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Cation-Exchange Resin-Catalysed Acylations and Esterifications in Fine Chemical and Perfumery Industries

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Abstract:

Acylation and esterification reactions are typically carried out by using homogeneous acids as catalysts which can be profitably replaced with heterogeneous solid acid catalysts to develop green chemistry. Solid acids that give the desired level of activity but which can be easily removed from the reaction mixture with no residual inorganic contamination of the organic products offer obvious advantages over existing methods. This contribution is concerned with eco-friendly synthesis of some commercially valuable products such as *p*-methoxyacetophenone, dimethyl phthalate, diethyl phthalate, methyl anthranilate, methyl salicylate, and methyl *p*-hydroxybenzoate (methyl paraben). The specifications require the esters to be free of halide impurities on ppm level for perfumery use, and thus use of chlorine-containing agents or catalysts must be avoided. The following catalysts were evaluated: Amberlyst-36, Bayer K2441, Amberlyst-15, Dowex 50Wx8, Indion-130, Deloxane ASP, Filtrol-24 clay, K-10 Montmorrilonite clay, and sulphated zirconia. Anisole was acylated with acetic anhydride to get 100% selectivity of *p*-methoxyacetophenone, and Amberlyst-36 was found to be the most active and reusable catalyst. A kinetic model is also presented. Amberlyst-36 was also the most active catalyst for the esterification reactions.

1. Introduction

Acylation and esterification reactions are commercially important with productions ranging from a few hundred to thousands of tonnes per year and are used to make ketones and esters which serve as precursors or additives for a variety of perfumes and flavours, pharmaceuticals, agrochemicals, and polymers. The waste generated in these industries ranges from 50 to 100 kg per kg of the desired product, depending on the number of stages and the type of functionality introduced in each stage. These esters and ketones are usually manufactured in batch reactors, in a multicampaign process plants, using homogeneous catalysts which include Lewis acids ($AlCl_3$, BF_3, $ZnCl_2$, $TiCl_4$, $SnCl_4$, $FeCl_3$, SbF_5, $ZrCl_4$, SiF_4, etc.) and Brønsted acids (HF, H_2SO_4, HCl, H_3PO_4, *p*-toluenesulphonic acid, dihydroxyfluoroboric acid, etc.), including finely divided metals such as tin, manganese, silver, copper, lead, and so forth in conjunction with a proper reagent where the acid is generated in situ.[1−3] The use of homogeneous catalysts leads to several problems such as corrosion of equipment, hazards of handling the corrosive acids which are not reused, neutralization of the resulting reaction mass, and generation of large quantities of dilute dissolved salts, including loss of conversion, yield, and selectivity. The biological oxygen demand (BOD), chemical oxygen demand (COD), and total dissolved solids (TDS) loads on effluent treatment plants become enormous. Since the prices of these fine chemicals are very high and volumes are low, no serious attempts were made until recently to recover the catalyst or change the processes.

In the case of the Friedel−Crafts acylation, apart from the fact that the use of homogeneous acids as catalysts is polluting and hazardous, they have to be employed in at least two molar excess quantities over the acylating agent. On the industrial scale, the use of metal halide types of acids, which are preferred catalysts, create workup and effluent problems. Indeed, during the workup of acylation mixtures, the destruction of catalysts produces relatively large amounts of hydrochloric acid in the off-gas or in the effluent. This hydrochloric acid, which has to be disposed of, originates both from the catalyst and also from acyl chloride employed for the acylation. In addition, the corrosion problem due to hydrochloric acid must be solved.

In the case of esterification reactions, the quantity of catalyst is not stoichiometric except for aromatics containing amine groups, but the same problems exist. Many synthetic routes are available to make esters, but most of them are not suitable to meet the stringent specifications.[3−4] The most acceptable method of making an ester is to react the corresponding acid with an alcohol. The reaction is catalysed by mineral acids and is reversible. Several methods are available to drive the reaction towards the product. One of them is to use an excess amount of alcohol, and another is to remove the ester formed (or the coproduct water) continuously.[3,4]

Pressure from legislative and environmental bodies together with a growing awareness within the chemical industry has led to a massive search for new eco-friendly processes to replace unacceptable outdated reactions. Therefore, a

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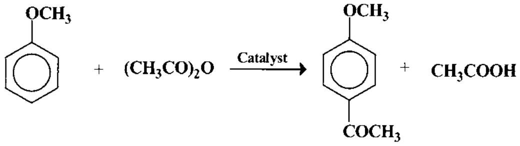
Scheme 1. **Acylation of anisole by acetic anhydride**



process that could be environmentally friendly and also inexpensive, with respect to the disadvantages indicated above, is the most desirable. Solid acids that give the desired level of activity, but which can be easily removed from the reaction mixture with no residual inorganic contamination of the organic products, offer obvious advantage over existing methods. Solid acids and superacids contain all their acidity within the pores, are easy to handle, and can be fine-tuned to get the desired activity and selectivity. The corrosion problems are avoided, and the cost of materials of construction is substantially reduced. There are several choices of reactor configurations, including modes of heat addition or removal, and the overall process safety is enhanced. Among several other researchers all over the world, considerable progress has been made in achieving these goals through recent developments in solid acid catalysis for fine chemical synthesis in our laboratory[5−20] including esterification[8−14] and acylation.[15−20]

This report is concerned with the eco-friendly synthesis of some commercially valuable products such as *p*-methoxyacetophenone, dimethyl phthalate, diethyl phthalate, methyl anthranilate, methyl salicylate, and methyl *p*-hydroxybenzoate (methylparaben). The specifications require that there be no halide impurities even on the ppm level for perfumery use; thus, use of chlorine containing agents or catalysts must be avoided. It is pertinent to review the pertinent literature related to these products.

