



UC BERKELEY COLLEGE OF CHEMISTRY

CHEMISTRY 112B

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Chemoselectivity in Transfer-Hydrogenation Reactions

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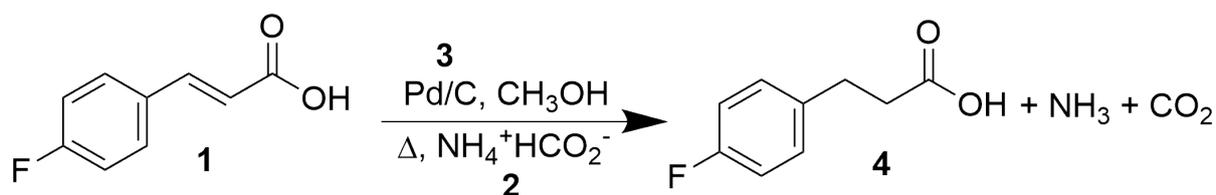
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1 Introduction

In this reaction, a variety of compounds were reacted using similar reagents and conditions chosen to selectively hydrogenate alkene double bonds (ammonium formate as a source for hydrogen and palladium on carbon as a catalyst), in order to inspect the varying products that would be created from a chemoselectivity standpoint. While many of the starting materials were chemoselectively converted into saturated compounds, several of the compounds reacted in more complex ways, including the hydrogenation of other double bonds, the cleaving of ester functional groups, and even ring formation. In the specific variation of the experiment run by our group, we synthesized 3-(4-fluorophenyl)propanoic acid from 4-fluorocinnamic acid, a simple hydrogenation that we correctly predicted would be entirely chemoselective to the alkene double bond.

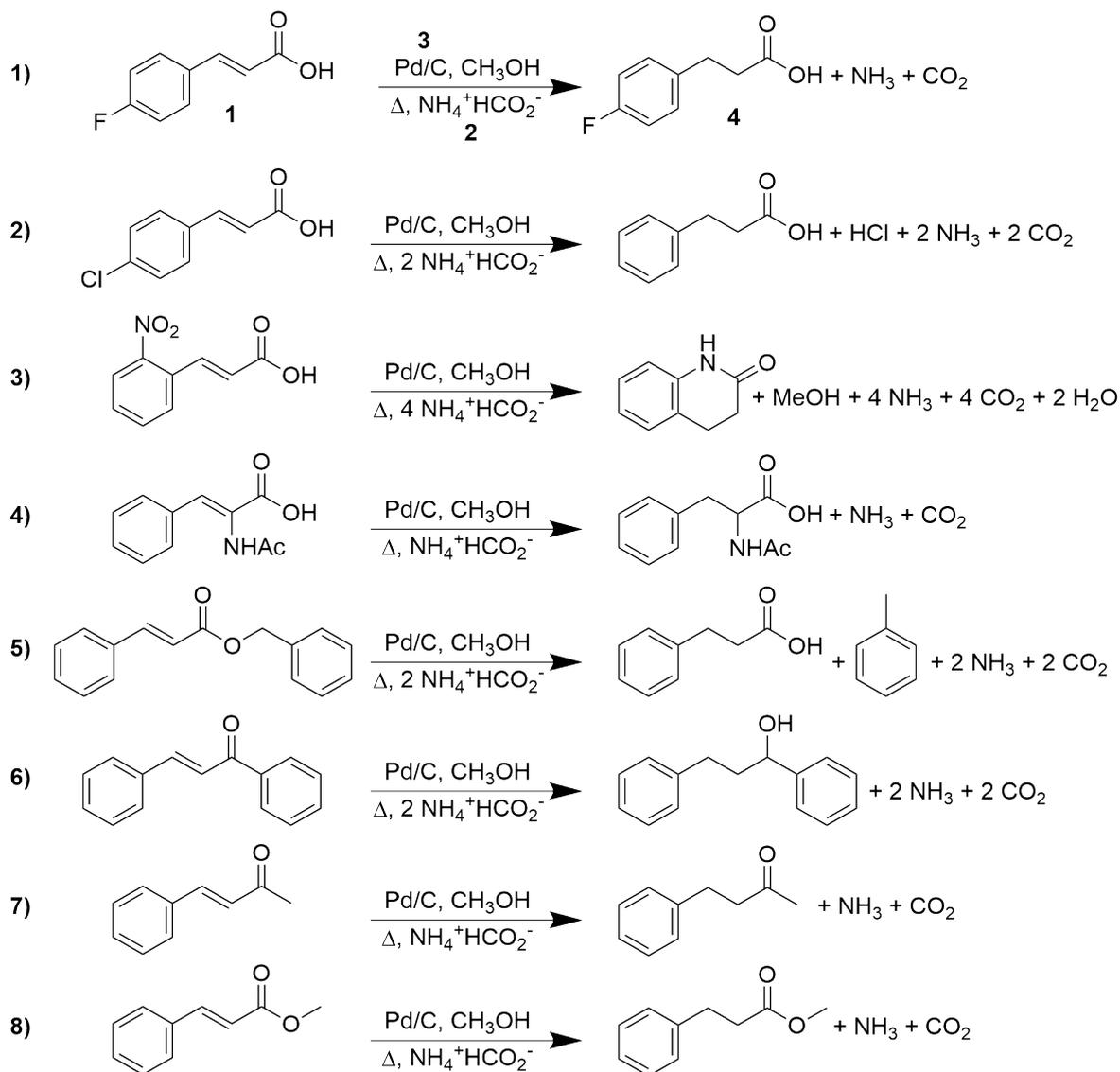
As Johnstone et. al.^[1] discusses in their review article, palladium on carbon is merely one of many reagents used to chemoselectively hydrogenate compounds. Transfer hydrogenation is an incredibly versatile and important tool, because it allows for easy conversion between various degrees of unsaturation during the synthesis of a compound. As such, chemoselectivity in this process is incredibly important, because it ensures that hydrogenation can be targeted at specific functional groups without drastically changing the entire structure of the compound. A variety of alternate catalysts, often organometallic, exist for chemoselective transfer hydrogenation, such as the fast and high-yielding Ir^{III} catalyst for selective aldehyde hydrogenation described in Wu et. al.^[2]. The wealth of transfer-hydrogenation catalysts that are tailor-made to work under specific conditions is a great asset to anyone working in synthetic organic chemistry.



