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Large scale synthesis of acetylene dicarboxaldehyde mono and diacetal ☆

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Abstract—An easy, high yield, large scale, and atom economical, synthesis of the valuable acetylene dicarboxaldehyde dimethyl and tetramethyl acetals was described starting from 2,5-dimethoxy-2,5-furan.

Acetylene dicarboxaldehyde (**1**)[1] and its precursors mono and bis acetals **2**, **3** (Fig. 1) are useful starting materials, which have found many applications in dipolar cycloaddition,[1a–e] Diels-Alder,[1a,f–i] Michael,[1a,f,g,j] or Wittig[1k] reactions. A major drawback for a larger use of these compounds is their high price[2] or difficulties in their preparation, which preclude their large scale synthesis.

The main literature procedures leading to acetals **2** or **3** are described in Schemes 1 and 2. According to Scheme 1,[1f,l] to obtain 100 g of diacetal **3a**, it would be necessary to use 350 g of triethyl orthoformate, 690 g of KOH and 1150 g of tetrabutylammonium hydrogen sulfate.

According to Scheme 2,[1f,g] it would be necessary to use 400 g of triethyl orthoformate, 38 g of magnesium, and 520 l of gaseous acetylene. During this last procedure, it is difficult to avoid precipitation of the intermediate bis magnesium salt of acetylene, which is very bulky and difficult to stir, leading to very bad yields.[1g]

We now report an easy, high yield, large scale preparation of acetals **2b** and **3b** from inexpensive 2,5-dimethoxy-2,5-dihydrofuran (**4**).[3] Indeed it appears to us that this compound contains all the carbon atoms of acetylene dicarboxaldehyde (**1**) and is a cyclic diacetal while **3** is a linear diacetal, and we envisioned the general process described in Scheme 3.

The first step was realized with only slight variation of a literature method.[4] This led to a near quantitative yield of 95% pure 3,4-dibromo-2,5-dimethoxytetrahydrofuran (**5**) as a mixture of three geometric isomers in a 43/40/17 ratio. This mixture was not purified[5] and was used directly for the next step. It was reported[1f,g] that when the previous syntheses were used it was easier to obtain **2a**

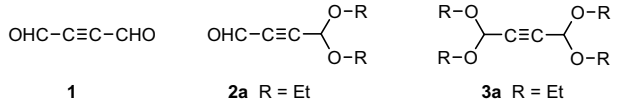
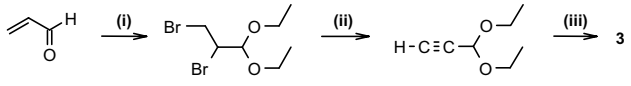
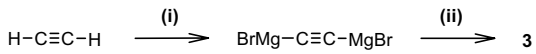


Figure 1.



Scheme 1. Synthesis of acetal **3a** from acroleine. Reactions conditions: (i) Br_2, $HC(OEt)_3$ (75%); (ii) KOH, $Bu_4N^+HSO_4^-$ (64%); (iii) $HC(OEt)_3$, $ZnCl_2$ (61%).



Scheme 2. Synthesis of acetal **3a** from acetylene. Reaction conditions: (i) EtBr, Mg; (ii) $HC(OEt)_3$ (65%).

Keywords: 2,5-Dimethoxy-2,5-dihydrofuran; Acetylene dicarboxaldehyde; Atom economy.

☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.01.022

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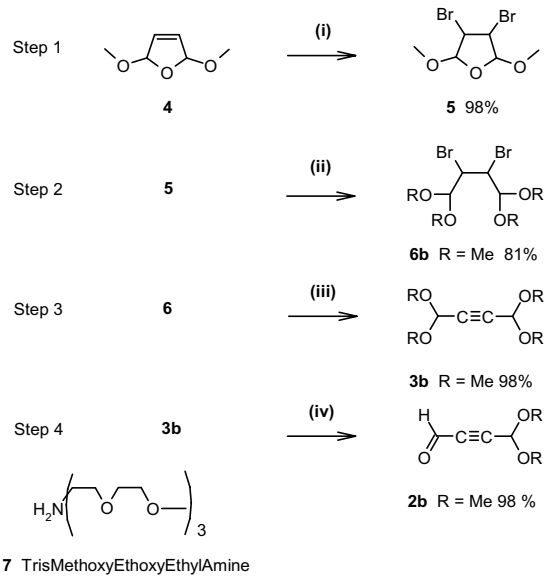