Acylation of anisole with a suitable acylating agent leads to *p*-methoxy acetophenone (Scheme 1). *p*-Methoxyacetophenone has a sweet, somewhat harsh, haylike floral animal note and is extensively used in soap formulations for it is relatively stable in mild alkaline conditions and is also used as a flavouring chemical. Acetyl chloride, acetic anhydride and acetic acid have been used as acylating agents in the presence of hazardous solvents such as nitromethane, nitrobenzene, carbon disulphide, methylene chloride and a variety of homogeneous Lewis acids and Brønsted acids which include $AlCl_3$, $TiCl_4$, $SnCl_4$, Cu, $AgClO_4$, $NaClO_4$, $Ag_3(PO_4)$, CF_3COOH, BF_3, $HClO_4$, ortho- and polyphosphoric acid, $ZnCl_2$, $ClCH_2COOH$, I_2, $(ClCH_2O)_2O$, $(CF_3CO)_2O$, and $(C_3F_7CO)_2O$ (see Table 1). The reactions are typically conducted in a semibatch mode and are highly exothermic. The reactant is mixed with the catalyst at low temperature, and on complete addition of the second reagent, the mass is refluxed over a period of time ranging from 3 to 12 h. The yields vary from 18 to 98%, and all processes are polluting. On industrial scale, acylation has been carried out using $AlCl_3$ in chlorobenzene or methylene chloride as a solvent and acetyl chloride as an acylating agent with 2.2 mol of $AlCl_3$ per mol of acetyl chloride. There are some recent reports on the reaction between anisole with acetic anhydride or acid chloride in the presence of reusable catalysts such as zeolites (H-ZSM5, H-Mordenite, H-β, H-Y),[41−44] clays and modified clays,[45] and lanthanide bis(trifluoromethylsulphonyl) amides.[46]

Most esters have a pleasant odour reminiscent of floral to fruity notes.[47] Methyl anthranilate is one such interesting ester that occurs naturally in several citrus fruits such as orange and also in some flowers such as neroli and ylang ylang. It finds more applications in flavouring rather than perfumery compositions because of its odour, which resembles the musty-fruity-dry floral note imitating concord grapes and orange blossoms. It blends very well with several flavours and finds more usage in the flavouring of soft drinks and alcoholic beverages. The annual production of methyl anthranilate was 186 t[48] in 1964 and is currently estimated to be over 1000 t. The major commercial routes are based

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Table 1. **Past work on synthesis of 4-methoxyacetophenone from anisole: use of polluting catalysts or hazardous solvents**[a]

	catalyst	acylating agent (AA)	catalyst to AA mol ratio	AA to anisole mol ratio	solvent	yield %	ref
1	$AlCl_3$	acetyl chloride	2:1	1:1	nitromethane	quant	21, 22
2	$TiCl_4$	acetyl chloride	2:1	1.5:1	CS_2	65	23
3	$SnCl_4$	acetyl chloride	2:1	1:1	nitromethane	81	24
4	Cu	acetyl chloride	2:1	1:1	CS_2	30	25
5	$AgClO_4$	acetyl chloride	2:1	1.5:1	acetic acid + acetic anhydride	70	26, 27
6	$NaClO_4$	acetyl chloride	2:1	1.5:1	acetic acid + acetic anhydride	50	28
7	Ag_3PO_4	acetyl chloride	2:1	1:1	acetic acid + acetic anhydride	59	1
8	H_2SO_4	acetyl chloride	2:1	1:1		2	1
9	CF_3COOH	acetyl chloride	2:1	1.5:1		91	29
10	$AlCl_3$	acetic anhydride	2.2:1	1.5:1	CS_2	94	30, 31
11	$AlCl_3$	acetic anhydride	2.2:1	1:1.06	methylene chloride	95	32, 33
12	BF_3	acetic anhydride	2:1	1.1:1	Acetic acid	95	1
13	$TiCl_4$	acetic anhydride	2:1	1.5:1		80	30
14	$HClO_4$	acetic anhydride	2:1	1:1		37	26
15	orthophosphoric acid	acetic anhydride	2:1	1:1		45	30
16	polyphosphoric acid	acetic anhydride	2:1	1.5:1		84	34
17	CF_3COOH	acetic anhydride	2:1	1.5:1		91	35
18	$ZnCl_2$	acetic anhydride	2:1	1:1		50	36
19	$ClCH_2COOH$	acetic anhydride	2:1	1.5:1		90	37
20	I_2	acetic anhydride	2:1	1:1		66	38
21	$(ClCH_2O)_2O$	acetic acid	2:1	1.5:1		90	37
22	$(CF_3CO)_2O$	acetic acid	2:1	1.5:1		78	39
23	$(C_3F_7CO)_2O$	acetic acid	2:1	1.5:1		18	39
24	polyphosphoric acid	acetic acid	2:1	1.5:1		64	40
22	BF_3	acetic acid	2:1	1.5:1		98	36

