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PALLADIUM CATALYZED ALLYLIC C-ALKYLATION OF HIGHLY ACIDIC AND ENOLIC HETEROCYCLIC SUBSTRATES: TETRONIC ACID AND TRIACETIC ACID LACTONE

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Summary.- Tetronic acid (pK_a 3.76) and triacetic acid lactone (pK_a 4.94) have been alkylated at their active carbon atoms by means of thermodinamically controlled palladium catalyzed allylic alkylations.

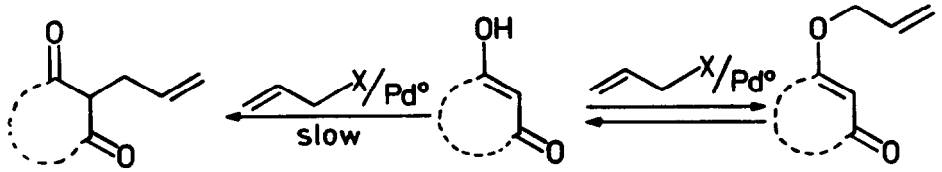
There are many heterocyclic β-dicarbonyl compounds having pKa values around 5 or even much less which frequently exhibit a high content of enol forms and which are particularly difficult to alkylate at the central carbon atom.

Among them, triacetic acid lactone, 1, (pK_a 4.94 (1), 100% enol form) and tetronic acid, 2, (pK_a 3.76 (2), 100% enol form) have attracted a great deal of attention. The pyrone 1 is itself a natural polyketide (3) and many related natural pyrones have been described with biogenetically relevant substituents at C-3, such as elasnin (4) which has a butyl chain at that position. Tetronic acid, 2, has the fundamental skeleton of a family of natural butenolides (5,6). Both 1 and 2 could be more important building blocks were it not for the difficulties experienced when alkylations at carbon are attempted. It is well known that compounds such as 1 and 2 have a great propensity to alkylate at the oxygen atom of the enol form. Thus the pyrone 1 can not be alkylated at C-3 through direct methods (7,8), and no useful C-alkylation is known for 2 (9,10).

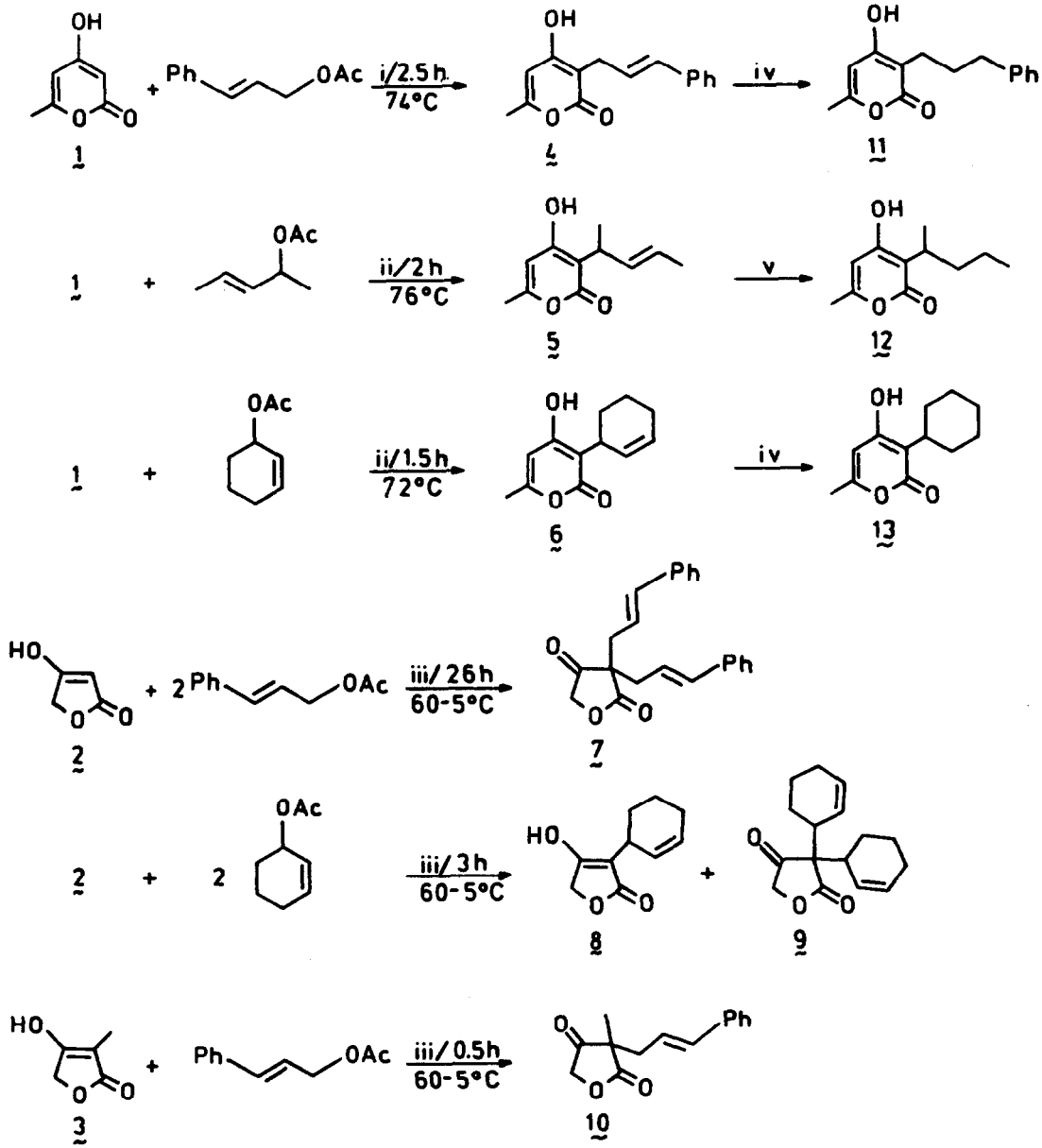
The palladium catalyzed alkylation of proton active substrates with allylic systems is a useful method of carbon-carbon bond formation (11-14). The acidity of the most frequently used proton active substrates ranges in between 10 pKa 24. However, more acidic substrates (pKa<8) have received much less attention.

