On the Use of 3-Bromopropyne as a Reagent for the Introduction of the Pyruvate Moiety

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In the presence of metallic zinc 3-bromopropyne reacts with aldehydes to give homopropynylic alcohols which are converted to the corresponding bromohomopropynylic acetates by acetylation followed by reaction with *N*-bromosuccinimide and a catalytic quantity of silver acetate; these derivatives are then oxidized to γ-acetoxy-α-ketoesters with osmium tetroxide and *tert*-butyl hydroperoxide resulting in a convenient four step sequence for the introduction of the pyruvate moiety.

The biosynthesis of the sialic and ulosonic acids is thought to involve the effective condensation of pyruvic acid, in the form of phosphoenol pyruvate, with aldoses.[1] Consequently considerable effort has been expended on the design of pyruvate anion equivalents for use in the laboratory. Nevertheless, to our knowledge, the successful development of a simple, general reagent or protocol suitable for use with both carbonyl and halogenoalkane type electrophiles has not yet been achieved.[2,3] In this communication we report a simple four step sequence for the effective introduction of the pyruvate moiety involving straightforward acetylene chemistry which is applicable to both aldehydes and alkyl halides as electrophiles.

The general principles of the approach are outlined for the more demanding case of aldehydes as electrophiles in Scheme 1. The three carbon chain is introduced in the form of a 1-metallo-2-propyne derivative. The requisite γ-hydroxy-α-oxo acid or ester is then revealed by a two step oxidative procedure. Advantages of the method principally involve the ability to protect the homopropynylic alcohol with a suitable blocking group and carry this latter derivative through a synthetic scheme only revealing the delicate γ-hydroxy-α-oxo acid or ester in the last step.

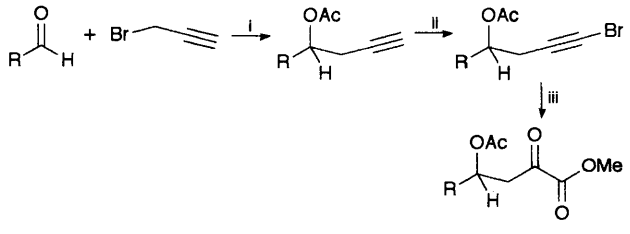
In the event, we chose to couple 3-bromopropyne to the aldehyde by stirring with zinc powder in tetrahydrofuran (THF) at room temperature when good yields were obtained of the required homopropynylic alcohols within 24 h (Table 1).[4] Significant increases in reaction rate were observed on sonication in a standard ultrasonic cleaning bath.[5] Acetylation gave the corresponding acetate esters which were converted to the bromo- or iodo-alkynes by reaction with 10 mol% of silver acetate and *N*-bromo- or *N*-iodosuccinimide, respectively, essentially as described by Hofmeister for steroidal propynylic alcohols (Table 1).[6]

We then turned to the oxidation step. Initially we studied the oxidation of 1-bromooct-1-yne **7** and 1-bromo-2-phenylacetylene **8** which themselves were produced from the corresponding alkynes by the *N*-bromosuccinimide (NBS)–AgOAc procedure. The oxidation reactions were run in dry methanol with a catalytic amount of OsO_4 and 5 mol. equiv. of

Table 1 Formation of halohomopropynylic alcohols[a]

Entry	Substrate	Alcohol (% Yield)	Acetate (% Yield)	Haloalkyne (Hal., % Yield)
1	**1a**	**2a**(85)	**3a**(96)	**4a**(Br, 89)
2	**1b**	**2b**(81)	**3b**(99)	**4b**(Br, 78; I, 82)
3	**1c**	**2c**(88)	**3c**(94)	**4c**(Br, 98)

[a] Yields refer to isolated, chromatographically and spectroscopically homogeneous compounds.