[a] Reaction conditions: All additions slowly over a period of time, allowing the temperature to rise to the reflux and then cooking over 3−8 h. Reagent itself served as a solvent in some cases.

on esterification of anthranilic acid with methanol or isatoic anhydride with methanol, and these employ homogeneous acid catalysts, posing problems of disposal. Typically, sulphuric acid is used as a catalyst with little more than stoichiometry over anthranilic acid to block the amino group as hydrogen sulphate and the remaining for catalysis.[15,47,48]

Methyl salicylate is a valuable ester, having a pungent-sweet, fruity odor with a burning sensation at high concentration. Methyl salicylate can be obtained from natural sources by the maceration and subsequent steam distillation of wintergreen leaves or sweet birch bark. Generally, the commercial product is synthesised by the esterification of salicylic acid with methanol. Other than aspirin, methyl salicylate is by far the most important commercial derivative of salicylic acid. As a pharmaceutical, it is used in liniments and ointments for the relief of pain in the lumbar and sciatic regions and for rheumatic conditions. As a flavor and fragrance agent, it is used in confectionery, dentifrices, cosmetics, and perfumes.[47] Methyl 4-hydroxybenzoate has been used as preservative for food, pharmaceuticals, and cosmetics for many years.[47−50] Similarly, phthalate esters such as dimethyl phthalate (DMP) and diethyl phthalate (DEP) are also used in the perfumery industry and these can be prepared by treating methanol and ethanol with phthalic anhydride.

From the several available catalysts, it was thought desirable to evaluate a number of solid acids, develop a suitable green process, and to include a kinetic model which will be useful for reactor design purposes.

2. Experimental Method

2.1. Chemicals and Catalysts. All chemicals and catalysts were procured from firms of repute: anthranilic acid (LR; Loba Chemie), anisole, salicylic acid, 4-hydroxybenzoic acid, phthalic anhydride, methanol, acetic anhydride, (AR; s.d. Fine Chem Ltd, India), ethanol (absolute GR; Merk KgaA, Germany), Filtrol-24 (Engelhard, U.S.A.), K-10 clay (Aldrich, U.S.A.), ion-exchange resins (IER) such as Indion-130 (Ion Exchange Ltd., India), Amberlyst-15, Amberlyst-36 (Rohm and Hass, U.S.A.), Dowex 50Wx8 (Dow Chemicals, U.S.A.), and Bayer K-2441 (Bayer, Germany), Deloxane ASP, (Degussa AG, Germany). These catalysts were dried and used as such.

Sulphated zirconia was prepared according to the method developed in this laboratory,[5,6] by adding aqueous ammonia solution to zirconium oxychloride solution at a pH of 10. The precipitate was thoroughly washed with distilled water, free from ammonium and chloride ions. It was then dried in an oven at 120 °C for 24 h. The sulphation of the prepared zirconia was done with 1.0 N sulphuric acid (15 mL/g). It was dried at 120 °C and calcined at 650 °C for 3 h.

2.2. Catalytic Experiments. *2.2.1. Acylation of Anisole.* Acylation of anisole with acetic anhydride or acetyl chloride gives *p*-methoxy acetophenone (Scheme 1).

The reactor consisted of a flat-bottom glass vessel of 100-mL capacity, equipped with baffles and a turbine stirrer. The assembly was kept in an isothermal oil bath at a constant known temperature and mechanically agitated with an electric

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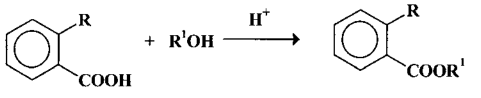
Scheme 2. **Esterification of aromatic carboxylic acids**



Where R = -COOR, -NH$_2$, -OH

motor. A typical reaction mixture consisted of 0.05 mol anisole and 0.15 mol acetic anhydride with a catalyst loading of 0.095 g/cm^3, based on the total volume of the reaction mixture. The total volume of the reaction mixture was 19.6 mL. The reaction was carried out at 50 °C at a speed of agitation of 1000 rpm. The conversions were based on the limiting reactant. The yields of the product were of the nonisolated product, defined as the amount of product formed with reference to the amount of limiting reactant reacted. The selectivity was based on the amount of desired product formed to the amount of all products formed. A material balance was done for a few experiments. In a typical experiment, after arriving at the best parameters, the catalyst was filtered off, and the reaction mixture was fractionated under vacuum. The isolated yield of the product was within 3−5% of the nonisolated yield.

A perfumery industry helped in determining the perfume value of the isolated product. *p*-Methoxyacetophenone was found to have a sweet, somewhat harsh, haylike floral, musky note.

