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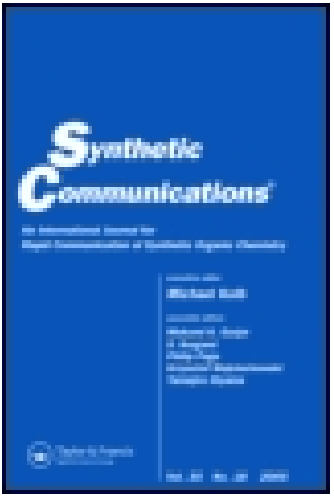

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Facile Synthesis of Steroidal Δ^4-3,6-Diones from Δ^5-3-Ols using Pyridinium Chlorochromate

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FACILE SYNTHESIS OF STEROIDAL Δ^4-3,6-DIONES FROM Δ^5-3-OLS USING PYRIDINIUM CHLOROCHROMATE

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ABSTRACT: Pyridinium chlorochromate (PCC) in dichloromethane under ambient conditions is found to oxidise steroidal Δ^5-3-alcohols to Δ^4-3,6-diketones in high yield.

In steroid chemistry, the transformation of commercially available Δ^5-3β -alcohols to synthetically and biologically more important Δ^4-3-ketones and Δ^4-3,6-diones is a well-studied reaction.[1,2] In connection with an ongoing project on the synthesis of A-ring modified aromatase inhibitors, we required 17-ethylenedioxy-4-androstene-3,6-dione as starting material. Perusal of literature revealed two procedures[3,4] related to our objective, both of which were found to be unsatisfactory upon closer examination. Piers and Worster[3] reported

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isolating a mixture of Δ^5-3-one and Δ^4-3,6-dione (9:1) upon oxidation of cholesterol with CrO_3.2Py complex. The procedure was synthetically unusable because the enedione is formed as a minor component of the mixture (<10% yield). Parish *et. al.*[4] reported recently that oxidation of steroidal Δ^5-3β-tetrahydropyranyl ethers with PCC in refluxing benzene afforded the corresponding Δ^4-3,6-diones in excellent yield (85-90%). Adapting this procedure to our substrate not only meant an extra protection step, but more importantly the compatibility of acid-sensitive ketal protecting group to the harsh reaction conditions was of concern to us. The use of TPAP/NMO oxidant system[5] for this transformation was not expedient because of the exorbitant cost of TPAP.[6] We report in this *Communication* a mild PCC oxidation of commercially available Δ^5-3-hydroxy steroids to Δ^4-3,6-diketones in a single step.

Treatment of 17-ethylenedioxy-5-androstene-3β-ol **2** with PCC (5 equi.) in CH_2Cl_2 at ambient temperature for 24 h afforded material after silica gel purification which exhibited the following spectral characteristics. It showed a broad IR absorption at 1680 cm^{-1} and a vinyl proton singlet at δ ~6.2 in its PMR spectrum. The ^{13}C NMR spectrum clearly exhibited two distinct carbon resonances at δ ~200 ppm. The ethylene ketal was intact in the product as concluded from its PMR and CMR spectra. From this data it was clear that the expected conjugated Δ^4-3-one was not isolated.[7] Furthermore, comparison with similar Δ^4-3,6-dione steroids[5,8] confirmed the structure of PCC oxidation product as **7**.

In order to test the generality and mildness of the novel homoallylic alcohol to enedione transformation, we carried out the reaction on a few representative hydroxy steroids. It may be noted that the reaction conditions are mild enough that the acid-sensitive acetal protecting group in **2** survives the

transformation. The acetyl group at C-17 in pregnenolone does not suffer any epimerisation as evident from the PMR and CMR spectra of **9**. The C-22 alkene in stigmasterol **5** also does not undergo any oxidative cleavage during the transformation in A-B ring of steroid nucleus.

Although the structure of Δ^4-3,6-diones is unambiguously assigned, the mechanism for their formation is less clear. When the reaction of **2** was carried out with lesser excess of PCC (2-3 equi.) and interrupted at short interval (1-2 h), the crude residue contained deconjugated Δ^5-3-one (δ 5.3, 6-H), conjugated Δ^4-3-one (δ 5.8, 4-H), and the product Δ-4,3,6-dione; no unreacted Δ^5-3-ol was detected. We propose that the PCC promoted oxidation at ambient temperature proceeds in the following manner.[9] The enol form **12** of Δ^5-3-one **11** reacts at C-6 vinylogously with the Cr=O of PCC to provide chromate ester **13** as shown in Scheme. Subsequent oxidation of C-6 alcohol smoothly provides the Δ^4-3,6-diones. Other possible pathways, such as allylic oxidation of Δ^4-3-one at C-6 or epoxidation of Δ^5-3-one, appear unlikely under the mild conditions of PCC at room temperature. Moreover, use of other Cr-based reagents such as CrO_3.2Py and PDC also afforded the enediones under similar conditions.

In summary, we disclose a mild and efficient preparation of steroidal Δ^4-3,6-diones from complex homoallylic alcohols. This procedure expands the utility of transformations accomplished by PCC reagent.

