A NEW 2-PYRONE SYNTHESIS AND ITS APPLICATION TO BUFADIENOLIDE SYNTHESIS

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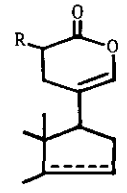
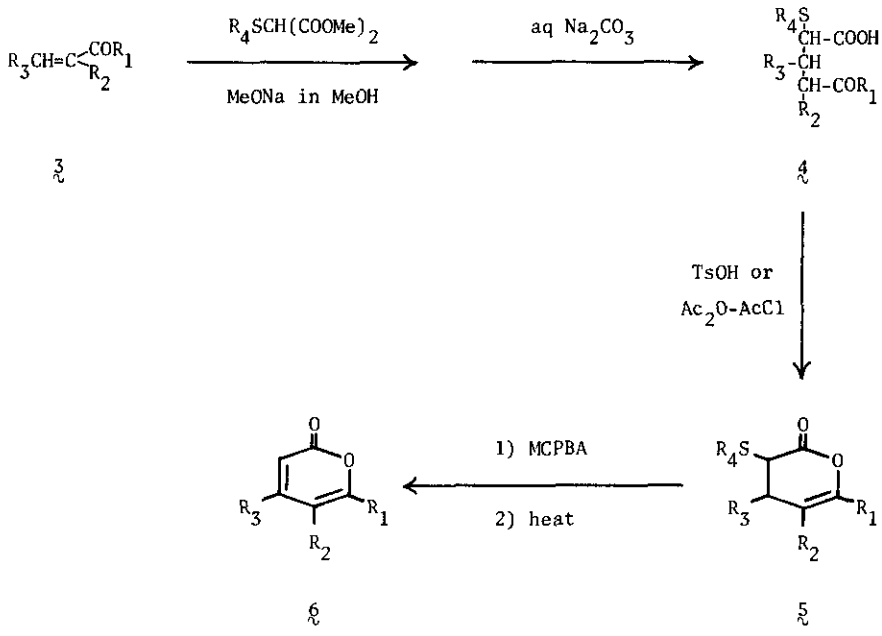
Abstract ——— A synthetic method of 4-, 5-, and 6-alkyl-2-pyrones from an appropriately substituted α,β-unsaturated ketone or aldehyde was presented. The reaction sequence consisted of 1) conjugate addition of a methylthio- or phenylthioacetate to the enone by use of the corresponding thiomalonate, 2) acid-catalyzed enol lactonization of the adduct, and 3) oxidative elimination of the thio group. Application of this method to a 21-oxo-20-methylenepregnane leading to a new method for the synthesis of bufadienolides was also described.

In our continuing effort aimed at establishing the effective synthetic route to bufadienolides from readily available steroids,[1] we required a new method for the synthesis of 2-pyrone ring which could be operated under such a mild condition not affecting the functional groups in steroid skeleton. It occurred to us that the bufadienolide synthesis reported by Hoechst workers[2] would become attractive, if one could improve the crucial step ——— dehydrogenation of 3,4-dihydro-2-pyrone ring(bufenolide 1), which was carried out in poor yield by heating with palladium on charcoal. One promissing alternative method for the dehydrogenation could be preparation and oxidative desulfurization[3] of the alkylthiobufenolide such as 2. This paper describes successful results obtained by the investigation along this line.



1 : R = H
2 : R = SR'

Scheme I illustrates our preliminary experiment leading to a methyl substituted 2-pyrone(6) from a conjugated ketone or aldehyde(3). Conjugate addition of α-methylthio- and α-phenylthiocarboxylates has already been reported by Schultz[4] and Uda.[5] The poor yields of 1,4 mode of addition products in case of the thioacetate anion with acyclic acceptors prompted us to employ methyl methylthio- or phenylthiomalonate in place of the acetate. Dimethyl methylthiomalonate(10 mmol) was treated with methyl vinyl ketone(3a)(11 mmol) in the presence of NaOMe(0.5 mmol) in MeOH(20 ml) at 0°C for 5h. The reaction mixture was stirred with



