Spring 2016

The synthesis of 1,3-Difluoro-2-methyl-4-phenylbenzene from a one-pot reaction of Difluorocarbene and 1-Phenyl-2-methylcyclobutene

Ruth Felicitas Menger
James Madison University

Follow this and additional works at: https://commons.lib.jmu.edu/honors201019

Part of the Medicinal-Pharmaceutical Chemistry Commons, Organic Chemicals Commons, and the Organic Chemistry Commons

Recommended Citation
https://commons.lib.jmu.edu/honors201019/232

This Thesis is brought to you for free and open access by the Honors College at JMU Scholarly Commons. It has been accepted for inclusion in Senior Honors Projects, 2010-current by an authorized administrator of JMU Scholarly Commons. For more information, please contact dc_admin@jmu.edu.
The Synthesis of 1,3-Difluoro-2-methyl-4-phenylbenzene from a one-pot Reaction of Difluorocarbene and 1-Phenyl-2-methylcyclobutene

An Honors Program Project Presented to the Faculty of the Undergraduate College of Science and Mathematics James Madison University

by Ruth Felicitas Menger

May 2016

Accepted by the faculty of the Department of Chemistry and Biochemistry, James Madison University, in partial fulfillment of the requirements for the Honors Program.

FACULTY COMMITTEE:

Project Advisor: Scott Lewis, Ph.D.
Associate Professor, Chemistry

Reader: Kevin Caran, Ph.D.
Associate Professor, Chemistry

Reader: Donna Amenta, Ph.D.
Professor, Chemistry

HONORS PROGRAM APPROVAL:

Bradley R. Newcomer, Ph.D.,
Director, Honors Program

PUBLIC PRESENTATION

This work is accepted for presentation, in part or in full, at Spring Symposium on April 14, 2015.
Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>List of Figures</td>
<td>3</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>4</td>
</tr>
<tr>
<td>Abstract</td>
<td>5</td>
</tr>
<tr>
<td>Chapter 1: Introduction</td>
<td>6</td>
</tr>
<tr>
<td>Chapter 2: Mechanistic and Synthetic Explanation</td>
<td>14</td>
</tr>
<tr>
<td>Chapter 3: Results and Discussion</td>
<td>18</td>
</tr>
<tr>
<td>Chapter 4: Experimental</td>
<td>22</td>
</tr>
<tr>
<td>References</td>
<td>24</td>
</tr>
<tr>
<td>Appendix</td>
<td>26</td>
</tr>
</tbody>
</table>
List of Figures

1. Examples of fluoroaromatic compounds with pharmaceutical applications 7
2. Blocking of unproductive metabolic pathways by fluorination of an inhibitor of cholesterol absorption 8
3. Structure of mefloquine, used to treat malaria 9
4. Examples of fluorinated fungicides 10
5. Examples of fluorinated insecticides 10
6. Balz-Schiemann fluorination of aryl diazonium tetrafluoroborates 11
7. Electrophilic aromatic substitution 12
8. Fluorine direct electrophilic aromatic substitution 12
9. Examples of industrially useful compounds with 1,3-difluorobenzene moieties 12
10. Reaction of Seyferth’s reagent and 1,2-diphenylcyclobutene to make 1,3-difluoro-2,4-diphenylbenzene 14
11. Formation of difluorocarbene from Seyferth’s reagent 14
12. Proposed cationic mechanism of the addition of 1 mol difluorocarbene to disubstituted cyclobutene 15
13. Addition of the second mole of difluorocarbene 15
14. Possible isomers formed from the reaction of difluorocarbene with 1-phenyl-2-methylcyclobutene 16
15. Resonance structure differences between fully and cross conjugated systems 17
16. Overall reaction scheme 18
17. Magnified view of aromatic region of 1H NMR of 1,3-difluoro-2-methyl-4-phenylbenzene 19
Acknowledgements