EXPERIMENTAL SECTION:

Steroid Δ^5-3β-alcohols were purchased from Aldrich or Sigma (USA) and used as such. PCC was obtained from Aldrich. The structures of isolated and purified reaction products were established by mp, IR, microanalysis, and ^1H and ^{13}C NMR.

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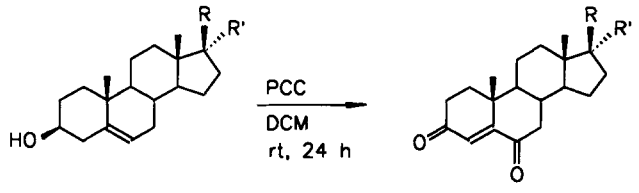

1	R,R'=O	6
2	R,R'=OCH_2CH_2O	7
3	R'=H,R=	8
4	R'=H,R=CH_3CO	9
5	R'=H,R=	10

Scheme

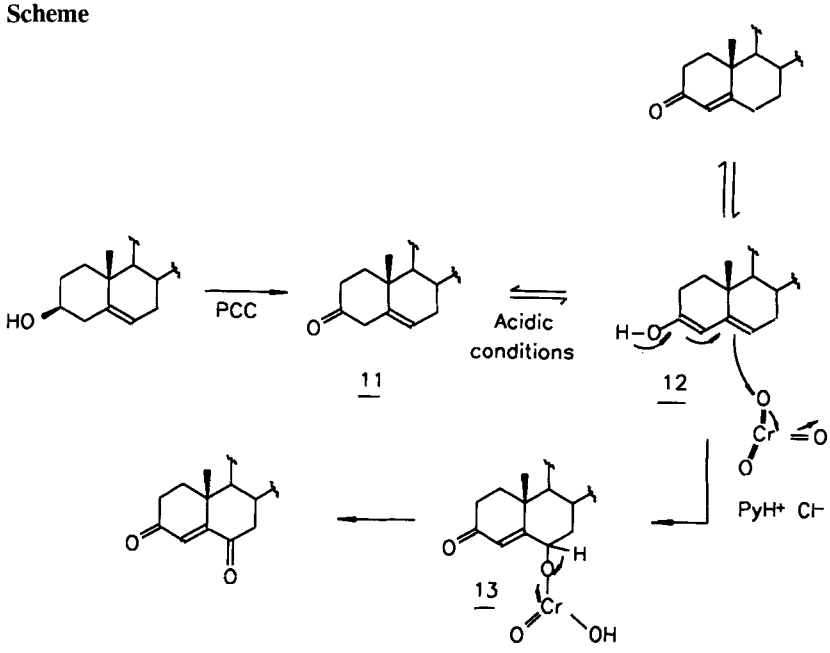

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Table: PCC oxidation of steroidal Δ^5-3-ols to Δ^4-3,6-diones

Entry	Substrate	Product	^{1}H NMR shifts δ in ppm	^{13}C NMR shifts δ in ppm	IR cm^{-1}	mp °C	Yield %
1)	**1**	**6**	6.21(s,1H,4-H) 1.20(s,3H,19-H) 0.94(s,3H,18-H)	218.9(17-C), 200.8(6-C) 198.8(3-C), 160.0(5-C) 125.4(4-C)	1736 1672	220-222°	78
2)	**2**	**7**	6.14(s,1H,4-H) 1.16(s,3H,19-H) 0.89(s,3H,18-H)	201.4(6-C), 198.8(3-C) 160.5(5-C), 125.2(4-C)	1684	162-164°	80
3)	**3**	**8**	6.18(s,1H,4-H) 1.16(s,3H,19-H) 0.70(s,3H,18-H)	201.9(6-C), 199.2(3-C) 160.9(5-C), 125.3(4-C)	1687	132-134°	70
4)	**4**	**9**	6.19(s,1H,4-H) 2.14(s,3H,21-H) 1.17(s,3H,19-H) 0.69(s,3H,18-H)	208.4(20-C), 201.3(6-C) 198.9(3-C), 160.3(5-C) 125.4(4-C)	1699 1674	188-190°	70
5)	**5**	**10**	6.17(s,1H,4-H) 1.15(s,3H,19-H 0.75(s,3H,18-H)	202.0(6-C), 199.2(3-C) 160.9(5-C), 125.4(4-C)	1691	150-152°	70

The UV spectrum of **6-10** exhibited λ_{max} at 250 nm (ε~12-13x10^3)

General procedure for PCC oxidation: To a solution of homoallylic hydroxy steroid (1 mmol) in dry CH_2Cl_2 (7 mL) was added PCC (5 mmol) in one portion. The reaction mixture was allowed to stir at ambient temperature (30-35 °C) for 24 h. Addition of Et_2O (25 mL), filtration through a short pad of silica gel, and solvent removal afforded pure Δ^4-3,6-dione steroid. The substrates, their characteristic spectral data, and yields are detailed in Table.

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