Journal of Organometallic Chemistry, 311 (1986) C35–C38
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands

Preliminary communication

AN IMPROVED PROCEDURE FOR THE GENERATION AND SELECTIVE TRAPPING OF 2,4′-DILITHIOPHENYLETHYNE

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(Received June 9th, 1986)

Summary

2,4′-Dilithiophenylethyne, prepared by treatment of 4-bromophenylethyne with two equivalents of butyllithium, reacts selectively with electrophilic reagents at the 4′-position provided the correct temperature and solvent combination are employed. The successive addition of two different electrophiles gives the 2,4′-dialkylated product in a regioselective manner.

4-Metallophenylethynes are useful synthetic intermediates [1]. An example is Grignard reagent **1** in which trimethylsilyl protection of the terminal alkyne is employed prior to generation of the organometallic reagent [1]. In principle, the need for a separate protection–deprotection sequence could be avoided by the conversion of 4-bromophenylethyne (**2**) into 2,4′-dilithiophenylethyne (**3**), provided electrophilic trapping could be achieved in a regioselective manner to give a 4-substituted product (**4**) after protonation (Scheme 1). By the successive addition of two electrophiles, such a procedure should also be applicable to the "one pot" synthesis of 2,4′-disubstituted derivatives (**5**). We required compounds of general structure **4** and **5** as starting materials in a programme to prepare novel leukotriene analogues [2] and therefore investigated the transformations outlined in Scheme 1.

A literature search revealed that the preparation of dilithio reagent **3** from 4-bromophenylethyne (**2**) and butyllithium in hexane using ether/THF (ca. 1/1) at −78°C had been reported by Salisbury [3]. However, regioselective trapping experiments, such as those shown in Scheme 1, were circumvented by the use of an

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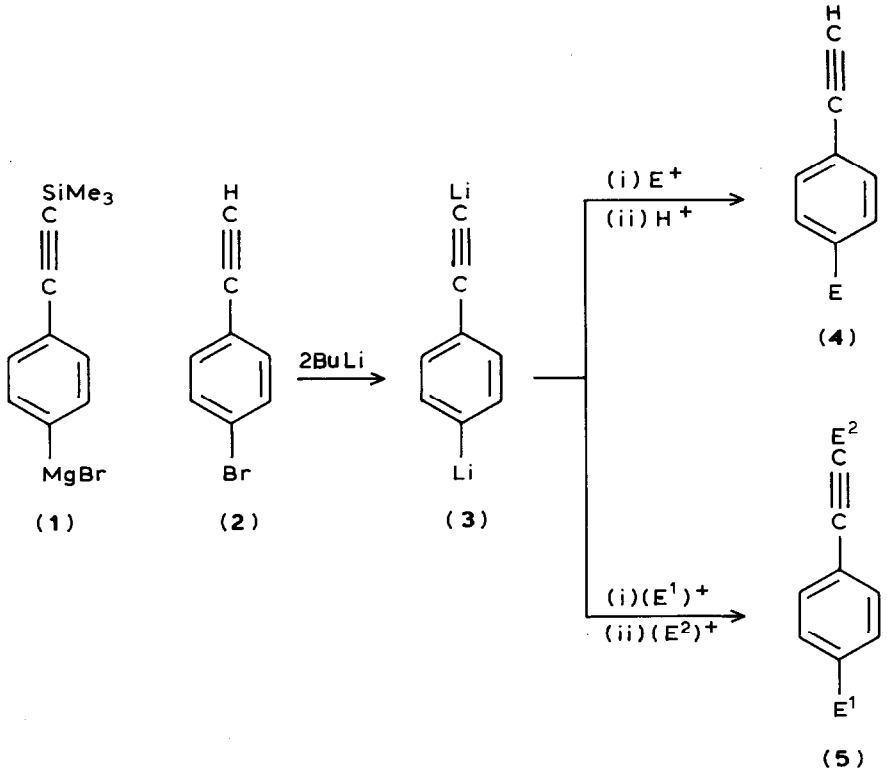
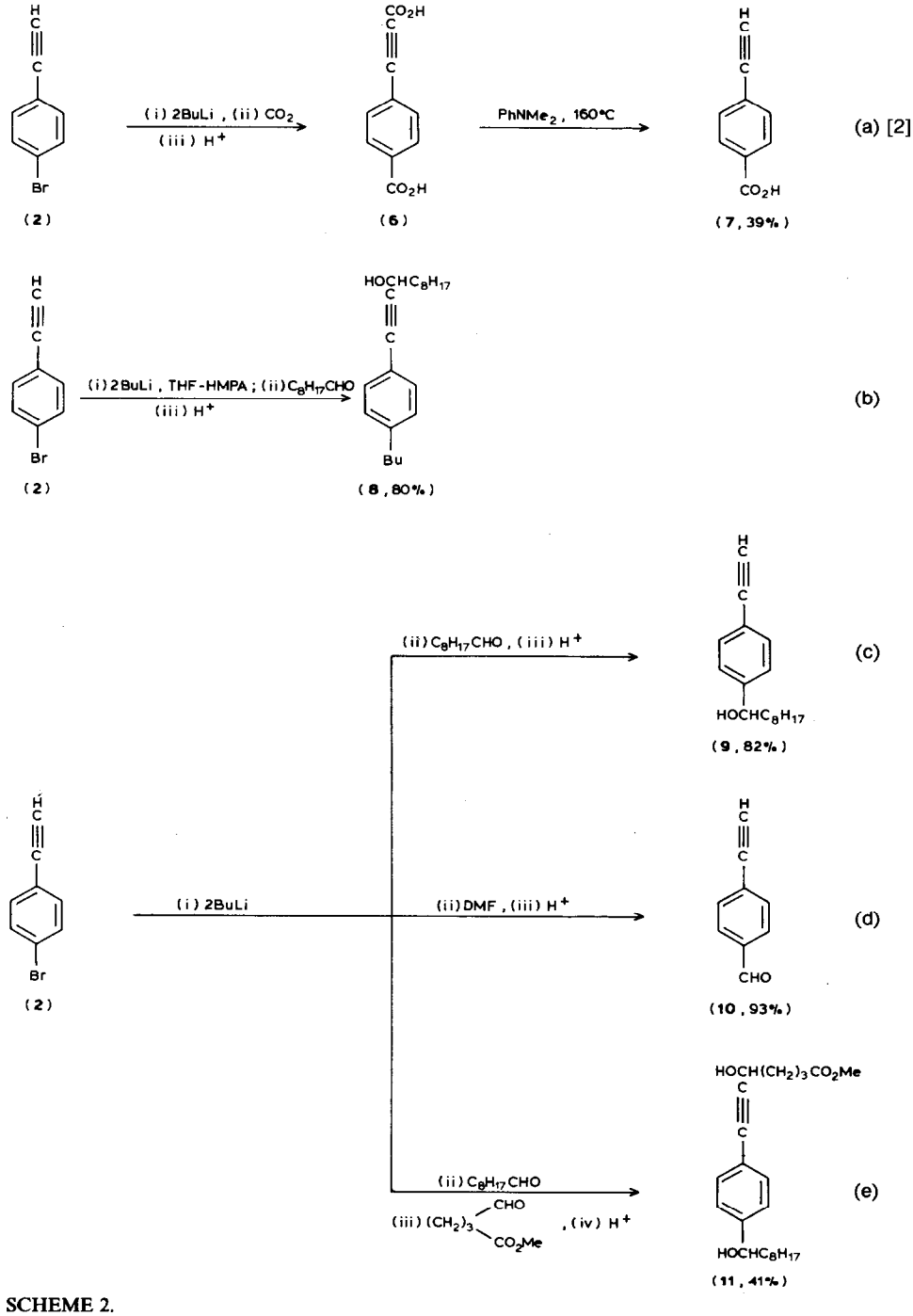


