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INTRAMOLECULAR ACYLATION DURING ACID CHLORIDE FORMATION OF SOME o-STYRYL PHENOXYACETIC ACIDS

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Abstract : o-Isopropenyl phenoxyacetic acids **1** and **8** on treatment with thionyl chloride followed by aqueous workup furnished the acylated products **4** and **9** in moderate yields. The corresponding acid chlorides could also be cyclised with stannic chloride. The acid chlorides from **10** and **11** however did not undergo cyclisation.

The key reaction in our synthesis[1] of aplysin involved intramolecular cycloaddition of ketene from acid chloride **2** to provide the cyclobutanone **3** which was consistently obtained in excellent yield. Subsequent to our communication[1a], a report appeared[2] which stated that the attempted reaction of acid chloride **2** with Et_3N gave poor yield of **3**. The major product was the mixture (endo and exo) of unsaturated ketones **4**. A 'preferred' ene reaction of the intermediate ketene involving the isopropenyl group was implicated for this unexpected result. Since our own results were contrary to this observation, this merited a closer look. That the isopropenyl group facilitates cycloaddition is amply borne out by the excellent yield of cyclobutanone obtained both from the acid chloride method as well as the one-pot procedure[1b] for such cycloadditions developed by Brady et al[3]. In a related system

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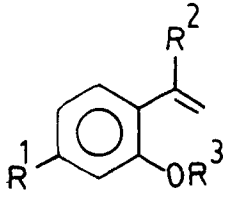
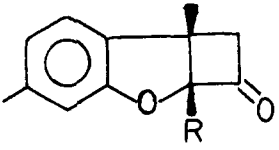
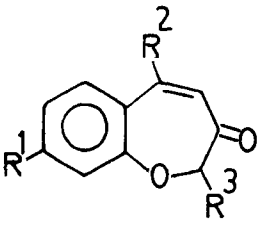






(**1**) $R^1=R^2=Me$, $R^3=CH(Me)CO_2H$ (**3**) R = Me (**4**) $R^1=R^2=R^3=Me$

(**2**) $R^1=R^2=Me$, $R^3=CH(Me)COCl$ (**6**) R = CH_2OMe (**7**) $R^1=R^2=Me$, $R^3=CH_2OMe$

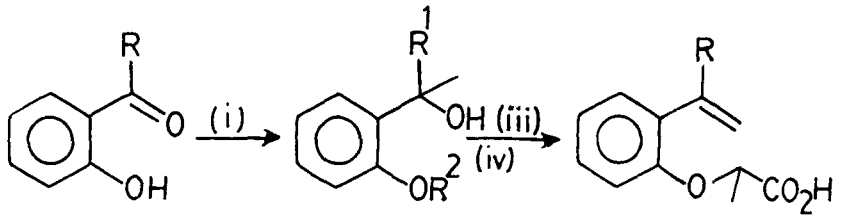
(**5**) $R^1=R^2=Me$, $R^3=CH(CH_2OMe)CO_2H$ (**9**) $R^1=H$, $R^2=R^3=Me$

(**8**) $R^1=H$, $R^2=Me$, $R^3=CH(Me)CO_2H$

(**10**) $R^1=R^2=H$, $R^3=CH(Me)CO_2H$

(**11**) $R^1=Me$, $R^2=H$, $R^3=CH(Me)CO_2H$

Shishido et al[4]. also have encountered no problem in such cycloadditions involving an isopropenyl group. It appeared to us that the intramolecular Friedel-Crafts product **4** could have arisen from the acid chloride **2** catalysed by some in situ generated HCl rather than from the ketene. This contention received additional support from our own observation[1b] during synthesis of aplysinol where the acid chloride from **5** on reaction with Et_3N afforded a mixture of cyclobutanone **6** and the acylation product **7** whereas under the one-pot condition, **5** furnished only the cyclobutanone **6**. Following these we deemed it appropriate to subject a few representative o-styryl phenoxyacetic acids to the conditions tried by Kher et al[2] for acid chloride formation and study the course of the reaction. Intramolecular acylation products[5] in intramolecular cycloadditions of certain keteniminium salts with alkenes have been encountered.



Scheme

(12) R = Me (ii) → (13) R^1=Me, R^2=H (8) R = Me
(15) R = H (ii) → (14) R^1=Me, R^2=CH(Me)CO_2Et (10) R = H

(ii) → (16) R^1=R^2=H
(ii) → (17) R^1=H, R^2=CH(Me)CO_2Et

Reagents : (i) MeMgI, Et_2O; (ii) Anhyd. K_2CO_3, KI, MeCH(Br)CO_2Et, dry acetone; (iii) $POCl_3$, Pyridine; (iv) KOH, MeOH.

