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# A New Synthetic Route to Dihydrobenzopyran Via Tandem Demethylation Cyclisation

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**Abstract:** A tandem demethylation-cyclisation reaction resulting in the formation of pyran rings using $AlCl_3$/EtSH reagent under mild reaction conditions is reported. X-ray diffraction studies on the intermediate support the suggested mechanism.

**Keywords:** Osthol, pyranocoumarins, demethylation, cyclisation, hard-soft interactions.

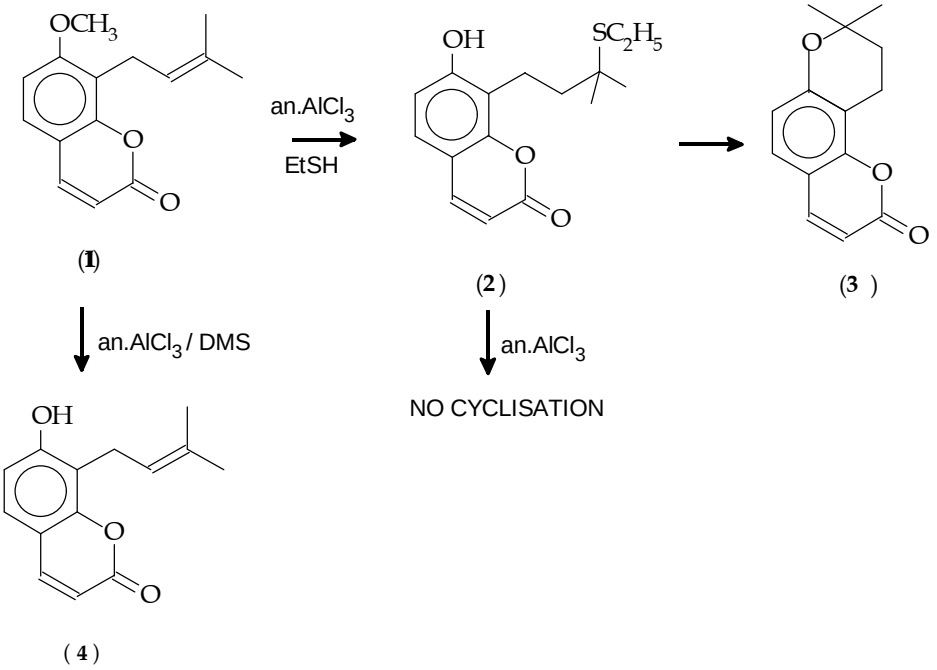
## Introduction

In our continuing search for bio-active leads from natural products, a coumarin analog, osthol **1** [1] and its derivatives were considered, since they are known to exhibit anti-inflammatory and anti-proliferatory activities[2]. While attempting to prepare a pyrano coumarin analog from osthol, a simple and convenient method for preparing the same was noted while the reported procedures failed to give the desired product in good yields.

Dihydrobenzopyrans are synthesised from phenols and isoprene in the presence of $AlCl_3$ [3] or phenols having isoprene units in the 2-position, in the presence of PTSA[4]. Allyl phenols undergo cyclisation to yield dihydrobenzopyrans, in the presence of phospate esters [5] or metal carbonyls [6] or zeolites [7] under high temperatures. Synthesis of dihydrobenzopyrans from aromatic ethers having isoprenyl group in 2-position involves either harsh acid conditions like refluxing with HBr/AcOH overnight [8] or multi step synthesis [9].

## Results and Discussion

The use of $AlCl_3$/EtSH reagent [10] for demethylation of aromatic ethers has been reported. However, treatment of osthol with $AlCl_3$/EtSH at room temperature resulted in direct cyclisation by transetherification reaction yielding pyrano coumarin, **3**. Reaction of osthol with $AlCl_3$-DMS complex yielded the demethylated product osthenol (**4**) [11] (Scheme-I).




**Scheme 1.**

It is noteworthy to mention that no cyclisation was observed while using other Lewis acid-ethane thiol complexes namely, $ZnCl_2$/EtSH, $BF_3.OEt_2$/ EtSH and $TiCl_4$/EtSH under different conditions. (Tab.1).

**Table 1.** Reactions of osthol.

| *S.No* | *Reagents* | Time(h) | Product[c] | Yield(%) |
|---|---|---|---|---|
| 1. | $BF_3.OEt_2$/ EtSH | 48[a] | - | - |
| 2. | $AlCl_3$/EtSH | 12[b] | **2**<br>**3** | 40<br>20 |
| 3. | $AlCl_3$/EtSH | 24[b] | **3** | 76 |
| 4. | HBr/AcOH | 12 | **3** | 40 |
| 5. | $AlCl_3$/DMS | 24[b] | **4** | 62 |
| 6. | $ZnCl_2$/EtSH | 48[a] | **4** | 24 |
| 7. | $TiCl_3$/EtSH | 48[a] | - | - |
| 8. | $TiCl_4$/EtSH | 48[a] | - | - |

[a] reflux; [b] room temperature stirring; [c] In all these reactions a certain amount of diethyldisulphide was formed and it was maximum in the reaction with $TiCl_4$/EtSH.

