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COPPER COMPLEX PROTECTION IN THE REGIOSELECTIVE ALKYLATION OF METHYL 3,5-DIOXOHEXANOATE. PREPARATION OF 3-ALKYL DERIVATIVES OF 4-HYDROXY-6-METHYL-2-PYRONE

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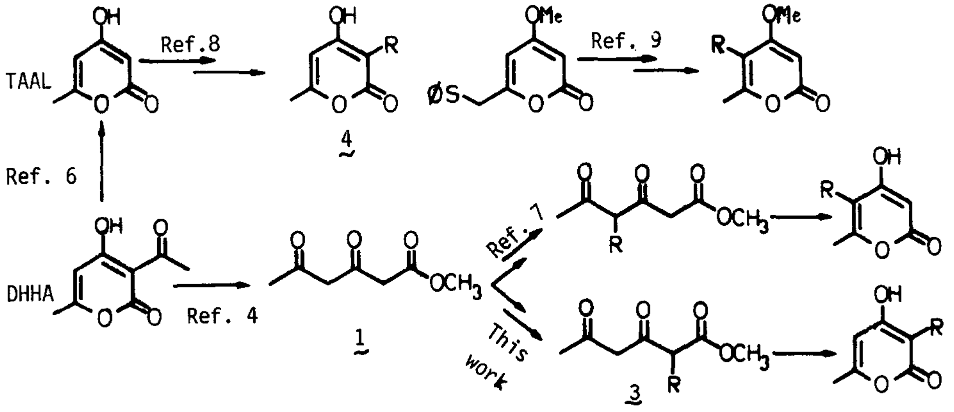
Summary.- Protection of the diketone moiety of the polyketide model methyl 3,5-dioxohexanoate by copper(II) complex formation followed by alkylation of the free C-2 position results in overall regioselective alkylation of the diketoester to afford methyl 2-alkyl-3,5-dioxohexanoates, which under cyclization afford 3-alkyl derivatives of triacetic acid lactone.

Regioselective alkylation of open-chain polyketides is an important elusive synthetic target. The only reported regioselective reactions of poly-β-ketoesters with electrophiles have been achieved at the terminal ω position through polyanion chemistry as developed by Harris(1,2). Indeed, conventional alkylation of the most simple open-chain polyketide model: methyl 3,5-dioxohexanoate, 1, results in the formation of a complicated array of products(3).

The diketoester 1 can be easily prepared from the industrially available dehydroacetic acid (3-acetyl-4-hydroxy-6-methyl-2-pyrone, DHAA)(4). The related 4-hydroxy-6-methyl-2-pyrone (triacetic acid lactone, TAAL) is a natural polyketide(5) which is prepared by deacetylation of dehydroacetic acid(6). Moreover, many related natural 2-pyrones have been described with biogenetically relevant substituents at C3 and C5. Therefore, methods to accomplish the regioselective alkylation of both the diketoester 1 and of the aforementioned 2-pyrones deserve some attention.

We have previously reported that the cobalt(II) complex of the diketoester 1 can be regioselectively alkylated at C4, the cobalt atom acting as activating factor for that position(7). The resulting methyl 4-alkyl-3,5-dioxohexanoates were efficienly cyclized to the difficultly accessible 5-alkyl derivatives of triacetic acid lactone. Also, methods to alkylate C3 and C5 of triacetic acid lactone and derivatives have been reported from our laboratories(8,9).

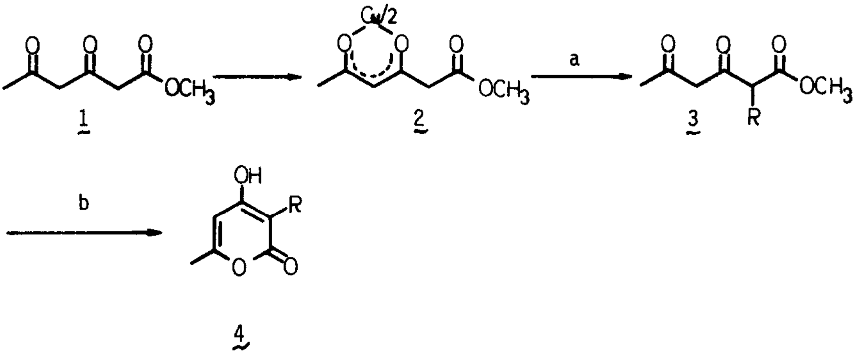


We report here the regioselective alkylation of the diketoester copper complex, **2**(10), at the position C2 by treatment with sodium hydride in THF followed by refluxing (0.3-5 hours) with excess of alkyl halides, the metal atom acting now as protector instead of as activator. The methyl 2-alkyl-3,5-dioxohexanoates, **3** (See Table), were formed in yields higher than 60%, and were cyclized to 3-alkyl-4-hydroxy-6-methyl-2-pyrones, **4**, (3-alkyl derivatives of triacetic acid lactone) by treatment with DBU in refluxing benzene (See Table).

TABLE . Methyl 2-alkyl-3,5-dioxohexanoates, 3 and 3-alkyl-4-hydroxy-6-methyl-2-pyrones, 4(11).

R-X	3[a]	mp°C or bp°C/mmHg[b]	yield	4	mp°C	yield
CH_3CH_2Br	**3a**	85-7/1.1	85%	**4a**	172-4	88%
$n\text{-}C_4H_9I$	**3b**	89-91/1.2	60%	**4b**	132-3[c]	65%
$CH_2{=}CHCH_2Br$	**3c**	83-4/1.2	83%	**4c**	149-52	100%
$C_6H_5CH_2Br$	**3d**	100-2/1.0	73%	**4d**	164-7[d]	86%
$MeOCOCH_2Br$	**3e**	56-60	94%	**4e**	179-84	77%

[a] Reaction with isopropyl bromide failed. [b] Oven temp. for bp. [c] Lit.(8), mp. 132-3. [d] Lit.(8), mp. 169-70.



a)1.-HNa, THF, ref., 5 min.; 2.- R-X, THF, ref.; 3.- H_3O^+. b)DBU, benzene, ref., 1.5h.

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REFERENCES AND FOOTNOTES

1.- T.M. Harris, C.M. Harris; Pure Appl. Chem., 1986, **58**, 283.
2.- C.P. Hauser, T.M. Harris; J. Am. Chem. Soc, 1958, **80**, 6360.
3.- S. Gelin, J. Rouet; Bull. Soc. Chim. Fr. 1972, 232.
4.- J.G. Batelaan; Synth. Commun., 1976, **6**, 81.
5.- R. Bentley, P.M. Zwitkowits; J. Am. Chem. Soc, 1967, **89**, 676 and 681.
6.- J.N. Collie; J. Chem. Soc, 1891, **59**, 607.
7.- J. Cervelló, J. Marquet, M. Moreno-Mañas; J.C.S. Chem. Commun., 1987, 644.
8.- M. Moreno-Mañas, R. Pleixats; Synthesis, 1984, 430.
9.- P. de March, M. Moreno-Mañas, I. Ripoll; Chem. Ber., in the press.
10.- Complex **2**, m.p.190-2°C was prepared by treatment of **1** with copper acetate in water-methanol. The formed precipitate was filtered and dried to afford **2**. Ir(KBr): 1730 cm^{-1}.
11.- All new compounds **3** and **4** gave correct elemental analysis.

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