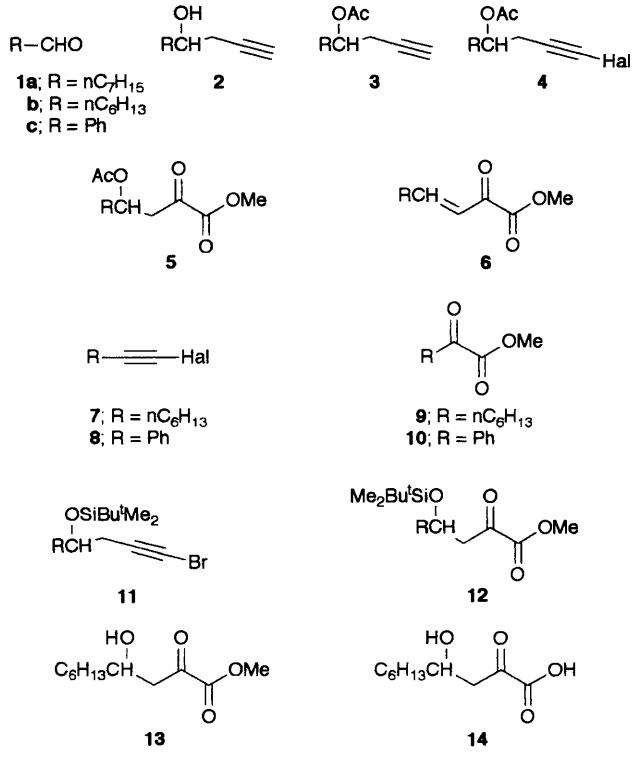


Scheme 1 *Reagents*: i, (*a*) Zn, THF (*b*) Ac_2O, pyridine; ii, NBS, AgOAc; iii, Bu^tOOH, OsO_4, MeOH, epichlorohydrin

Table 2 Oxidation of haloalkynes to α-ketoesters[a]

Entry	Substrate (Hal.)	Time/ days	Epichlorohydrin/ equiv.	Products (% Yield)
1	**7**(Br)	4	0	**9**(67)
2	**7**(I)	2	0	**9**(86)
3	**8**(Br)	10	0	**10**(82)
4	**4a**(Br)	4	0	**5a**(19) + **6a**(47)
5	**4a**(Br)	4	7	**5a**(47) + **6a**(11)
6	**4b**(Br)	3	7	**5b**(64) + **6b**(12)
7	**4b**(I)	2	20	**5b**(62) + **6b**(8)
8	**4c**(Br)	4	0	**5c**(13) + **6c**(52)
9	**4c**(Br)	3	7	**5c**(50) + **6c**(18)
10	**11**(Br)	3	7	**12**(47)

[a] Yields refer to isolated, chromatographically and spectroscopically homogeneous compounds.



tert-butyl hydroperoxide in isooctane.[7] In this manner satisfactory yields of the α-ketoesters **9** and **10** were obtained after 4 days at room temperature: the reaction times could be halved by use of the corresponding iodoalkyne (Table 2; entries 1–3). Attempted oxidation of the acetate **4a** under these conditions resulted in the isolation of the desired product **5a** in only 19% yield together with 47% of the elimination product **6a** (Table 2; entry 4). Clearly elimination of the acetate moiety from **5a** was occurring owing to the stoichiometric amount of HBr produced in the course of the reaction. Attempts to remove HBr from the reaction mixture with both inorganic and organic bases resulted in the complete failure of the reaction. Eventually however, success was achieved by carrying out the reaction in the presence of the organic buffer epichlorohydrin (Table 2; entry 5). The use of iodoalkynes in place of bromoalkynes (Table 2; entries 6 and 7) increased the reaction rate but not the isolated yields. We also briefly investigated the use of the *tert*-butyldimethylsilyl ether protecting group as in **11** (Table 2; entry 10) with moderate success.

Hydrolysis of the γ-acetoxy-α-oxoester function was best achieved by a two step procedure involving treatment with hydrogen chloride in methanol followed lithium hydroxide in aqueous THF. In this manner **5b** yielded **13** in 78% isolated yield on standing with HCl in methanol at room temperature for 24 h. Saponification then gave the acid **14** in 75% yield. Attempts at the saponification of **5b** resulted mainly in elimination. However treatment of **5b** with a combination of lithium hydroxide and hydrogen peroxide at room temperature did provide the required product **13** in 50% yield but we were unable to suppress completely the competing elimination reaction.

We believe that the protocol presented here is an attractive, and viable, alternative to the currently available pyruvate equivalents and will be of use in organic synthesis.

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