We chose the four acids **1**,**8**, **10** and **11**. Acid **1** had been prepared earlier[1]. Acid **8** was synthesised as follows. Addition of methylmagnesium iodide to o-hydroxyacetophenone **(12)** furnished a diol **13** which was alkylated with ethyl α-bromopropanoate to provide the hydroxyester **14**. This was directly subjected to a dehydration followed by hydrolysis to afford the acid **8** (Scheme). The same sequence of reactions was applied on salicylaldehyde (**15**) and furnished the acid **10** (Scheme). Acid **11** was prepared from alkylation of 2-vinyl-5-methylphenol with α-bromopropanoic acid as per previous conditions[1].

Initially an intramolecular acylation was tried on acid **1**. To this end this was converted to the acid chloride as per previous condition[1] and treated with stannic chloride[6] and afforded the acylation product **4** in a moderate yield. Analytical and spectral data were fully supportive of the

structure. Conversion of the acid **1** to the acid chloride was next attempted using thionyl chloride following conditions of Kher et al[2]. The product showed in the IR peak at 1780 cm^{-1} and additional weak peaks at 1720 and 1655 cm^{-1}. The ^{1}H NMR spectra showed a complex pattern. The product was directly decomposed with water and worked up and purified by plc to afford **4** in a moderate yield along with some recovered acid **1.** Clearly some HCl generated in situ is catalysing the acylation reaction - resulting also in an initial exo methylene product which during workup and purification isomerises to the more stable endo α,β -unsaturated compound. This proved unambiguously that the intramolecular acylation takes place at the acid chloride stage.

In a similar fashion acid **8** was converted to an acid chloride and cyclisation with stannic chloride afforded the acylation product **9** in low yield. Reaction of the acid **8** with thionyl chloride followed by aqueous workup also furnished the same acylation product **9** attesting to the generality of competetive acylation pathway under the conditions of the reaction.

In contrast to above results acids **10** and **11** on reaction with thionyl chloride furnished only the corresponding acid chlorides and no intramolecular acylation resulted either by direct workup or using stannic chloride procedure. From this it appears that presence of vinyl methyl group is necessary for the cyclisation providing additional stabilisation to the cationic intermediate.

In conclusion intramolecular cycloaddition of ketenes from o-isopropenyl phenoxyacetic acids to provide cyclobutanones can be successfully carried out following a proper set of conditions. The formation of the acid chloride is crucial for the success of the reaction and the one-pot procedure would seem to offer the best choice to obviate unwanted competing intramolecular acylation in the event of difficulty to form the acid chloride under standard conditions.

Experimental Section

All the compounds described and having asymmetric centres are racemic forms. Melting and boiling points are uncorrected and melting points were taken in open capillary in sulphuric acid bath. All of the dry solvents and reagents were prepared from reagent grade materials by conventional methods. Petroleum refers to the fraction of bp 60-80°C and ether refers to diethyl ether. All reactions were carried out in nitrogen atmosphere. Product purities were routinely checked by TLC using silica gel $60HF_{254}$ (E. Merck). Preparative-layer chromatography was done with silica gel $60HF_{254}$ (E. Merck) plates, thickness 1 mm. Drying of organic layers was done with sodium sulphate. ^1H NMR spectra were determined at 60 MHz on a varian T-60A, at 200 MHz on a varian XL-200 spectrometers. Peak positions are indicated in ppm downfield from internal TMS in δ units. ^1H NMR spectra were taken in $CDCl_3$ solution in XL-200 spectrometer. Spectra in CCl_4 refer to T-60A instrument. IR spectra were recorded on Perkin-Elmer 298 infrared spectrophotometer and were taken in $CHCl_3$ solution. Yields have not been optimised.

2-(2-Isopropenylphenoxy)propanoic acid (8). : To a magnetically stirred solution of methylmagnesium iodide [prepared from magnesium (0.9 g, 0.037 g atom) methyl iodide (5.32 g, 37 mmol) in dry ether (20 ml)] a solution of o-hydroxyacetophenone **(12)** (4.08 g, 30 mmol) in dry ether (20 mL) was added at room temperature. The reaction mixture was then heated under reflux for 3 h, cooled to 0°C, decomposed with saturated ammonium chloride and stirred at room temperature for 10 min. After separating the ether layer, the aqueous layer was extracted with ether. The combined ether layer was washed with water, then dried and concentrated. The residual oil was evaporately distilled to afford 2-(2-hydroxyphenyl)propan-2-ol

(13) (2.7 g, 59%) : bp 85-90°C/(0.5 mmHg); ^{1}H NMR (CCl_4) δ 1.6 (s, 6H); 6.5-7.07 (m, 5H).