Without the help of many people, this project would never have been a success. I would first like to thank the collective faculty of the Department of Chemistry and Biochemistry at James Madison University for the preparation they have provided in all aspects of chemistry. Without their teaching, I never would have become interested in research and delving further into solving the mysteries of organic chemistry. To my readers, Drs. Donna Amenta and Kevin Caran, thank you for providing the expertise in organic chemistry to fill in the blanks and make my writing comprehensive. Drs. Jun Yin and Daniel Ralston, you were invaluable in assisting with the use and interpretation of the NMR and GC-MS, respectively. My biggest thanks goes to my advisor, Dr. Scott Lewis. Your organic chemistry class is the one class that inspired me to pursue a career in chemistry. I am incredibly thankful for your continued support and guidance over the past three years. I can only dream of being a professor and advisor as inspirational as you have been. And finally, I cannot thank my parents enough for instilling in me a curiosity and drive that ultimately led to the desire to take on this project. Your support and encouragement kept me motivated throughout the entire process.
Abstract

Previous studies show that 1,2-disubstituted cyclobutenes can be used in reaction with difluorocarbene to produce 1,3-difluorobenzenes. A pathway to the synthesis of these types of compounds is of interest due to their presence in fluoroquinolone antibacterials, resins, and insecticides. The synthesis is unique because the fluorine atoms from the difluorocarbene are not adjacent to each other when the ring expands to a benzene ring. This study focuses on the reaction of difluorocarbene with 1-phenyl-2-methylcyclobutene, which was synthesized in one-pot in 4 steps starting from 1-phenyl-1-propyne and zirconocene dichloride.
Chapter 1

Introduction

One of the most unique elements that has yet to be fully explored is fluorine. Since first being successfully isolated by Ferdinand Frederic Henri Moissan in 1886, it has been used in a variety of industries, from medicine and health, to agriculture and synthetic polymers.\(^1\) With an electronegativity value of 4.0, the highest of all the elements, fluorine has the capability of reacting with almost any element. Despite its high reactivity, it can still form some of the most stable and inert substances, such as Teflon. Some common applications include fluoride in toothpaste and drinking water, synthetic blood substitutes, and the production of insulators, flame-retardants, and batteries.\(^2\)

Elemental fluorine is extremely toxic and corrosive. When in contact with organic compounds, it will spontaneously combust or explode. Its unique smell, similar to a mixture of chlorine and ozone, is detectable by smell even at 10 ppm. Elemental fluorine is so unusual, it can even react with noble gases like krypton and xenon. Its homolytic dissolution into radicals makes it dangerous for living organisms but also contributes to its reactivity, causing high redox potentials. Due to its high electronegativity, smallest ion size (ion radius 133 pm) and being the least polarizable monatomic anion, it can stabilize other elements in their highest and otherwise inaccessible oxidation states. The compatible size also make it an excellent match for the corresponding 2s or 2p orbitals of carbon, producing a highly polar bond with a dipole moment of around 1.4 D. The strength of this bond (think Teflon) and the electrostatic interactions that result from the polarity lend themselves to be very useful in a variety of industries.\(^3\)

Interestingly, fluorine has been found to have an increasingly larger effect on the pharmaceutical industry over the past few decades. Despite its reactivity, the chemical and
physical properties of fluorine have been utilized to increase the efficacy of a number of drugs to treat all kinds of diseases (Figure 1). In general, pharmaceuticals depend on a specific interaction with a target structure in an organism. The strength of this interaction can be determined by the structure of the drug which then affects its function. Fluorine has become an obvious choice to replace a hydrogen atom. Both atoms are similar in size so the replacement will not significantly change the size or geometry of the molecule due to steric hinderance.

![Figure 1. Examples of fluorine-containing pharmaceuticals: non-steroidal anti-inflammatory drugs (Roflumilast, Celebrex), modulators of cholesterol metabolism (Cerivastatin, Ezetimibe), anti-depressants (Fluoxetine), antibiotic (Ciprofloxacin), and anti-virals (Efavirenz, Gemcitabine).]

However, because fluorine is so electronegative, it can greatly affect the functionality of a part of the molecule and change its interactions with other molecules. It changes the electron distribution of the overall molecule while also affecting the acidity or basicity of the neighboring groups.

