Tetrahedron Letters,Vol.30,No.28,pp 3655-3656,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

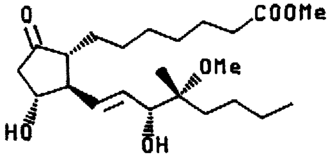
A PRACTICAL PROCEDURE FOR THE CONVERSION OF ALDEHYDES TO TERMINAL ALKYNES BY A ONE CARBON HOMOLOGATION

Luc Van Hijfte*, Michael Kolb and Pascale Witz
Merrell Dow Research Institute, Strasbourg Center
16 rue d'Ankara, 67084 Strasbourg Cedex, France

Abstract. A convenient method for the conversion of aldehydes to terminal alkynes via the corresponding 1,1-dibromoalkenes is described. The key feature of the process is the use of magnesium in tetrahydrofuran for the debromination step.

In connection with a study directed towards an enantioselective synthesis of the prostaglandin derivative MDL 646 (1)[1], a method for the transformation of the aldehyde 2a to the alkyne 4a was needed which was applicable to large scale preparations.

The well-known procedure described by Corey and Fuchs[2] for the conversion of 2a to 4a via the corresponding dibromo olefin 3a employes either n-BuLi at - 78°C or lithium amalgam for the debromination step. However, both techniques proved to be impractical for large scale preparations; problems of heat transfer, handling of large quantities of alkyllithiums, and the unavailability of lithium amalgam, a reagent rather difficult to prepare[3], can be cited as considerable drawbacks. The appeal of using a more convenient reagent such as magnesium[4], has led us to investigate this alternative, despite the reported negative results[2,4].



1

$$\underset{2}{\mathrm{RCHO}} \xrightarrow[\substack{\mathrm{CH_2Cl_2},\ r.t.\\ 80-90\%}]{\mathrm{Ph_3P},\ \mathrm{CBr_4}} \underset{3}{\mathrm{RCH{=}CBr_2}} \xrightarrow[\substack{\text{reflux}\\ 75-95\%}]{\mathrm{Mg},\ \mathrm{THF}} \underset{4}{\mathrm{RC{\equiv}CH}}$$

a: R = $C_4H_9C(OMe)(CH_3)CH(OTBS)$

b: R = C_6H_5

c: R = $C_6H_5CH(CH_3)$

d: R = $n.C_7H_{15}$

e: R = $C_6H_5CH_2CH(COOt.Bu)CH_2$

f: R = $CH_3CH(OTHP)$

As it turned out, the dibromoolefins 3, obtained from the aldehydes 2 by reaction with carbontetrabromide and triphenylphosphine[2,7], led to the corresponding alkynes 4 in good yield when treated with magnesium[5] in THF at reflux temperature[6]. Examples 2a-f demonstrate the efficiency of the process. The yields obtained with magnesium are comparable to those obtained with n-BuLi. Only in the case 3b approximately 10% of overreduction of the alkyne to the alkene was observed. Magnesium converted the dibromide 3e to the alkyne 4e in a clean fashion and in good yield, whereas n-BuLi afforded an uncharacterized reaction mixture. Tetrahydropyranyl ethers (entry 2f) are well tolerated; cleavage due to in situ formed $MgBr_2$ did not occur in THF[8]. Finally, but most important for our purpose, a stereogenic center next to the aldehyde function (entry 2a) is not epimerized during the two step transformation.

Experimental procedure: to magnesium turnings (4.2 g, 175 mmol) in dry THF (50 mL) was added a trace of iodine, and the mixture was heated till the yellow color disappeared[9]. A solution of the dibromide 3a (60 g, 135 mmol) in THF (600 mL) was added at a rate to keep the mixture at a gentle reflux (on smaller scale, heating was sometimes necessary). The solution was refluxed for an additional 30 min or, alternatively, stirred at room temperature for 2 h. Hexane (600 mL) was added to precipitate the formed $MgBr_2$, the mixture was filtered through a short path of silica gel and the filter cake was rinsed with ether. Distillation (65-67°C, 0.01 torr) afforded 31.4 g (82%) of the alkyne 4a.

The advantages of magnesium over n-BuLi with respect to its safety and ease of handling, especially for large scale preparations, and its non reactivity towards alkyllithium sensitive groups such as esters, recommend its preferential use for the conversion of 1,1-dibromoolefins to terminal alkynes.

REFERENCES

1. U. Guzzi, R. Ciabatti, G. Padova, F. Battaglia, M. Cellentani, A. Depaoli, G. Galliani, P. Schiatti, G. Spina, **J. Med. Chem.**, 29, 1826-1832 (1986).
2. E.J. Corey, P.L. Fuchs, **Tetrahedron Lett.**, 3769-72 (1972).
3. R. Criegee, G. Louis, **Chem. Ber.**, 90, 423 (1957).
4. Theoretically, magnesium has a reduction potential sufficiently negative to transfer its electrons to a vinyldibromide, to convert it, most probably through a carbene intermediate and an insertion reaction, to an acetylene. It is unclear why the reaction was unsuccessful in the hands of Corey and Fuchs, since no experimental details are given (for example, we have found that the reaction does not work in ether).
5. Purchased from Janssen Chimica.
6. Satisfactory spectral data were obtained for all reaction products.
7. The dibromides 3a-f were obtained in essentially pure form by reaction of the corresponding aldehydes 2a-f with triphenyl phosphine (4 equiv.) and carbon tetrabromide (2 equiv.) in dichloromethane at 0°C, followed by extractive workup with water and ether, concentration, precipitation of triphenyl phosphine oxide using pentane and filtration through a short path of silica gel.
8. Tetrahydropyranyl ethers are cleaved by magnesium bromide in ether but not in THF: see S. Kun, J.H. Park, **Tetrahedron Lett.**, 28, 439-440 (1987).
9. A trace of methyl iodide or ethylene dibromide can also be used to activate the magnesium metal.

(Received in France 15 March 1989)