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THE CHEMISTRY OF γ-OXOSULFONES. II. 4-HYDROXYCYCLOPENTENONES

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We wish to report a general synthesis of 4-hydroxycyclopentenones through the use of α-sulfonyl carbanions. Some 4-hydroxycyclopentenones of interest include the alcohol moieties of the pyrethrum esters and a key intermediate in the synthesis of prostaglandins in the E and F series.[1] This route is outlined in Scheme I.

For the butyl compound 9a, p-toluenesulfinic acid and acrolein were allowed to react in aqueous THF at 25° to yield 3-(p-toluenesulfonyl)-propanal 3, which was immediately converted to the ethylene acetal 4 in 69% yield after crystallization from hexane/ether (m.p. 83-85°) (NMR: 7.78 (2H,d,J=8 hz), 7.34(2H,d,J=8 hz), 4.94(1H,t,J=4 hz), 3.85(4H,m), 3.2(2H,m), 2.47(3H,s), 2.1(2H,m).

Attempted acylation[2,3,4] of the α-sulfonyl carbanions derived from 4 or 5 gave low conversions (<50%). Transformation of 4 to the acylated compound 14 via a two step procedure--formation of the magnesium α-sulfonyl carbanion and addition of acetaldehyde,[5,6] followed by chromium trioxide[7] oxidation of the carbinol 13--gave the crystalline ketosulfone 14 (m.p. 96-97°) in good yield. However, numerous attempts to alkylate the ketosulfone anion gave largely O-alkylation except with CH_3I. The slightly longer approach of alkylation, hydroxyethylation and oxidation proved to be the sequence of choice.

Formation of the α-sulfonyl carbanion with BuLi in THF, followed by addition of n-butyl iodide gave the butylated sulfone 5a in 81% yield without purification (NMR: 7.74(2H,d,J=8 hz), 7.32(2H,d,J=8 hz), 4.98(1H,t,J=5 hz), 3.82(4H,m), 3.2(1H,m), 2.46(3H,s), 1.6-2.0(4H,m), 1.1-1.6(4H,m), 0.7-1.0 (3H,m). The alkylated sulfone was treated with ethyl magnesium bromide in dry benzene, followed by addition of acetaldehyde to give the diastereomeric mixture of alcohols 6a. These alcohols could easily be separated from the small amount (ca.10-15%) of 5a by thin layer chromatography (2% MeOH/$CHCl_3$) but as the final product was easy to purify, the mixture was generally oxidized directly, affording the ketosulfone 7a in 50% yield from 5, (NMR: 7.62

