Pergamon

Tetrahedron Letters, Vol. 35, No. 21, pp. 3529-3530, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0622-5

An Improved Procedure for Aldehyde-to-Alkyne Homologation via 1,1-Dibromoalkenes; Synthesis of 1-Bromoalkynes

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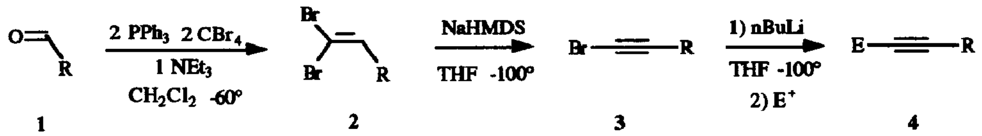
Abstract: *1,1-Dibromoalkenes, 1-bromoalkynes and alkynes could be obtained in excellent yields by homologation of functionnalized aldehydes through a modified Mc Kelvie-Corey procedure.*

Alkynes are useful and versatile intermediates in organic synthesis.[1] One of the most convenient access to alkynes is the one-carbon homologation originally developed by McKelvie[2] *et al.* and later extended by Corey and Fuchs.[3] This procedure requires the formation of a 1,1-dibromoalkene by addition of dibromomethylene triphenylphosphorane to an aldehyde. The alkyne derivative is subsequently obtained from the 1,1-dibromo alkene by treatment with n-butyl lithium. Although widely used, this procedure suffers from serious drawbacks when applied to highly functionnalized and/or sensitive aldehydes.[4] Although alternative routes have been developed,[5] the aldehyde-to-alkyne homologation via 1,1-dibromoalkenes is an interesting process, especially since 1,1-dibromoalkenes are useful intermediates.[6] In this communication, we present our modification of the McKelvie-Corey procedure allowing for the preparation of 1,1-dibromoalkenes and the corresponding 1-alkynes from sensitive aldehydes (Scheme 1).[7]

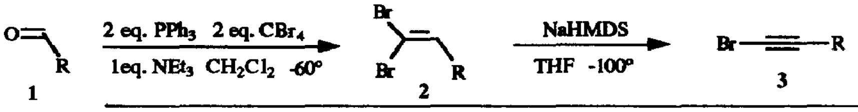
As mentioned by McKelvie[2] *et al.*, the actual reagent for dibromoolefination is always contaminated by dibromotriphenylphosphine generated *in situ*. However this dibromophosphine is known to be a strong electrophile[8] as well as a brominating agent[9] and therefore the probable source of side-reactions. For instance, in our hands 2,3-epoxyaldehydes decomposed when submitted to the CBr_4-PPh_3 mixture.[10] *In situ* reduction of dibromotriphenylphosphine by metallic zinc prior to aldehyde addition[3] also led to decomposition.[11] We finally found that addition of a single equivalent of triethylamine prior to the addition of the CBr_4-PPh_3 mixture suppressed side reactions[12] and allowed us to prepare the expected epoxydibromoalkenes **2** in good yields (Table 1).



Scheme 1

The formation of alkynes from dibromoalkenes **2** can also be cumbersome. For example, from the epoxides **2a-d**, the reported procedure[3] consistently gave very low yields of the expected products **4a-d**. Since β-elimination then metal-halogen exchange are the probable steps in the Mac Kelzie-Corey procedure and since *trans* elimination of halogen across a double bond is a favored process, we looked for a more selective and milder base than nBuLi, NaHMDS proved to be the best choice, giving very cleanly and quantitatively the bromoalkyne[13] 3 (Table 1). The bromine in 3 was then exchanged with 1 equivalent of nBuLi to the corresponding lithiated alkyne, which could be trapped by various electrophiles in high yields (Scheme 1). This two step sequence can also be performed in one pot. In this case, however, a second equivalent of nBuLi is required to neutralize the proton of the HMDS liberated *in situ*.

The overall sequence has been applied to various aldehydes with consistent results (Table 1) and high overall yields, especially on multigram scale. Common protecting groups were well tolerated. Even sensitive ester groups survived to the conditions described here, although the lowest yields were obtained in this case.



