An efficient method for synthesis of 2-ethyl hexyl-4-methoxy cinnamate:
A raw material for cosmetic industry

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Methyl, ethyl and isopropyl esters of 4-methoxy cinnamic acid could be synthesized by Claisen condensation of anisaldehyde with the respective alkyl acetate at a temperature of 0 - 5°C using stoichiometric amount of sodium and a few drops of methanol, the latter being used as an initiator. The yield of the ester of cinnamic acid was about 77%. When the reaction was extended to the synthesis of 2-ethylhexyl ester of cinnamic acid, the reaction rates were rather very poor and it was necessary to carry out the reaction at the temperature of 28°C which resulted in the extensive hydrolysis of the starting acetate and the product ester. In the case of 2-ethyl hexyl ester, therefore, it may be desirable to resort to the synthesis of ethyl / methyl ester of the cinnamic acid by Claisen condensation followed by transesterification of the ethyl / methyl ester. Thus, transesterification of ethyl 4-methoxy cinnamate with excess of 2-ethyl hexanol and p-toluenesulfonic acid as catalyst at 150°C gave a yield of 93% in 6 h.

In recent years market projections indicate that sunscreen chemicals are the growing category of the cosmetic industry1. This growth in demand for the sunscreen products has been sparked, in part, by an ever increasing understanding of the effects of sunlight on the skin, with regard to both skin cancer and premature aging. A few years back esters of p-amino benzoic acid (PABA), viz., octyl N,N-dimethyl-p-amino benzoate (Padimate O) was extensively used as a sunscreen chemical. Due to the irritation and sensitization effect of PABA and its derivatives, these chemicals were, however, phased out. Of late, esters of 4-methoxy cinnamic acid are extensively used as sunscreen chemicals. Of these 2-ethyl hexyl 4-methoxy cinnamate which has a SPF (Sun protection factor) of 15 and not causing any irritation or sensitization to the skin is the most widely used sunscreen chemical in the US and the developed world2.

There is no detailed procedure available in the literature for the synthesis of 2-ethylhexyl 4-methoxy cinnamate3-6. It was thought worthwhile to study the synthesis of this chemical by various alternate routes and they are as follows:

(i) Transesterification of ethyl 4-methoxycinnamate with 2-ethylhexanol using catalysts such as p-toluenesulfonic acid or ion exchange resin such as Indion-13078.

(ii) Direct synthesis of 2-ethylhexyl 4-methoxy cinnamate by Claisen condensation9.

(iii) Direct esterification of 4-methoxy cinnamic acid with 2-ethylhexanol using p-toluenesulfonic acid as catalyst.

Experimental Procedure
Materials
Ethyl 4-methoxy cinnamate, 2-ethyl hexyl acetate, iso-propyl acetate, 4-methoxy cinnamic acid (prepared in the laboratory), anisaldehyde, Indion-130 (commercial grade), sodium metal, methanol, isopropanol, 2-ethyl hexanol (laboratory grade), p-toluenesulfonic acid, xylene and toluene (technical grade) were used for the above study.

Synthesis of esters of 4-methoxy cinnamic acid
Ethyl, isopropyl and 2-ethyl hexyl 4-methoxy cinnamate were synthesized by Claisen condensation as reported in the literature9.

Synthesis of isopropyl and 2-ethylhexyl esters of acetic acid
Predetermined quantity of 2-ethyl hexanol or isopropanol, toluene, excess of acetic acid and catalytic amount of sulfuric acid were taken in a round bottom flask fitted with a condenser. The reaction mixture was refluxed for 4 h. Unreacted acetic acid was re-
moved by washing the toluene layer several times with water until free of acetic acid. Toluene layer was finally dried using anhydrous sodium sulfate. Toluene was distilled under vacuum and the product was further purified by distillation under vacuum in the case of 2-ethylhexyl acetate and under atmospheric pressure in the case of isopropyl acetate. Distilled acetates were stored in air tight bottles and a small amount of anhydrous potassium carbonate was added to the bottle to keep the ester anhydrous during storage (Table 1).

### Synthesis of 4-methoxy cinnamic acid

Prepared amount of ethyl 4-methoxy cinnamate, sodium hydroxide and ethanol were taken in a round bottomed flask fitted with a condenser. The reaction mixture was refluxed at 80°C for 3 h. Sodium salt of 4-methoxy cinnamic acid having less solubility in ethanol precipitated out. Part of the solvent was distilled under vacuum and the reaction mixture was acidified with dilute hydrochloric acid. 4-Methoxy cinnamic acid was filtered and washed with water until free of acid and then it was dried in an oven (Table 1).