2.2.2. Esterification of Aromatic Carboxylic Acids. The general reaction for esterification of aromatic carboxylic acid is as follows (Scheme 2).

The reaction was carried out in a Parr autoclave of 100-mL capacity. In a typical reaction for methyl anthranilate preparation, 0.05 mol of anthranilic acid, 1.7 mol of methanol, and 3.0% w/w catalyst were charged to the autoclave. The reaction mixture was allowed to reach the desired temperature, and the initial sample was collected. Agitation was then commenced at a known speed. Samples were withdrawn periodically for analysis. In most of the cases, methanol was taken in far molar excess over carboxylic acid to drive the equilibrium away towards the ester formation. It was interesting to note that the reaction mixture developed an intense odour of aromatic ester as the reaction proceeded as in the case of esterification of anthranilic acid and salicylic acid.

2.3. Analysis and Isolation of Product. *2.3.1. Acylation.* Analysis was performed by GC, (Chemito gas chromatograph, model 8510) by using a 2 m × 3.2 mm i.d., SS column packed with 10% OV-17 on Chromosorb WHP, coupled with a flame ionisation detector. Pure samples of the reactants and products and their synthetic mixtures were used to calibrate the chromatograms. For isolation of product, the catalyst was filtered off, and the excess unreacted acetic anhydride, anisole, and acetic acid (byproduct) were removed from the reaction mixture by using a rotovac. The products were isolated by standard procedures and characterised by IR and NMR spectroscopies. The product (*p*-methoxyacetophenone) was purified by vacuum distillation. It was confirmed by ^{1}H NMR (60 MHz Hitachi, Japan).

2.3.2. Esterification. After filtration of the catalyst the reaction mixture was analysed without any removal of alcohol. The analysis was carried out by high performance liquid chromatography (Tosoh, UV-8010) at ambient temperature. The Merck 50983 column with a stationary phase of Lichrospher 100 RP-18, particle size 5 μm, prepacked on a 250 mm × 4 mm i.d. with Tosoh UV-8010 detector set at 254 nm was used for methyl anthranilate, methyl salicylate, and methyl 4-hydroxybenzoate and 245 nm was used for phthalate esters. The eluent used for the analysis for phthalate esters was HPLC grade methanol with a flow rate of 1.0 mL/min, and for other esters it was an 80:20 methanol−water mixture with a flow rate of 0.8 mL/min. Pure samples of the reactants and products and their synthetic mixtures were used to calibrate the chromatograms.

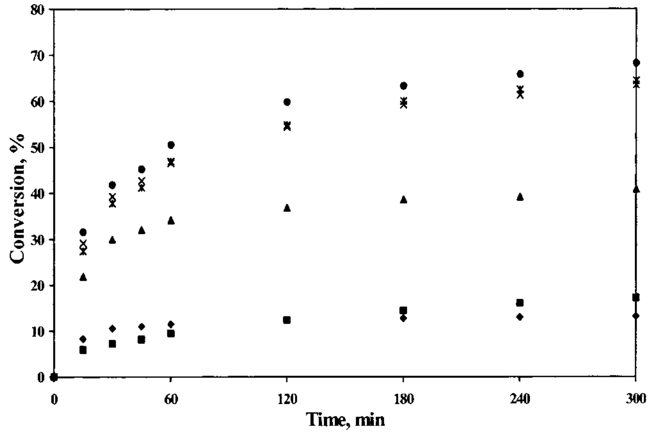


Figure 1. **Effect of different catalysts on conversion of anisole. Catalyst loading: 1.86 g, temperature: 50 °C, speed of agitation: 1000 rpm, particle size: 400−500 μm, Anisole: 5.4 g, Ac$_2$O: 15.3 g (mole ratio: 1:3), total volume: 19.6 cm^3. (◆) K-10. (■) F-24. (▲) S−ZrO$_2$ × Indion-130. (★) Amb-15. (●) Amb-36.**

For isolation of product, the catalyst was filtered off, and the excess unreacted methanol was removed from the reaction mixture by using a rotovac. The products were isolated by standard procedures and characterised by IR and NMR spectroscopies. In the case of methyl anthranilate, after removing the excess methanol, the remaining mass was treated with hexane in which only the ester was extracted, leaving behind unreacted anthranilic acid. The hexane phase was treated with charcoal and filtered. The product was purified by distillation. It was confirmed by ^{1}H NMR (60 MHz Hitachi, Japan) and FTIR (Bruker IFS-88 single channel Fourier transform spectrophotometer). Its odour was also evaluated vis-à-vis the pure commercial sample. The final product was a very pale, yellow liquid with a dry odour resembling that of concord grapes and had a boiling point of 255 °C matching the reported value.

