Coupling of Oxidative and Reductive Processes: Catalytic Carbonylation of Acetals of Prop-2-ynal

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Acetals of prop-2-ynal undergo double carbonylation with concomitant cleavage of an alkoxy group and stereoselective isomerisation to a vinyl ether under the catalytic action of a palladium iodide complex with thiourea.

Coupling of thermodynamically favoured and disfavoured processes is a well-known feature of biological cycles, but it has not found many applications in chemistry. Sometime ago we reported[1] that the palladium-catalysed carbonylation reaction of phenylacetylene at 25 °C in alcohols, gave equal amounts of products deriving from oxidative and reductive carbonylation, *e.g.* in methanol as solvent [eqn. (1)]. Separate carbonylation processes would have required a stoichiometric amount of palladium, while their coupling led to a catalytic reaction.

$$2PhC{\equiv}CH + 4CO + 2MeOH \xrightarrow{Pd^{II}\ cat.} Ph\text{–}C(CO_2Me){=}CH(CO_2Me) + \text{Ph-substituted butenolide} \quad (1)$$

This result overcomes the need for a reoxidant such as oxygen in oxidative carbonylation reaction[2] but the concomitant formation of two products is not convenient from a practical point of view. It could therefore be interesting to apply the coupling concept to substrates containing reducible functions, so that a single product would result. To this aim we chose the diethyl acetals of propynal and attempted to effect oxidative carbonylation of the triple bond coupled with acetal reduction. The catalyst, PdI_2 + 3 equiv. thiourea,[3] allowed working at room temp. and atmospheric or slightly higher pressure in alcoholic solvents. At 7 bar, using 3 mmol of the substrate diethyl acetal and 0.15 mmol of the catalyst in 30 ml of ethanol, the main product corresponded to the desired coupling of oxidative carbonylation with reduction. The double bond shifted towards the ethereal oxygen, however [eqn. (2), ethanol as solvent].

$$HC{\equiv}CCH(OEt)_2 + 2CO + EtOH \xrightarrow{Pd^{II}\ cat.} EtO_2C\text{–}CH_2\text{–}C(CO_2Et){=}CHOEt \quad (2)$$
1

Compound **1** was obtained in a 65% yield† at 95% conversion. The *E* stereoisomer was formed exclusively. Little conversion into the *Z* isomer was observed to occur with time.

Another compound **2**, deriving from additive (catalytic) carbonylation accounted for a 15% yield [eqn. (3)].

$$HC{\equiv}CCH(OEt)_2 + CO + EtOH \xrightarrow{Pd^{II}\ cat.} EtO_2C\text{–}CH{=}CHCH(OEt)_2 \quad (3)$$
2

The stereochemistry of this product is *E*, as expected for a *cis*-CO_2Et and -H addition.[4] Finally *ca.* 8% of the oxidative carbonylation product, corresponding to the pathway shown in eqn. (1), $EtO_2CCH{=}C(CO_2Et)CH(OEt)_2$ **3**, was also formed. The corresponding reductive carbonylation product could not be detected, however, because the reduced palladium catalyst (*ca.* 5%) was progressively converted into other soluble but inactive species. Other unidentified products make up for the balance (2%).

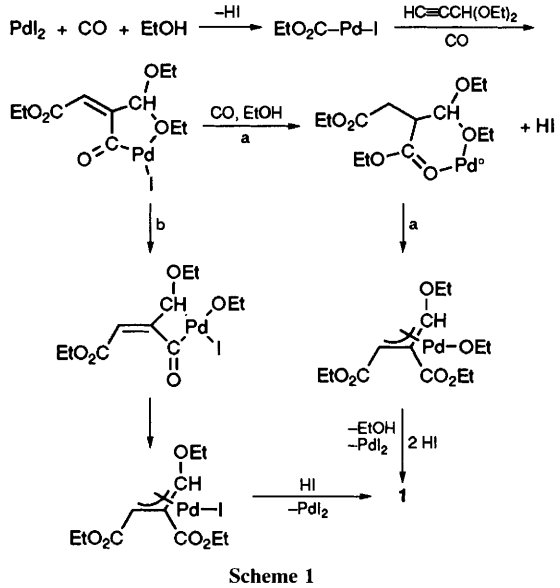
Working at atmospheric pressure of carbon monoxide alters the product distribution in favour of compound **2**, which reaches 33%. Increasing the substrate to catalyst ratio from 20 to 40 equiv. does not give significantly different results but the conversion decreases to *ca.* 85%.

To gain insight into the formation of compound **1**, the intermolecular version of reaction (2) was studied using phenylacetylene as the substrate for the carbonylation shown in equation (1) and benzaldehyde diethyl acetal as the reducible substrate. No significant reduction of the acetal occurred, the pattern of eqn. (1) involving reductive carbonylation to phenylbutenolactone still being preferred. When we used acetal **3** in the same reaction, reduction to ether **1** took place, however, with complete suppression of phenylbutenolactone formation, thus pointing to the involvement of an allylpalladium complex. Accordingly, the latter must be present in reaction (2) as an intermediate (Scheme 1, non reactive ligands are omitted).

Cleavage of an EtO- group, by oxidative addition of compound **3** to a soluble palladium(0)-thiourea complex (or possibly to a palladium–thiourea complex containing the elements of HI[5]) generates an allylpalladium intermediate which is decomposed to **1** by HI (route *a*). We cannot however, exclude an oxidative addition of the acetal to the palladium-bonded precursor of **3**, followed by intramolecular ethoxy group transfer to the palladium-bonded carbonyl group (route *b*).