### Synthesis of isopropyl 4-methoxy cinnamate by esterification reaction

Calculated quantity of 4-methoxy cinnamic acid, respective alcohol, xylene as solvent and p-toluene sulfonic acid as catalyst were taken in a reactor. The reaction mixture was refluxed for 6 h. 4-Methoxy cinnamic acid having less solubility than the ester precipitated out on concentrating the solvent. It was filtered and weighed whereas the ester remained in the solvent. Traces of 4-methoxy cinnamic acid in xylene were removed by washing the xylene layer with 10% sodium bicarbonate solution. It was then washed with water and dried using sodium sulfate. The solvent was distilled under vacuum and the product weighed. Its purity was checked by gas chromatography. The unreacted 4-methoxy cinnamic acid and the product were estimated by isolation and weighed.

### Synthesis of 2-ethylhexyl 4-methoxy cinnamate by transesterification reaction

#### Experimental set-up

The reaction was carried out in a 250 mL borosilicate glass reactor provided with a stirrer, four baffles, a dropping funnel, a thermometer pocket and a condenser. The desired temperature of the reaction mixture was maintained by immersing the reactor in a constant temperature bath.

#### Procedure

Pre-determined amount of ethyl 4-methoxy-cinnamate, 2-ethylhexanol and the catalyst such as p-toluene sulfonic acid and Indion-130 were taken in the reactor. After the reaction, the solvent was distilled under vacuum. To the bottoms was added benzene. Benzene layer was washed with 10% sodium carbonate solution and then with water. Traces of water in the benzene layer was removed by adding anhydrous sodium sulfate. Benzene was removed by distillation under vacuum. The product was further purified by vacuum distillation.

#### Analysis

The amount of unreacted ethyl 4-methoxy-cinnamate and its conversion to 2-ethylhexyl 4-methoxy cinnamate was estimated by gas chromatography. The column and the conditions used were as follows: Column, S.S., 3.2 mm, i.d. and 2 m long; Stationary phase, 10% OV - 17 on chromosorb - W; Carrier gas, N₂; Rate, 0.138 MPa; Detector, F.I.D.; Oven temperature, 80°C, 1 min. isothermal, ramp 10°C/ min. to 300°C; Injector temperature, 300°C; Detector temperature, 300°C.

#### Results and Discussion

### Synthesis of esters of 4-methoxy cinnamic acid by Claisen condensation

When ethyl 4-methoxy cinnamate was synthesized by Claisen condensation an overall conversion of...
89% of anisaldehyde with a yield of 70% was obtained in 3.5 h at 5°C (Table 3).

During the synthesis of isopropyl 4-methoxy cinnamate by Claisen condensation the temperature was maintained at about 0°C because the isopropyl acetate is relatively more susceptible to hydrolysis than ethyl acetate, particularly when temperature is more than 0°C. In the present work, the temperature was maintained at 0°C by using a cryostat. In 3.5 h an overall conversion of 90% with 77% yield of the product was obtained (Table 3). One of the by-products was hydrogenated cinnamate. The conversion to isopropyl 4-methoxy-dihydro cinnamate was only 4%. The other by-products could have resulted from the reaction of sodium metal and anisaldehyde which were not isolated and characterized. Since Claisen condensation gives the ester in one step, it was thought desirable to synthesize 2-ethylhexyl 4-methoxy cinnamate by this route. Claisen condensation was usually performed at 0-5°C to avoid the hydrolysis of 2-ethylhexyl acetate and the product ester at higher temperature. During the synthesis of 2-ethylhexyl 4-methoxy cinnamate by Claisen condensation it was observed that no significant conversion to product was obtained at 0-5°C. Therefore, the reaction was performed at 28°C. At this temperature, as expected, part of 2-ethylhexyl acetate and 2-ethylhexyl 4-methoxy cinnamate did undergo hydrolysis, thus affecting the yield of the product. The product of hydrolysis of 2-ethylhexyl acetate, viz., 2-ethylhexanol, was recovered by distillation and could be re-used. 4-Methoxy-cinnamic acid obtained due to the hydrolysis of 2-ethylhexyl 4-methoxy-cinnamate was recovered from the aqueous 10% sodium bicarbonate wash stream on acidifying with dil. hydrochloric acid. It was filtered, washed and dried (Table 3). Thus, at 28°C, 89.7% conversion of anisaldehyde with 43.4% conversion to product was obtained in 2 h. The major side product was 4-methoxy cinnamic acid.

