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A GENERAL APPROACH TO THE SYNTHESIS OF 5,6-DIHYDRO-2(2H)PYRANONES ; SIMPLE SYNTHESIS OF α-PYRONE, (±)-ARGENTILACTONE AND (±)-GONIOTHALAMIN

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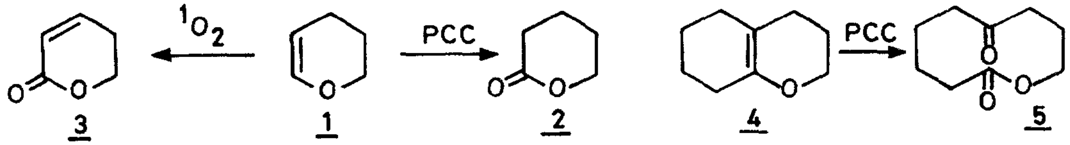
Summary : Easily accessible dihydropyrans undergo oxidation with PDC/t-BuOOH to yield the corresponding 5,6-dihydro-2-(2H)-pyranones in good yield. The methodology is exemplified with the synthesis of α-pyrone, (±)-argentilactone and (±)-goniothalamin.

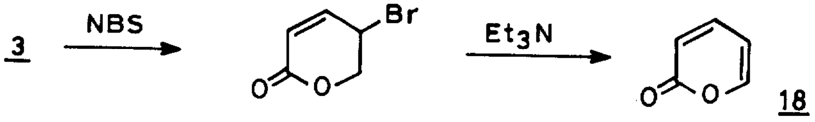
It has been shown that the oxidation of enol ethers with chromium(VI) reagents like pyridinium chlorochromate lead to the corresponding δ-lactones and keto-lactones[1] whereas oxidation with singlet oxygen results in the formation of the corresponding dihydropyranones[2] (Scheme 1). The procedure utilising singlet oxygen for the conversion of 1 to 3 is not generally amenable for large scale manipulation and hence there is a need for the development of a new synthetic methodology for effecting this important transformation. In the course of our studies on oxidation, we recently reported a mild method for effecting allylic and benzylic oxidations using pyridinium dichromate (PDC) and tert-butyl hydroperoxide.[3]



SCHEME 1

In this paper, we report our results on the successful one step conversion of 3,4-dihydro-(2H)-pyrans to 5,6-dihydro-2-(2H)-pyranones under very mild conditions. The reaction is generally performed at 0°C in dichloromethane with PDC/t-BuOOH (2:3) for 2-4 h. The results of this oxidation are summarized in the Table. Dihydropyran 1 on treatment with PDC/t-BuOOH gave the dihydropyranone 3[4] (50%) and the t-butyl peroxy compound 3a (6%). 3a on treatment with triethylamine at 80°C for 0.5 h got converted to 3 raising the overall yield of 3 to 55%. Bromination of 3 followed by dehydrobromination yielded α-pyrone 18[5] (70%) (Scheme 2).

SCHEME 2



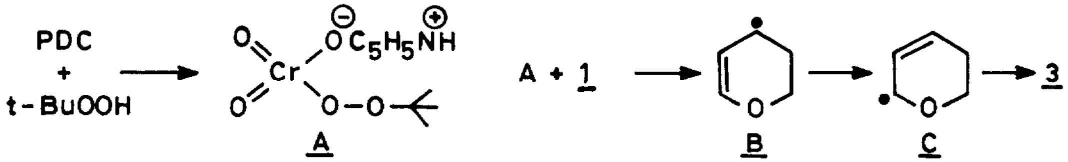
Similarly, dihydropyrans 6[6] and 8[7] under the same reaction conditions with PDC/t-BuOOH yielded 7 (70%) and 9 (52%) respectively.

It is interesting to note that enol ether 10 with a primary hydroxylic group in the molecule on oxidation with this reagent system gave the α,β-unsaturated lactone 11 (30%) and the t-butyl peroxy compound 11a (14%) where the hydroxyl group was not affected. The oxidation of hydroxyl group by this reagent is rather slow that one can use this chemoselectivity to advantage in organic synthesis.

The spiroenol ether 12[8] on the other hand under the same reaction conditions yielded only the enone 13 (51%) which is not a product of oxidation. This obviously arises by acid catalysed hydrolysis of the acetal followed by aldol reaction of the intermediate carbonyl compound. Here again it is worth noting that the primary hydroxy group in 13 was not affected by PDC/t-BuOOH.

