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ALKYLATION OF ACTIVE HYDROGEN COMPOUNDS WITH ALLYLIC AND BENZYLIC ALCOHOLS UNDER $CoCl_2$ CATALYSIS. A USEFUL SYNTHESIS OF GRIFOLIN†

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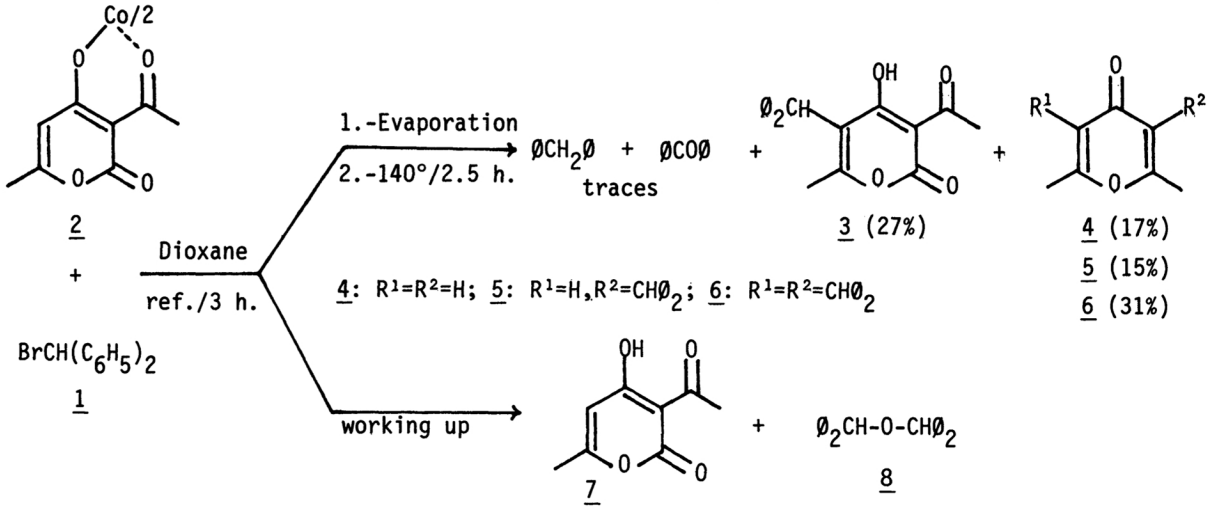
$CoCl_2$ is a useful catalyst for the condensation of allylic and benzylic alcohols with active hydrogen compounds. Under these neutral conditions orcinol and farnesol react to afford the antibiotic grifolin.

The alkylation of active hydrogen compounds in neutral media is a subject of general interest since acid and alkaline conditions reduce the range of suitable starting reagents and can deteriorate the initial alkylation products. The reactions of alkaline salts of β-dicarbonyl compounds with alkyl halides offer typical examples of such limitations[1,2,3].

In our search for better alkylating methods of β-dicarbonyl compounds we found that bis-(pentane-2,4-dionato)cobalt(II) reacts with several reactive alkyl halides. The final products are the alkylated pentane-2,4-diones[4]. When this method was applied to benzhydryl bromide, 1, and the cobalt(II) complex of dehydroacetic acid, 2[5], alkylation at C-3 was not observed. Instead, upon heating in the absence of solvent, 3-acetyl-5-benzhydryl-4-hydroxy-6-methyl-2-pyrone, 3[5] (m.p. 135-7°; ν(KBr): 1725, 1630(sh), 1600 cm^{-1}; pmr($CDCl_3$): δ 17,6(s., 1H), 7,45-7,00(m., 10H),



5.80(s., 1H), 2.65(s., 3H), 2.00(s., 3H); mass spectrum: m/e 334(M^+,5), 206(24),178(17), 168(28), 153(27), 129(36), 125(25), 115(20), 111(24), 98(21), 85(98), 83(100), 77(25), 69(42), 43(94); UV(cyclohexane): λ 322 nm (log ε: 4.09)), was isolated. Also the pyrones 4 (m.p. 127-30°), 5[8] (oil, never isolated in pure form), and 6[5,8] (m.p. 161-2°) were characterized by standard methods. Product 4 must be formed by ring opening of dehydroacetic acid, 7, followed by decarboxylation and cyclization. Similarly 5 can derive from 3 although alkylation of 4 is also possible. Most probably 6 comes from alkylation of 5 since dialkylation on 2 (or 7) was never observed.