Scheme 3. Synthesis of acetal **3a** from dimethoxydihydrofuran. Reactions conditions: (i) Br_2, CH_2Cl_2 (98%); (ii) MeOH, H_2SO_4 (81%); (iii) THF, KOH, TMEEA (98%); (iv) HCO_2H/CH_2Cl_2 (98%).

and **3a** than their methoxy analogs **2b** and **3b**. Consequently, in a first approach to Step 2 we tried to obtain the *tetraethy* l diacetal **3b**, and opening of the furan ring was performed in ethanol. This led to about 40% of a mixture of **6a** (R = Et) and **6b** containing large amounts of by-products **8** (two isomers), **9**,[6] and **10**[6] (Fig. 2). In order to suppress the trans-acetalization giving **8**, ethanol was replaced by methanol. *Tetramethyl* diacetal **6b** was then obtained contaminated by a low amount of ester **11**, which probably comes from the solvolysis of lactone **10**. Addition of trimethyl orthoformate as scavenger of the water formed[7] did not improve the yields, but working with a large amount of methanol and one equimolar quantity of sulfuric acid yield leads to a better yield of bromoacetal **6b**. At the end of the reaction, sulfuric acid was neutralized by addition of triethylamine, and methanol was evaporated. Extraction of the residue with heptane gives 81% of isolated product **6b**, with purity better than 90%. This compound was not purified but used directly for the next reaction.[8]

First attempts to obtain compounds **3** were realized by treatment of **6a** with potassium *tert*-butoxide in DMSO (80% yield), or NaOH (2 equiv 60 °C, 36 h) in H_2O/THF, in the presence of tetrabutylammonium chloride. In this last reaction, diacetal **3a** (47%) and by-product **12** (47%) were isolated. Modification of these conditions led to use solid KOH and THF (reflux, 24 h), in the presence of trismethoxyethoxyethylamine as a phase transfer agent. The near quantitative (98% isolated, 95% pure) yield of **3b** reflects the efficiency of this inexpensive phase transfer agent. Only evaporation of solvents and CH_2Cl_2/H_2O partition was necessary to obtain tetramethoxy diacetal **3b**, which was not purified but used directly for the next reaction.[9]

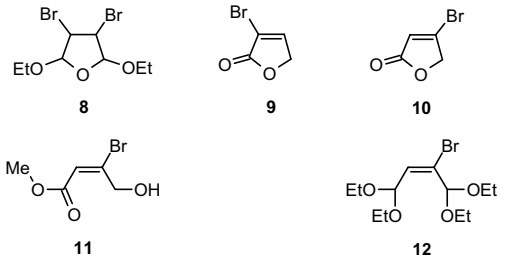

Figure 2. By-products observed during the study of steps 2 and 3.

In previous works it was reported that the formic acid[10,11] monodeprotection of diacetal **3a** (R = Et) (50/100 $HCO_2H/CHCl_3$, 12 h, 20 °C, 75%) was easier than the one of **3b**,[1g] which was then deprotected in harsher conditions (50/100 $HCO_2H/CHCl_3$, 3 h, 40 °C, 52%). We have found that a near quantitative yield (98% isolated, 95% pure) of **2b** was obtained when a HCO_2H/CH_2Cl_2 solution of **3b** was allowed to stand in the dark at room temperature for 3 days. The good purity (Figs. 3 and 4) of crude mono protected acetal **2b** was sufficient for most of the uses.[12]

