

Application of a Novel Directing Effect in an Organocopper/Orthoester Reaction to the Synthesis of Deuterium Labeled Unsaturated Esters

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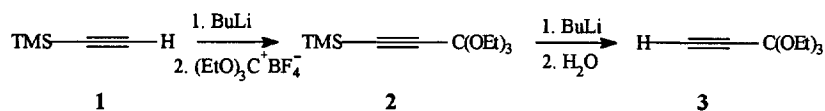
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Abstract: Deuterium labeled methacrylates (5,6), tiglates (10,12), and senecioates (13,14,16,17), important for biosynthetic studies on the synthesis of carboxylic acids in carabid beetles, have been prepared using organocopper-alkyne coupling reactions. With 1,1,1-triethoxypropyne as a coupling partner, a novel directing effect was observed; the "branched" product was formed exclusively.

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We required a number of specifically deuteriated, branched, unsaturated acids in connection with a study of the biosynthesis of defensive compounds in carabid beetles. In the course of applying Normant and Alexakis organo-copper alkyne couplings¹ to these syntheses, we found that an orthoester substituent brings about a novel orientation effect. We here describe these results, which may be particularly useful for the preparation of a variety of specifically labeled compounds.

Labeled methacrylates were prepared as outlined in Schemes 1 and 2.² Commercially available trimethylsilylacetylene (**1**) (Farchan Laboratories) was deprotonated with *n*-butyllithium and treated with triethoxycarbonium tetrafluoroborate to give **2**³ (Scheme 1). Treatment with additional *n*-butyllithium followed by water gave **3**, the desired starting material for the organocopper reaction, in 77% yield.²

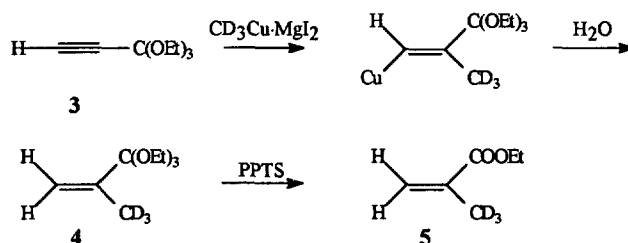


Scheme 1

Deuteriated methylcopper was prepared by addition of commercially available trideuteriomethylmagnesium iodide to copper(I) bromide-dimethyl sulfide complex⁴ at -55°C in THF/methyl sulfide (1:1). The mixture was warmed to -40°C and stirred for two hours. Alkyne **3** was added at -60°C and warmed to -15°C. After stirring for four days, the reaction was quenched with water affording orthoester **4** in 39% yield (Scheme 2). Side reactions of dimer formation and dimethylation account for the reduced yield. Hydrolysis of **4** with the mild acid catalyst pyridinium *p*-toluenesulfonate (PPTS)⁵ (10 mole percent) in ethanol/water (8 mL to 0.2 mL) at 0°C for four hours gave **5**.

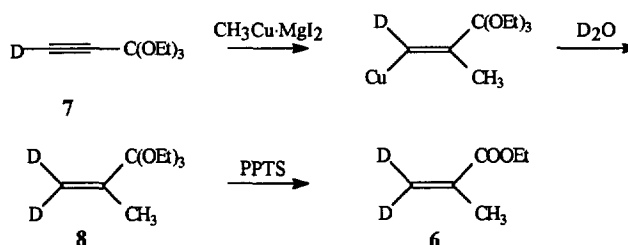
In the successful formation of the "branched" product **5**, no trace of the "linear" regio-isomer was observed in GC/MS analysis of the reaction mixture. This is the first example, to the best of our knowledge, of

an organocopper reaction with an alkyne bearing a carbon in the oxidation state of a carboxylic acid giving the branched adduct as the major product. The complete regio-control observed in this reaction makes it a potentially desirable synthetic route to compounds with similar stereo- and regio-control demands.



Scheme 2

Another required ethyl methacrylate, 6, could be made simply by modifying the above described procedure. In the synthesis of 3, deuterium oxide substitution for water gave 7 (Scheme 3). Using non-deuteriated methylcopper and deuterium oxide quenching afforded 8 in 39% yield. Subsequent PPTS-catalyzed hydrolysis gave ester 6.