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	R_1	R_2	R_3	R_4
a	Me	H	H	Me or Ph
b	H	Me	H	Me or Ph
c	H	H	Me	Me or Ph

Scheme I

5% Na_2CO_3 at 50°C for 3h, and then acidified to give 2-methylthio-5-oxohexanoic acid(4a, R_4=Me) as a homogeneous oil in 96% yield. Dimethyl phenylthiomalonate also afforded a 2-phenylthio analog(4a, R_4=Ph) in 93% yield. By employing essentially the same procedure, methacrolein(3b) and crotonaldehyde(3c) produced the corresponding Michael adducts(4b and 4c, R_4=Me and Ph) in 91-96% yields. Enol lactonization of the adducts 4(10 mmol) was then carried out by heating them at reflux either with acetic anhydride(30 mmol) containing a small amount of acetyl chloride[6] for 5h(4a) or with p-toluenesulfonic acid(6 mmol) in benzene(200 ml)[7] for 6-8h(4b, 4c). Physical and nmr spectral data for the 3-thio derivatives(5) of 3,4-dihydro-2-pyrone were shown in Table 1.[8] Finally, the compounds 5(6 mmol) were oxidized with m-chloroperbenzoic acid(6 mmol)

Table 1. 3,4-Dihydro-2-pyrone Derivatives 5

Compound	R	bp,°C(torr)	Yield(%)	nmr($CDCl_3$)δ, J in Hz
5a	Me	122(15)	90	1.83(diff s, 3H, Me), 2.17(s, 3H, SMe), 3.23(dd, J=6.0 and 3.0, 1H, 3-H), 2.2-3.1(m, 1H, 4-H), 4.85(m, 1H, 5-H)
	Ph	112(0.06)	83	1.88(s, 3H, Me), 2.1-3.0(m, 2H, CH_2), 3.75(t, J=5.0, 1H, 3-H), 4.83(m, 1H, 5-H), 7.1-7.6(m, 5H, Ph)
5b	Me	140(15)	63	1.72(s, 3H, Me), 2.20(s, 3H, SMe), 2.16(dd, J=19.0 and 3.5, 1H, CH_2), 2.90(br dd, J=19.0 and 7.0, 1H, CH_2), 3.37(dd, J=7.0 and 3.5, 1H, 3-H), 6.23(br s, 1H, 6-H)
	Ph	150(0.16)	75	1.68(s, 3H, Me), 2.67(dd, J=17.0 and 5.0, 1H, CH_2), 2.80 (br dd, J=17.0 and 6.0, 1H, CH_2), 3.73(t, J=5.0, 1H, 3-H), 6.72(m, 1H, 6-H), 6.9-7.4(m, 5H, Ph)
5c	Me	135(26)	45	1.16(d, J=6.5, 3H, Me), 2.17(s, 3H, SMe), 2.2-2.8(m, 1H, 4-H), 3.07(m, 1H, 3-H), 5.13(dt, J=6.0 and 2.0, 1H, 5-H), 6.17(d, J=6.0, 1H, 6-H)
	Ph	——	21	1.15(d, J=6.5, 3H, Me), 2.3-3.1(m, 1H, 4-H), 3.67(br s, 1H, 3-H), 5.23(m, 1H, 3-H), 6.43(d, J=6.0, 1H, 6-H), 7.1-7.7(m, 5H, Ph)

