Design and Synthesis of Specifically Substituted 5-Arylisoxazolines and 5-Arylisoxazoles

An Honors Thesis (HONRS 499)

by

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Fipronil, a potent insecticide and major component of many crop and animal protection products, acts as a noncompetitive inhibitor of the GABA-gated chloride channel. The success of this phenylpyrazole (arylpyrazole) has led to the development of similar compounds including 3-phenylisoxazoles, 1-phenyltriazoles, fiproles, and other phenylpyrazoles. This particular research deals with the development of sixteen new 5-phenyl heterocyclic compounds similar in structure to fipronil, eight 5-arylisoxazolines and eight 5-arylisoxazoles. These novel heterocycles were synthesized via 1,3-dipolar cycloaddition reactions between a styrene or phenylacetylene and a nitrile oxide. To obtain a variety of compounds four different substituents were added to the 5-position of the phenyl ring and two different substituents were used at the para-position of the benzene ring. Each new compound was analyzed for structure and purity by NMR spectroscopy and elemental analysis.

Introduction

The GABA-gated chloride channel is a popular target for many insecticidal compounds. During the early 1990s a new class of phenylpyrazole compounds was thought to be potentially useful as pesticides. Studies of receptor-binding and neurotransmitter flux assays with house flies and mice, as well as cross-resistance studies with insecticide-resistant house flies, provided evidence that phenylpyrazoles act at the GABA-gated chloride channel, and the suitability of these compounds as insecticides indicated that optimizations could lead to successful products. Fipronil is a major insecticide and component of pet products and is included in such products as Frontline, MaxForce, and Regent. Fipronil, as with other phenylpyrazoles, acts by inhibition of the GABA receptor. Noncompetitive binding blocks the passage of chloride ions through the GABA-gated chloride channel leading to over-excitation of the central nervous system. Fipronil’s major advantage is not just its potency but also its selectivity; insects are much more susceptible to fipronil than mammals. However, fipronil is still a highly toxic compound and this toxicity and the fact that insects are known to become resistant to other insecticides makes the study of new, similar compounds desirable.
Other compounds structurally related to fipronil have been synthesized and biologically tested. It was found that the potency of fipronil remained intact when altering the structure of the compound. Substitution included replacing the trifluoromethylsulfinyl substituent of the pyrazole with isopropyl or tert-butyl and replacing the phenyl’s trifluoromethyl substituent with chloro or bromo.\(^5\)

Triazoles (phenylheterocycles) are another class of compounds that have been synthesized and shown to block the GABA-gated chloride channel.\(^6\) Another phenylpyrazole, ethiprole which has ethylsulfinyl in place of trifluoromethylsulfinyl, compares favorably with fipronil and is similar in potency.\(^7\)

Our interest in arylisoxazoles and arylisoxazolines (4,5-dihydroisoxazoles) is due to their similarity to fipronil and other related compounds (Fig. 2). These compounds are of biological significance. A study of the selective inhibition of human transglutamine 2 demonstrates the potential of 4,5-dihydroisoxazoles. The TG2 enzyme is suspected of relating to human diseases like cancers and neurological disorders such as Alzheimer’s. Evidence has been found supporting 3-halo-4,5-dihydroisoxazole containing compounds as selective inhibitors of human TG2 by active site binding.\(^8\) Another study presented an efficient one-pot synthesis of 4,5-dihydroisoxazoles using a 1,3-dipolar cycloaddition reaction between dipolarophiles and nitrile oxides. The potential of isoxazolines as pharmaceutical agents was also described.\(^9\)