3. Results and Discussion

3.1. Results and Discussion: Acylation. *3.1.1. Effect of Various Catalysts.* The efficacy of different catalysts under otherwise similar conditions was tested at 50 °C (Figure 1). Among the catalysts used cation-exchange resins showed very high activities followed by sulphated zirconia, Filtrol-24, and K-10. Catalysts based on zeolite Y did not show any activity at these reaction conditions. It appears that the pore sizes of these catalysts pose considerable intraparticle

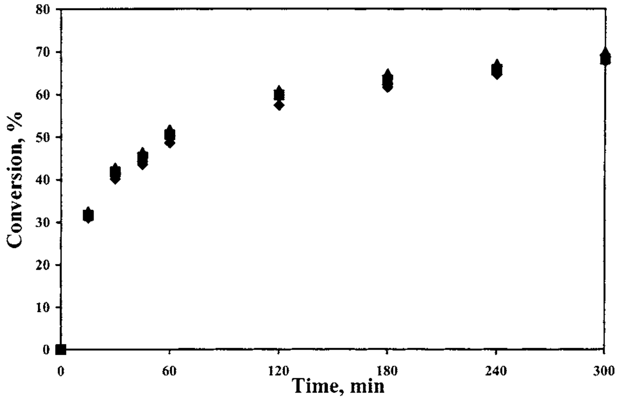


Figure 2. **Effect of speed of agitation on conversion of anisole. Catalyst: Amberlyst-36: 1.86 g, temperature: 50 °C, particle size: 400−500 μm, Anisole: 5.4 g, Ac_2O: 15.3 g (mole ratio: 1:3), total volume: 19.6 cm^3. (◆) 800 rpm. (■) 1000 rpm (▲) 1200 rpm.**

resistance for the reactant anisole to access the catalytic sites. Further experiments were conducted with cation-exchange resin Amberlyst-36, which was the most efficient heterogeneous catalyst. The meq/g exchange capacity on dry basis for Amberlyst-36, Indion-130, and Amberlyst-15 are >5.45, 4.8, and 4.9, respectively. The value of meq/g for Amberlyst-36 is maximum, and also the final conversion by using this catalyst was observed to be the maximum. It is obvious that the Brønsted acidity is mainly responsible for the activity with acetic anhydride as acylating agent, and therefore other catalysts were ineffective. Amberlyst-36 was used as the catalyst for all further experiments.

3.1.2. Effect of Speed of Agitation. The effect of the speed of agitation on the reaction rate and conversion was studied at 800, 1000, and 1200 rpm (Figure 2). There was no significant change in conversion patterns. This implies that there was no resistance to mass transfer of acetic anhydride to the external surface of the catalyst. All subsequent reactions were conducted at 1000 rpm.

3.1.3. Effect of Particle Size. The effect of intraparticle diffusion resistance was studied by varying the average catalyst particle size in the range of 250−650 μm at the same loading, and the results are shown in the Figure 3. It was observed that as the particle size was reduced from the range 550−650 μm to 450−500 μm there was an increase in conversion. However, further decrease in size to 250−350 μm did not increase the conversion appreciably. This suggests the internal diffusion resistance was absent. A theoretical analysis based on the Wiesz−Prater criterion was also performed to confirm the experimental observation.[15] Determining the activation energy as will be discussed later provided a further proof of the absence of intraparticle diffusion resistance.

3.1.4. Effect of Catalyst Loading. The reaction was conducted at four different loadings of Amberlyst-36 in the range of 0.0316−0.127 g/cm^3 of the total volume of the reaction mixture (Figure 4). The conversion had increased with an increase in catalyst loadings, which was due to the proportional increase in the number of acidic sites and surface area with catalyst loadings.

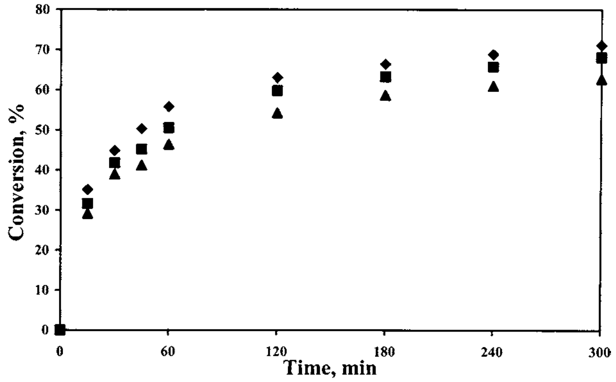


Figure 3. **Effect of particle size on conversion of anisole. Catalyst: Amberlyst-36: 1.86 g (0.095 g/cm^3), temperature: 50 °C, speed of agitation: 1000 rpm, Anisole: 5.4 g, Ac_2O: 15.3 g (mole ratio: 1:3), total volume: 19.6 cm^3. (◆) 250−350μm. (■) 400−500μm. (▲) 550−650μm.**

