

COPPER PROTECTION IN THE PALLADIUM CATALYZED REGIOSELECTIVE
ALLYLATION OF A MODEL POLYKETIDE: METHYL 3,5-DIOXOHEXANOATE

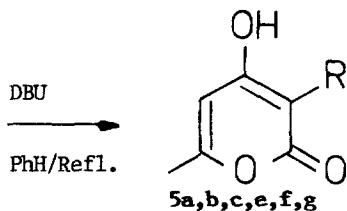
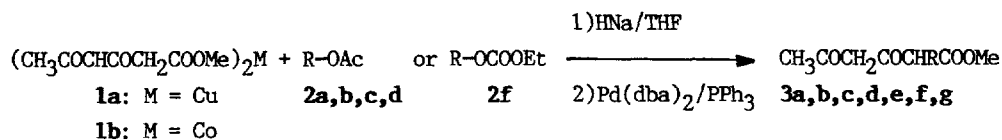
Jorge Marquet, Marcial Moreno-Mañas*, María Prat
Departamento de Química. Universidad Autónoma de Barcelona.
Bellaterra. 08193-Barcelona. Spain.

Summary.— Regioselective allylation of the model polyketide system methyl 3,5-dioxohexanoate at the C-2 position can be accomplished even with secondary and tertiary radicals by palladium catalyzed allylation of its copper(II) complex, **1a**. Initial results indicate that the cobalt(II) complex, **1b**, can be also useful. Cyclizations of the resulting diketooesters, **3**, afford triacetic acid lactone derivatives, **5**, regioselectively allylated at C-3.

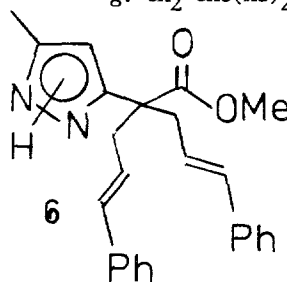
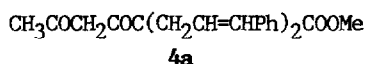
Regioselective alkylation of open chain polyketides is an important although elusive target due to the many nucleophilic centers present in these molecules. Reactions with electrophiles have been achieved at the terminal ω position by means of the polyanion chemistry developed by Harris^{1,2}. However, regioselective alkylation at the activated intercarbonyl non terminal positions remains a synthetic goal for which a general solution is still to be found.

We have reported regioselective alkylations at C-2³ and at C-4⁴ of a simple open chain polyketide model: methyl 3,5-dioxohexanoate, available itself from dehydroacetic acid⁵. Transition metals (e.g. cobalt(II), copper(II) and nickel(II)) form complexes with the β -diketo moiety of the diketooester. Moreover, cobalt(II) complexes of β -dicarbonyl compounds are known to activate the central position towards alkylation by a broad choice of alkyl halides⁶ whereas copper complexes are inactive. Therefore, the cobalt(II) complex of methyl 3,5-dioxohexanoate, **1b**, has been regioselectively alkylated at C-4⁴ whereas the corresponding copper(II) complex, **1a**, has been regioselectively alkylated at C-2 under more conventional conditions³. Since allylations of active positions under palladium catalysis constitute a powerful carbon-carbon bond formation method⁷ we planned to apply combined cobalt-palladium and copper-palladium methodologies to broaden the scope of the original cobalt and copper based methods.

Complex **1a** was sequentially treated with sodium hydride and with the corresponding allylic acetates, **2a-d**, (or ethyl carbonate **2f**) under palladium catalysis to give good yields of products **3** from regioselective allylation at C-2 (See table). The reactions were successful with primary (entries 1 and 2) as well as with secondary acetates (entries 4-6) although with the primary acetate **2a** diallylation presented an unsolved problem (entries 1 and 2). Also, no reaction was observed in the absence of base (entry 3). Finally, the

TABLE^a

For products **2-5** R =
 a: (E)-Ph-CH=CHCH₂-
 b: 2-Cyclohexen-1-yl-
 c: (E)-MeCH=CHCH(Me)-
 d: Me₂C=CHCH(Me)-
 e: MeCH=CH(Me)₂-
 f: Me₂C=CHCH₂-
 g: CH₂=CHC(Me)₂-



