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# Highly Efficient Synthesis of α,β-Acetylenic Aldehydes From Terminal Alkynes Using DMF As the Formylating Reagent.

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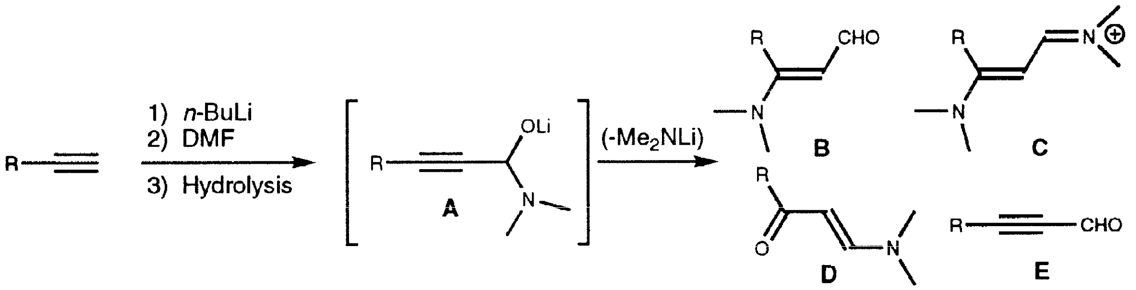
**Abstract**: *The formylation of lithium acetylides with DMF led to α,β-acetylenic aldehydes in excellent yields (>94%). A reverse quench into a phosphate buffer (10% aqueous $KH_2PO_4$ ,4 equiv) proved to be the key for this high-yielding reaction.* © 1998 Elsevier Science Ltd. All rights reserved.

The preparation of α,β-acetylenic aldehydes from terminal alkynes is a common transformation in organic synthesis. These alkynals have been widely used as Michael acceptors,[1] dienophiles in Diels-Alder reactions,[2] or as key intermediates in the synthesis of important natural products such as cembranolide,[3] neocarzinostatin[4] or calicheamicin.[5] Whereas the direct formylation of an acetylide with DMF is the shortest access to these compounds, the yields are modest[4a,5,6] due to over-addition of the organometallic species generating the secondary alcohol. To overcome this other formamide derivatives have been designed,[7] or a two step procedure,[3,4b-c] involving addition of paraformaldehyde followed by oxidation, has been used.

Herein, we wish to report that the high-yielding formylation of lithium acetylides can be accomplished simply with DMF by quenching the α-aminoalkoxide into aqueous monobasic potassium phosphate. The reaction itself proceeds in nearly quantitative yields without over-addition of the organolithium reagent. The incipient intermediate aldehyde shown (Scheme 1) is stable under the reaction conditions. As reported by Olah,[7b] the formylating reagent does not need to bear additional ligands to stabilize **A** making the cheap, readily available DMF a convenient reagent. However, the distribution of the reaction products can be complicated during hydrolysis where side-reactions occur easily. Indeed, intermediate **A** collapses to release the strong nucleophile dimethylamine which can subsequently react with the alkynal **E**. We isolated and identified three byproducts **B**-**D** all arising from a Michael addition of the dimethylamine. Their formation depended on the way the reaction was hydrolyzed. By addition of water, **E** was isolated in <50% yield, **B** being the very major byproduct. On the other hand, an acidic workup (aqueous acetic acid) provided the stable iminium acetate **C** which was slowly hydrolyzed to the enaminoketone **D** upon aging. When harsher conditions were used (3N HCl), crude $^1$H-NMR showed only acetylenic aldehyde but the isolated yield was 40-45%. In fact, reverse-phase HPLC analysis[8] of the aqueous layer revealed that the three Michael adducts **B**, **C** and **D** had formed and had been extracted into the aqueous layer as their hydrochloride salts.

**Scheme 1**



Therefore, in order to obtain an effective, high-yielding preparation of α,β-acetylenic aldehydes an appropriate hydrolysis must be achieved with an efficient trapping of the dimethylamine that would circumvent

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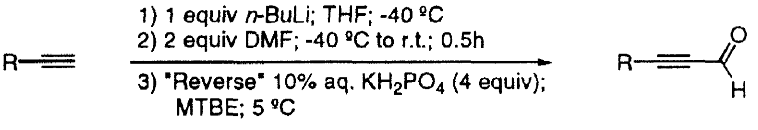
these side-reactions. This was accomplished by a reverse addition of the reaction mixture into a phosphate buffer (10% aqueous $KH_2PO_4$, 4 equiv) affording the alkynals in >94% isolated yield without any trace of Michael adducts (Scheme 2). It is noteworthy that due to the mild conditions of the hydrolysis (pH4.1→6.7), this procedure was compatible with the presence of acid sensitive functional groups such as an acetal (*e.g.*, THP protecting group). All examples gave essentially quantitative yields with the only impurity being a small amount of the starting material (ca. 1-2%).

**Scheme 2**



| R | Yield (%) |
|---|---|
| Ph | 97 |
| $TBSO(CH_2)_3$ | 98 |
| $THPO(CH_2)_2$ | 97 |
| $THPOCH_2$ | 94 |
| $n$-$C_4H_9$ | 95 |

In summary, we have demonstrated that lithium acetylides can react with DMF to give α,β-acetylenic aldehydes in excellent yields as long as a reverse quench into a monobasic phosphate solution is employed.

***General Experimental Procedure:*** The alkyne (50 mmol) was dissolved in dry THF (125 mL) and the solution was cooled to -40 °C under nitrogen. *n*-Butyllithium[9] (1.53M in hexanes, 32.7 mL, 50 mmol) was added dropwise over ca. 2 minutes maintaining the temperature between -35 and -40 °C. After completion of the addition, anhydrous DMF (7.75 mL, 100 mmol) was added in one portion and the cold bath was removed. The reaction mixture was allowed to warm to room temperature and aged for 30 minutes. The THF solution was poured into a vigourously stirred biphasic solution prepared from a 10% aqueous solution of $KH_2PO_4$ (270 mL, 200 mmol) and MTBE (250 mL) cooled over ice to ca. +5 °C. Layers were separated and the organic extract was washed with water (2x200 mL). Combined aqueous layers were back extracted with MTBE (150 mL). Combined organic layers were dried over $MgSO_4$, filtered and concentrated to give the crude acetylenic aldehyde as an oil which was filtered through a pad of silica gel (40g) using a 90/10 mixture of Hexanes/AcOEt as the eluent.

**References and notes:**

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