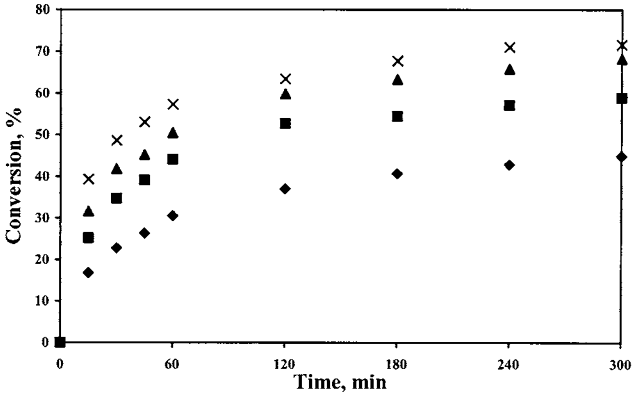


Figure 4. **Effect of catalyst loading on conversion of anisole. Catalyst: Amberlyst-36, temperature: 50 °C, speed of agitation: 1000 rpm, particle size: 400−500 μm, Anisole: 5.4 g, Ac_2O: 15.3 g (mole ratio: 1:3), total volume: 19.6 cm^3: (◆) 0.0317 g/cm^3. (■) 0.0633 g/cm^3. (▲) 0.095 g/cm^3 × 0.127 g/cm^3.**

3.1.5. Effect of Mole Ratio. The effect of mole ratio was studied at an anisole-to-acetic anhydride ratio of 1:1 to 1:5 without adding any solvent. The catalyst loading for all four reactions was maintained at 0.095 g/cm^3. The conversion was found to increase with the amount of acetic anhydride concentration (Figure 5). However, the selectivity towards the monoacylated product was found to decrease with an increase in acetic anhydride concentration. Between the mole ratio of 1:1 to 1:3 no significant change in the selectivity was observed. Therefore, all the reactions were conducted at a mole ratio of 1:3 without any solvent.

3.1.6. Effect of Temperature. The effect of temperature for the reaction of anisole with acetic anhydride was studied from 30 to 90 °C (Figure 6). The conversion was found to increase substantially with increasing temperatures. Although an increase in temperature gave a substantial increase in the conversion of anisole, the selectivity towards the monoacylated product PMAP was found to decrease. The selectivity of *p*-methoxy acetophenone was 98.3, 97.8, 94.2, and 84.4% at 30, 50, 70, and 90 °C respectively, after 5 h. There was a diacylated product formed with an increase in temperature. Therefore, a temperature 50 °C was selected as the most suitable condition for further experiments.

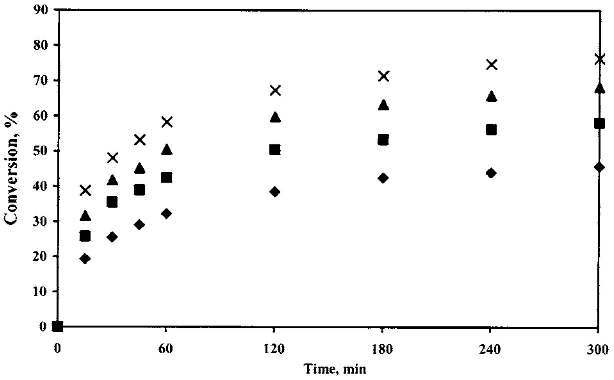


Figure 5. **Effect of mole ratio on conversion of anisole. Catalyst: Amberlyst-36 (0.095 g/cm^3), temperature: 50 °C, speed of agitation: 1000 rpm, particle size: 400−500 μm: (◆) 1:1. (■) 1:2. (▲) 1:3 × 1:5.**

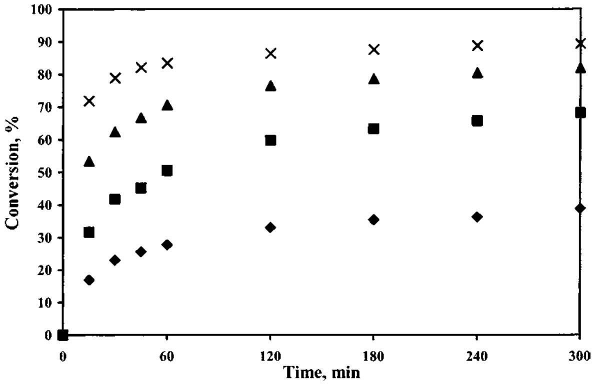
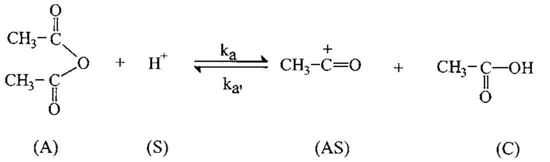


Figure 6. **Effect of temperature on conversion of anisole. Catalyst: Amberlyst-36: 1.86 g (0.095 g/cm^3), speed of agitation: 1000 rpm, particle size: 400−500 μm. Anisole: 5.4 g; Ac$_2$O: 15.3 g (mole ratio: 1:3), total volume: 19.6 cm^3; (◆) 30 °C. (■) 50 °C. (▲) 70 °C × 90 °C.**

