Acylation of activated aromatics without added acid catalyst

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Phenol and resorcinol can be acetylated to the corresponding esters and ketones in aqueous and neat acetic acid at high temperature (250–300 °C) to substantial equilibrium conversion without any added acid catalyst.

Friedel–Crafts and other acylations generally require stoichiometric quantities of strong mineral acids, such as H_2SO_4, H_3PO_4, and HCl, or nonregenerable Lewis acids, such as $AlCl_3$.[1] These acids require neutralization and disposal, and disposal costs can be considerable. The conventional acylation of one mol of phenol with acetic acid consumes stoichiometric quantities of $AlCl_3$. Neutralizing this $AlCl_3$ requires land-filling several pounds of $Al(OH)_3$ salt for every pound of product produced.[2,3] In addition, many of these reactions require polar organic solvents, such as methylene chloride, that can simultaneously dissolve the reactants as well as the reactant–catalyst complex.[1,3]

Aromatic acylations have also been performed successfully without salt production over solid acids, such as zeolites,[4] as well as polymer supported alkyl sulfonic acid.[5] Heterogeneous catalysis of this type, however, generally requires the operating expense of vaporizing the reactant and the increased capital cost of the large vessels needed for solid–vapor contacting. In addition, the need for periodic regeneration or replacement of the rapidly deactivating zeolite catalysts may preclude their use in commercial applications where reactants readily form coke. Ghibaudi and Colassi attempted the Fries rearrangement of phenyl acetate at low pressure and very high temperatures ($T > 675$ °C) without catalyst, but only phenol and ketene were detected as products.[6] Photo-Fries rearrangements of phenyl acetate[7] and 2,5-dimethylphenyl acetate[8] have been run successfully to produce the corresponding ketones.

Another alternative to acid catalysts that require neutralization and disposal are polar-protic solvents at elevated temperature that can simultaneously act as the solvent, catalyst, and, in certain cases, the reactant. Liquid water ($T_c = 374$ °C) in the nearcritical region (250–300 °C) exhibits some beneficial properties that make it a good solvent and catalyst for acid-catalyzed organic reactions. As the temperature is increased from room temperature to 275 °C, the dieletric constant decreases from 80 to 20, and nearcritical water readily dissolves both organic and ionic compounds. Even non-polar organics, such as toluene, become miscible above 300 °C.[9–10] In addition, the dissociation constant of water increases by three orders of magnitude from room temperature to 275 °C, making it a source of hydronium and hydroxide ions that may catalyze reactions. Nearcritical water has been used as a solvent, catalyst, and reactant for a number of hydrolyses that require added mineral acid at ambient conditions.[9,12–15] It has also been successfully used for the Friedel–Crafts alkylation of phenol and *p*-cresol with *tert*-butyl alcohol.[16]

Nearcritical acetic acid ($T_c = 319$ °C) is another polar, protic solvent that may simulateneously act as the solvent, catalyst, and reactant in some reactions. Similar to nearcritical water, nearcritical acetic acid readily dissolves organics, and it has a higher acid strength and dissociation constant than water. Acetic acid can also be distilled from reaction products unlike other Lewis acid catalysts, such as $AlCl_3$, that require neutralization to salts and subsequent disposal.

We have successfully acetylated phenol and resorcinol in nearcritical water, as well as in neat acetic acid, in the temperature range 250–300 °C without any added acid catalyst or UV light. Performing Friedel–Crafts acylations and Fries-rearrangements in neat or aqueous acetic acid at elevated temperatures is also attractive as no additional organic solvent is required, and any unused acetic acid may be recycled for further reaction.

The reactions were performed in 3.2 ± 0.2 ml titanium batch vessels as described elsewhere.[16] Each vessel was loaded with phenol or resorcinol, an excess of acetic acid (Aldrich, HPLC grade), and, in certain experiments, deoxygenated water (Aldrich, HPLC grade). For reactions in neat acetic acid, the molar ratio of reactant to acetic acid was 1:50. For reactions in aqueous acetic acid, the molar ratio of reactant to acetic acid to water was 1:12:47, respectively. Products were identified by GC–MS (EI mode) and by comparison of the GC retention times and EI mass spectra to those of commercially available compounds. The composition of the each product mixture was quantified by GC-FID.

The Friedel–Crafts alkylations of phenol and *p*-cresol with *tert*-butyl alcohol in nearcritical water previously reported[16,17] were found to be reversible, with equilibrium yields of *ca.* 20 mol%. In this work, we report that the acetylations of phenol and resorcinol are also reversible at high temperature in the presence of water, but with less favorable equilibrium yields. These acylations are generally irreversible with traditional Friedel–Crafts catalysts due to the complexation of the acid catalyst with the carbonyl oxygen of the product. In this work, however, products were not stabilized by complexation with catalyst and were free to react back to starting material. In aqueous acetic acid at 290 °C, phenol was primarily converted to 2′-hydroxyacetophenone, 4′-hydroxyacetophenone, and phenyl acetate in roughly equal amounts, with a combined equilibrium yield of less than 1%. Under the same conditions, resorcinol was converted to primarily 2,4-dihydroxyacetophenone (Scheme 1) with a modest equilibrium yield of 4%.