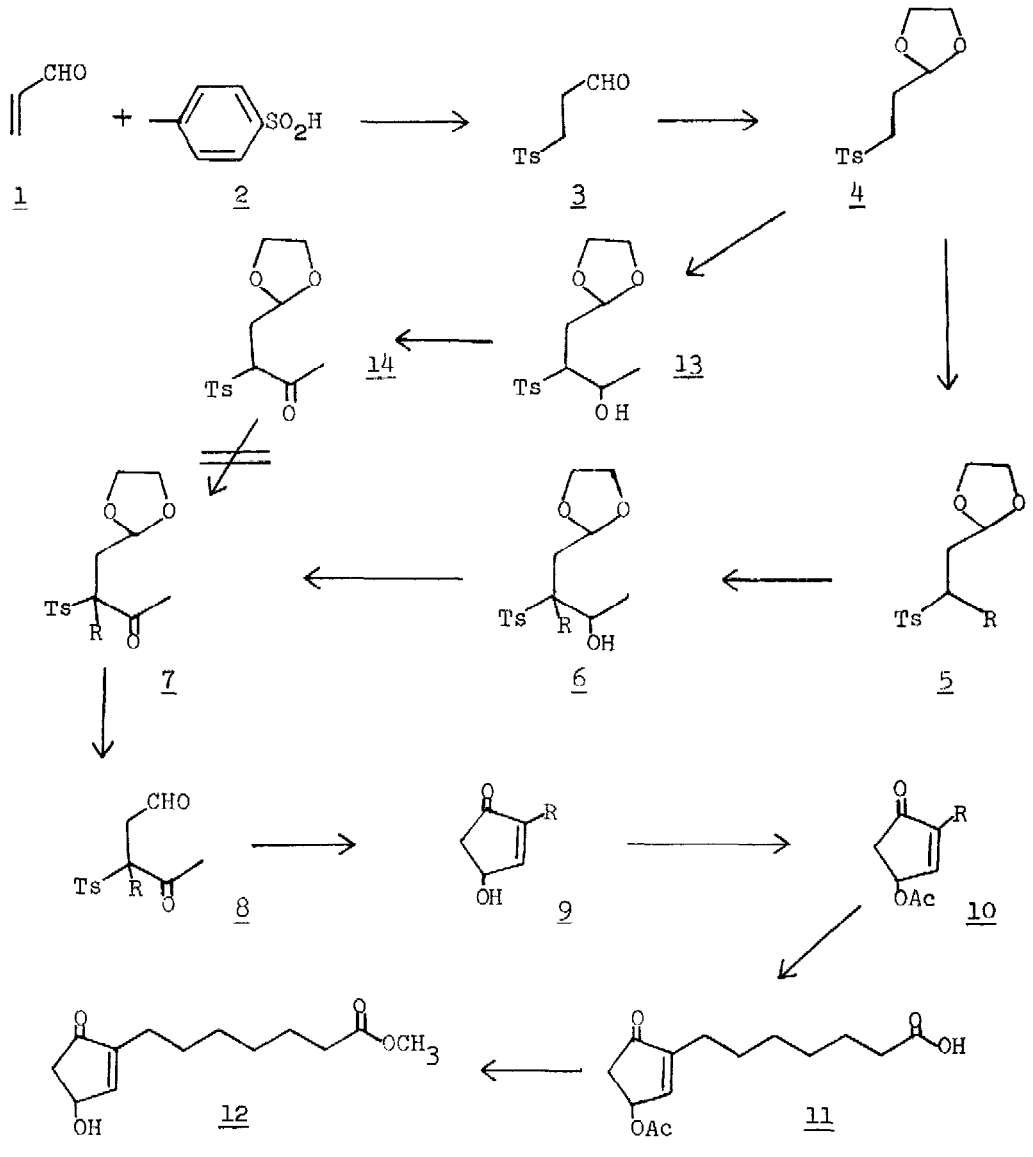
(2H,d,J=8 hz), 7.53(2H,d,J=8 hz), 5.08(1H,t,J=5 hz), 3.84(4H,m), 2.44(6H,s) 2.0-2.2(2H,m), 1.6-2.0(2H,m), 1.1-1.5(4H,m), 0.8-1.0(3H,t,J=6 hz)). The ketosulfone acetal 7a was hydrolyzed (50% aq. $HClO_4$, dioxane 1:1 at 0° for 3 hr.) to give the ketoaldehyde 8a. The ketoaldehyde was immediately dissolved in aqueous dioxane, with 4 equiv. K_2CO_3 (0.4 M in CO_3^{2-}) containing a catalytic amount of thiophenol and the mixture stirred 18 hr. at 25° to give hydroxycyclopentenone 9a. Replacing carbonate with triethylamine gave the same result. Omission of the thiophenol from the reaction mixture led cleanly to (E)-3-acetyl 2-heptenal (NMR:10.25(1H,d,J=7 hz), 6.55(1H,d,J=7 hz), 2.76(2H,t(broad),J=7 hz), 2.40(3H,s), 1.2-1.6(4H,m), 0.9(3H,t,J=6 hz)). This shows the necessity for thiophenol-catalyzed trans/cis equilibration with the less favored (Z)-3-acetyl 2-heptenal prior to cyclization to the hydroxycyclopentenone. The fact that the p-toluenesulfinate salt produced in the elimination did not catalyze this isomerization indicates that the elimination of sulfinate is irreversible in this instance. The hydroxycyclopentenone 9a could be readily purified by preparative thin layer chromatography (1% MeOH/$CHCl_3$) to give 2-n-butyl-4-hydroxycyclopent-2-en-1-one in 30% yield from 7 (7% from acrolein) (NMR:7.20(1H,m(sharp)), 4.98 (1H,m(broad)), 3.0(1H,s(broad)), 2.8(1H,d of d,J=19 hz,6 hz), 2.3(1H,d of d,J= 19 hz,2 hz), 2.2(2H,t(broad),J=7 hz), 1.2-1.8(4H,m), 0.8-1.1(3H,t,J=7 hz)).