Entry	1:2	1:HNa:2: Pd:PPh ₃	t ^a (°C), time(h)	1[M]	Products (%)
1	1a 2a	1:2:2:0.02:0.2	75 19	0.25	3a (17), 4a (50)
2	1a 2a	1:4:4:0.04:0.4	70-75 65	0.125	3a (0), 4a (71)
3	1a 2a	1:0:2:0.02:0.2	75-80 19	0.24	—
4	1a 2b	1:2:2:0.02:0.2	80 17	0.25	3b (89)
5	1a 2b	1:2:2:0.02:0.2	70 18	0.25	3b (80)
6	1a 2c	1:2:2:0.02:0.2	75-79 17	0.25	3c (72)
7	1a 2d	1:2:2:0.02:0.2	80-95 27	0.25	3d (8), 3e (33)
8 ^b	1a 2f	1:0:2:0.02:0.2	70 5	0.25	3f (25), 3g (33)
9	1b 2a	1:0:2:0.02:0.2	60 5	0.25	3a (5), 4a (56)

^aTo a mixture of NaH (dispersion in mineral oil) and **1** the following products were added under argon atmosphere in the indicated order: half of the THF and a solution of **2**, Pd(dba)₂ and PPh₃ in the rest of the THF. The mixture was kept under the conditions specified in the table, poured into 1N HCl and worked up as usual. **3a**: b.p.: 185°C/0.04mmHg¹¹; **3b**: m.p. 47-9°C¹¹; **3c**: b.p. 115°C/0.2mmHg¹¹; **3e**: b.p. 85-90°C/0.03mmHg¹¹; **3f**: b.p. 60-75°C/0.01mmHg¹¹; **3g**: b.p. 55-60°C/0.01mmHg¹¹; **4a**: oil¹¹. **3d** was an oil which exhibited spectroscopic behaviour as expected. The limited amount available did not allow an elemental analysis.

^bNo base was added in this experiment since the ethoxide anion liberated in the formation of the cationic π -allylpalladium complex is basic enough.

copper-palladium combination permits the introduction of heavily substituted radicals; thus, 4-methyl-3-penten-2-yl acetate, **2d**, produced only 8% yield of the product of allylation at the less substituted terminus of the allylic system, **3d**; instead and curiously enough the product of attack at the most substituted terminus, **3e**, was isolated in excellent yield (entry 7). Also, reaction of **1a** with ethyl 3-methyl-2-butenyl carbonate, **2f**, afforded **3f** in 25% yield but also **3g** in 33% yield (entry 8). It has been previously reported that the presence of copper militates favouring the nucleophilic attack at the most substituted end of the π -allylpalladium system⁸, although no clear explanations are evident.

Also complex **1b** reacted with cinnamyl acetate under palladium catalysis in the absence of base to afford methyl 2-cinnamyl-3,5-dioxopentanoate, **3a**, (5%) and the dialkylation product **4a** (56%) (entry 9) instead of the expected 4-cinnamyl isomers. The free C-2 position was active enough as to allylation to predominate there instead of at C-4. It should be remembered that the formation of a cationic π -allylpalladium complex from Pd(0) and an allylic acetate results in the liberation of acetate anion which can act as a strong base in THF. It is interesting to have at hand a method to alkylate C-2 without added base. Its scope will be studied further. At present we do not have yet a mechanistic explanation for the different requirements for added base observed for the copper (base needed) and cobalt (base not essential) complexes **1**.

Compounds **3** were efficiently cyclized to the 3-allyl-4-hydroxy-6-methyl-2-pyrones, **5**, by treatment with DBU in refluxing benzene; **5a**: m.p. 218-24°C (Lit.⁹ m.p. 221-2.5°C); **5b**: m.p. 208-9°C (Lit.⁹ m.p. 200-1°C); **5c**: m.p. 133-5°C (Lit.⁹ m.p. 131-2°C); **5e**: m.p. 93-8°C¹¹; **5f**: m.p. 152-3°C (Lit.¹⁰ m.p. 152-3°C); **5g**: m.p. 136-8°C (Lit.⁹ m.p. 129-30°C). The importance of these derivatives of triacetic acid lactone regioselectively allylated at the ring C-3 position has been emphasized elsewhere^{3,4,9}. The dialkylated compound **4a** did not cyclize under these conditions but it was converted into the oily pyrazole **6**¹¹.

ACKNOWLEDGEMENTS.— Financial support from DGICYT (Ministry of Education and Science of Spain) through project n° 0030-87 and a predoctoral grant (to M.P.) are gratefully acknowledged.

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- 11.- Correct elemental analysis was secured for these compounds.

(Received in UK 8 March 1989)