UC Berkeley College of Chemistry

Chemistry 112B

Organic Chemistry

The Friedel-Crafts Reaction

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1   Introduction

Friedel-Crafts alkylation is an important method for adding alkyl chains to aromatic rings through the use of a strong Lewis acid, generally $AlCl_3$ or $FeCl_3$, as a catalyst. Though the reaction has some limitations (namely the potential for carbocation rearrangement limiting the types of alkyl chains that can be substituted), its relative simplicity makes it an important tool when dealing with aromatic syntheses.

Though the Friedel-Crafts mechanism has been known for over a century[1], the sheer simplicity of the process means it is frequently the best alkylation reaction available. It is thus through sheer ubiquity that research on the parameters of the reaction is still ongoing (mostly revolving around the specific substituents and catalysts that can participate in the reaction, according to a 2011 review[1]). One such paper explores the mechanics of breakthrough catalytic approaches in enantioselective Friedel-Crafts alkylation[2]; through the use of specific catalysts, the Friedel-Crafts reaction can be "tuned" to specific enantiomers, a process known as asymmetric catalysis. Because of the differing properties of enantiomers, especially pharmaceutically, and the widespread use of Friedel-Crafts as an alkylation technique, enantioselective Friedel-Crafts reaction could allow for higher-efficiency production of many compounds. The Friedel-Crafts reactions are the focus of so much research because of their widespread utility in many spheres of organic chemistry, and it is likely that research on them will continue for many decades to come.
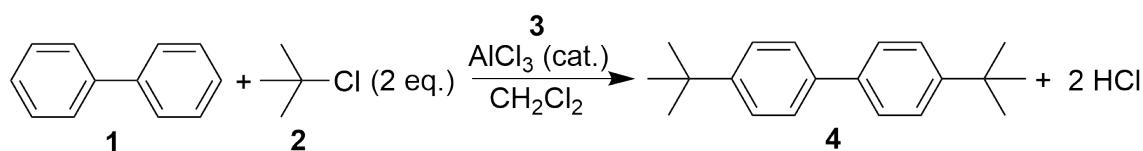
Scheme 1: Overall Reaction Scheme of Friedel-Crafts Alkylation

The Friedel-Crafts Alkylation that was performed in lab involved the reaction of biphenyl (**1**) with two equivalents of *tert*-butyl-chloride (**2**) to form 4,4'-di-*tert*-butylbiphenyl (**4**), in the presence of catalytic aluminum chloride (**3**) and in a dichloromethane solvent. Because of the activating effects of the phenyl substituent (and the steric bulk of *t*-butyl),

the substituents are added on both sides of the biphenyl reactant, while the aluminum and dichloromethane serve to facilitate the reaction.
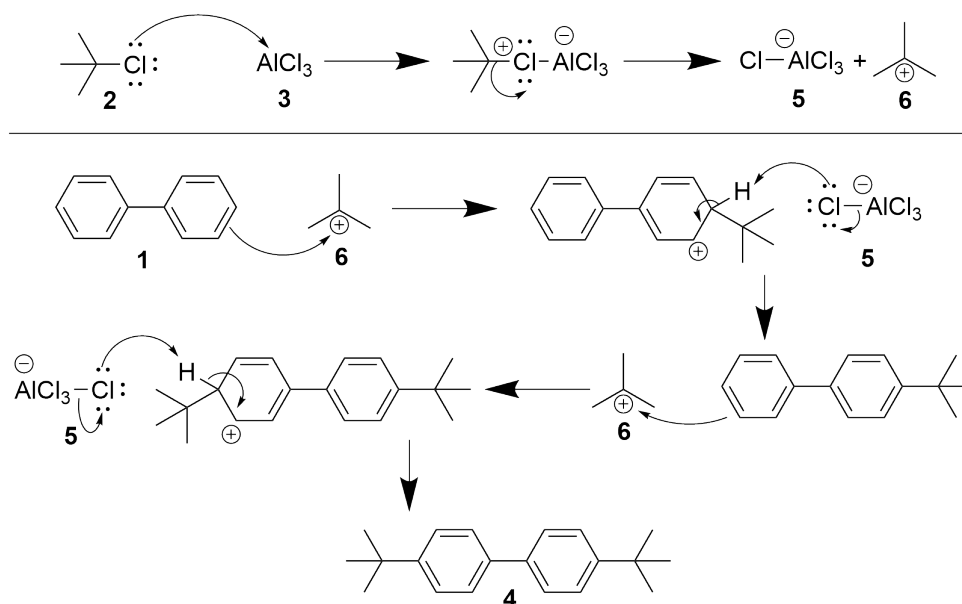
Scheme 2: Primary Reaction Mechanism of Friedel-Crafts Alkylation

The preparation of the activated electrophile begins with the attack of a unit of t-butyl-chloride on aluminum chloride (**3**) (formed by the interaction of aluminum metal and the dichloromethane solvent). Following this, the t-butyl dissociates from the chloride, leaving a negatively charged Cl-AlCl$_3^-$ complex (**5**) and an activated t-butyl-chloride electrophile (**6**). The electrophilic addition starts with an attack from the biphenyl (**1**) on this activated electrophile to form a σ-complex. Meanwhile, the aluminum chloride complex (**5**) returns and abstracts a hydrogen, creating an HCl molecule and reforming the aromatic ring. With one of the t-butyl substituents attached, the exact same process occurs on the opposite side of the phenyl, eventually coupling another t-butyl substituent onto the biphenyl on the opposing ring, producing our 4,4'-di-t-butylbiphenyl product (**4**).