The prostaglandin precursor 12 (2-(6-carbomethoxy hexyl) 4-hydroxycyclopent-2-en-1-one) was synthesized in a similar manner. The sulfone acetal 4 was allowed to react with n-BuLi in THF, followed by 7-iodoheptanal dimethyl acetal to give the alkylated material in 96% yield (NMR: 7.76(2H,d,J=8 hz), 7.34,(2H,d,J=8 hz), 5.0(1H,t,J=5 hz), 4.33(1H,t,J=5 hz), 3.85(4H,m), 3.30(6H,s), 3.2(1H,m), 2.44 (3H,s), 2.0-2.3(∿2H,m), 1.0-2.0(∿12H,m)). The ω-iodoheptanal acetal was prepared by diborane reduction of 7-bromoheptanoic acid, chromium trioxide/pyridine oxidation, dimethyl acetal formation, followed by the Finkelstein reaction. Attempted alkylation with t-butyl 7-iodoheptanoate gave unavoidable acylation (50%). The alkylated sulfone 5b was hydroxyethylated as before. The diastereomeric mixture of sulfone alcohols 6b was purified by preparative TLC (33% EtOAc/67% hexanes) to give an 80% yield of alcohols, which were then oxidized by Corey's procedure[8] (NCS/DMS) to give a 70% yield of pure ketosulfone 7b (NMR: 7.62(2H,d,J=8 hz), 7.34(2H,d,J=8 hz), 5.10(1H,t,J=5 hz), 4.38(1H,t,J=6 hz), 3.9(4H,m), 3.34(6H,s), 2.46(6H,s), 2.2(2H,m), 1.2-2.0(∿12H,m)). Hydrolysis of 7b as before (0° for 20 min.) gave 8b, which was immediately converted to hydroxycyclopentenone aldehyde 9b with 0.1 M $Ba(OH)_2$ in dry methanol (1 equiv. $Ba(OH)_2$)[9] for 10 min. at 25°, giving 80% conversion. The crude product (NMR:9.77(1H,t,J=2 hz), 7.16(1H,m), 4.96(1H,m), 2.92(1H,d of d, J=18 hz, 6 hz), 2.30(1H,d of d,J=18 hz, 2 hz), 2.40 (2H,t,J=7 hz), 2.10(2H,t,J=7 hz), 1.2-2.0(∿8H,m)) was also characterized by high resolution mass spec (m/e 210.123 ± 0.010 for $C_{12}H_{18}O_3$). The divalent cation in non-aqueous solution was a necessity because, in this case, the K_2CO_3 conditions

SCHEME I

5-9a: R= n-butyl
5-7b: R= $-(CH_2)_6CH(OCH_3)_2$
8b, 9b, 10: R= $-(CH_2)_6CHO$

Ts= p-toluenesulfonyl



failed, as did aqueous KOH, Et_3N, Triton B and aqueous $Ba(OH)_2$.

The crude aldehyde was acetylated with acetic anhydride/pyridine in methylene chloride overnight at 25° to give the 4-acetoxycyclopentenone aldehyde 10. The aldehyde was oxidized with Jones reagent (0°, 3 min.) to give the heptanoic acid derivative 11, which was transesterified (dry HCl/MeOH) from AcCl/MeOH) for 2 hr. at 25°) to yield the desired final product 12. Preparative TLC (33% EtOAc/67% hexanes) gave 53% yield of about 90% pure compound from aldehyde 9b. Methyl-ester 12 was purified by crystallization and short path distillation to give better than 98% pure hydroxycyclopentenone heptanoate methyl ester (m.p. 46-49°, lit.[1] 48-50°). The NMR spectrum was identical with the reported[1] spectrum. The yield based on acrolein was 14% overall.

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