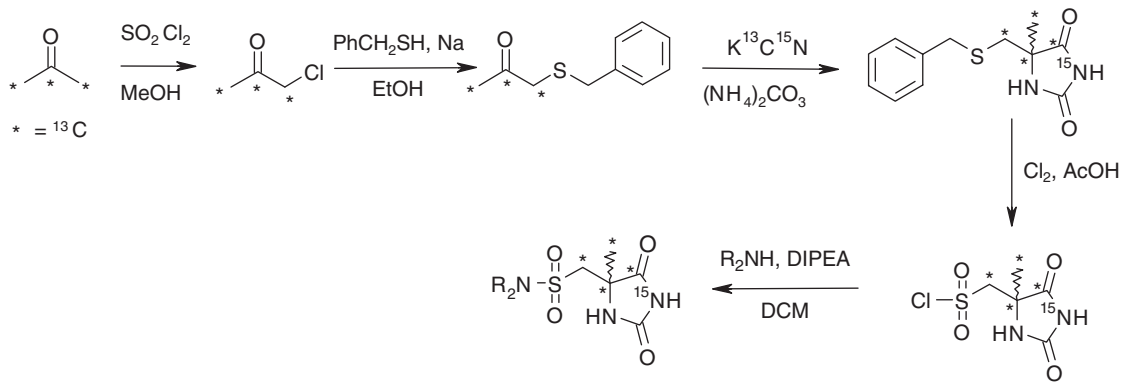


Scheme 4



Scheme 5

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