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# A ONE STEP SYNTHESIS OF ω-HYDROXYACETYLENIC CARBOXYLIC ACIDS

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Abstract : A convenient chemioselective method to prepare ω-hydroxyacetylenic carboxylic acids from unprotected ω-alkyn-1 ols and ω-bromo acids is described.

Condensation of alkylhalides with ω-acetylenic acids (1) amides (2) or halides (3) involves usually the lithium salts (4,5) or the corresponding Grignard derivatives (6) of the acetylenic function. Similarly, the dilithio salts of ω-alkyn-1 ols 1 were reported to react with ω-bromoacids with yields about 50 to 60% (7), unfortunatly we were unable to reproduce this reaction with satisfactory yields. We report here that the direct condensation can occur readily in THF in the presence of HMPA at -30°C |eq.1, table I| with yields up to 85%. Furthermore, the chemioselectivity depends on the conditions of the reaction.

|1| $H\text{-}C{\equiv}C\text{-}(CH_2)_n\text{-}OH$ (1) + $X\text{-}(CH_2)_m\text{-}CO_2H$ (2) $\xrightarrow[\text{THF - HMPA}\ -30°C]{\text{n Buli, 2 eq}}$ $HO\text{-}(CH_2)_n\text{-}C{\equiv}C\text{-}(CH_2)_m CO_2H$ (3)

n = 1,2 ; m = 4,5,10,11 ; X = Br,I

Two side reactions can compete with the formation of 3 |eq 2, table II| which depend on the temperature of the reaction mixture and on the structure of the acid.

|2| $H\text{-}C{\equiv}C\text{-}(CH_2)_n\text{-}OH$ (1) + $X\text{-}(CH_2)_m CO_2H$ (2) $\xrightarrow[\text{HMPA}\ \text{THF}\ -110°C \text{ or } -80°C]{\text{n Buli}}$ $HO\text{-}(CH_2)_m\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}(CH_2)_n C{\equiv}C\text{-}H$ (4) + $H\text{-}C{\equiv}C\text{-}(CH_2)_n\text{-}O\text{-}(CH_2)_m CO_2H$ (5)

In every case, the formation of ω-ethylenic acid $CH_2{=}CH\text{-}(CH_2)_{m-2}CO_2H$ 6 is observed (mostly from the ω-iodoacid).

**Table I**

| | Base | $H\text{-}C{\equiv}C\text{-}(CH_2)_n\text{-}OH$ | $X\text{-}(CH_2)_m\text{-}CO_2H$ | | 3 | 6 |
|---|---|---|---|---|---|---|
| 1 | n Buli | n = 1, 2 | m=4,5,10,11 | X=Br | 75-85% | 5% |
| 2 | n Buli | n = 1, 2 | m=5 | X=I | 65% | 15% |
| 3 | NaH, $NaNH_2$ $Na/NH_2/LiBr$ | n = 2 | m=5 | X=Br | - | - |

As shown in table I, the formation of 3 is only efficient when lithium was used as counterion, with 3 equivalents of HMPA and a controlled temperature of -30°C.

At lower temperatures, the formation of two other condensation products was observed (4 and 5) (equation 2, table II, runs 5-6).

**Table II**

| Run | Base | t° | $H-C\equiv C-(CH_2)_n-OH$ | $Br-(CH_2)_m CO_2H$ | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|---|
| 4 | n Buli | - 80°C | n = 1 | m = 4, 5 | - | 70% | - | 5% |
| 5 | n Buli | -110°C | n = 2 | m = 4, 5 | 5% | 55-65% | - | 10% |
| 6 | n Buli | -110°C | n = 2 | m = 7 | - | - | 55% | 5% |
| 7 | n Buli | -110°C → -30°C → -110°C | n = 1, 2 | m = 4 | 70% | - | - | 5% |

It seems that the dilithiosalt of 1 can only be formed when the temperature of the reaction mixture is high enough (-30°C)(run 7, table II). The comparison between runs 1 and 4, 1 and 5 shows that at -80°C, or -110°C, the dianion formation was considerably slow and only one equivalent of n Butyllithium was consumed to give the mono lithio derivative of 1. At -80°C or below, the second equivalent of n Butyllithium transformed the bromoacid 2 into its corresponding salt, when this compound was introduced into the reaction mixture (equation 3). In the case of m = 4 or 5 (run 4), the formation of the lactone was favoured and its opening by the alkoxide of 1 led to 4. When m = 7 (run 6), the lactonisation was not favoured for entropic reasons and only the product of O-alkylation 5 was detected.

|3|

$$H-C\equiv C-(CH_2)_n\,O^- + Br-(CH_2)_4CO_2^- \longrightarrow$$

$$H-C\equiv C-(CH_2)_n\,O^- + \text{7} \longrightarrow HO-(CH_2)_4-\underset{\underset{O}{\|}}{C}-O-(CH_2)_n-C\equiv C-H$$

Experimental procedure :

*Synthesis of 3* : To a solution of 1 (5.5 mmoles, 2 eq) in THF (5 ml) and HMPA (1.3 ml, 6 eq) at -80°C was added n Buli in hexane (4.3. ml, 4 eq). The temperature was progressively raised to -30°C and maintained for 45 mn. The ω bromoacid 2 (1 eq) was added dropwise at -30°C. After complete addition of 2, the solution was stirred at room temperature for 18 hours. The solution was neutralized with HCl 3N(20 ml) and extracted with ethylacetate (3x50 ml). Purification on TLC plates and elution with ethylacetate/hexane 50% led to 3 (8).

*Synthesis of 4 and 5* : To a solution of 1 (5.5 mmoles, 2 eq) in THF (5 ml) and HMPA (1.3 ml, 6 eq) at -80°C (n=1) or at -110°C (n=2) was added n Buli in hexane (4.3 ml, 4 eq). After 15 min. at -80°C or -110°C, the ω bromoacid was added dropwise and the solution was stirred at room temperature for 18 hours. The work-up was identical to the preceeding one.

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