Scheme 1: Chemoselective transfer-hydrogenation of 4-fluorocinnamic acid

The transfer-hydrogenation reaction our group performed (Scheme 1) began with a 4-

fluorocinnamic acid starting material (**1**), which we reacted with ammonium formate (**2**) and palladium on carbon (**3**) in the presence of methanol and heat to produce a 3-(4-fluorophenyl)-propanoic acid product (**4**), along with ammonia and carbon dioxide. In this reaction, the conversion of ammonium formate to ammonia and carbon dioxide produces two hydrogen atoms as a byproduct, which are then used by the palladium on carbon catalyst to saturate the alkene double bond of the the starting material.



Scheme 2: The eight transfer-hydrogenation reactions performed in class

However, this was not the only transfer-hydrogenation reaction run by the class. Eight different starting materials were all subjected to the same reagents (ammonium formate, palladium on carbon, methanol, and heat), as can be seen in Scheme 2. While all the

reactions produced some degree of saturation in the final product, they did not do so in any consistent manner. While reactions (1), (4), (7), and (8) all produced hydrogenated versions of the alkene starting material, reaction (2) additionally caused the loss of a chlorine substituent, while reaction (3) caused a ring to form due to hydrogenation of the nitro group. Over and above the hydrogenation of the alkene double bond, reaction (5) induced an ester cleavage, while reaction (6) caused the additional hydrogenation of a carbonyl substituent.