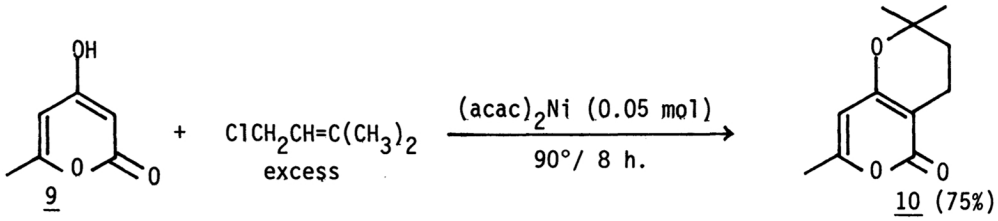
However, when a sample was taken off after refluxing for 3 h. in dioxane, only 7 and dibenzhydryl ether were characterized as organic products.

The unusual reaction at C-5 of the dehydroacetic acid ring, position which is not activated by the cobalt complex, together with the other facts above described, strongly suggested the operativity of a catalytic effect of the cobalt species, the ether 8 acting as a real alkylating agent. Indeed, when 7 and 1 were reacted under the catalytic influence of the complex 2, similar results were obtained.

$$7 + 1 \xrightarrow{2(\text{cat}),\ 100\text{-}5^\circ,\ 9\ \text{days}} 3\ (33\%) + 4 + 5 + 6$$

As a consequence we undertook a research on the catalytic effects of some metallic complexes and salts.

The adoption of alkyl halides as alkylating agents results on the undesirable formation of one equivalent of hydrogen halide. We have observed that this has a deletereous effect upon the direct alkylation products. For instance, in one of our best experiments, treatment of 4-hydroxy-6-methyl-2-pyrone, 9, with 1-chloro-3-methyl-2-butene,under bis-(pentane-2,4-dionato)nickel-(II) catalysis[6], led to the cyclized 2,8-dioxa-3,3,9-trimethylbicyclo{4.4.0}deca-1(6),9-dien-7--one, 10 (oil, pmr ($CDCl_3$) δ 5.75(s., 1H), 2.45(t., J ca. 6.7 Hz, 2H), 2.20(s., 3H), 1.79(t., J ca. 6.7 Hz, 2H), 1.35(s., 6H).