SCHEME 1.

excess of solid carbon dioxide as trapping agent and subsequent partial decarboxylation of diacid **6** to produce the 4′-carboxylic acid **7** (Scheme 2, eq. a). We repeated Salisbury's lithiation procedure but found that it produced reagent **3** as an insoluble, viscous gum and all attempts to obtain regioselective trapping were unsuccessful. We found that a homogeneous solution was obtained when THF/HMPA was used as solvent but addition of nonanal as trapping agent gave adduct **8** as the sole product in 80% yield (Scheme 2, eq. b). Under these conditions the bromobutane generated during transmetallation acts as the initial trapping agent, nonanal then reacting at the acetylide site. Though unexpected, this result demonstrated that selective reaction at the 4′-position is possible.

We eventually found conditions which enable the dilithio reagent **3** to be generated in a form suitable for selective trapping reactions. Bromophenylethyne (**2**) in ether is treated with two molar equivalents of butyllithium at $-70°C$. The reaction mixture is then warmed to $-40°C$ and THF is added dropwise until lithium/bromine exchange occurs. Under these conditions reagent **3** is formed as a bright pink suspension. The addition of nonanal followed by protonation now gives the expected regioselectivity, alcohol **9** being obtained in 82% yield (Scheme 2, eq. c). The use of DMF as trapping agent gives the 4′-aldehyde (**10**) in 93% yield after hydrolysis (Scheme 2, eq. d) and the addition of nonanal followed by methyl 4-oxopentanoate produces diol **11** in 41% yield (Scheme 2, eq. e). Although more



SCHEME 2.

work is required to optimise the yield of the double trapping process, the procedures outlined in this paper should prove to be of value for the synthesis of a wide range of 2,4′-disubstituted phenylethynes.

Acknowledgements.

We are grateful to the S.E.R.C. and Fisons Pharmaceutical Division for a C.A.S.E. award to Mark Furber.

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