The replacement of hydrogen with fluorine also increases the lipophilicity of the molecule, which affects resorption. This helps the drugs get to their target organ more quickly.
Additionally, drugs that target the central nervous system need a specific lipophilicity to cross the blood-brain barrier so the degree of fluorination can be used to manipulate this property. The electronegativity of fluorine substituents on aromatic rings renders the other aromatic hydrogen atoms more acidic, contributing to their potential as hydrogen bond donors.³

The replacement of hydrogen with fluorine can also prevent excessively rapid degradation of the drug. Metabolic pathways that usually depend on the functionality of hydrogen will be rendered useless with a fluorine in that position instead. The select placement of a fluorine atom can prevent the premature degradation of the drug, leaving the intended reaction sites open for the biological activation of the prodrug.³ For example, Figure 2 shows the

![Chemical Structure](attachment:image.png)

**Figure 2.** Blocking of unproductive metabolic pathways by fluorination as a design tool for an orally active inhibitor of cholesterol absorption. The result of this rational approach (SCH 58235) is 50 times more active than the conceptual starting compound SCH 48461. (ED₅₀ refers to reduction of liver cholesterol esters in hamsters).⁶
changes made in an orally active inhibitor of cholesterol absorption to prevent oxidation and increase efficacy. Without fluorine atoms on the left and right phenyl groups, one phenyl group is oxidated while the methoxy substituent becomes demethylated under normal biological conditions. The addition of fluorine atoms prevents this “non-productive” metabolism and helps activate the metabolism that is needed for the activation of the drug. It was found that this change increased activity by 50 times compared to the starting compound.  

The presence of fluorine on aromatic rings (and thus the synthesis of aryl fluorides) is of particular interest. In fact, more than 20% of pharmaceuticals currently contain fluorinated aromatic substructures. These are mostly fluoroquinolones, which are a group of antibacterial drugs that are necessary to combat infections that have arisen due to the growing resistance to the traditional antibacterials like penicillins, cephalosporins, and tetracyclines. Norfloxacin was one of the first to be introduced in 1980. Since then, many more fluorine-containing antibacterials have been designed and produced. They have been found to treat a multitude of diseases, including lower respiratory, urinary tract, and prostate infections. The only current treatment for malaria, mefloquine has two trifluoromethyl groups attached to aromatic rings (Figure 3).

![Figure 3. Structure of mefloquine, used to treat malaria.](https://via.placeholder.com/150)

The agricultural industry has even more applications of fluorinated aromatic substances, making up more than 50% of newly introduced compounds. Although it can be more expensive
to make these compounds, the increased effectiveness greatly outweighs the cost. This reduces the amount of chemicals that need to be put into the environment, making it safer overall.

Fluorine is found in herbicides, insecticides, and pesticides. Fungicides in particular have been synthesized with fluorine attached to a benzene moiety integrated into the molecule (Figure 4). They act as sterol biosynthesis inhibitors by blocking a crucial demethylation step in ergosterol biosynthesis. Insecticides like benzoylureas function by inhibiting chitin biosynthesis (Figure 5).

![Figure 4](image1.png)

**Figure 4.** Examples of fluorinated fungicides that function as sterol biosynthesis inhibitors.\(^5\)

![Figure 5](image2.png)

**Figure 5.** Examples of the different types of fluorinated insecticides. From top to bottom: benzoylureas and pyrethroids.\(^5\)
The use of fluoroaromatics in these various industries presents the need for an effective and selective synthetic method. Fluorobenzenes have proven to be especially difficult to synthesize. Previous pathways of achieving this aromatic C-F bond resulted from the reaction of aromatic C-H bonds with F₂; however, this reaction often produces large amounts of explosive waste.³ Another synthetic route is the Balz-Schiemann reaction, which is still the primary method of fluorinating benzene rings. This multi-step process involves the diazotization of an aromatic amine in the presence of tetrafluoroboric acid (Figure 6). However, this reaction also produces a large amount of waste, which is something to avoid, especially in a large-scale manufacturing industry. It has been a long-standing goal to make the production of fluoroaromatics more efficient in order to more easily capitalize on fluorobenzene as a reagent in further reactions.⁷