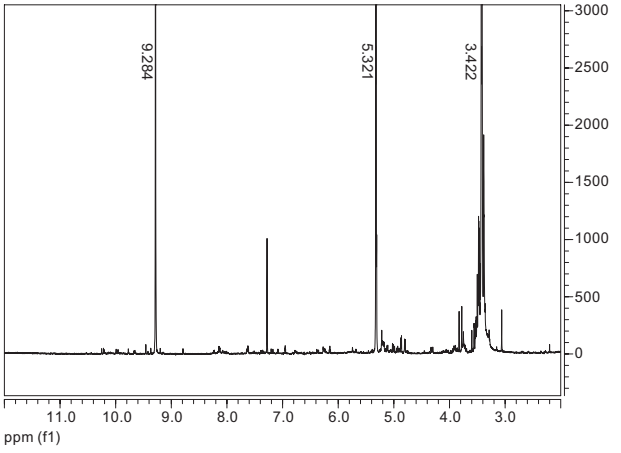

Figure 3. NMR spectrum of the crude monoacetal **2b** showing the main impurities.

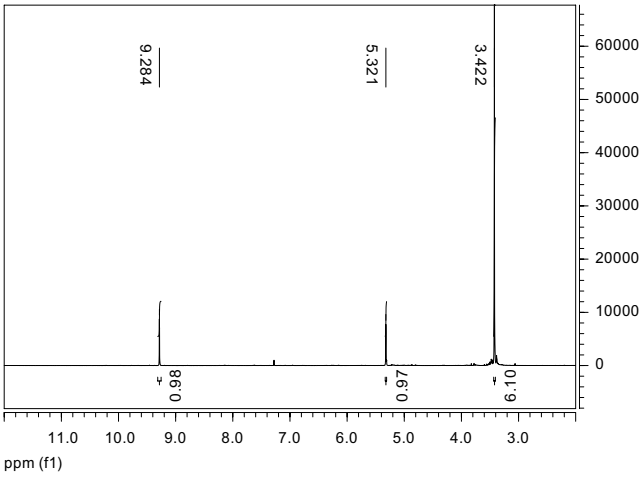

Figure 4. NMR spectrum of the crude monoacetal **2b**.

In summary, by using easily available 2,5-dimethoxy-2,5-dihydrofuran as starting material, we have accomplished an efficient and economic synthesis of acetylenic acetals **2a** and **2b**. We have performed these reactions in 100–300 g scale with no purification of intermediates and without appreciable changes in the yields. The experimental simplicity, the mild reaction conditions and the atom economy of the processes described are especially noteworthy.

1. Experimental procedure

^{1}H and ^{13}C NMR spectra were obtained on a Varian Gemini 2000 at 200 and 50 MHz, respectively.

Step 1.

3,4-Dibromo-2,5-dimethoxytetrahydrofuran (**5**): While controlling the reaction temperature (15 °C), bromine (122.8 g, 0.77 mol) was added to a cooled (ice) solution of **4** (100 g, 0.77 mol) in CH_2Cl_2. Upon decolorization, solvent was evaporated and the crude, low colored semisolid mass (**5**), was used in the next step. Mixture of three isomers; ^{1}H NMR ($CDCl_3$) δ ppm: 43% of isomer mp 88 °C [3.48 (s, 3H), 3.50 (s, 3H), 4.16 (dd, $J = 9.6$, 3.9 Hz, 1H), 4.26 (dd, 9.6, 3.9 Hz, 1H), 4.94 (d, $J = 3.9$ Hz, 1H), 5.21 (d, $J = 3.9$ Hz, 1H)], 17% of isomer mp 56 °C [3.47 (s, 6H), 4.42 (dd, $J = 1.9$, 0.7 Hz, 2H), 5.23 (dd, 1.9, 0.7 Hz, 2H)], 40% of isomer mp 72 °C [3.50 (s, 6H), 4.18 (dd, $J = 2$, 1.3 Hz, 2H), 5.29 (dd, 2, 1.3 Hz, 2H)].

Step 2.