3.1.7. Kinetics of Reaction. The kinetics of the acylation reaction has already been developed by Yadav and coworkers[17,20] for 2-methoxynaphthalene and acetic anhydride. According to this model, acetic anhydride is adsorbed on a site to generate carbocation (AS) and acetic acid (C). This model was found to hold for the current case. The final integrated form of the said equation is eq 2 given below:



$$CH_3C(=O){-}O{-}C(=O)CH_3 + H^+ \underset{k_{a'}}{\overset{k_a}{\rightleftharpoons}} CH_3{-}\overset{+}{C}{=}O + CH_3{-}C(=O){-}OH \quad (1)$$

$$\left(\frac{M}{M-1}\right)\ln\left(\frac{M-X_B}{M}\right) - \left(K_a + K_aM + \frac{1}{M-1}\right)\ln(1-X_B) + X_B = k_{sr}K_a wt \quad (2)$$

This is the complete solution for all ratios of M other than 1. Where M is the molar ratio of acetic anhydride to anisole, K_a is the adsorption equilibrium constant for chemisorption of acetic anhydride, k_{sr} is the surface reaction rate constant, w is the catalyst loading (mass per unit liquid volume), X_B is the fractional conversion of the limiting reactant (anisole in most cases), and t is the time. A plot of left-hand side terms (LHS) versus t for a known K_a will be a straight line passing through the origin. Otherwise, K_a can be assumed and the equation fitted to get results.

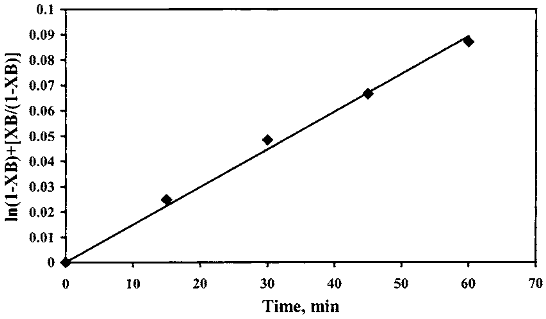


Figure 7. **Kinetic plot in integrated from of eq 3 for acylation of anisole. Catalyst: Amberlyst-36, temperature: 50 °C, speed of agitation: 1000 rpm, particle size: 400−500 μm. Anisole: 5.4 g; Ac$_2$O: 15.3 g (mole ratio: 1:3), total volume: 19.6 cm^3.**

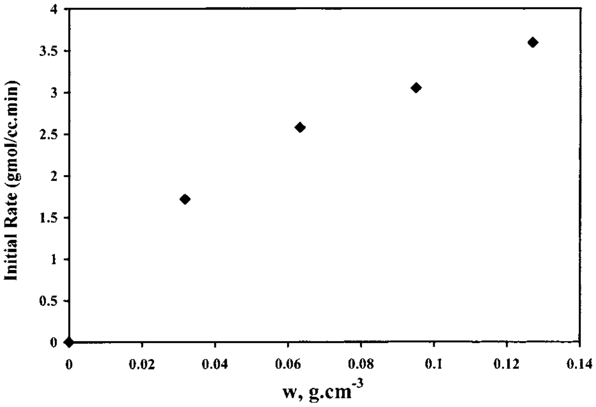


Figure 8. **Plot of initial rate vs catalyst loading (w) for acylation of anisole. Catalyst: Amberlyst-36, temperature: 50 °C, speed of agitation: 1000 rpm, particle size: 400−500 μm. Anisole: 5.4 g; Ac$_2$O: 15.3 g (mole ratio: 1:3), total volume: 19.6 cm^3.**

For $M = 1$, the final integrated form of the said equation is:

$$\ln(1-X_B) + K_aX_B + \left(\frac{X_B}{1-X_B}\right) = k_{sr}K_a wt \quad (3)$$

A plot of LHS versus time of eq 3 will be a straight line passing through the origin (Figure 7) with a slope of $k_{sr}K_aw$. The adsorption constant k_a was very small, and hence the term contribution k_aX_B was negligible.

The initial rate of the reaction is proportional to w. A plot was made of initial rate versus w as shown in the Figure 8 to confirm the same.

3.1.8. Reusability of the Catalyst. Ion-exchange resin catalysts are generally reusable, and therefore the catalyst was filtered and reused thrice. There was a drop of 5−8% in the final conversion from the previous run. This may be due to the loss of catalyst during filtration. Thus, it can be assumed to be reasonable because the quantity used is quite small in laboratory experiments.

3.2. Esterification. The esterification of phthalic anhydride with alcohols involves two steps. The first reaction giving the monoester is very fast and is completed in a short

Table 2. **Esterification of anthranilic acid and phthalic anhydride with methanol in the presence of solid acid catalysts**

entry	catalyst	H^+ Capacity (meq/g)	conversion (%)[b]	conversion (%)[c]
1.	Indion −130	4.8	57.0	73.1
2.	Dowex 50w x 8	*a*	57.1	73.3
3.	Amberlyst −36	5.45	68.7	80.4
4.	Amberlyst −15	4.9	61.0	75.1
5.	Deloxane ASP	0.7−1.1	37.0	51.0
6.	Bayer K2441	*a*	55.0	76.9
7.	Filtrol-24	0.3	5.2	30.7
8.	K-10 clay	0.35	<1.0	6.3

[a] Not available in catalogue (should be around 5). [b] Conversion of anthranilic acid. [c] Conversion of phthalic acid monoester.

time without any catalyst; thus, the kinetics of the overall reaction is normally studied by considering the diester formation in the second stage for the reaction between the monoester and alcohol, wherein the catalyst can have a real influence.