The biological properties of 5-arylisoxazoles and 5-arylisoxazolines and the similarity in structure to fipronil of these heterocycles led us to develop an efficient synthesis of heterocycles utilizing a 1,3-dipolar cycloaddition reaction with a nitrile oxide.\(^10\) Substituted styrenes are used to prepare the 5-arylisoxazolines and substituted phenylacetylenes are used to prepare the 5-arylisoxazoles. We used four different substituents at the 5-position of the phenyl ring: tert-butyl, isobutyl, ethylpropyl, and isopropyl. These substituents were selected due to their short, bulky nature to ensure they would fit the same binding site as the other phenylpyrazole derivatives and be active at the receptor.\(^5,6\) We also used two different substituents at the para-position of the benzene ring: chloro and trifluoromethyl. We are hopeful that the synthesis of 5-arylisoxazolines and 5-arylisoxazoles will lead to the development of potentially useful compounds that interact at the GABA-gated chloride channel as noncompetitive inhibitors similar to other phenylpyrazoles.

**Results and Discussion**

The synthesis of 5-arylisoxazoles and 5-arylisoxazolines involved similar procedures, both utilizing a 1,3-dipolar cycloaddition reaction between a dipolarophile and a nitrile oxide generated from an aldoxime. The main difference between the two synthesis reactions involved the reactant which was paired with the nitrile oxide; styrenes are the dipolarophiles used to generate the isoxazolines while phenylacetylenes are used to form the isoxazoles. Therefore, our
first goal was to determine an efficient method of synthesizing the styrene and phenylacetylene derivatives.

Initial attempts at generating a styrene utilized the knowledge that 2,4,6-trichlorobenzaldehyde (1) could be prepared from 1,3,5-trichlorobenzene upon lithiation with n-butyllithium and quenching with DMF.\(^\text{11}\) The 2,4,6-trichlorostyrene (2) was subsequently prepared by a Wittig reaction.\(^\text{12}\) The problem with this method was that 2,4,6-trichlorobenzaldehyde was substituted at both ortho positions and it was a challenge to get the reaction to occur. Also, since a strong base was used in this synthesis we were concerned about other undesirable reactions occurring which would lead to lack of product formation or impurities that we would not be able to separate from the substituted styrene. Due to these restrictions we looked into other methods of creating a substituted styrene.

We discovered another possible method of creating the 2,4,6-trichlorostyrene using 2,4,6-trichloroaniline. The first step of this synthesis involved the 2,4,6-trichloroaniline undergoing a Sandmeyer reaction to create 2-bromo-1,3,5-trichlorobenzene (3).\(^\text{13}\) The second and final step resulted in 2,4,6-trichlorostyrene (2) by having 2-bromo-1,3,5-trichlorobenzene undergo a Stille coupling.\(^\text{14}\) This reaction succeeded in producing the desired product but with a few inconveniences. Initial attempts at carrying out the Stille coupling were followed according to the reference and approximately 10% more tributylvinyltin and 10% more palladium catalyst than 2-bromo-1,3,5-trichlorobenzene was used. The extra tributylvinyltin resulted in the formation of divinyls which were impossible to separate using column chromatography techniques. We solved this issue by using a 1:1 ratio of tributylvinyltin and 2-bromo-1,3,5-trichlorobenzene, along with less catalyst and heat. While this change eliminated divinyl formation, it also led to the result that 2-bromo-1,3,5-trichlorobenzene remained unreacted along with small amounts of tributylvinyltin. These compounds were unable to be separated from each other and were also difficult to separate from the substituted styrene. This reaction method was also attempted with 2,6-dichloro-4-trifluoromethylaniline as the starting material. The Sandmeyer reaction produced 2-bromo-1,3-dichloro-5-(trifluoromethyl)benzene (4), and the subsequent Stille coupling produced 1,3-dichloro-5-(trifluoromethyl)styrene (5). The results of this procedure were identical to those observed previously with the 2,4,6-trichlorostyrene.