![Figure 6. Balz-Schiemann fluorination of aryl diazonium tetrafluoroborates.](image)

The synthesis of fluorobenzene leads one to attempt to synthesize difluorobenzenes. This problem proves to be even more difficult due to the extreme electronegativity of the fluorine atoms and its directing influence during a typical electrophilic aromatic substitution reactions. During an EAS reaction, an electrophile interacts with the π system of the electron-rich benzene. A carbocation intermediate is created but is stabilized by resonance and then an aromatic proton is lost to restore the aromatic six-membered ring (Figure 7). Fluorine has the ability to donate electrons to participate in resonance, stabilizing the ring, but also directing the next atom to attach to the ortho or para position, to yield 1,2- or 1,4-difluorobenzene (Figure 8). In addition,
once on the ring, fluorine deactivates the ring by inductively withdrawing electron density away from the ring, making it difficult to add any additional substituents. For fluorine (and the other halogens) the inductive withdrawal is great than the resonance donation, leading to a net deactivation towards electrophilic aromatic substitution.

This leaves a large gap in the literature for methods to achieve a 1,3 orientation on a benzene ring. This moiety is present in compounds like Hexaflumuron, Ci-934, and Diflunisal. Hexaflumuron is sold as a commercially useful termite poison while compound CI-934 is a potent antibacterial agent against Gram-positive isolates and Diflunisal is a steroidal anti-inflammatory drug. Used to treat arthritis pain, its mechanism of action involves preventing protein mis-folding that occurs due to minor mutations.

![Figure 7. Electrophilic aromatic substitution.](image)

![Figure 8. Fluorine directed electrophilic aromatic substitution of a second substituent to the ortho position.](image)

![Figure 9. Examples of industrially useful compounds with 1,3-difluorobenzene moieties.](image)
This leads to the purpose of this project – to improve the methodology of synthesizing 1,3-difluorobenzenes but not by the reaction of elemental fluorine to an already intact benzene ring. We propose the reaction of substituted cyclobutenes with difluorocarbene to achieve a difluorobenzene with the fluorine atoms *meta* to each other. In addition to adding to the literature by discovering more about the mechanism of this reaction, the resulting compounds have the potential to be used in a variety of industries.
Chapter 2

Mechanistic and Synthetic Explanation

In 1994, Lewis and Borden presented the use of difluorocarbene to synthesize a difluorobenzene via a cyclobutene intermediate. This ring expansion was achieved by the addition of Seyferth’s reagent (phenyl(trifluoromethyl)mercury(II)) to 1,2-diphenylcyclobutene (Figure 10). Later it was shown the synthesis could be successful using various substituted cyclobutenes. The use of a non-benzene precursor for the synthesis of fluorobenzenes eliminates the production of large amounts of explosive waste that comes from the Balz-Schiemann reaction. Hopefully the ability to produce compounds with a larger variety of substituents can be realized using this approach.

![Figure 10. Reaction of Seyferth’s reagent and 1,2-diphenylcyclobutene to make 1,3-difluoro-2,4-diphenylbenzene.](image)

Difluorocarbene is very reactive and has a short half-life on its own, justifying the use of Seyferth’s reagent, Ph-Hg-CF$_3$. The precursor undergoes an $S_N2$ style reaction in the presence of NaI, replacing the trifluoromethyl group with iodine. The leaving group, CF$_3$, is unstable and spontaneously separates into a fluoride ion and difluorocarbene (Figure 11). The difluorocarbene is now free to attack the cyclobutene.

![Figure 11. Formation of difluorocarbene from Seyferth’s reagent.](image)
This reaction is believed to follow a cationic mechanism (Figure 12). When the difluorocarbene is added to the cyclobutene, it forms a strained housane intermediate. One fluoride ion leaves, allowing the ring to expand and relieving the strain. The allylic ion expands into a five-membered ring. A proton is immediately expelled, forming a double bond and leaving behind an even more stable, neutral fluorocyclopentadiene structure. A second equivalent of difluorocarbene is then added and reacts with the non-fluorinated double bond of the cyclobutadiene (Figure 13). It is thought that the non-fluorinated double bond is attacked in the second step because it is more electron rich than the other double bond, which is under the electron withdrawing effect of the fluorine substituent.\(^{11}\) The 1,3-difluorobenzene is complete with the loss of a fluoride ion and proton to form the aromatic ring.