**Synthesis of isopropyl 4-methoxy cinnamate by direct esterification reaction**

As the yield of the desired product was poor by the above process, and the side product obtained was an acid, it was thought desirable to synthesize 2-ethylhexyl 4-methoxy cinnamate by direct esterification of 4-methoxy cinnamic acid with the respective alcohol. The esters of 4-methoxy cinnamic acid are very high-boiling and, therefore, purification of the product by distillation is very cumbersome. Hence, a process which gave the ester without employing complicated separation techniques is desirable. The direct esterification process looked very attractive from the view point of ease of separation of the acid from the ester. To start with, the possibility of esterifying 4-methoxy cinnamic acid with isopropyl alcohol was explored. Xylene was used as a solvent with p-toluenesulfonic acid as the catalyst. 4-Methoxy cinnamic acid had very poor solubility in xylene and therefore large excess of xylene had to be used to increase the solubility. The yield of isopropyl 4-methoxy cinnamate was 41.9% in 6 h (Table 2). Since the rate of esterification of 4-methoxy cinnamic acid with 2-ethylhexanol is going to be less than that with isopropanol and the latter, itself is rather poor, the synthesis of 2-ethylhexyl 4-methoxy cinnamate by esterification was not considered. It was thought desirable to synthesize it by transesterification reaction.

**Synthesis of 2-ethylhexyl 4-methoxy cinnamate by transesterification reaction**

Transesterification of ethyl 4-methoxy cinnamate with 2-ethyl hexanol was studied using catalysts, such as p-toluene sulfonic acid and ion-exchange resin, viz., Indion-130. Transesterification of ethyl 4-methoxy cinnamate with Indion-130, it was observed that with an increase in catalyst loading, the conversion was found to increase. The catalyst loading, expressed as w/v of the reaction volume, was varied in the range of 0.04 - 0.1 g/cm³. At the end of 6 h, yield
of 29.4, 47.5 and 60% were obtained with loadings of 0.04, 0.08 and 0.1 g/cm³ respectively (Table 4). The reusability of Indion-130 was considered at a catalyst loading of 0.1 g/cm³. The yield dropped from 60% to 49.5% in the second run but remained almost constant in the subsequent two runs (Table 5). The reaction rates with Indion-130 as a catalyst were rather poor mainly because the temperature had to be restricted to about 100°C since the ion-exchange resin was not stable at higher temperatures. Using p-toluenesulfonic acid as catalyst at 150°C gave 91% conversion of ethyl 4-methoxy cinnamate with a yield of 91% of 2-ethylhexyl 4-methoxy cinnamate in 6 h. The product was purified by distillation under vacuum (Table 6).

Conclusion

Ethyl and isopropyl esters of 4-methoxy-cinnamic acid could be synthesized by Claisen condensation of anisaldehyde with respective alkyl acetate at a temperature of 0-5°C using stoichiometric amount of sodium and a few drops of methanol, the latter being used as an initiator. The conversion of anisaldehyde was about 90% and the yield of the ester of the cinnamic acid was about 70 - 77%. When the reaction was extended for the synthesis of 2-ethylhexyl ester of the cinnamic acid, the reaction rates were rather very poor and it was necessary to carry the reaction at the temperature of 28°C which resulted in the extensive hydrolysis of the starting acetate and the product. In the case of 2-ethylhexyl ester, therefore, it may be desirable to resort to the synthesis of ethyl / methyl ester of the cinnamic acid followed by transesterification of the ethyl / methyl ester. It may be argued that if two steps synthesis is followed, the possibility of converting anisaldehyde to 4-methoxy-cinnamic acid followed by esterification to the ethylhexyl ester may be also worth considering. In this context it was observed that the rates of esterification of the cinnamic acid with even isopropanol were rather poor. The strategy of synthesizing the 2-ethylhexyl ester using transesterification reaction was, therefore, found to be more attractive. The rates of transesterification reaction at a temperature level of about of 100°C, at which cation exchange resins can be used were rather poor. The transesterification at 150°C with p-toluenesulfonic acid gave acceptable reaction rates. Under suitable reaction conditions [ethyl 4-methoxy-cinnamate, 0.145 gmol; 2-ethylhexanol, 100 ml; catalyst, p-toluenesulfonic acid; catalyst loading, 0.03 g/cm³ of the reaction volume; temperature, 150°C; speed of agitation, 1000 rpm] 93% overall conversion of ethyl 4-methoxy-cinnamate with a yield of almost 100% could be obtained in 6 h. The product could be isolated by vacuum distillation.

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References