A mixture of the above diol, **13** (2.7 g, 17.7 mmol), ethyl-α-bromopropanoate (3.2 g, 17.7 mmol), anhydrous potassium carbonate (2.44 g, 17.7 mmol) and a pinch of potassium iodide in dry acetone (50 mL) was heated under reflux with stirring for 12 h. It was then concentrated to one-third of the volume, diluted with water and extracted with ether. The combined organic layer was washed with cold sodium hydroxide solution (1.25 N) and water, dried and concentrated. The residue was passed through a column of silica gel and eluted with petroleum to afford the alkylated product, **14** (3.5 g, 78%); ^{1}H NMR (CCl_4) δ 1.17 (t, J = 6 Hz, 3H); 1.56 (s, 6H); 1.63 (d, J = 6 Hz, 3H); 4.13 (q, J = 6 Hz, 2H); 4.83 (q, J = 6 Hz, 1H); 6.53-7.43 (m, 4H), and was directly subjected to dehydration.

A solution of this alkylated product, **14** (3.38 g, 13.4 mmol) in dry pyridine (10 mL) was cooled to 0°C, and with stirring phosphorous oxychloride (2.04 g, 13.4 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. It was diluted with H_2SO_4 (7N), and then extracted with ether. The ethereal layer was washed with saturated sodium hydrogen carbonate and saturated brine and then dried. Removal of ether afforded an oil (1.73 g) which showed expected spectral feature; ^{1}H NMR (CCl_4) δ 1.2 (t, J = 6 Hz, 3H); 1.59 (d, J = 6 Hz, 3H); 2.13 (br s, 3H); 4.13 (q, J = 6 Hz, 2H); 4.66 (q, J = 6 Hz, 1H); 5.00 (br s, 2H); 6.5-7.2 (m, 4H), and was directly hydrolysed.

To a magnetically stirred solution of the above (1.73 g, 7.4 mmol) in methanol (10 mL) was added a cold aqueous solution of potassium hydroxide (5 mL, 5N). The reaction mixture was stirred at room temperature for 24 h. It was then diluted with water, acidified with cold dilute HCl (6N) and extracted with ether. The ethereal layer was washed with

saturated brine and water, dried and concentrated to afford the desired acid **8** as a crystalline solid (910 mg, 60%); crystallised from petroleum; mp 68-69°C; ^{1}H NMR ($CDCl_3$) δ 1.66 (d, J = 6 Hz, 3H); 2.16 (s, 3H); 4.82 (q, J = 6 Hz, 1H); 5.12 (m, 1H); 5.2 (m, 1H); 6.82 (d, J = 8 Hz, 1H); 6.96-7.07 (m, 1H); 7.18-7.3 (m, 2H).

Anal. calcd. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84
Found : C, 70.22; H, 6.96

2-(2-Vinylphenoxy)propanoic acid (10). - Starting from salicylaldehyde **(15)** the steps of Grignard reaction (MeMgI), alkylation [Me-CH(Br)CO_2Et], dehydration and hydrolysis were carried out as for **8** to furnish the 2-(2-vinylphenoxy)propanoic acid **10** in an overall yield of 18% : crystallised from ether-petroleum; mp 106-107°C; ^{1}H NMR ($CDCl_3$) δ 1.68 (d, J = 6 Hz, 3H), 4.82 (q, J = 6 Hz, 1H); 5.32 (d, J = 12 Hz, 1H); 5.8 (d, J = 20 Hz, 1H); 6.8 (d, J = 8 Hz, 1H); 6.96-7.08 (m, 1H); 7.12-7.3 (m, 2H); 7.54 (br d, J = 8 Hz, 1H).

Anal. calcd. for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29
Found : C, 68.39; H, 6.34

2-(2-Vinyl-5-methylphenoxy)propanoic acid (11). - A mixture of 7-methylcoumarin (5.72 g, 35.7 mmol), KOH pellets (10.01 g, 178.7 mmol), water (10 mL) and ethylene glycol (55 mL) was heated under reflux for 3 h. It was then cooled, poured into crushed ice, covered with ether (50 mL) and acidified with cold dilute HCl (6N) with constant stirring. After separating the ether layer, the aqueous layer was extracted with ether. The combined ethereal layer was washed with water and dried. Removal of ether furnished a solid product which was pyrolysed at 250-260°C/(15 mmHg). The solution of distillate in methylene chloride was extracted with cold dilute KOH solution (12.5 N). The alkaline solution was cooled (0.5°C), acidified with dilute HCl (6N) and extracted with ether. The ether

extract was washed with water, dried and concentrated to afford 2-vinyl-5-methylphenol (1.43 g, 30%); ^{1}H NMR (CCl_4) δ2.2 (s, 3H); 5.03-5.72 (m, 2H); 6.36-7.23 (m, 4H). The methylene chloride layer was washed with water and then dried. Removal of solvent furnished a solid product (3 g) which was identified as 7-methylcoumarin. Based upon recovered coumarin, the yield of styrenol was 62%. The styrenol was used in the next step without further purification.