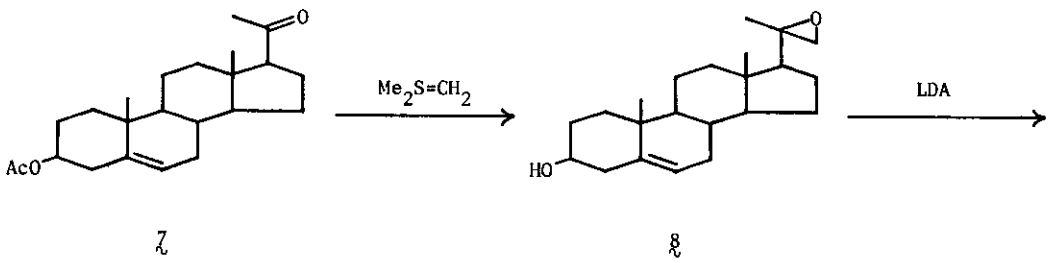
in methylene chloride(100 ml)[9] at 0°C for 1h and the intermediate sulfoxides were subjected to thermal elimination either by heating them in toluene(25 ml)(R_4=Me) or by allowing them to stand at room temperature(R_4=Ph). Monomethyl-2-pyrones(6) thus obtained by the simple three-step procedure were characterized by nmr spectral data shown in Table 2.[8]

We next advanced our synthetic method of 2-pyrones mentioned above to an application to a steroidal vinyl aldehyde 10. This compound was previously obtained by Hoechst workers[2] from 21,21-dimethoxypregnenolone by the reaction with triphenylphosphonium methylid and the subsequent deacetalization. On the other hand, we have prepared the vinyl aldehyde(10) from pregnenolone .

Table 2. Monomethyl-2-pyrones 6

Compound	bp,°C(torr)	Yield(%) A[a]	Yield(%) B[b]	nmr($CDCl_3$)δ, J in Hz
6a	112(14)	76	64	2.27(s, 3H, Me), 6.0(br d, J=6.0, 1H, 5-H), 6.11(br d, J=9.5, 1H, 3-H), 7.28(dd, J=9.5 and 6.0, 1H, 4-H)
6b	130(24)	63	64	2.03(s, 3H, Me), 6.26(dd, J=10.0 and 1.5, 1H, 3-H), 7.24(dd, J=10.0 and 2.0, 1H, 4-H), 7.3(br s, 1H, 6-H)
6c[10]	125(19)	70	74	2.16(s, 3H, Me), 6.05(dd, J=6.0 and 1.5, 1H, 5-H), 6.10(br s, 1H, 3-H), 7.40(dd, J=6.0 and 1.0, 1H, 6-H)

a, from 5(R_4=Me) b, from 5(R_4=Ph)



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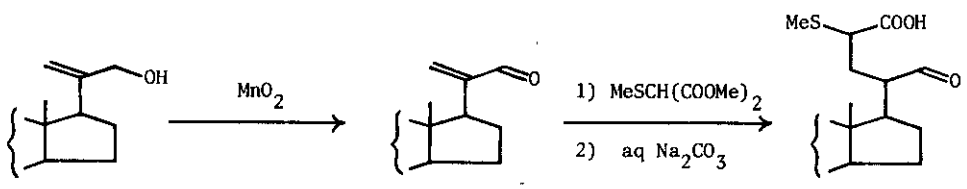

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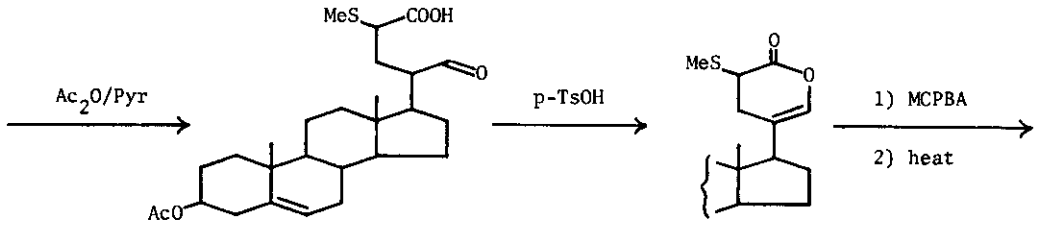

