Acetylenedicarbaldehyde: Isolation and some Examples of Exclusive Dienophilicity under Neutral Conditions

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Acetylenedicarbaldehyde (**1**) is isolated in the pure state after acidolysis of its monoacetal (**2**) with an excess of formic acid followed by dehydration of residual HCO_2H into CO with P_2O_5; under neutral conditions, (**1**) reacts with conjugated dienes as a dienophile only, in contrast to what occurs in acidic medium.

We have previously shown that acetylenedicarbaldehyde (ADCA) (**1**) and its monoacetal (**2**), both attractive synthetic intermediates,[1,2,3b] were readily generated by the acidolysis of the diacetal (**3**) with a large excess of formic acid, equation (1) and (2), respectively.[4]

Whereas (**2**) is easily isolable,[3,4]† the unstable ADCA could neither be isolated in the pure state, nor conveniently obtained in aprotic solutions.[4] Although formic acid solutions of (**1**), see equation (1), can be used in some syntheses,[1,2,4] residual HCO_2H is often incompatible in many reactions (*e.g.* with carbanionic species, dipolar compounds etc.), or can strongly modify the reactivity of ADCA[4] (*vide infra*). Here we describe procedures for eliminating HCO_2H, from the formolysis reactions in order to get aprotic solutions of ADCA, and for isolating ADCA in the pure form. They are based on the use of P_2O_5, an electrophilic reagent which promotes the dehydration of formic acid into CO.[5]

After treatment of (**2**) (2.5 g), under nitrogen and in the dark, HCO_2H (5 ml; dried over anhydrous $CuSO_4$) and anhydrous $CuSO_4$ (2 g), for 1.5 h at 20 °C (or 1 h at 25 °C) (see equation 3), and dilution with CH_2Cl_2 (200 ml), the resulting solution was added dropwise to a 100 ml CH_2Cl_2 suspension of P_2O_5 (17 g) for 10—15 min, at room temperature and in the dark. When CO was evolved (1—1.5 h of stirring), the reaction mixture was filtered and concentrated to 100 ml (rotary evaporation under reduced pressure, bath 20—25 °C); this solution A contains (**1**) (50—55% yield), ethyl formate, and only a small amount of HCO_2H[6] (<10% with respect to ADCA).

$$\underset{(\mathbf{3})}{(OEt)_2CHC{\equiv}CCH(OEt)_2} + 4\,HCO_2 \rightarrow \underset{(\mathbf{1})}{OHCC{\equiv}CCHO} + 4\,HCO_2Et + 2H_2O \tag{1}$$

$$(\mathbf{3}) + 2\,HCO_2H \rightarrow \underset{(\mathbf{2})}{HOC{\equiv}CCH(OEt)_2} + H_2O + 2HCO_2Et \tag{2}$$

$$(\mathbf{2}) + 2HCO_2H \rightarrow (\mathbf{1}) + 2HCO_2Et + H_2O \tag{3}$$

It was necessary to use a purification procedure consistent with the explosive character of ADCA in the dry state (*vide infra*) which allows the elimination of the remaining HCO_2H. Thus, to the solution A, diethyl phthalate (10 ml) (as a high boiling solvent) and P_2O_5 (0.5 g) were added, and the greater

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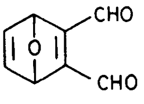
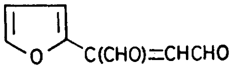
† Compounds (**2**), (**3**), and 5,6-dimethyl-4,7-dihydroisobenzofuran are marketed by Janssen Pharmaceutica.



(4)



(5)

$OHCC\equiv CCHO$

(1)

$OHCC\equiv CCH(OEt)_2$

(2)

part of the dichloromethane and ethyl formate slowly distilled off under reduced pressure (bath 15 °C, nitrogen capillary) for 1 h (completion of HCO_2H decomposition). When the temperature of the bath was raised to 50—60 °C, ADCA condensed (column 20—22 °C) in the refrigerant cooled to −40 °C as pale-yellow needles that explode, even under nitrogen, on melting (m.p. −11 to −10 °C). This explosion can be avoided by dissolving the solid at a temperature well below −11 °C in an aprotic solvent (CH_2Cl_2, $CHCl_3$, CCl_4), the resulting solutions (up to 0.4 mol/l) being fairly stable for a week when stored at −20 °C [30% yield of (**1**)].‡

For synthetic purposes, HCO_2H-free solutions of (**1**) can be more readily obtained by a further treatment of the solution A with P_2O_5 (5.7 g) in CH_2Cl_2: thus is obtained solution B [30% yield of (**1**)]. If ethyl formate and CH_2Cl_2 cannot be used in subsequent reactions, both can be distilled off under reduced pressure (bath 15—20 °C) after dilution of solution B with another higher boiling solvent (*e.g.* toluene) without any significant decrease in yield.

Whereas under HCO_2H conditions, ADCA shows a variety of reactivity towards conjugated dienes[1,4] (*i.e.* Diels–Alder and/or pseudo-Michael adducts), in contrast, under neutral conditions (from freshly prepared solutions of pure ADCA or from solution B), only the dienophilic behaviour is observed irrespective of the aromaticity of the diene.

The most significant example is provided by furan which leads to the exclusive formation of (**5**) in the presence of formic acid,[4] and of (**4**) (pale yellow solid, m.p. 70—73 °C, 98% yield) in the presence of pure ADCA collected into CCl_4.§ It should be noted that the addition of formic acid to a $CHCl_3$ solution of (**4**) does not give rise to (**5**), which suggests a kinetically controlled formation of the latter under acidic conditions.[4,7] Similarly, the dienes diphenylfulvene, anthracene, 4,7-ethano-4,7-dihydrobenzofuran,[8] and 5,6-dimethyl-4,7-dihydroisobenzofuran react to form the cycloadduct analogous to (**4**) instead of the mixture of products which is formed when the reaction takes place in the presence of HCO_2H.

With non-aromatic, or α,α'-disubstituted aromatic, dienes which are not subject to electrophilic substitution and will therefore form cycloadducts only, cycloaditions take place more slowly, but more cleanly in neutral solutions. For example, the product between cyclopentadiene and (**1**) was formed in 80% yield and that between cyclohexa-1,3-diene was formed in 75% yield, both from solution B. Also, 2,3-dimethylbuta-1,3-diene forms a cycloaddition product with (**1**) (pale yellow solid, m.p. 106—107 °C) in a neutral medium but only a tarry material in the presence of HCO_2H. Finally, the non-isolated, sensitive cycloadducts between (**1**) and 2,5-dimethylfuran and (**1**) and 1,3,3-trimethyl-2-vinyl cyclohexene[9] could be characterised only by starting with neutral solutions of ADCA.

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‡ Estimated by ^1H n.m.r. with an internal standard; i.r. (CCl_4) 1685 cm^{-1} (C=O), and no band in the C≡C absorption range; ^1H n.m.r. ($CDCl_3$) δ 9.50 (s, CHO); M^+, *m/z* 82.0057 (calc. 82.0055).

§ 1.8 mmol ADCA in CCl_4 (6 ml) reacted with 1.7 mmol furan for 2 h at 20 °C.