In the case of $AlCl_3$/EtSH, the reactive species, $Al(SEt)_3$, has a pronounced hard-hard interaction resulting in demethylation followed by cyclisation, compared to other Lewis acids. Both the nucleophilicity of the phenoxy oxygen and the presence of a good leaving group at the appropriate position in the intermediate complex (V) seems to influence the cyclisation reaction. Both these factors are satisfied when $AlCl_3$/EtSH is used. The intermediate **2**, which has been isolated and crystallised, underwent cyclisation only in the presence of $AlCl_3$/EtSH and not with $AlCl_3$ alone. The X-ray diffraction data obtained on the intermediate II confirmed its structure (Fig-1).

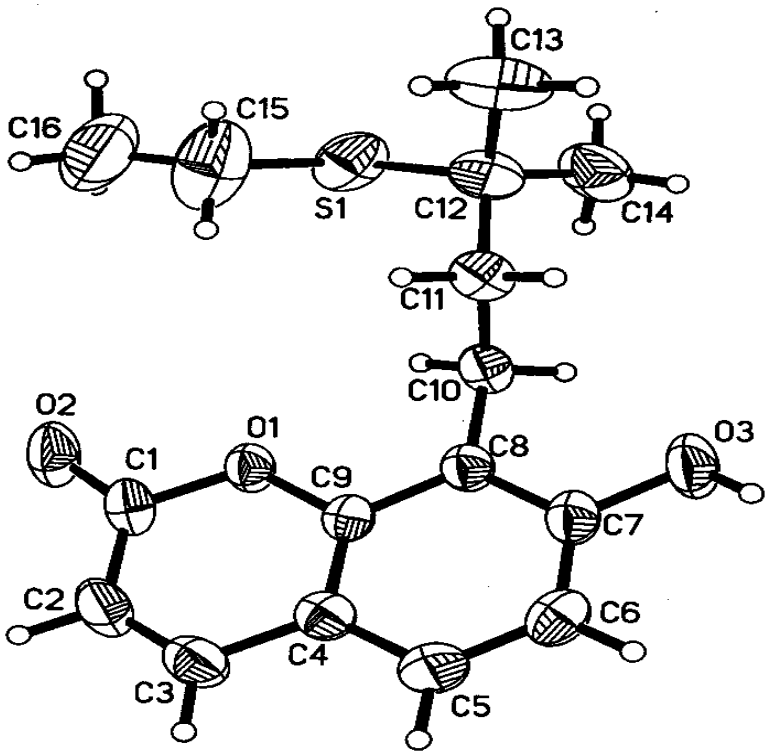
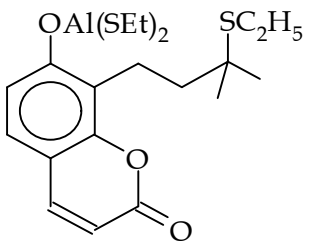
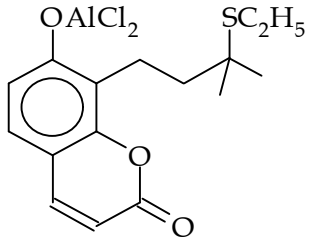



**Figure 1.**

These observations prove the fact that nucleophilicity of the phenoxy oxygen is increased in the complex **5** compared to that of the oxygen in the complex **6**.




(**5** )




(**6** )

**Scheme 2.**

The need for the good leaving group is demonstrated by the reaction of osthol with $AlCl_3$-DMS complex. Though the nucleophilicity of the phenoxy oxygen is the same as in the reaction with $AlCl_3$/EtSH, cyclisation is not observed in the former reaction due to the lack of good leaving group.

## Experimental

### *General*

Melting points were determined using a Toshniwal (India) apparatus and are uncorrected. Both $^1$H- and $^{13}$C-NMR spectra were recorded with a BRUKER DPX-200 MHz instrument using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were recorded in Shimadzu QP-5000 instrument.