We reasoned that C-alkylation on 1, 2 and 3 could be better achieved if the kinetically preferred O-alkylation would be performed under reversible conditions thus permitting the slower C-alkylation to predominate under thermodynamic control. Palladium catalyzed allylic alkylation should met the above conditions since the enol ether initially formed under kinetic control should act itself as an alkylating agent. The enolate anion, being the conjugate base of a relatively strong acid, is itself an efficient leaving group. In other words, O-alkylation should be reversible (Scheme I).

Scheme I



Scheme II



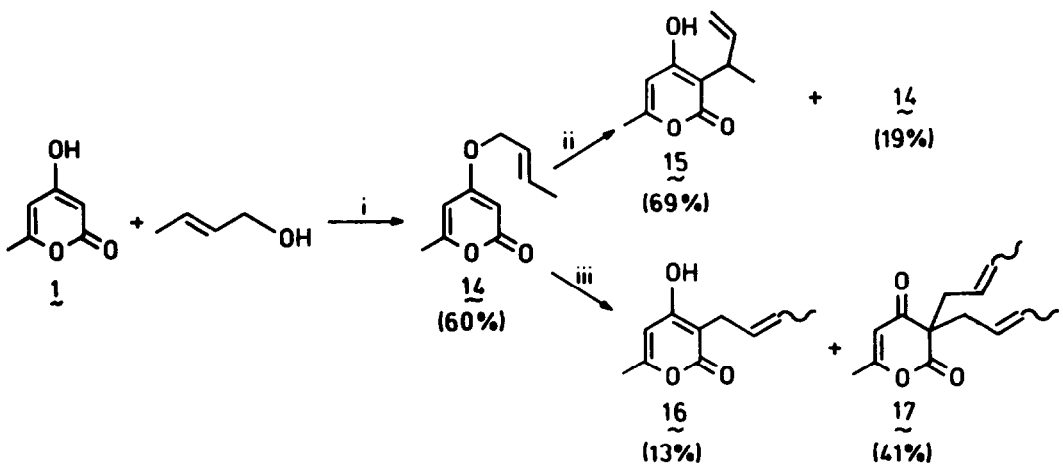
SCHEME II.- Allylic C-alkylations compounds 1, 2 and 3.

[a] Yields refer to isolated pure products and they are based on the starting amount of the respective lactone. The new compounds gave correct elemental analyses. i.- Toluene, $Pd(acac)_2$ (5% molar), $(C_6H_5)_3P$ (20% molar); ii.- Toluene, DBU (1 equiv.), $Pd(acac)_2$ (5% molar), $(C_6H_5)_3P$ (20% molar); iii.- THF, DBU (1 equiv.), $Pd(acac)_2$ (5% molar), $(C_6H_5)_3P$ (20% molar); iv.- H_2, Pd-C, EtOH; v.- H_2, Pd-C, EtOAc.

Our initial results are collected in the Scheme II. Monoalkylations have been achieved with pyrone **1** upon working in toluene. Thus, the C-monoalkylation product **4** (83%, m.p. 221-2 °C) was isolated as the only product. Secondary radicals can also be introduced at C-3 of pyrone **1**, for example to afford **5** (47%, m.p. 131-2 °C) and **6** (58%, m.p. 200-1°C). Tetronic acid **2** is efficiently alkylated with cinnamyl acetate to afford **7** (38%, m.p. 99-100°C). By using 2-cyclohexenyl acetate the monoalkylated lactone **8** (57%, m.p. 167-9°C) was obtained although minor amounts of the dialkylated butanolide **9** (14%,m.p. 88-90°C) were also isolated. 3-Methyltetronic acid, **3**(15), behaved similarly, affording the oxobutanolide **10** (32%, m.p. 93-4°C). Selective hydrogenations of **4**, **5** and **6** at the side chains double bonds to afford **11** (97%, m.p. 129-31°C), **12** (98%, m.p. 123-5°C) and **13** (100%, m.p. 264-5°C) broadens the scope of the method which should be formally considered as a C-alkylation method including allylic and saturated primary and secondary chains.

In order to obtain information about the reversibility of the O-alkylation step under palladium catalysis we prepared the enol ether **14** (m.p. 64-6°C; lit. m.p.65-6°C (16)) (Scheme III). The pyrone **14** was converted into **15** (m.p. 173-4°C) through a thermal Claisen rearrangement. However, under palladium catalysis **14** afforded a mixture of the pyrones **16** and **17**. Product **16** (16) was formed as a 4:1 mixture of **E** and **Z** isomers. Product **17** (b.p. 75°C/0.05mmHg in a bulb-to-bulb distillation) was also a mixture of isomers. These experiments support our hypothesis of a prior reversible O-alkylation on our C-alkylation reactions.

Scheme III



SCHEME III

i.- Benzene, $(C_6H_5)_3P$, EtOCO-N=N-COOEt, r.t., 9h; ii.- Toluene, reflux, 19h; iii.- Toluene, $Pd(acac)_2$ (5% molar), $(C_6H_5)_3P$ (20% molar), 85°C, 1h.

Our initial results here described show that a general method for C-alkylation of highly acidic and enolic heterocyclic compounds is now available.

A full paper reporting on the synthetic scope and the mechanistic aspects of the alkylations herein described will be published elsewhere.

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