2,5-Dibromo-1′1′4′4-tetramethoxybutane (**6b**): Sulfuric acid (75.4 g, 0.77 mol) was added (30 min) to a hot solution of crude **5** (from the previous reaction) in MeOH (3900 mL) (nitrogen). The solution was refluxed for 72 h then cooled at room temperature. Triethylamine (98 mL, 0.77 mol) was added then solvents were evaporated. Residue was stirred and refluxed three times with 500 mL of heptane. The crude, yellow oil **6b**, obtained after evaporation of heptane was used in the next step.^{1}H NMR ($CDCl_3$) δ ppm: 3.45 (s, 12H), 4.35 (d, $J = 7.9$ Hz, 2H), 4.59 (d, $J = 7.9$ Hz, 2H).

Step 3.

1,1,4,4-Tetramethoxybut-2-yne (**3b**): A stirred mixture of crude **6b** (from the previous reaction), KOH (140 g, 2.5 mol) and TMEEA (0.06 mol, 20.2 g) in THF (300 mL) was refluxed for 24 h. Solvent was evaporated, water (500 mL) was added, and the solution was partitioned three times with ether (500 mL). The crude, yellow oil **3b**, obtained after drying ($MgSO_4$) and evaporation of ether was used in the next step.

Alternatively, it is not necessary to perform an heptane extraction of compound **6b**: the crude mixture obtained after neutralization of **6b** with triethylamine was evaporated. Potassium hydroxide (5.5 mol equiv), TMEEA and THF were added and the mixture was refluxed for 24 h. Part of THF was evaporated, water was added and the mixture was extracted with ether, leading to 75% yields of **3b** (95% pure) for steps 2 and 3. ^{1}H NMR ($CDCl_3$) δ ppm: 3.85 (s, 12H), 5.22 (s, 1H).

Step 4.

4,4-Dimethoxybut-2-ynal (**2b**): A mixture of crude **3b** (from the previous reaction) in CH_2Cl_2 (600 mL) and formic acid (556 g, 12 mol) was kept in the dark for three days. The solution was partitioned three times with water (200 mL). The organic phase was dried ($MgSO_4$) and evaporated giving 74 g of **2b** (75% from **4**) as a brown-yellow oil whose purity (95%) was sufficient for most of the utilizations. ^{1}H NMR ($CDCl_3$) δ ppm: 3.42 (s, 6H), 5.32 (d, $J = 0.5$ Hz, 1H), 9.28 (d, $J = 0.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ ppm: 53.1, 83.1, 88.4, 92.7, 176.4.

NMR spectra of crude monoacetal **2b** are displayed in Figures 3 and 4.

Acknowledgements

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2. 3,3-Diethoxy-1-propyne (Scheme 1): 329 €/25 g (Lancaster); **3a**: 75 €/1 g (Acros); **2a**: 78 €/1 g (Acros); **4**: 191 €/1000 g (Alfa Aesar).
3. 2,5-dimethoxy-2,5-dihydrofuran (**4**) is a commercial synthon, which is very versatile: Kass, N. C.; Limborg, F.; Fakstorp, J. *Acta Chem. Scand.* **1948**, *2*, 109–115; Baussanne, I.; Chiaroni, A.; Riche, C.; Royer, J.; Husson, H. -P. *Tetrahedron Lett.* **1994**, *35*, 3931–3934; Merz, A.; Meyer,

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5. If one needs very pure product for another use, the three optical isomers of dibromide **3** can be separated then purified as described in literature (chromatography and crystallization)[4].
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8. Product **6b** is difficult to purify but remaining impurities are removed during the treatment of the next step.
9. If one needs very pure product for another use, **3b** can be purified by distillation: $E_{13} = 101–103\,^{\circ}C$;[10] $E_1 = 70–73\,^{\circ}C$.[1g]
10. Acid hydrolysis of acetal **3a** is very difficult: Wohl, A.; Bernreuter, E. *Ann. Chem.* **1930**, *481*, 1–29.
11. Gorgues, A. *Bull. Soc. Chim. Fr.* **1974**, 529–530.
12. If one needs very pure product **2b** can be purified by distillation: $E_{14} = 75–78\,^{\circ}C$.[1g] This compound remains unaltered for years when kept at $-40\,^{\circ}C$.