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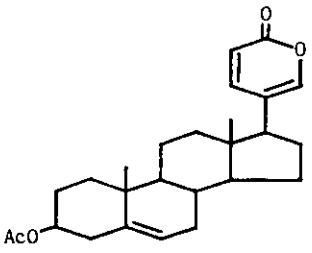

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Scheme II

acetate(7) by the following sequence of reactions, which seems to be more straightforward and have more general applicability(Scheme II). To a solution of pregnenolone acetate(7)(4.50 g) and trimethylsulfonium iodide(5.13 g) in DMSO(70 ml) and THF(90 ml) was added dropwise a solution of dimsyl potassium(2.64 g) in DMSO(15 ml) and THF(15 ml) at 0°C and the resulting mixture was stirred for 30min. The solution was then extracted, after acidification, with $CHCl_3$ giving the oxirane 8 in 95% yield(mp 149-150°C(acetone); m/e 330(M^+)). A mixture of the oxirane(8)(1.50 g, 4.55 mmol) and LDA(9.1 mmol) in THF(50 ml) was heated at reflux for 2h. Acidification and concentration of the solution gave the allylic alcohol 9 in 70% yield(mp 186-7°C(acetone); m/e 330 (M^+); Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.89; H, 10.10; nmr($CDCl_3$)δ 4.11 (br s, $-CH_2OH$), 4.98 and 5.26(two br s, $=CH_2$)). A mixture of the alcohol(9)(1.67 g) and active MnO_2(17 g) in $CHCl_3$(170 ml) was stirred at room temperature for 20h. Filtration of the mixture and concentration of the filtrate afforded the vinyl aldehyde 10 in 91% yield(mp 136-140°C(MeOH); m/e 328(M^+); ir(KBr) 1675cm^{-1}(-CHO); nmr($CDCl_3$)δ 6.11 and 6.28(two s, $=CH_2$), 9.52(s, -CHO); Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.53; H, 9.77).

Reaction conditions of the successive procedures(10 ⟶ 14) were adapted from those of the nonsteroidal experiments. Reaction of the aldehyde(10) with dimethyl methylthiomalonate was, however, found to be too sluggish at such low temperatures and required heating at reflux for 2 days. After usual workup, the adduct 11 was isolated in 81% yield(mp 170-2°C(acetone); nmr ($CDCl_3$)δ 6.07(br, -OH and -COOH), 9.54(m, -CHO); ir(KBr) 1710 and 1675cm^{-1}(C=O)). Treatment of the adduct(11) with Ac_2O/Pyr at room temperature for 15h gave the 3-acetoxy derivative 12 in 95% yield(nmr($CDCl_3$)δ 2.07(s, CH_3CO)). The acetate(12) was subjected to acid-catalyzed enol lactonization with p-toluenesulfonic acid in benzene to produce the dihydro-2-pyrone 13 in 38% yield[11] (nmr($CDCl_3$)δ 3.50(t, J=5.0 Hz, CH-CO), 6.39(br s, =CH-O)). The final stage was accomplished by oxidation of the enol lactone(13) followed by thermal elimination of the resulting sulfoxide giving the bufadienolide 14 in 38% yield[11](mp 196-7°C(MeOH); nmr($CDCl_3$)δ 6.35(d, J=8.5 Hz, 23-H), 7.33(m, 21-H and 22-H); ir(KBr) 1760 and 1730cm^{-1}(C=O); m/e 350(M - AcOH); Anal. Calcd for $C_{26}H_{34}O_4$: C, 76.06; H, 8.34. Found: C, 76.20; H, 8.18), which was identified by comparison of the data with those of a related compound.[1]

References and Notes

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8. Satisfactory elemental analyses(±0.3% for C and H) and exact mass molecular weights were obtained on all the compounds in the table.

9. Oxidation with periodic acid[3] resulted in inferior yield of the sulfoxide producing unidentified byproducts.

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11. Modified reaction conditions are now being tried for obtaining optimum yields.

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