Selective Hydrogenolysis of a Benzyl Group in the Presence of an Aromatic Chlorine over Supported Palladium Catalysts

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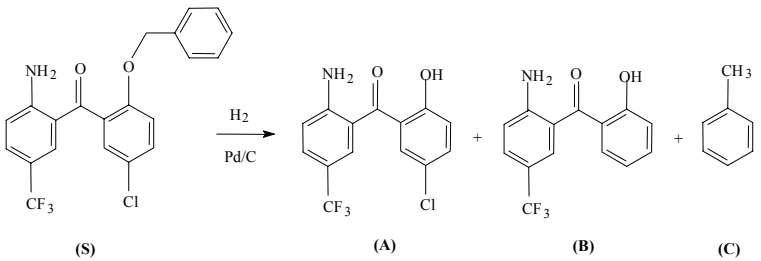
Introduction

An important goal in pharmaceutical process development is the design of highly selective chemical transformations leading to cost-effective processes in which separation or purification steps are minimized.

The hydrogenolysis of benzyl protecting groups using a supported palladium catalyst is well documented. However, in the presence of an aromatic halogen, selective debenzylation versus dehalogenation has received little attention (1).In our study, selective debenzylation versus dehalogenation was required for an intermediate (S) containing a benzyl ether protecting group and an aromatic chloride.



(S) (A) (B) (C)

The goal was to select a suitable catalyst and develop an optimized catalytic process in which the level of the dechlorinated impurity (B)was minimized. A variety of palladium catalysts with different metal content, metal dispersion, and oxidation states was prepared employing different techniques. Catalyst screening and kinetic studies were carried out in the Endeavor and Autoclave reactor/FTIR systems. The effect of catalyst variables on the activity and selectivity of the debenzylation was investigated. Our study indicated that with proper selection of the catalyst and control of the reaction conditions, selectivity for the desired product **(A)** can be as high as >99%. The undesired by-product, dechlorinated compound **(B)**, can be controlled to <1%. A sequential debenzylation/dehalogenation reaction is proposed to explain the observed catalytic behavior.

Results and Discussion

Figure 1 shows hydrogen uptake curves on three different types of 5%Pd/C catalyst. It is clear that ESCAT 147 (5% Pd/C edge coated, unreduced) gives the highest activity, followed by ESCAT 142 (5% Pd/C edge coated, reduced) and ESCAT 168 (5% Pd/C uniform, reduced) under the same reaction conditions.

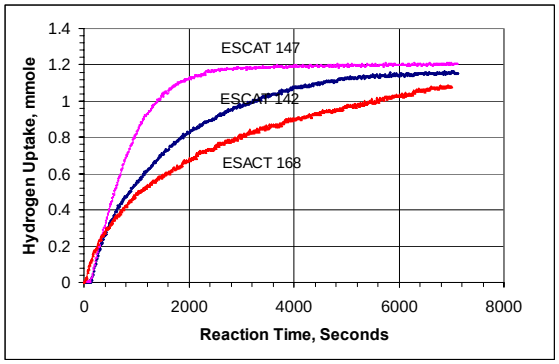


Figure 1. Hydrogen uptake curves for debenzylation of intermediate (S) on three different types of 5% Pd/C catalyst. Reaction conditions: 25°C, 45 psig, 0.5 g starting material in 5 mL ethyl acetate, 0.15 g catalyst.

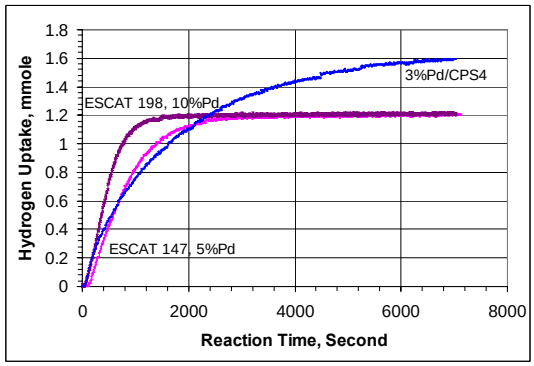


Figure 2. Hydrogen uptake curves for debenzylation of intermediate (S) on Pd/CP catalyst with three different metal loadings: 3%, 5% and 10% Pd/C. Reaction conditions are same as in Fig.1.

Based on these results, catalyst screening was continued on the edge coated, unreduced catalysts. Figure 2 shows the hydrogen uptake curves for three different Pd loading levels. When the same amount of palladium metal was used, ESCAT 198 (10%Pd, edge coated, unreduced) give the best activity and selectivity. 3% Pd/C (non-standard catalyst) has similar activity asESCAT 147, but has poor selectivity. With this catalyst, hydrogen uptake was 30% more than theoretical value of 1.2 mmole for debenzylation. Over reduction of the product (A) to generate the dechlorinated by-product (B) was confirmed by HPLC analysis.

Figure 3 shows the concentration profile of reactant and products during hydrogenation over ESCAT 198. Under the given conditions, the descholoro content was less than 0.8% even after 19 hr reaction, thus establishing that dehalogenation occurs primarily, if not exclusively from the desired product (A).

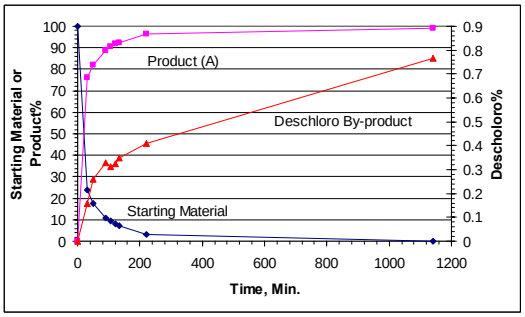


Figure 3. Product distribution as a function of time for debenzylation of intermediate (S) on ESCAT 198. Reaction conditions: Parr reactor, 25°C, 45 psig hydrogen, 6 g starting material in 60 mL ethyl acetate.

Under similar reaction conditions, the 3% Pd/C catalyst resulted in generating >8% descholoro undesired by-product

References

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2. J.P. Chen, et al.,Catalysis of Organic Reactions, Ed. By D. Morrell, Marcel Dekker, New York, pp. 313-328, (2002).