One other reaction scheme with the possibility of forming substituted styrene was discovered and attempted that involved carbinol formation. This method employed 1,3,5-trichlorobenzene as the starting compound. The addition of acetaldehyde to the lithiated intermediate led to formation of 1-(2,4,6-trichlorophenyl)ethanol (6). Dehydration of the carbinol with potassium bisulfate produced 2,4,6-trichlorostyrene (2).\(^\text{15}\) A similar procedure was attempted with 2-bromo-1,3-dichloro-5-(trifluoromethyl)benzene. This led to formation of 1-[2,6-dichloro-4-(trifluoromethyl)phenyl]ethanol (7), which following dehydration of the carbinol with potassium bisulfate produced 1,3-dichloro-5-(trifluoromethyl)styrene (5). The addition of toluene was required for the formation of (7) to prevent benzyne formation during the lithium-halogen exchange.\(^\text{16}\) Yields for these reactions were poor. However, an advantage for this method was the purity of the product due to coupling which changes the polarity. This method produced products that were more pure than any of
the other schemes, but the amount of product obtained was always very small.

Each of the methods used to generate substituted styrene succeeded, although some methods worked better than others. The Stille coupling was the most successful and produced the best yield, along with recovery of starting material. The problems with this scheme were the separation of starting material from each other. The Wittig reaction didn’t always produce the desired product and was often difficult to get working. The carbinol dehydrations generally had poor yields but products were pure. Our method of choice when producing substituted styrenes was the Stille coupling reaction scheme.

\[
\text{Stille coupling reaction scheme.}
\]

Potassium carbonate was used to deprotect the compound, removing the TMS group and forming 2,4,6-trichlorophenylacetylene (9). A similar procedure was followed with 2,6-dichloro-4-trifluoromethylaniline. This compound was halogenated to form 1,3-dichloro-2-iodo-5-(trifluoromethyl)benzene (10) which was protected and deprotected to form 1,3-dichloro-5-(trifluoromethyl)phenylacetylene (11). The Sonogashira coupling and deprotection reactions may at first seem like unnecessary steps to generate the phenylacetylene. The reason that the reaction is carried out in this manner is that the compound would be a terminal alkyne if not protected and the product could couple more than once leading to unwanted dimer formation. Also, if Sonogashira coupling was not used acetylene would have to be used in the reaction which is a gas and difficult to work with.

\[
\text{Scheme 2. Reaction scheme to generate phenylacetylene from aniline precursor.}
\]

The other crucial component of the 1,3-dipolar cycloaddition reaction besides the dipolarophile was the aldoxime which would react with the substituted styrene or phenylacetylene to give the final product. The aldoximes are important because they provide the necessary functional groups for the various 5-phenylisoxazoles and 5-phenylisoxazolines. As a result, four different aldoximes (Fig. 3) were created to coincide with the desired four functional groups: isopropyl (A), isobutyl (B), t-butyl (C), and 1-ethylpropyl (D). These functional groups were selected because of their short, bulky nature so that they would fit the appropriate binding site. This was
based on the knowledge of the structure and activity of other phenylpyrazole derivatives. The aldoximes were prepared from the corresponding aldehyde and hydroxylamine hydrochloride by a standard method. The only difference among the four aldoximes was the volatility and/or water solubility based on number of carbons.

![Figure 3. Four aldoximes used to generate phenylisoxazoles and phenylisoxazolines via 1,3-dipolar cycloaddition.](image)

The desired phenylisoxazoline (12A-D, 13A-D) was formed by a 1,3-dipolar cycloaddition reaction between a substituted styrene (2, 5) and an aldoxime (A-D) in the presence of bleach and dichloromethane. Initial attempts to create the phenylisoxazoline used excess oxime which led to the formation of furoxan dimers. We preferred to use the styrene derivatives as limiting agents because of the effort required for their synthesis, but the furoxan dimers could not be separated from the product. Subsequently a 1:1 ratio of styrene derivative and oxime was employed which reduced dimer formation. In some cases we actually used excess dipolarophile. Yields varied (Table 1) but were generally good. Lower yields were generally caused by purification problems rather than the reaction.