To determine the effect of water on the equilibrium limitation of these reactions, the stability of the products was checked in water at nearcritical conditions. The product of the forward reaction of resorcinol and acetic acid, 2,4-dihydroxyacetophenone, was placed in liquid water at 250 °C. The concentration
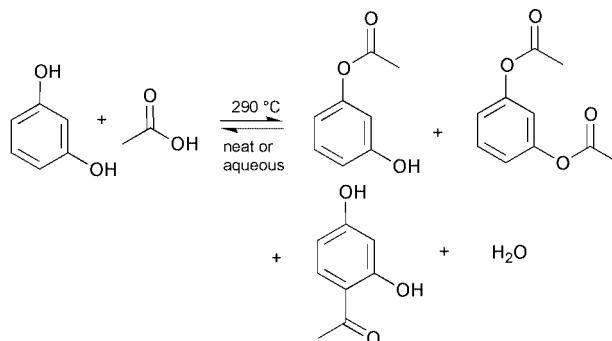
Scheme 1
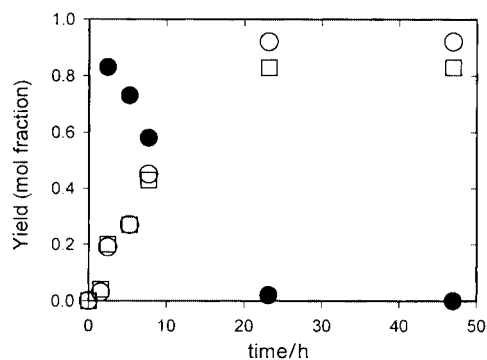
Fig. 1 Back reaction of 2,4-dihydroxyacetophenone (●) to resorcinol (□) and acetic acid (○) using water at 250 °C as solvent.
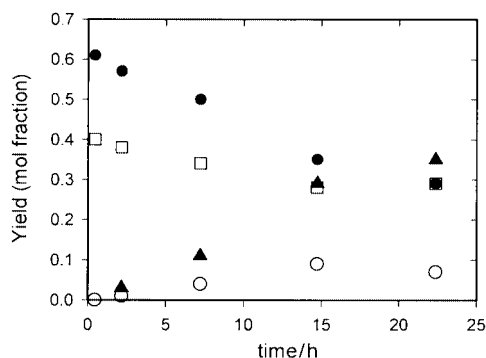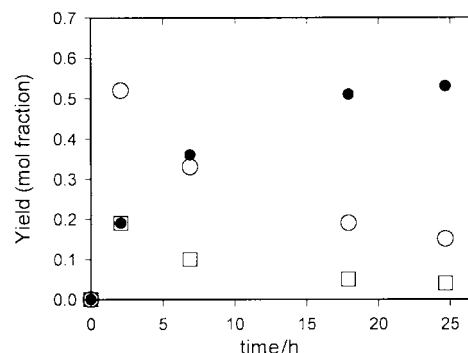

Fig. 2 Reaction of phenol (□) and acetic acid to phenyl acetate (●), 2′-hydroxyacetophenone + 4′-hydroxyacetophenone (○), and byproducts (▲) at 290 °C.

Fig. 3 Reaction of resorcinol and acetic acid to 2,4-dihydroxyacetophenone (●), resorcinol monoacetate (○), and resorcinol diacetate (□) at 290 °C.

vs. time data of the almost complete conversion of 2,4-dihydroxyacetophenone back to the corresponding amounts of resorcinol and acetic acid are shown in Fig. 1. The products of the phenol acetylation, 2′-hydroxyacetophenone, 4′-hydroxyacetophenone, were also converted to phenol and acetic acid when high-temperature water was used as a solvent.

The tunable solvent properties of nearcritical water allow for the facile separation of products upon cooling, but excess water imposes too severe an equilibrium limitation on this reaction. To overcome the equilibrium limitation in the presence of excess water, the acetylations of phenol and resorcinol were run in neat acetic acid. Unlike water, acetic acid does not require elevated temperature to solubilize organics, so phenol was first refluxed in neat acetic acid for 24 h (*ca.* 117 °C). This resulted in an equilibrium conversion of 16% entirely to phenyl acetate with no detectable quantities of 2′-hydroxyacetophenone or 4′-hydroxyacetophenone. In neat acetic acid at 290 °C, however, phenol was converted to 2′-hydroxyacetophenone, 4′-hydroxyacetophenone, and phenyl acetate, with a combined equilibrium yield of 8 mol% (Fig. 2). Byproducts included 2-methyl chromone and 4-methyl coumarine. These same byproducts have been found in the Fries rearrangement of phenyl acetate over zeolites and are a result of the intramolecular reaction of 2-acetoxyacetophenone.[18] Under the same conditions, resorcinol was successfully converted to primarily 2,4-dihydroxyacetophenone, with an equilibrium yield of more than 50%, in less than 12 h. The yield of 2,4-dihydroxyacetophenone *vs.* time is shown in Fig. 3.

Although no water was added initially, the reactions in neat acetic acid remain equilibrium limited. In contrast to the Fries rearrangement of phenyl acetate, however, water is produced from the reaction of acetic acid and phenol or resorcinol. This implies that the water produced by the forward reactions in neat acetic acid may also promote the reverse reaction to phenol or resorcinol and acetic acid. The production of water could be avoided by starting the reaction with the corresponding monoesters of phenol and resorcinol.

In summary, Friedel–Crafts acylations of activated aromatic compounds can be run homogeneously at high temperature in nearcritical water without added Lewis acid catalysts, which have an undesirable environmental impact. While nearcritical water allows for subsequent separation of products upon cooling, it limits the reaction equilibrium yield of desired products when present in excess. Running the same reaction in neat acetic acid allows for a ten-fold increase in yield, while still avoiding the unwanted salt byproducts associated with strong mineral and Lewis acid catalysts.

Notes and references

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