Figure 12. Proposed cationic mechanism of the addition of 1 mol difluorocarbene to disubstituted cyclobutene.

Figure 13. Addition of the second mole of difluorocarbene.
This cationic mechanism is consistent with the results of reactions using symmetrically substituted cyclobutenes as precursors. This study investigates an asymmetric cyclobutene which will result in the possible formation of various isomers (Figure 14). By determining which isomer is the major one, the validity of the cationic mechanism can be determined. Using a cation-stabilizing substituent like benzene should allow for the control of the preferred location of the cation after the addition of the first mole of difluorocarbene.

![Diagram showing isomer formation](image)

**Figure 14.** Possible isomers formed from the reaction of difluorocarbene with 1-phenyl-2-methylcyclobutene.

Investigation of the potential cyclopentadiene intermediates shows differences in stability based on the orientation of the \( \pi \) system. The presence of a phenyl group on the cyclopentadiene provides the possibility for conjugation or cross-conjugation. This is related to a conjugated \( \pi \) system, where an alternating pattern of single and double bonds allows the general delocalization of electrons. The flow of electrons through the system stabilizes the molecule, which is present in benzene for example. Cross conjugation occurs when only a limited number of a set of \( \pi \) bonds interact with each other. While these molecules may look like normally conjugated
molecules, inspection of their resonance structures shows that not all the $\pi$ bonds participate in resonance (Figure 15). The cross-conjugated molecules are higher in energy because of reduced intramolecular electron delocalization and resonance capability than are their fully conjugated systems relatives.\textsuperscript{12} Of the two potential intermediates that would be formed by the cationic mechanism, one is cross-conjugated and one is fully conjugated, leading to the formation of compounds 1 and 3 respectively (Figure 14). The identification of the major isomer formed will provide more evidence toward the validity of this cationic mechanism and the ability to use this synthesis for the production of 1,3-difluorobenzenes from disubstituted cyclobutene.

\textbf{Figure 15.} Resonance structure differences between fully conjugated (top) and cross conjugated (bottom) systems.
Chapter 3

Results and Discussion

The synthesis of 1,3-difluoro-2-methyl-4-phenylbenzene was achieved by the addition of Seyferth’s reagent (Ph-Hg-CF₃) to 1-phenyl-2-methylcyclobutene (Figure 16). A solution of 1-phenyl-2-methylcyclobutene (5) was added to dried NaI and Seyferth’s reagent. After heating to reflux for 24 hours, the reaction was filtered and concentrated.

Previous attempts have shown this reaction with Seyferth’s reagent to be very temperamental. The reagent itself is not reliable to work on a consistent basis. The reaction will also only work if the starting cyclobutene is extremely pure. The purification of this molecule was found to be difficult, especially the separation from its starting material, Z-1,4-diiodo-4-phenyl-3-methyl-3-butene (4). Extreme care was taken to combine only the fractions of the column that had completely separated products. All reagents used in the ring expansion reaction were dried under vacuum to ensure the absence of water. Despite these efforts, trace contaminants could still prevent the production of the 1,3-difluorobenzene product.

Figure 16. Overall reaction scheme.
The product 3 was characterized using GC/MS, which showed the major peak at 6.5 minutes with a parent ion peak having a 204 mass to charge ratio. This matches the expected value for either isomer of the difluorobenzene that was expected from this reaction. A $^{19}$F NMR confirmed the addition of two fluorine atoms and therefore the structure of 3 (Figure 16). Aromatic fluorine atoms have a chemical shift in the -100 to -150 ppm region. Two signals were found at around -120 ppm which are consistent with expected peaks for the placement of the fluorine atoms on the benzene ring. With the purification of the product, exact peaks could be assigned but due to impurities, just the existence of signals in the aromatic region confirms the addition of two fluorine atoms to the benzene ring. The exact structure was confirmed by the cleaner $^1$H NMR.