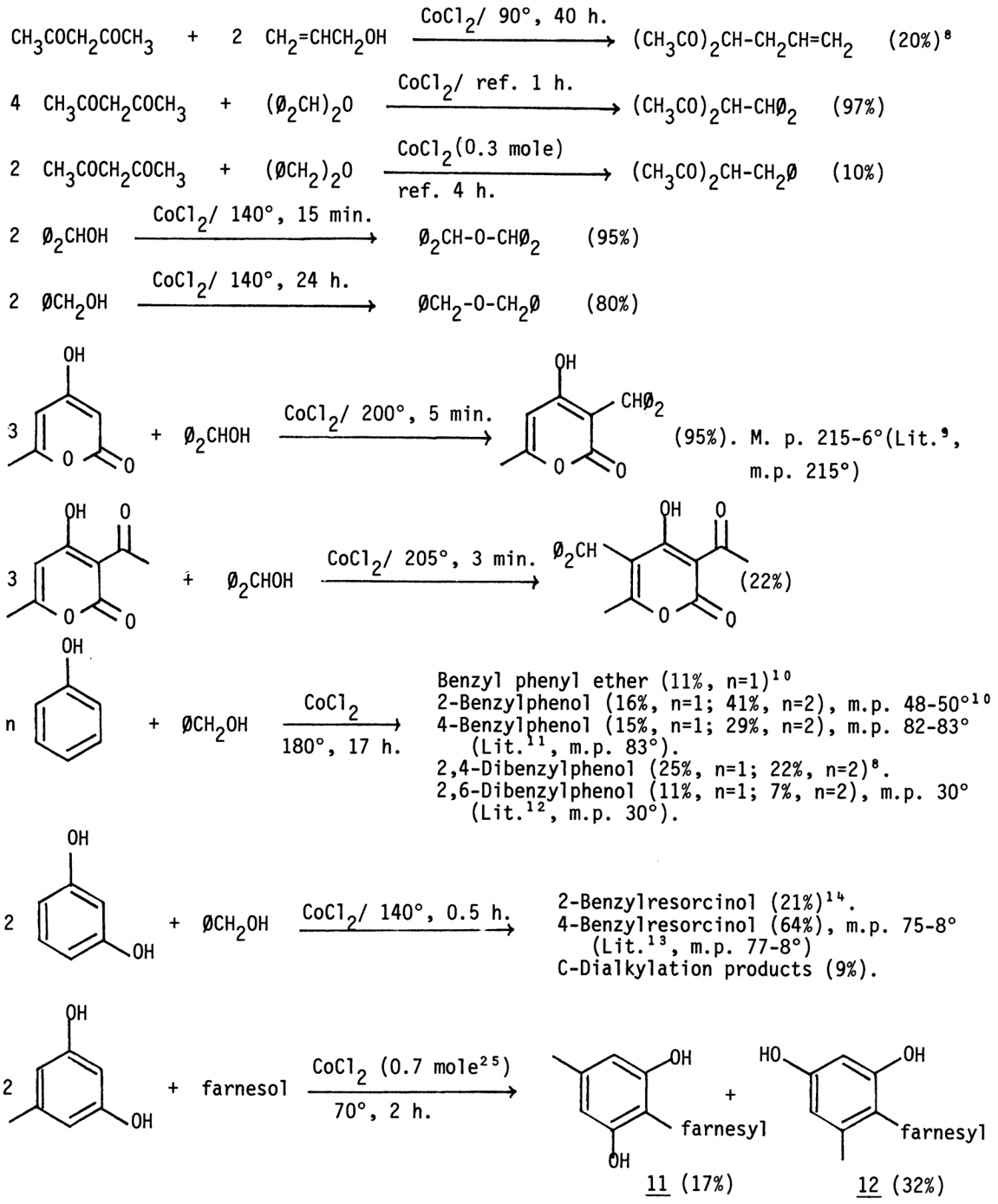


Therefore, we turned upon alcohols as alkylating agents. For a variety of substrates, and in the absence of solvent, anhydrous $CoCl_2$ is an efficient catalyst although its conversion into an hexahydrate makes necessary its use in rather large quantities (0.2 mol unless otherwise stated). Our initial results are collected below:

$$3\ CH_3COCH_2COCH_3 + Ø_2CHOH \xrightarrow{CoCl_2/\ \text{ref.}\ 3.5\ \text{h.}} (CH_3CO)_2CH\text{-}CHØ_2\ \ (96\%)$$

M. p. 114-5°(Lit.[4], m. p. 113-5°)

$$3\ CH_3COCH_2COCH_3 + ØCH_2OH \xrightarrow{CoCl_2/\ \text{ref.}\ 17\ \text{h.}} (CH_3CO)_2CH\text{-}CH_2Ø\ \ (65\%)^7$$



Two natural products, the antibiotics grifolin, 11[15,16,17] and its isomer neogrifolin, 12 [16,17], were prepared from orcinol and farnesol (having ca. 30% of the 2-Z isomer). After careful chromatography on silica gel, the yields of isolated 11 and 12 were respectively 17 and 32%, which compares well with those previously reported from non neutral condensation techniques[18-23].

The ir of 11 was identical to that reproduced in the literature[18]. However, the presence of minor amounts of the 2'-Z isomers of both 11 and 12[8,24] can not be excluded.

At present we are investigating the scope of this method.

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