

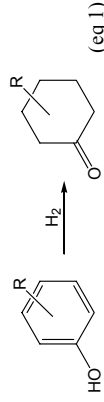
Substituted Phenol to Substituted Cyclohexanone: Influence of Gas / Liquid Mass Transfer Rates on Selectivity

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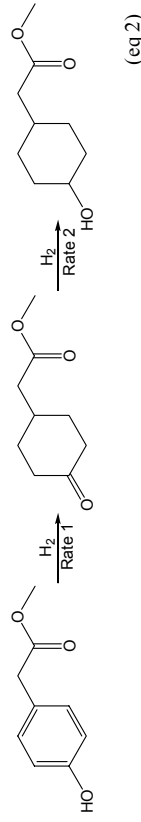
Introduction

The production of substituted cyclohexanone molecules is of great value to the pharmaceutical and specialty chemical industry. While the gas phase conversion of phenol to cyclohexanone has been optimized and practiced on commercial scale [1], substituted phenols offer new challenges, especially in small volume production facilities with liquid phase batch processing, equation 1. In these scenarios high conversion processes, which can be easily



transferred among generic manufacturing facilities are essential. Additionally, the products may not be amenable to distillative refining.

The hydrogenation of methyl-4-hydroxy-phenylacetate to the corresponding cyclohexanone is an important reaction in fine chemicals, equation 2. Over-hydrogenation of the ketone to the alcohol is an unwanted side reaction. Reaction



parameters influencing the selectivity of such reactions include the surface character of the catalyst and its affinity for binding phenol versus ketone, the intrinsic reaction rates for the two sequential reactions and dependence of the reaction rates on hydrogen concentration, which is influenced by hydrogen solubility in the medium, the pressure of hydrogen and the gas / liquid mass transfer rate.

Materials and Methods

Reactions were conducted in pressure reactors fabricated by Parr Instrument Co and with overhead stirring or in pressurized glass tube reactors with magnetic stir bar stirring. Reaction pressures were varied from atmospheric pressure to 90 psig (621 kPa). Reagents and solvents were purchased from Aldrich Chemical Co. or Fluka and utilized as received. The catalyst 10% Pd/C was used for all experiments. Gas chromatography was utilized for analysis of product mixtures (30m, 1 μ m, HP5 column; flame ionization or mass spec detector).

Results and Discussion

During assessment of the hydrogenation of methyl-4-hydroxyphenylacetate, we discovered that the reaction selectivity was significantly influenced by the rate of gas / liquid mass transfer in batch or semi-batch reactions. Notably, systems with slow hydrogen diffusion into the liquid phase provided higher selectivity to the ketone product than systems with more efficient gas / liquid mass transfer. In one case, head to head reactions were conducted in a glass tube reactor with magnetic stir bar stirring and in a steel Parr reactor with rapid overhead stirring using 10% Pd/C. The reactions were each conducted at 40 psig (276 kPa) with identical substrate, catalyst and solvent compositions. In these otherwise identical reactions, the faster gas / liquid mass transfer rate associated with the Parr reactor led to a decrease in selectivity compared to the reactor with stir bar stirring (Figure 1). In this presentation we will discuss a kinetic model describing the reaction series as well as reaction parameters influencing the selectivity.

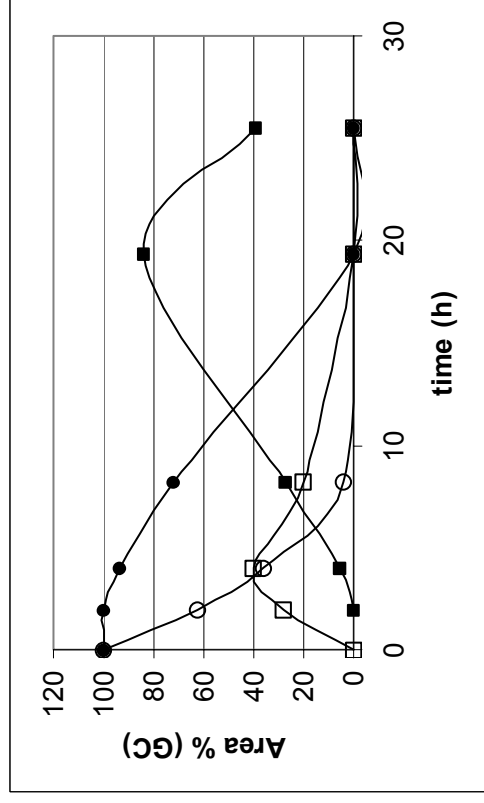


Figure 1. Comparison of reaction profiles for the hydrogenation of methyl-4-hydroxyphenylacetate (eq 2). For simplicity the cyclohexanol product(s) are not shown. ○) phenol – Parr Reactor, ●) phenol – glass tube reactor, □) ketone – Parr Reactor, ■) ketone – glass tube reactor

Significance

This paper describes challenges to the production of a pharmaceutically relevant class of molecules and provides mechanistic insight for overcoming these challenges.

References

1. Dodgson, I.; Griffin, K.; Barberis, G.; Pignataro, F.; Tauszik, G. *Chem. Ind.* Dec, 830 (1989).