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AN UNUSUAL SYNTHESIS OF MALONATES

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Abstract - The reaction of palladium diacetate, triethylamine, ethyl chlorocarbonate and carbon monoxide in acetonitrile at room temperature gives a good yield of diethyl malonate. By ^{13}C labelling of each of the reagents in turn it has been proven that the methylene group of the malonate comes from an acetate originally bonded to Pd^{II}.

The insertion of Pd(O) into organic halides having little or no propensity for β-elimination constitutes the initial step of numerous synthetically useful transformations, such as carbonylation, Heck arylation, oxidative coupling etc.[1] Despite the extensive use of aryl, vinyl, acyl, methyl, benzyl and neopentyl-like alkyl halides as substrates, examples of Pd(O) insertion into chlorocarbonates are known[2] but rare. Herein, we report our studies on the reaction of palladium diacetate with ethyl- and isobutyl chloroformates in the presence of NEt_3 and CO.

The initial experiments with ethyl chloroformate under stoichiometric conditions showed that diethyl malonate **1** was the only product left after removal of solvent (CH_3CN). In its optimized form a typical procedure involved dissolving palladium diacetate (93 mg, 0.41 mmol) and Et_3N (168 mg, 1.66 mmol) in dry CH_3CN (5 ml) under argon. Ethyl chloroformate **3** (183 mg, 1.66 mmol) was then added and the solution was stirred under a static pressure of CO (in a balloon) at room temperature overnight. Ethyl malonate **1** (59 mg, 80%, based on palladium diacetate) was obtained after filtration of the reaction mixture through a short silica column. Similarly, isobutyl chloroformate **4** afforded diisobutyl malonate **2** (82%).

Formation of this unexpected product led us to seek the origin of the methylene carbon. We ascertained the necessity of Et_3N, CO, Ethyl chloroformate **3** and palladium acetate in malonate formation. Each of these compounds could, in principle, be the source of the methylene carbon. There was no ^{13}C incorporation into the malonate from triethylamine labelled at C-1 or at C-2. The use of ^{13}C enriched CO again gave no incorporation. A ^{1}H-n.m.r. analysis of malonate formed using deuterated palladium acetate showed some deuterium to be present in the malonate CH_2, especially when moisture was excluded during work up.

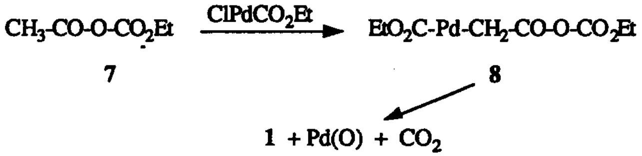
The use of palladium dipropionate afforded diethylmethylmalonate **5** (38%). The slower reaction rate with palladium dipropionate enabled us to isolate, after one hour of reaction at room temperature, the mixed anhydride **6** in 90% yield based on palladium diacetate.

We then prepared the acetate mixed anhydride **7**. This was used in the normal reaction sequence using palladium dichloride instead of palladium diacetate and gave diethyl malonate (44%). The presence of the other reagents was essential.

Finally, the origin of the methylene group was proven to be the acetates of the palladium diacetate. 2-^{13}C labelled acetic acid was converted to its Hg^{II} salt. This exchanged ligands with palladium dichloride in CH_3CN to furnish $Pd(OCO\,^{13}CH_3)_2 \cdot 2CH_3CN$. Using this 99.3% ^{13}C enriched diacetate the diethyl malonate formed was 99% enriched in ^{13}C in its methylene group. The extent of ^{13}C incorporation was determined by comparing the intensities of NMR peak(s) of ^{13}C-coupled ($J_{13C\text{-}H}$ = 132 Hz) and uncoupled (δ = 3.36 ppm) methylene protons of the malonate.

The Scheme proposes one way in which diethyl malonate might be formed. There is no reaction between palladium diacetate and ethyl chlorocarbonate **3** in the absence of CO. So Pd(O) formation is essential. The latter may, or may not, play a role in formation of the mixed anhydride **7**. Starting with **7** the Pd(O) must participate in the activation of **3** to furnish, by reaction with **7**, an intermediate which in turn affords diethyl malonate. The structure **8** for the intermediate satisfies these requirements. It implies that the methyl group of the anhydride is sufficiently acidic (NEt_3) to permit displacement of chloride from EtO-CO-Pd-Cl.

Scheme



$$CH_3\text{-}CO\text{-}O\text{-}CO_2Et \xrightarrow{ClPdCO_2Et} EtO_2C\text{-}Pd\text{-}CH_2\text{-}CO\text{-}O\text{-}CO_2Et$$

$R^1O\text{-}CO\text{-}CHR\text{-}CO\text{-}OR^2$

1 R = H ; $R^1 = R^2$ = Et

2 R = H ; $R^1 = R^2$ = *iso*-Bu

5 R = Me; $R^1 = R^2$ = Et

ClCO-OR

3 R = Et

4 R = *iso*-Bu

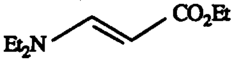
$R^1\text{-}CO\text{-}O\text{-}CO\text{-}OR^2$

6 $R^1 = R^2$ = Et

7 R^1 = Me ; R^2 = Et

CH_3CONEt_2

9



10

We also investigated variation of the partial pressure of CO. Reducing the CO pressure reduced the malonate yield with concomitant formation of two other products **9** and **10**, both of which arose by palladium diacetate oxidation of triethylamine. We considered **10** as a potential intermediate but it was recovered unchanged under malonate synthesis conditions.

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