It is worth noting that the formation of compound **1** is highly regio and stereoselective. Double bond isomerization appears to occur non-stereoselectively in conventional substitution reactions not involving palladium as catalyst: for example if the allylic bromide **4** (derived from double carbonylation of propynyl alcohol,[2] followed by bromination with PBr_3) is treated with sodium methoxide in methanol at room temp. a mixture of two stereoisomers (*Z* and *E*) is formed [eqn. (4)].

$$MeO_2CCH{=}C(CO_2Me)CH_2Br + NaOMe \longrightarrow \underset{\mathbf{4}}{} \quad \underset{\mathbf{1}\ (Z\text{ and }E)}{} + NaBr \quad (4)$$



Scheme 1

The synthesis leading to product **1** provides a simple and direct method for preparing a stereochemically defined enol ether. The latter has an interesting synthetic potential deriving from the presence of readily reactive functions. This aspect is being currently investigated.

We wish to thank Consiglio Nazionale delle Ricerche, Progetto Finalizzato Chimica Fine 2, for financial support and for the grant to A. B. The facilities of Centro Interfacoltà di Misure of the University of Parma have been utilized for MS and NMR determinations.

Received, 12th July 1994; Com. 4/04244A

Footnote

† **1**-*E*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, 3H, *J* 7.1 Hz, Me), 1.22 (t, 3H, *J* 7.1 Hz, Me), 1.28 (t, 3H, *J* 7.1 Hz, Me), 3.23 (s, 2H, CH_2), 4.03 (q, 2H, *J* 7.1 Hz, OCH_2), 4.09 (q, 2H, *J* 7.1 Hz, OCH_2), 4.13 (q, 2H, *J* 7.1 Hz, OCH_2), 7.44 (s, 1H, =CH); *m/z*: 230 (M^+, 10), 202 (1), 185 (16), 184 (11), 157 (32), 141 (2), 129 (50), 110 (7), 101 (73), 83 (100), 55 (15), 45 (4); IR ν/cm^{-1} (film): 2983 (ms), 2937 (m), 2905 (m), 1741 (vs), 1704 (vs), 1653 (s), 1448 (w), 1369 (m), 1305 (ms), 1213 (vs), 1178 (vs), 1103 (vs), 1033 (ms).

1-*Z* ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, 3H, *J* 7.1 Hz, Me), 1.25 (t, 3H, *J* 7.1 Hz, Me), 1.36 (t, 3H, *J* 7.1 Hz, Me), 3.07 (s, 2H, CH_2), 4.06 (q, 2H *J* 7.1 Hz, OCH_2), 4.14 (q, 2H, *J* 7.1 Hz, OCH_2), 4.18 (q, 2H, *J* 7.1 Hz, OCH_2), 6.56 (s, 1H, =CH); *m/z*: 230 (M^+, 4), 185 (11), 184 (7), 157 (33), 129 (54), 101 (77), 99 (4), 83 (100), 69 (7), 55 (22), 44 (30); IR ν/cm^{-1} (film): 2982 (ms), 2938 (m), 2905 (m), 1737 (vs), 1691 (s), 1647 (s), 1447 (m), 1370 (m), 1303 (ms), 1264 (ms), 1185 (vs), 1102 (s), 1032 (s).

2-*E*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, 6H, *J* 7.1 Hz, 2 Me), 1.27 (t, 3H, *J* 7.1 Hz, Me), 3.52 (q, 2H, *J* 7.1 Hz, OCH_2), 3.62 (q, 2H, *J* 7.1 Hz, OCH_2), 4.19 (q, 2H, *J* 7.1 Hz, OCH_2), 5.04 (dd, 1H, *J* 4.2, *J* 1.3 Hz, $CH(OEt)_2$), 6.12 (dd, 1H, *J* 15.8, *J* 1.3 Hz, $=CHCO_2Et$), 6.79 (dd, 1H, *J* 15.8, *J* 4.2 Hz, $=CHCH(OEt)_2$); *m/z*: 202 (M^+, absent), 201 (1), 173 (2), 157 (98), 145 (3), 129 (100), 127 (5), 117 (4), 103 (16), 101 (41), 83 (56), 73 (29), 57 (11), 55 (24), 45 (5); IR ν/cm^{-1} (film): 2979 (ms), 2934 (m), 2881 (m), 1726 (vs), 1447 (w), 1371 (m), 1299 (s), 1178 (ms), 1139 (ms), 1057 (vs), 977 (mw).

3-*E*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, 6H, *J* 6.9 Hz, 2 Me), 1.27 (t, 3H, *J* 7.2 Hz, Me), 1.31 (t, 3H, *J* 7.1 Hz, Me), 3.55 (q, 2H, *J* 7.1 Hz, OCH_2), 3.65 (q, 2H, *J* 7.2 Hz, OCH_2), 4.19 (q, 2H, *J* 7.2 Hz, OCH_2), 4.29 (q, 2H, *J* 7.2 Hz, OCH_2), 5.25 (d, 1H, *J* 1.4 Hz, $CH(OEt)_2$, 6.24 (d, 1H, *J* 1.4 Hz, CH); *m/z*: 274 (M^+, absent), 273 (0.5), 245 (1), 229 (38), 201 (10), 199 (10), 184 (5), 171 (18), 155 (100), 143 (67), 127 (48), 103 (35), 99 (32), 83 (7), 81 (7), 75 (22), 69 (9), 55 (18), 53 (10), 47 (16); IR ν/cm^{-1} (film): 2980 (ms), 2955 (m), 1730 (vs), 1178 (m), 1218 (s), 1203 (s), 1104 (vs).

Elemental analyses were satisfactory for all compounds.

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