The desired phenylisoxazoles (14A-D, 15A-D) were obtained from an identical 1,3-dipolar cycloaddition reaction, this time between a substituted phenylacetylene (9, 11) and an aldoxime (A-D) in the presence of bleach and dichloromethane. Yields were typically good (Table 2).

![Scheme 3. Reaction scheme for phenylisoxazolines.](image)

<table>
<thead>
<tr>
<th>5-Phenylisoxazoline</th>
<th>Yield</th>
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<tbody>
<tr>
<td>12A</td>
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</tr>
<tr>
<td>12B</td>
<td>27%</td>
</tr>
<tr>
<td>12C</td>
<td>69%</td>
</tr>
<tr>
<td>12D</td>
<td>48%</td>
</tr>
<tr>
<td>13A</td>
<td>59%</td>
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<td>13B</td>
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<tr>
<td>13C</td>
<td>49%</td>
</tr>
<tr>
<td>13D</td>
<td>36%</td>
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</table>

Table 1. Yield data for the eight target 5-phenylisoxazolines.

![Scheme 4. Reaction scheme for phenylisoxazoles.](image)

<table>
<thead>
<tr>
<th>5-Phenylisoxazole</th>
<th>Yield</th>
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<tbody>
<tr>
<td>14A</td>
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</tr>
<tr>
<td>14B</td>
<td>25%</td>
</tr>
<tr>
<td>14C</td>
<td>50%</td>
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<tr>
<td>14D</td>
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<td>15A</td>
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<td>15C</td>
<td>61%</td>
</tr>
<tr>
<td>15D</td>
<td>50%</td>
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Table 2. Yield data for the eight target 5-phenylisoxazoles.
Following synthesis of our target compounds we ran competition reactions to determine rates of reaction. These reactions were run with styrene, phenylacetylene, and oxime in solution. The organic layer was analyzed by $^1$H NMR and integration of the peaks was used to determine the ratio of the isoxazoline and isoxazole products. These reactions were carried out with styrene, substituted styrene (2, 5), phenylacetylene, and substituted phenylacetylene (9, 11). The results provided information on the relative reactivity (rates of reaction) of the compounds (Table 3). The 1,3-dipolar cycloaddition reaction with phenylacetylene was slower than that with styrene. This was expected. An interesting observation from our data was that the substituted styrenes had lower reactivity than styrene while the substituted phenylacetylenes had higher reactivity than phenylacetylene.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Relative Reactivity (Rates)</th>
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<tbody>
<tr>
<td>Styrene</td>
<td>1.00</td>
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<tr>
<td>(2)</td>
<td>0.52</td>
</tr>
<tr>
<td>(5)</td>
<td>0.59</td>
</tr>
<tr>
<td>Phenylacetylene</td>
<td>0.13</td>
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<tr>
<td>(9)</td>
<td>0.19</td>
</tr>
<tr>
<td>(11)</td>
<td>0.26</td>
</tr>
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</table>

Table 3. Relative reactivities (rates) for styrene, substituted styrenes, phenylacetylene, and substituted phenylacetylene with 2-methylpropanenitrile oxide.

Experimental

Thin layer chromatography (TLC) was performed using Baker-Flex silica gel IB-F plates and an ultraviolet lamp was used to visualize the plates. A solution of KMnO$_4$ was used to stain the plates. Column chromatography was used to separate and purify components; both silica gel from Acros and pre-packaged AnaLogix Flash Columns were used. All reagents were used as they were received from the manufacturer without purification. All $^1$H NMR and $^{13}$C NMR spectra were obtained with either a 400 MHz or 300 MHz JEOL Eclipse spectrometer. Elemental analysis of products was carried out at MidWest Microlab in Indianapolis, IN.

Standard Procedure for Oxime Preparation.

Hydroxylamine hydrochloride (30 mmol), water (13 mL), ethanol (13 mL), and the aldehyde of choice were added in the listed order and the mixture was stirred for five minutes. Sodium acetate (45 mmol) was then added and the mixture was stirred for five hours. The product was extracted with dichloromethane (2 x 25 mL) and concentrated via rotary evaporation.