The $^1$H NMR showed interesting coupling due to the fluorine atoms and confirmed that isomer 3 was formed, with the methyl group situated between the two fluorine atoms on the benzene ring. Since fluorine is similar to hydrogen in size, there is very strong coupling between

![Figure 17. Magnified view of aromatic region of $^1$H NMR of 1,3-difluoro-2-methyl-4-phenylbenzene 3.](image-url)
protons and fluorine atoms. Fluorine can couple up to seven bonds away due to electron pairs, causing extra splitting in the $^1$H spectrum. The peak assigned to the protons on the methyl substituent at 2.09 ppm ($J = 5.16 \text{ Hz}$) appeared to be a triplet because of coupling from fluorine atoms on either side of it. The presence of a doublet in this peak would suggest only one fluorine neighbor and the formation of isomer 1, with the phenyl group in between the two fluorine atoms instead of the methyl group.

A magnified view of the aromatic region of the $^1$H NMR of 3 showed two smaller peaks on either side of the multiplet assigned to the phenyl substituent group at 7.39 ppm (Figure 17). An apparent triplet was found at 7.14 ppm ($J = 7.65 \text{ Hz}$) and a doublet of doublets was found at 7.72 ppm ($J = 8.34 \text{ Hz}, J = 1.17 \text{ Hz}$). These were assigned to $H_b$, next to $F_b$, and $H_a$, next to the phenyl substituent, respectively. These splitting patterns are expected with the structure of this isomer. The atom $F_b$ and $H_a$ split $H_b$ at 7.14 ppm into an apparent triplet while $F_a$ and $H_b$ split $H_a$ at 7.72 ppm into a doublet of doublets. This splitting pattern combined with the splitting of the methyl substituent protons supports the formation of isomer 3 over isomer 1 and provides further evidence for the validity of a cationic mechanism with a fully conjugated fluorocyclopentadiene intermediate for the addition of difluorocarbene to an asymmetric disubstituted cyclobutene.

It has not yet been confirmed whether Seyferth’s reagent can be recommended without a doubt for the use of this ring expansion reaction to make 1,3-difluorobenzenes. The lack of consistent success of the reaction invites further studies to improve the reaction. Other investigations are being done using differently substituted alkenes to make various cyclobutenes. This will demonstrate the regioselectivity of the reaction and how substituents with different sizes and properties affect the reaction. It is still a desire to declare with more certainty the
successful completion of this reaction for efficiency in production of various industrially useful compounds.
Chapter 4
Experimental

General Procedure

All reagents were used as received from the manufacturer. All solutions were prepared in dry solvents from the solvent purification system separately right before use and cannula transferred to the reaction flask. All reactions were performed under inert gas conditions. Product concentration was accomplished using a Buchi Rotavapor R-114. An Agilent 6890N gas chromatograph with an HP-5MS 0.25mm x 30m x 0.25 um column coupled to an Agilent 6460 triple quadrupole (QqQ) mass spectrometer was used to confirm products. A Bruker 400 MHz NMR was used to characterize all products. CDCl₃ was used as the solvent, and chemical shifts are reported in ppm downfield from tetramethylsilane (δ scale). Procedures were modified from the original procedure by Morrison et al.¹³

Preparation of Z-1,4-diiodo-4-phenyl-3-methyl-3-butene (4)

Compound 1 was prepared by dissolving 1.26 g ZrCp₂Cl₂ (4.3 mmol) in dry THF in a 250 mL round bottomed flask. To this, 4.5 mL EtMgBr (8.6 mmol) in ether was added dropwise to the flask and reaction allowed to stir at -78°C for one hour. Phenylpropyne (0.5 g, 4.3 mmol) in dry THF was added and stirred at 0°C for 6 hours and at room temperature overnight. The reaction was brought back to 0°C before adding 3.28 g I₂ (12.9 mmol) in dry THF and stirred at room temperature overnight. Work-up involved removal of THF under reduced pressure followed by the addition of ether. The ether solution was treated with 3M HCl and allowed to stir for 10 minutes. The organic layer was separated and sequentially washed with 10% NaHCO₃ and 10% Na₂SO₃. The organic layer was retained, dried over Na₂SO₄, gravity filtered, and concentrated. The crude product was purified on a silica gel column eluted with cyclohexanes to
give a yield of 64%. The structure of the product was confirmed by GC-MS and NMR analyses.

