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Short Research Article

A novel synthesis of ($^2H_6$)2-methyl-3-butyn-2-ol[†]

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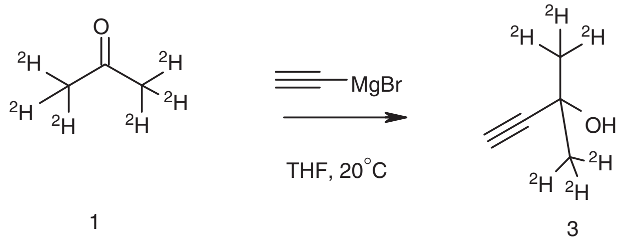
Introduction

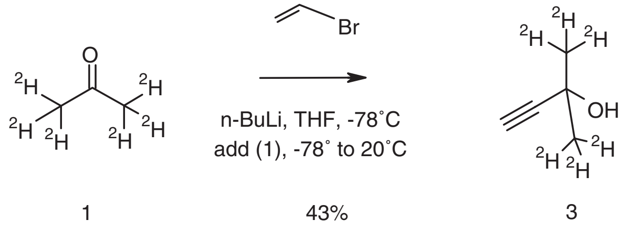
[$^2H_6$]2-methyl-3-butyn-2-ol **3**, synthesized[1] from hexadeuteroacetone **1** and acetylenic Grignard reagent **2**, was required as an intermediate in the synthesis of a mass labelled internal standard. In general an increase of at least 3 a.m.u. over the test substance and a very high degree of isotopic incorporation (typically $<0.1\%$ unlabelled) is required for such a standard. MS analysis, however, of an advanced intermediate, showed $\sim 0.5\%$ of the corresponding unlabelled molecular ion clearly deriving from the butynol. It seemed likely that this arose from contamination of the acetylenic Grignard reaction with unlabelled acetone.



Scheme 1

Results and discussion

A second batch of **3** was prepared as above (Scheme 1), taking extra precautions to avoid contamination by adventitious acetone. The [$^2H_6$] acetone **1** showed (NMR) no trace of unlabelled acetone. The product **3** was derivatized by a Mannich reaction[2] (HCHO, pyrrolidine, CuI) prior to LC-MS analysis, which confirmed 0.5% M0. Acetone is used in the commercial packing of acetylene[3] into gas cylinders, so is likely to be a contaminant in commercial acetylenic Grignard reagents. An alternative source of an acetylenic organometallic reagent, guaranteed acetone-free, was required. Generation of acetylene by dehydrobromination[4] of readily available vinyl bromide, under conditions that would lead to the eventual formation of monolithium acetylide, was chosen. The generation of vinyllithium from vinyl bromide and *t*-butyllithium is carried out at -120°C. Above -110°C, however, competitive formation of acetylene by dehydrobromination occurs.[4a] An attempt to prepare vinyllithium from vinyl bromide and *n*-butyllithium in diethyl ether at 0°C resulted, after quenching with carbon dioxide, in a 34% yield of acetylenedicarboxylic acid, presumably via the formation[4b] of dilithium acetylide. The stoichiometric reaction of acetylene with *n*-butyllithium at -78°C is known[4c] to favour the formation of monolithium acetylide over that of dilithium acetylide. Treatment of vinyl bromide with one equivalent of *n*-butyllithium at -78°C generated lithium monoacetylide[5], which was treated with hexadeuteroacetone at -78°, allowed to warm to room temperature, and the desired product **3** isolated in 43% yield. Mannich derivatization of a sample followed by LC-MS analysis confirmed that the desired product **3** had formed and contained no detectable M0 (Scheme 2).



Scheme 2

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Conclusion

A novel method of preparing acetone-free monolithium acetylide from vinyl bromide has been developed in order to prepare [$^2H_6$]2-methyl-3-butyn-2-ol **3** suitable for use in the synthesis of a mass labelled internal standard.

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