### *7-Hydroxy-8-(3-methyl-3-thioethylbutyl)-coumarin (**2**)*

To a magnetically stirred supension of anhydrous $AlCl_3$ (0.33 g, 2.5 mmol) in $CH_2Cl_2$ (5 mL) at 0°C was added ethanethiol (2.0 mL) followed by osthol **1** (0.24 g, 1.0 mmol) in $CH_2Cl_2$ (3 mL) added dropwise over a period of 10 min. The temperature of the reaction mixture was allowed to raise to room temperature (30°C) and stirring continued (12 hrs). The reaction was quenched with cold dilute HCl (10 mL) and extracted with $CH_2Cl_2$ (2 x 15 mL). Removal of the solvent yielded a dark viscous gum, which on column chromatography (silica gel, 60-120 mesh) with 95:5 hexane: ethyl acetate furnished the cyclised product **3** (0.04g, 20%). Further elution of the column with 90:10 hexane : ethyl acetate yielded the demethylated compound **2** as a solid which was recrystallised from ethyl acetate. (0.11 g, 40%). m.p-112-114$^0$C.

$^1$H-NMR (δ, ppm) : 1.25 (t, 3H, J=7.4 Hz), 1.30 (s, 6H), 1.67 (bs, 1H), 1.81 (t, 2H, J=7.4 Hz), 2.53 (q, 2H, J=7.4 Hz), 2.95 (t, 2H, J=7.3 Hz), 6.25(d, 1H, J=9.4 Hz), 6.85 (d, 1H, J=8.3 Hz), 7.25 (d, 1H, J=8.3 Hz), 7.65 (d, 1H, J=9.4 Hz).

$^{13}$C-NMR: 14.2, 18.8, 22.1, 28.8, 40.7, 46.5, 112.3, 112.5, 113.3, 116.3, 126.4, 144.1, 157.7. MS (EI, m/z) 292 ($M^+$).

### Crystal data

$C_{16}H_{20}O_3S$, M=292.38, monoclinic, a=8.4325(1), b=10.8293(1), c=17.8545(1) Å, β=101.565(1)°, U=1597 Å, T = 293K, space group $P2_1/n$, Z = 4,

$D_c$ =1.216Mg$^{-3}$, μ =0.207 mm$^{-1}$, F(000) =624, crystal dimensions 0.48 x 0.34 x0.32 mm. Of the 12378 reflections collected by a Siemens SMART CCD area detector diffractometer with graphite monochromated Mo-K α radiation ( λ=0.71073 Å) between 2.21 to 28.29°, -11 < h < 7, -14 < k < 14, -20 < l < 23, 3901 were independent ($R_{int}$ =0.054) and 2966 were considered and observed.

Structure solution and refinement

The crystal structure was solved by direct methods (SHELXS-97) [12] and refined anisotropically by full matrix least-squares on $|F|^2$ (SHELXL-97) [13]. Most of the H-atoms were located in a difference map and refined freely with isotropic displacement parameters. The final R indices were R=4.41% for observed reflections and $wR(F^2)$=12.76% for all data. The final difference map extremes were +0.315 and -0.364 e $Å^{-3}$, and the final shift/esd was 0.001.

*7,8-(11,11-Dimethyl pyrano)coumarin (**3**)*

The above reaction was quenched after 24 hrs. Usual workup and purification of the crude product by column chromatography (silica gel, 60-120 mesh, 95:5 hexane : ethyl acetate) yielded the title compound as a colourless crystalline solid. (0.17 g, 76%). m.p-101-103$^0$C.

$^1$H-NMR: (δ, ppm) 1. 38 (s, 6H), 1.85 (t, 2H, J=6.8 Hz), 2.90 (t, 2H, J=6.8 Hz), 6.21 (d, 1H, J=9.3 Hz), 6.75 (d, 1H, J=8.6 Hz), 7.25 (d, 1H, J=8.6 Hz), 7.65 (d, 1H, J=9.3 Hz).

$^{13}$C-NMR:(δ, ppm)16.4, 26.6, 31.5, 75.6, 109.3, 111.5, 111.9, 114.4, 119.5, 126.2, 144.0, 153.2, 157.5, 161.6. Mass (EI, m/z) 230 ($M^+$).

*Osthenol (**4**)*

Dimethyl sulphide (2.5 ml) was added dropwise to a suspension of anhydrous $AlCl_3$ (0.33g, 2.5 mmol) in $CH_2Cl_2$ (5mL) at 0°C with stirring to yield a completely dissolved $AlCl_3$/DMS solution. To this solution, osthol **1** (0.24g, 1.0 mmol) in $CH_2Cl_2$ (3mL) was added over a period of 10 min.at the same temperature. Then the reaction mixture was allowed to raise to room temperature (30°C) and stirring continued (24 hrs). The reaction mixture was quenched with cold 1N HCl (10mL) and extracted with $CH_2Cl_2$ (2 x 15mL). Purification of the crude product by column chromatography yielded osthenol (**4**) [11] (0.14g, 62%).

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*Samples Availability*: Available from MDPI.