$^1$H NMR (CDCl$_3$) δ: 1.78 (s, 3H), 3.04 (t, 2H, $J = 7.52$), 3.35 (t, 2H, $J = 6.96$), 7.28 (m, 5H); 
GC/MS (EI) m/z = 272, r.t. = 18 min.

Preparation of 1-phenyl-2-methylcyclobutene (5)

Pure products of 1 were combined and solvent was removed in vacuo. Dry ether was added to 500 mg of product (1.837 mmol), followed by the syringe addition of 0.346 mL $n$-butyllithium (3.675 mmol, 2.5 M in hexanes). The reaction was stirred for 1 hour at -78°C, after which 1 mL H$_2$O was added to quench the reaction. The reaction was allowed to stir until coming to room temperature. Crude product was purified on a silica gel column eluted with pentanes to give a yield of 17%. The structure of the product was confirmed by GC-MS and NMR analyses. $^1$H NMR (CDCl$_3$) δ: 1.28 (m, 4H), 1.56 (s, 3H), 7.29 (m, 5H); GC/MS (EI) m/z = 115, r.t. = 7 min.

Preparation of 1,3-difluoro-2-methyl-4-phenylbenzene (3)

A large excess of NaI was ground into a powder in a mortar and pestle and then added to a 25-mL 3-necked round bottom flask with a stir bar. It was dried under vacuum at 150°C for 24 hours. Phenyl(trifluoromethyl)mercury(II) (Seyferth’s reagent) (264 mg, 0.763 mmol) was added to the flask and dried under vacuum at room temperature for 24 hours. A solution of 10 mL dry benzene (Na/benzophenone) added to 50 mg of 2 (0.347 mmol) was added to the reaction flask. The flask was heated to reflux for 24 hours. The structure of the product solution was gravity filtered. The product was confirmed by GC-MS and NMR analyses. $^1$H NMR (CDCl$_3$) δ: 2.09 (apparent t, 3H, $J = 5.16$), 7.13 (t, 1H, $J = 7.65$), 7.39 (m, 5H), 7.72 (d, 1H, $J = 8.34$, $J = 1.17$); GC/MS (EI) m/z = 204, r.t. = 6.5 min.
References


Appendix

Z-1,4-diiodo-4-phenyl-3-methyl-3-butene (4): GC/MS
Z-1,4-diiodo-4-phenyl-3-methyl-3-butene (4): \(^1\)H NMR
Z-1,4-diiodo-4-phenyl-3-methyl-3-butene (4): \(^{13}\text{C} \text{NMR}\)
1-phenyl-2-methylcyclobutene (5): GC/MS

File: D:\Data\Lewis Group\RM\CYBU 9.11 C01 F72.D
Operator: RM
Acquired: 4 Mar 2016 19:20 using AcqMethod LEWISMAN.M
Instrument: Agilent GCMS
Sample Name: CYBU 9.11 C01 F72
Misc Info:
Vial Number: 1
1-phenyl-2-methylcyclobutene (5): $^1$H NMR
1-phenyl-2-methylcyclobutene (5): $^{13}$C NMR
1,3-Difluoro-2-methyl-4-phenylbenzene (3): GC/MS

File: D:\Data\Lewis Group\RM\DFBEN 2.D
Operator: RM
Instrument: Agilent GCMS
Sample Name: DFBEN 2
Vial Number: 1
1,3-Difluoro-2-methyl-4-phenylbenzene (3): $^1$H NMR
1,3-Difluoro-2-methyl-4-phenylbenzene (3): $^1$H NMR aromatic zoom
1,3-Difluoro-2-methyl-4-phenylbenzene (3): $^{19}$F NMR
1,3-Difluoro-2-methyl-4-phenylbenzene (3): $^{19}$F NMR aromatic zoom