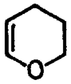
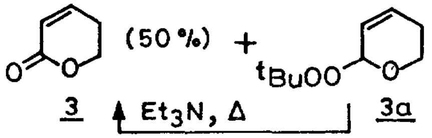
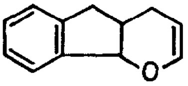
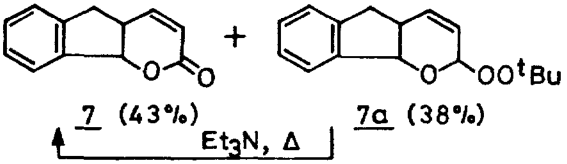
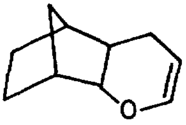
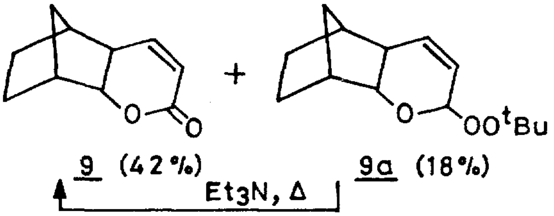
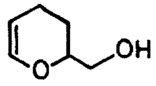
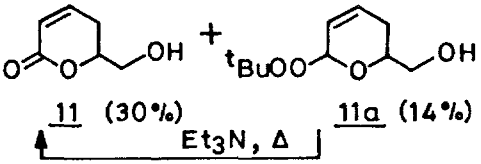
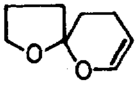
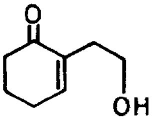
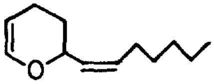
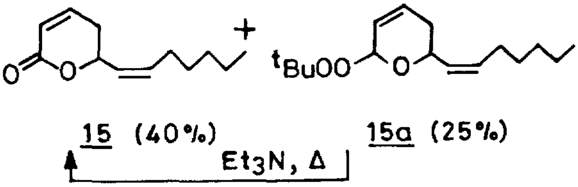
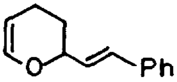
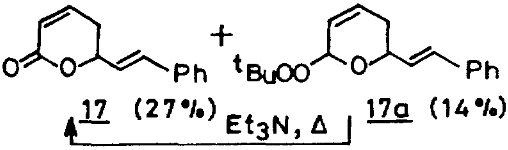
Having shown that this is a general methodology for the synthesis of 5,6-dihydro-2-(2H) pyranones from 3,4-dihydro-2H-pyrans, it was then extended to the synthesis of (±)-argentilactone 15[9] and (±)-goniothalamin 17[10]. Thus enol ether 14[2] on treatment with PDC/t-BuOOH yielded (±)-argentilactone 15[9] (40%) alongwith t-butyl peroxy compound 15a (25%). However, 15a could be smoothly converted into 15 on exposure to triethylamine giving a total yield of 52%. In a similar manner the enol ether 16 on oxidation with PDC/t-BuOOH afforded (±)-goniothalamin 17[10] (27%) alongwith the peroxy compound 17a (14%). After exposing 17a to triethylamine (±)-goniothalamin 17 was obtained in 35% yield.

The mechanism of this reaction is unclear. It is likely that the actual reagent in these oxidations is the peroxochromium species A which reacts with 1 to produce the allylic radical B which rearranges readily to the more stable radical C which then reacts with the oxidant to give the products (Scheme 3).



SCHEME 3

Table : Oxidation of Enol Ethers with PDC/t-BuOOH[a]

Entry	Substrate	Time(h)	Products[b] (Yield)[c]
1	 1	2	 3 (50%) + 3a (6%) Et$_3$N, Δ
2	 6	4	 7 (43%) + 7a (38%) Et$_3$N, Δ
3	 8	3	 9 (42%) + 9a (18%) Et$_3$N, Δ
4	 10	3	 11 (30%) + 11a (14%) Et$_3$N, Δ
5	 12	2	 13 (51%)
6	 14	4	 15 (40%) + 15a (25%) Et$_3$N, Δ
7	 16	3	 17 (27%) + 17a (14%) Et$_3$N, Δ

a) In all the reactions substrate : PDC:t-BuOOH = 1:2:3 was employed; b) All the products gave satisfactory spectral and analytical data; c) Yields refer to pure isolated products.

Muzart[11] and Firouzabadi[12] have reported the use of similar peroxochromium reagents for various oxidative transformations.

PDC/t-BuOOH Oxidation of Dihydropyran 1 : Pyridinium dichromate (4.123 g, 10.96 mmol) was taken in a 25 ml round bottomed flask in dichloromethane (12 ml) and the flask was cooled in an ice bath. t-Butyl hydroperoxide (70%) (1.482 g, 16.44 mmol, 1.50 ml) was added to PDC and was stirred for 15 min. The reagent generated in solution was quickly filtered over a cotton plug into another 25 ml round bottomed flask kept in an ice bath. The residue was washed with dichloromethane (3 ml) and filtered. To this dihydropyran 1 (0.461 g, 5.48 mmol) in dichloromethane (5 ml) was added dropwise and the reaction mixture was stirred at 0°C for 2 h. Dichloromethane was evaporated under reduced pressure and ether (15 ml) was added and filtered over a pad of Celite. The residue obtained after removal of solvent was purified by flash chromatography on silica gel (ethyl acetate : petroleum ether, 5:95) to give the peroxy compound 3a (0.056 g, 6%). IR($CHCl_3$) : 3000, 2950, 1660, 1365, 1090, 955 cm^{-1} and ^1H NMR($CDCl_3$) : δ 1.26(s, 9H), 2.17 (m, 2H), 3.67-4.1(m, 2H), 4.27(bs, 1H), 4.6-4.85(m, 1 H) and 6.5(d, 1 H, J=6Hz). $C_9H_{16}O_3$ requires : C, 62.79; H, 9.30; Found : C, 63.18; H, 9.42. Further elution (ethyl acetate:petroleum ether, 20:80) afforded the dihydro-2-pyrone 3[4] (0.269 g, 50%).

Conversion of 3a to 3 : To a stirred solution of 3a (0.05 g) in toluene (4 ml) was added triethylamine (0.229 g). The reaction mixture was then heated at 80°C for 0.5 h. Usual work up and purification by chromatography yielded 3 (0.025 g).

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