The results of the screening experiments carried out on anthranilic acid and methanol at a mole ratio of 1:34 at 120 °C and an agitation speed of 800 rpm with 3.0% w/w loading of different cation-exchange resins and clays are presented in Table 2.

The values of the exchange capacity, meq/g-dry resin, for Amberlyst-36, Indion-130, and Amberlyst-15 are >5.45, 4.8, and 4.9, respectively. The value of meq/g dry for Amberlyst-36 is maximum, and also the final conversion by using this catalyst was observed to be maximum.

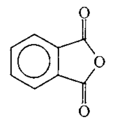
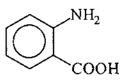
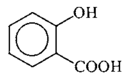
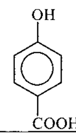
The conventional inorganic catalysts such as H-ZSM-5, acid-treated clays Filtrol-24 and K10, as well as heteropolyacid (dodecatungstophosphoric acid, as homogeneous catalyst) did not show much activity for this reaction. These catalysts are well-known for their sensitivity towards aqueous conditions, and that might have caused the deactivation of these catalysts. The reaction requires catalysts of a hydrophobic nature such as IERs because the catalysts with the hydrophilic surface deactivate rapidly in the presence of water formed during the reaction. It was found that Amberlyst-36 showed higher conversions vis-à-vis other catalysts. Hence, further experiments were conducted with Amberlyst-36 as the catalyst. The effect of different substrates by using Amberlyst-36 as the catalyst is presented in Table 3.

3.2.1. Reusability of Catalyst. The catalyst was employed as such without any posttreatment/washings for three runs. It was found that the activity had decreased with each use, but the subsequent reduction in activity was marginal. Thus, after the third use, the catalyst was washed with methanol to see that the same activity was maintained at the end of fourth use.

4. Economic Evaluation

The successful application of heterogeneous catalysts for the preparation of these products demonstrates that the product can be economically produced. Since ion-exchange resins are commercially available and reusable, the major problems of effluent treatment and the cost associated with it are overcome. There is no halide present in the products for their use in perfumery industry, and this fetches a higher price. The current bulk prices of these important esters are in the range of $1.70−8.20 (U.S.) per kg: *p*-methoxyacetophenone, $3.50; dimethyl phthalate, $1.72; diethyl phthalate, $2.20; methyl anthranilate, $8.14; methyl paraben, $7.7; and methyl salicylate, $5.53. The product separation using solid acids is very easy, and thereby the overall yields are also increased. The scale-up of these reactions for a mechanically agitated contactor is straightforward, wherein the same tip speed would be a criterion. In the case of *p*-methoxyacetophenone for the process based on $AlCl_3$ as a catalyst, the cost of catalyst is more than the raw materials on a kilogram basis since 2 mol are used per mole of anisole, apart from the effluent treatment cost. The catalyst cost on the basis of laboratory experiments with a minimum of 10 recycle times turns out to be less than 5% of the product cost in most of the cases, which is economical. In the case of esterifications, the homogeneous catalysts are cheaper. We can compare this with a typical sulphuric acid-based process for which the cost is 1% including the cost of neutralisation of the liquid acid. However, the corrosion and treatment of salt generated after neutralisation of the liquid acid would be much greater.

Table 3. **Esterification reactions of different subtracts using Amberlyst-36 as catalyst**

Entry	Carboxylic acid or Anhydride	Alcohol	Temp. (°C)	Conv. (%)
1.		CH_3OH	120	80.4
1a.	1	C_2H_5OH	140	77.3
2.		CH_3OH	120	68.7
3.		CH_3OH	120	79.3
4.		CH_3OH	120	96.4

Conditions: Entry 1-1a; 0.06 moles phthalic anhydride, 1.5 moles appropriate alcohol, 2.5% (w/w) of Amberlyst -36 for 5h. Entry 2; 0.05 moles anthranilic acid, 1.7 moles methanol, 3.0% (w/w) of Amberlyst -36 for 5h. Entry 3-4; 0.05 moles of appropriate carboxylic acid, 1.25 moles methanol, 3.0% (w/w) of Amberlyst -36 for 5h. Selectivity was 100 %.

5. Conclusions

This contribution has addressed an important problem related to green chemistry, wherein the polluting homogeneous acids can be replaced by cation-exchange resins in acylation and esterification reactions. Anisole was efficiently acylated in liquid phase with cation-exchange resins as the catalyst under mild conditions, without undergoing demethylation, giving rise only to the para isomer. The coproduct acidic acid can be easily recovered. Amberlyst-36 was found to be the best catalyst. Esterification reactions of phthalic anhydride with methanol and ethanol, and those of anthranilic acid, salicylic acid, and 4-hydroxybenzoic acid with methanol were studied by using a variety of catalysts: The order of catalytic activity was found to be as follows: Amberlyst-36 > Bayer K2441 > Amberlyst-15 > Dowex 50Wx8 > Indion-130 > Deloxane ASP > Filtrol-24 > K-10 Montmorrilonite.

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