A Convenient Synthesis of Alkylated 4-Hydroxy-2-pyrones

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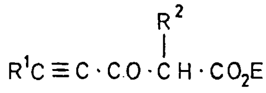
Summary Various alkylated 4-hydroxy-2-pyrones were synthesized from the $\beta\delta$-diketo-esters (**11**), (**13**), and (**14**), which were easily prepared from the $\gamma\delta$-acetylenic β-keto-esters (**3**), (**4**), and (**7**) *via* the corresponding enamino-β-keto-esters (**8**)—(**10**).

The present study was undertaken to establish a convenient method for the preparation of 3,6- and 5,6-dialkyl- and 3,5,6-trialkyl-4-hydroxy-2-pyrones corresponding to the pyrone units in luteoreticulin,[1] citreoviridin,[2] and aureothin.[3] Syntheses of 3,6-[4] and 5,6-dialkyl-4-hydroxy-2-pyrones[5] have been carried out extensively in recent years, but no 3,5,6-trialkyl derivatives have been synthesized.

The Grignard reagents (**1**) and (**2**) reacted with a solution of ethyl methylmalonyl chloride in tetrahydrofuran at −20° to give the $\gamma\delta$-acetylenic β-keto-esters (**3**) (65%) and (**4**) (85%), respectively, as viscous oils. The imidazolide of tetrolic acid reacted with the malonate magnesium enolates (**5**) and (**6**)[6] in tetrahydrofuran to give the esters (**3**) (50%) and (**7**) (50%). Addition of diethylamine to (**3**), (**4**), and (**7**) in ether afforded the corresponding enamino-β-keto-esters, (**8**) (74%), (**9**) (48%), and (**10**) (41%). Hydrolysis of the enamine (**9**) with N-hydrochloric acid at 50° gave ethyl 2-methyl-3,5-dioxoheptanoate (**11**) (81%). Ring closure with polyphosphoric acid at 100° for 2 h then furnished 6-ethyl-4-hydroxy-3-methyl-2-pyrone (**12**) (51%), m.p. 182—183°. When the enamines (**8**) and (**10**) were heated with 3 equiv. of methyl iodide at 100° for 12 h, predominant *C*-alkylation was observed on the carbon atom of the enamine function. Without purification, the alkylated enamines were hydrolysed with boiling water for 1 h to give ethyl 2,4-dimethyl-3,5-dioxohexanoate (**13**) (54%) and ethyl 4-methyl-3,5-dioxohexanoate (**14**) (74%). Treatment of (**13**) with polyphosphoric acid at 100° for 1 h afforded 3,5,6-trimethyl-4-hydroxy-2-pyrone (**15**) (54%), m.p. 153—154°. 5,6-Dimethyl-4-hydroxy-2-pyrone (**16**) was prepared (50%) from (**14**) in the same way. The physical properties (m.p., i.r., and n.m.r.) of (**16**) were in good agreement with those cited in the literature.[5a]

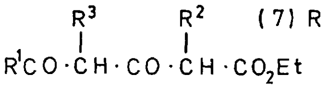
$\mathrm{RC{\equiv}CMgBr}$

(1) R = Me
(2) R = Et



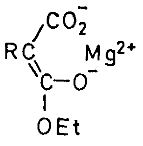
$\mathrm{R^1C{\equiv}C\cdot CO\cdot \overset{R^2}{C}H\cdot CO_2Et}$

(3) $\mathrm{R^1 = R^2 = Me}$
(4) $\mathrm{R^1 = Et, R^2 = Me}$
(7) $\mathrm{R^1 = Me, R^2 = H}$

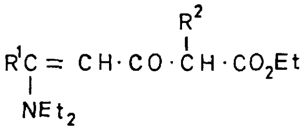


$\mathrm{R^1CO\cdot \overset{R^3}{C}H\cdot CO\cdot \overset{R^2}{C}H\cdot CO_2Et}$

(11) $\mathrm{R^1 = Et, R^2 = Me, R^3 = H}$
(13) $\mathrm{R^1 = R^2 = R^3 = Me}$
(14) $\mathrm{R^1 = R^3 = Me, R^2 = H}$

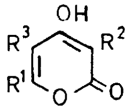


(5) R = Me
(6) R = H



$\mathrm{R^1\underset{NEt_2}{C}{=}CH\cdot CO\cdot \overset{R^2}{C}H\cdot CO_2Et}$

(8) $\mathrm{R^1 = R^2 = Me}$
(9) $\mathrm{R^1 = Et, R^2 = Me}$
(10) $\mathrm{R^1 = Me, R^2 = H}$



(12) $\mathrm{R^1 = Et, R^2 = Me, R^3 = H}$
(15) $\mathrm{R^1 = R^2 = R^3 = Me}$
(16) $\mathrm{R^1 = R^3 = Me, R^2 = H}$

All new compounds gave satisfactory spectral and analytical data.

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