To a magnetically stirred solution of 2-vinyl-5-methylphenol (1.39 g, 10.3 mmol) and α-bromopropanoic acid (1.58 g, 10.3 mmol) in dry THF (20 mL) at -10°C was added sodium hydride (1.2 g, 50% dispersion in mineral oil, 25 mmol) portionwise during 30 min. Stirring was continued at -10°C for 20 min and at room temperature for 30 min. The reaction mixture was then refluxed with vigorous stirring for 10 h. Upon cooling the reaction was diluted with water, acidified with dilute HCl (6N) and extracted with ether. The ether extract was washed with water, dried and concentrated to furnish the desired alkylated acid, **11** (1.28 g, 60%); crystallised from ethylacetate-petroleum; mp 114-116°C; ^{1}H NMR ($CDCl_3$) δ 1.68 (d, J = 6 Hz, 3H); 2.32 (s, 3H); 4.82 (q, J = 6 Hz, 1H); 5.24 (d, J = 11 Hz, 1H); 5.72 (d, J = 16 Hz, 1H); 6.62 (s, 1H); 6.84 (d, J = 8 Hz, 1H); 7.00-7.14 (m, 1H); 7.42 (d, J = 8 Hz, 1H).

Anal. calcd. for $C_{12}H_{14}O_3$: C, 69.9; H, 6.79
Found : C, 69.52; H, 6.49

2,3-Dihydro-2,5,8-trimethyl-1-benzoxepin-4-en-3-one (4):

Method A. - 2-(2-Isopropenyl-5-methylphenoxy)propanoic acid **(1)** (440 mg, 2 mmol) was converted to the acid chloride **2**,[1b] and taken in dry 1,2-dichloroethane (120 mL) and cooled to -5°C. To this magnetically stirred solution of acid chloride was added a solution of stannic chloride (0.5 mL) in dry 1,2-dichloro-

ethane (5 mL) dropwise during 15 min. Stirring was continued at -5°C for 1.5 h. Before attaining room temperature the mixture was poured into crushed ice and extracted with ether. The combined organic layer was washed with saturated sodium hydrogen carbonate, saturated brine and water, and dried. The residual oil after removal of solvent was evaporatively distilled to afford **4** (60 mg); bp 95-100°C/(0.15 mmHg); IR 1655 cm^{-1}; ^1H NMR δ1.48 (d, J = 7 Hz, 3H), 2.35 (d, J = 1.1 Hz, 3H); 2.38 (s, 3H); 4.36 (q, J = 7 Hz, 1H); 6.37 (br s, 1H); 7.08 (m, 2H); 7.44 (d, J = 7 Hz, 1H).

Anal. calcd. for $C_{13}H_{14}O_2$: C, 77.2; H, 6.98
Found : C, 76.85; H, 7.26

The alkaline extract on acidification and workup furnished some recovered acid **1** (330 mg). Based on this recovered acid the yield of the acylated product is around 55%.

Method B. - To a solution of acid, **1** (90 mg, 0.41 mmol) in dry benzene (5 mL) was added freshly distilled thionyl chloride (112 mg. 0.94 mmol). The reaction mixture was heated under reflux for 3 h. It was then cooled and excess thionyl chloride was removed by azeotropic distillation under vacuum with fresh addition of dry benzene (3 x 5 mL). The acid chloride thus obtained [IR 1780 (s), 1720 (w), 1655 cm^{-1} (br)] was decomposed with crushed ice and then extracted with ether. The combined ethereal layer was washed with saturated sodium hydrogen carbonate, saturated brine and water, and dried. The residual oil obtained after removal of ether was subjected to preparative-layer chromatography. Elution with 5% ethyl acetate in petroleum furnished the α,β-unsaturated ketone **4** (30 mg, 60% based on recovered **1** from the alkaline extract).This material was identical with the sample obtained from method A.

2,3-Dihydro-2,5-dimethyl-1-benzoxepin-4-en-3-one (9). Method A : Following similar procedure as in method A for acid **1**, the acid **8** furnished the acylation product **9** in 60% yield (based on recovered acid); bp 100-105°C/(1.5 mmHg); IR 1655 cm^{-1}; ^1H NMR δ 1.52 (d, J = 7 Hz, 3H); 2.4 (s, 3H); 4.36 (q, J = 7 Hz, 1H); 6.46 (br s, 1H); 7.22-7.60 (m, 4H).

Anal. calcd. for $C_{12}H_{12}O_2$: C, 76.58; H, 6.43
Found : C, 76.23; H, 6.57

Method B : Similar treatment as in method B for acid 1of the acid **8** afforded **9** in 55% yield.

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