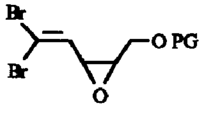
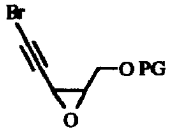
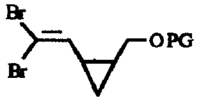
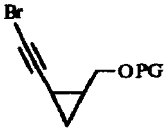
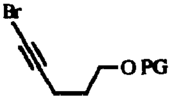
	PG = SiMe₂tBu SiPh₂tBu SEM COPr	2a 2b 2c 2d	80 % 85 % 93 % 74 %		PG = SiMe₂tBu SiPh₂tBu SEM COPr	3a 3b 3c 3d	92 % 96 % 95 % 94 %
	PG = SiPh₂tBu COPr	2e 2f	96 % 91 %		PG = SiPh₂tBu COPr	3e 3f	98 % 98 %
	PG = SiPh₂tBu COMe	2g 2h	96 % 80 %		PG = SiPh₂tBu COMe	3g 3h	98 % 86 %

Table 1

References

1) Pataï, S. Ed. *The Chemistry of Carbon-Carbon Triple Bond*; Wiley: New-York, 1978.
2) Ramirez, F; Desai, N. B.; Mc Kelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745-1747.
3) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769-3772.
4) see, for example: Mattes, H.; Benezra, C. *Tetrahedron Lett.* **1987**, 28, 1697-1698.
5) Larock, R. C. *Comprehensive Organic Transformations*; VCH:Weinheim, 1989, pp 295-296
6) Grandjean, D.; Pale, P. *Tetrahedron Lett.* **1993**, *34*, 1155-1158 and references therein.
7) Taken in part from the DEA report of D. Grandjean, 1987, Université de Reims-Champagne-Ardenne.
8) PPh_3Br_2 can cleave THP group (Wagner, A.; Heitz, M. P.; Mioskowski, C. *Chem. Commun.* **1989**, 1619-20; *ibid. Tetrahedron Lett.* **1989**, *30*, 557-58) and open ethers (*ibid. Tetrahedron Lett.* **1989**, *30*, 1971-74) as well as oxiranes (Palumbo, G.; Ferreri, C.; Caputo, R. *Tetrahedron Lett.* **1983**, *24*, 1307-1).
9) Aizpurrua, J. M.; Cossio, F. P.; Palomo, C. J. *J. Org. Chem.* **1986**, *51*, 4941-4943.
10) 3-bromo-4-hydroxy-1,1-dibromoalkenes were isolated, although in low yield. Control experiments[7] showed that the same products were obtained from 3,4-epoxy-1,1-dibromoalkenes when treated by PPh_3Br_2.
11) Such treatment produced zinc dibromide which is a Lewis acid probably strong enough in these conditions to initiate degradation.
12) A similar modification was very recently achieved for the formation of a 1,1-dibromoalkene derived from L-arabinose McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4823-4832.
13) Bromo alkynes are also useful intermediates, see: Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron Lett.* **1992**, *33*, 4905-4908 and *Tetrahedron* **1993**, *49*, 5225-5236.

Typical procedure: To a solution of CBr_4 (2 eq.) in dry CH_2Cl_2 (10 mL/mmol) under argon, was added at -20°C a solution of PPh_3 (2 eq.) in dry CH_2Cl_2 (20 mL/mmol). An intense yellow color developed which darkened after 15 mn at this temperature. Then, a solution of aldehyde (1 eq.) and NEt_3 (1 eq.) in dry CH_2Cl_2 (10 mL/mmol) was added at -60°. After warming up, addition of petroleum ether (1 to 2 vol.), filtration and solvent evaporation, the 1,1-dibromoalkene was obtained and purified by flash-chromatography (FC).

To a cold (-100°) solution of 1,1-dibromoalkene (1 eq) in THF (10 mL/mmol) was added a commercial solution of NaHMDS (1M in THF, 1 eq). After 10 mn, the reaction was quenched by addition of a saturated NH_4Cl solution. Ether extraction and solvent evaporation provided the 1-bromo alkyne, which is purified by FC.

(*Received in France* 24 *February* 1994; *accepted* 24 *March* 1994)