2 Results and Discussion

The final product was a white crystal obtained to the percent yield of 77.8%. This yield is not great, and this sentiment is exacerbated by the fact that our final product contains large quantities of diethyl ether, methanol, and acetone impurities, identifiable through their characteristic peaks in the ^1H NMR spectra. However, we managed to achieve the stated goal of our experiment, using TLC, NMR, and melting-point analysis to confirm that the product synthesized was indeed the chemoselective product. Our TLC analysis indicated that our product and starting material had very similar R_f values (0.701 for the starting material and 0.707 for the product), an observation that is in line with the near-identical polarities of our product and starting material. ^1H NMR analysis corroborates this sentiment, and we can see by careful observation of the spectrum that the alkene hydrogen doublet peaks at 7.0-7.5 ppm in the reactant spectra become triplet hydrogen peaks at 2.5-2.7 ppm in our product, corresponding with the hydrogenation from an alkene to an alkane. Our melting point range (60.8°C-61.7°C), while inconsistent with literature values (88°C-92°C^[3]) was consistent with values reported by the other 3 students performing the same reaction. A purer product could have been obtained simply by more precise extraction and drying of the final product, as NMR data indicated that our sample still contained significant amounts of methanol and diethyl ether impurities despite having been “dried” after the extractions with these solvents. More time spent drying would surely increase the purity of the final product, though whether this increase

would be worthwhile for the amount of time it would take is debatable.

Based on the collective results of this experiment, we can determine the functional groups that palladium on carbon was capable of chemoselectively reducing or otherwise altering: alkene double bonds, phenyl ketones and esters, aryl-chloride bonds, and nitro groups. However, Pd/C was ineffective at reducing carboxylic acids, aromatic ring systems, methyl esters and ketones, and aryl-fluoride bonds. The aryl-halogen bonds are not, strictly speaking, "reduced" in the same way that the other functional groups are reduced; rather, chlorine is a more capable leaving group than fluorine and is more capable of dissociating from the compound during the reaction. The rest of the functional groups, however, became saturated by the hydrogenation reaction, and several compounds cleaved or formed rings in response to the saturation process. We can hypothesize that this chemoselectivity is due to the precise mechanism of the palladium catalyst hydrogenation, which appears to selectively reduce functional groups with lower dipole moments over more polar functional groups. We can make this assessment based on the fact that the Pd/C process hydrogenates the neutral C=C bond and is more capable of hydrogenating phenyl ketones and esters over methyl ketones and esters, probably due to the activating quality of aromatic rings. To understand how and why this occurs, however, further information about the catalyst and the mechanism by which it operates is necessary.

2.1 Conclusion

In this experiment, we successfully performed the selective transfer-hydrogenation of 4-fluorocinnamic acid to 3-(4-fluorophenyl)-propanoic acid, with a reasonable percent yield. NMR analysis indicated that our reaction was successful, by making it possible to identify the transformation from the starting material's alkene hydrogen peaks to the product's alkane hydrogen peaks, while also indicating the presence of diethyl ether, methanol, and acetone impurities in our final sample. Though our yield was not phenomenal, and our product was not pure, we still managed to definitively create the saturated product from an unsaturated precursor, the precise experimental goal.

3 Experimental

3-(4-fluorophenyl)-propanoic acid (4):

4-fluorocinnamic acid (156 mg, 0.939 mmol) and 10% palladium on carbon (36 mg) were weighed into a reaction vessel along with 1 mL of methanol. Next, ammonium formate (449 mg, 7.13 mmol) was added into the reaction vessel along with a further 1 mL of methanol. The reaction mix was heated to reflux while stirring, with TLC spots taken occasionally, for a total of 50 minutes. The reaction mix was then filtered and cooled in an ice-water bath. The methanol was then evaporated off and an HCl extraction was performed using diethyl ether. The ether layer was dried, spotted by TLC one last time, and then evaporated to produce 130 mg (0.773 mmol, 77.8% yield) of 3-(4-fluorophenyl)-propanoic acid as a white, powdery crystal, mp 60.8°C-61.7°C (lit^[3] 88°C-92°C). TLC: R_f 0.707 (silica gel, 80:20 hexane:ethyl acetate, UV/I₂). ¹H NMR (400 MHz, DMSO): δ 12.3 (s, 1H), 7.2 (d, $J=6.7$ Hz, 2H), 7.1 (d, $J=8.5$ Hz, 2H), 2.7 (t, $J=7.3$ Hz, 3H), 2.5 (t, $J=7.5$ Hz, 3H). EIMS m/z : M+ 168 (0.40), 122 (0.25), 109 (1.00), 103 (0.05), 96 (0.07), 83 (0.06).

References

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