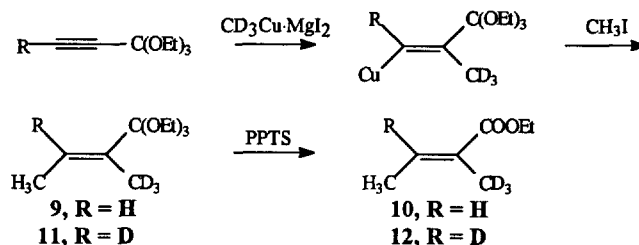
Scheme 3

With both desired deuterium labeled ethyl methacrylates in hand, our interest turned towards adapting this synthetic methodology to other targets. Two ethyl tiglates (10 and 12) with a deuterium labeling pattern required for a different biosynthetic study were obtained using methyl iodide as the electrophile to quench the vinylcopper species rather than water.

Under the conditions for the preparation of 4, hexamethylphosphorous triamide (HMPT) (2 equiv.), triethyl phosphite (3 equiv.)⁶, and methyl iodide reacted with the vinylcopper reagent at 25°C, giving 9 in 43% yield (Scheme 4). Acidic hydrolysis afforded ethyl ester 10. Repeating the procedure using alkyne 7 gave orthoester 11 in 48% yield. This orthoester was then hydrolyzed to the desired labeled ethyl tiglate, 12.

Spectroscopic evidence for the labeling pattern in esters 10 and 12 was obtained by ¹H NMR analysis. In ester 10, the vinylic proton gives a quartet at 6.82 ppm with a *J* value of 7 Hz. The methyl signal is a

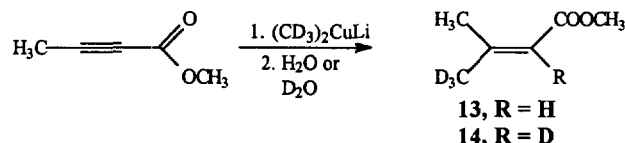
doublet at 1.75 ppm with a J value of 7 Hz. In ester **12**, the methyl group appears as a singlet at the same chemical shift as in **10** (1.75 ppm), and the vinylic proton signal is absent.



Scheme 4

In a different study involving senecioic acid biosynthesis, four deuterium labeled senecioates were needed. In this case, the “linear” regio-isomer was desired, and the orthoester substituent on the alkyne starting material was therefore replaced with an ester group.

The procedure described by Anderson⁷ was easily adapted to give the esters **13** and **14** (Scheme 5). Methyl-2-butyynoate (Aldrich) reacted with deuterium labeled methyl Gilman reagent at -78°C in THF/methyl sulfide (3:1) for 30 minutes. Quenching with water and acidic deuterium oxide⁸ gave **13** and **14** in 54% and 83% yields respectively. The anticipated “linear” isomer was obtained exclusively.

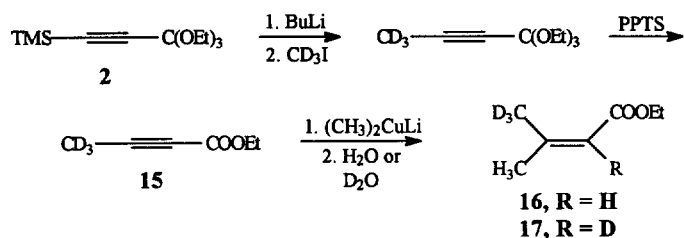


Scheme 5

Two other desired senecioates were synthesized from ethyl ester **15**, itself obtained from trideuteriomethyl iodide reaction with the anion of triethylorthopropionate and subsequent hydrolysis. Coupling with unlabeled methyl cuprate and quenching with either water or deuterium oxide gave **16** and **17** in yields of 41% and 66% respectively. (Scheme 6)

Assignments of the anticipated stereo- and regio-chemistry of the four labeled senecioates were confirmed on the basis of ^1H NMR spectral data. Collin and Sternhell⁹ showed that in senecioic acid, the *Z* methyl (2.18 ppm) is farther downfield than the *E* methyl group (1.92 ppm). Both **13** and **14**, the methyl senecioates with the unlabeled methyl *cis* to the ester group, have chemical shifts at 2.12 and 2.14 ppm,

respectively. Ethyl esters **16** and **17**, with the unlabeled methyl group *trans* to the ester group show methyl shifts of 1.86 ppm.



Scheme 6

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