2   Results and Discussion

The final product created via this reaction was a white, flaky crystal which appeared to consist almost entirely of the desired product (4, 4'-di-$tert$-butylbiphenyl), according

to melting-point, NMR, and TLC analysis. Impressively, this quite-pure product was isolated with a percent yield of 62%, significantly greater than the single-digit yields reported by some other students. While this loss of product was significant, it can largely be attributed to physical losses in mass transfer during the extraction, rather than missteps in the procedure. It is worth pointing out that an excess amount of *t*-butyl-chloride was erroneously added to the reaction mixture (0.50 mL instead of 0.35 mL), but NMR analysis suggests that the quantity of this excess reagent in the final product is negligible (and, in fact, it may have increased the yield of our final product by providing more reagent to react).

Meanwhile, melting-point, ^{1}H NMR, and TLC analyses all attest to the purity of our product, a feat which was likely attributable to the extensive separation procedures used to remove excess starting products and solvents from the final product. Excess *t*-butyl-chloride (as well as spare aluminum) was removed by the ethanol extractions, whereas the dichloromethane was separated out during the ethanol boiling stage due to its low boiling point (40℃[3]). The presence of [significant] unreacted biphenyl in our final product can be ruled out by our melting-point and NMR analysis, indicating that it mostly reacted to completion and any remainder was removed in the water extraction. While minute contaminant peaks are visible in the NMR spectrum, their size shows that the quantity of any adulterants is incredibly small. In sum, though minute discrepancies exist in the data that could be explained by trace amounts of impurities, the product appears to be mostly pure.

We performed both pure- and mixed-melting-point analysis on our sample. Our pure product melted at 122.6-125.6℃, compared to a literature value of 126-130℃[4]. While this slight downward offset from our expected melting point *could* be due to the presence of unreacted biphenyl (which has a melting point of 69-72℃[5]), the difference from the literature value is small enough that it could merely be due to the instrument or the qualitative nature of melting-point analysis. Our mixed-melting-point analysis, however, is far more telling. A mixture of our product and biphenyl produced a sample with the very broad melting-point 55.5-107.6℃, an incredibly wide range that indicates both that

the two components of the mixture have largely differing melting points and that they were present in roughly equal quantities – something that requires that our final product be pure and contain little biphenyl. Both forms of melting-point analysis point toward relatively high purity of the the 4,4'-di-t-butylbiphenyl product.

Our NMR data is incredibly clean, with the three largest peaks corresponding to our product's spectra and none of the other peaks having significant areas. Our splittings are exactly as predicted (singlets for the t-butyl hydrogens, doublets for the hydrogens on the phenyls), and all other readings are nominal. Our NMR data is by far the best case for the purity of our final product.

Four distinct TLC lanes were spotted at various points in the lab: a dichloromethane solution of biphenyl starting material, a spot of pre-extraction product, a spot of pure product, and a mixture of pure product and the biphenyl starting material. While there is little quantitative data that can be received from the TLC due to the broad spots and middling separation, noticeable differences in the retention factors of our final product and our starting material can be observed. While this isn't enough to guarantee the purity of our product, it at least shows that significant changes occured between our starting compounds and our final product.

2.1   Conclusion

In this lab, we successfully completed a Friedel-Crafts alkylation reaction with acceptable purity (as measured by TLC, melting-point, and NMR analysis) and comparatively excellent yield. Though minor errors were made (most notably the addition of an excess of t-butyl-chloride), our TLC and melting-point data showed significant differences of our final product from the initial reactant, and our NMR analysis showcased the excellent purity of our final product.

3 Experimental

4,4'-Di-*tert*-butylbiphenyl (4):

A flame-dried reaction tube connected to an HCl gas trap was charged with biphenyl (0.166 g, 1.08 mmol), *t*-butyl chloride (0.50 mL, 4.5 mmol), dichloromethane (0.50 mL), and a 4 mm^2 square of aluminum foil with the aluminum oxide coating scratched. Once bubbling subsided, the reaction mixture was extracted with water (3×1.0 mL). 95% ethanol (1.0 mL) was then added to the organic layer and the mixture was heated to 80℃ for 5 minutes, at which point the solids in the mixture dissolved. The reaction tube was then cooled to 0℃ to crystallize out the 4,4'-di-*t*-butylbiphenyl (a white crystalline solid), and the product was vacuum filtered to a final yield of 0.172 g (62%).

Melting Point:

mp (pure)	125.6-127.6℃ (lit[4] 126-129℃)
mp (mixed)	55.5-107.6℃ (lit[4][5] 69-72℃, 126-129℃)

¹H NMR: (400 MHz, CDCl$_3$): δ 7.58 (d, *J*=8.0 Hz, 4H), 7.50 (d, *J*=8.4 Hz, 4H), 1.42 (s, 18H).

TLC: R$_f$ 0.37 (silica gel, hexane, UV/I$_2$).

References

[1] Price, C. C. The Alkylation of Aromatic Compounds by the Friedel-Crafts Method. *Org. React.* [Online] **2011**, 1-82.

[2] Bandini, M.; Melloni, A.; Umani-Ronchi, A. New Catalytic Approaches in the Stereoselective FriedelCrafts Alkylation Reaction. *Angew. Chem. Int. Ed.* [Online] **2004**, *43*, 550-556.

[3] *dichloromethane*; Chemspider ID 6104 [Online]; Royal Society of Chemistry. http://www.chemspider.com/Chemical-Structure.6104.html (accessed Feb 22, 2014).

[4] *4,4'-di-t-butylbiphenyl*; Chemspider ID 66804 [Online]; Royal Society of Chemistry. http://www.chemspider.com/Chemical-Structure.66804.html (accessed Feb 22, 2014).

[5] *biphenyl*; Chemspider ID 6828 [Online]; Royal Society of Chemistry. http://www.chemspider.com/Chemical-Structure.6828.html (accessed Feb 22, 2014).

TMS

3.94
4.00

18.04

f1 (ppm)