2-Methylpropanal oxime (A). The general procedure for oxime preparation was followed with isobutyraldehyde as the aldehyde. 31% yield, E:Z 2.1:1.0, $^1$H NMR (300 MHz) 8: 8.26 (d, $J = 5.8$ Hz, 1H), 7.35 (d, $J = 5.8$ Hz, 1H), 2.59-2.43 (m, $J = 6.9$ Hz, 1H), 1.10 (d, $J = 6.9$ Hz, 6H); Z: 8.56 (d, $J = 7.4$ Hz, 1H), 6.54 (d, $J = 7.4$ Hz, 1H), 3.29-3.13 (m, $J = 6.9$ Hz, 1H), 1.07 (d, $J = 6.9$ Hz, 6H).

2,2-Dimethylpropanal oxime (B). The general procedure for oxime preparation was followed with trimethylacetaldehyde being used as the aldehyde. 69% yield, only E observed, $^1$H NMR (400 MHz) 8: 7.99 (s, 1H), 7.35 (s, 1H), 1.11 (s, 9H); $^{13}$C NMR (75 MHz) 8: 159.1, 33.64, 27.5.

2-Ethylbutanal oxime (C). The general procedure for oxime preparation was followed with 2-ethylbutyaldehyde being used as the aldehyde. 44% yield, E:Z 2.2:1.0, $^1$H NMR (400 MHz) 8: 7.24 (d, $J = 8.0$ Hz, 1H), 2.11-2.03 (m, 1H), 1.58-1.30.
(m, 4H), 0.904 (t, J = 7.7 Hz, 6H); Z: 6.47 (d, J = 8.8 Hz, 1H), 3.00-2.91 (m, 4H), 1.58-1.30 (m, 4H), 0.911 (t, J = 7.4 Hz, 6H); 13C NMR (100 MHz) δ E:155.7, 43.0, 25.4, 11.5; Z: 155.7, 43.0, 25.3, 11.7.

3-Methylbutanal oxime (D). The general procedure for oxime preparation was followed with isovaleraldehyde being used as the aldehyde. 85% yield, E:Z 1.2:1.0, 1H NMR (300 MHz) δ E 7.31 (s, 1H), 2.08 (t, J = 6.6 Hz, 2H), 1.92-1.76 (m, 1H), 0.95 (d, J = 6.6 Hz, 6H); Z: 6.74 (t, J = 5.5 Hz, 1H), 2.28 (dd, 7.1,5.5 Hz, 2H), 1.92-1.76 (m, 1H), 0.97 (d, J = 6.6 Hz, 6H).

Standard Competition Reaction. A solution of styrene (0.5 mmol) and phenyl acetylene (0.5 mmol) was prepared in CDCl3 followed by addition of 2-methylpropanal oxime (0.1 mmol). Bleach (8.29 g (4.04%), 4.5 mmol) and water (7 mL) were mixed and added drop wise to the CDCl3 solution over 30 minutes. The reaction mixture was allowed to stir for two hours. A sample of the organic layer was analyzed via 1H NMR and the corresponding peaks were integrated to determine the ratio of the corresponding 5-arylisoxazoline and 5-arylisoxazole products. Following this procedure, styrene was compared with the two substituted styrenes [(2,4,6-trichlorostyrene, 1,3-dichloro-5-(trifluoromethyl)styrene)] and phenylacetylene was compared with the two substituted phenylacetylenes [(2,4,6-trichlorophenylacetylene, 1,3-dichloro-5-(trifluoromethyl)phenylacetylene)].

Trichlorobenzaldehyde (1).11

2,4,6-Trichlorostyrene (2) via Wittig reaction. Tetrahydrofuran (20 mL) and methyltriphenylphosphonium iodide (1.98 g, 4.9 mmol) were mixed in the presence of argon. The reaction mixture was cooled to 78 °C with stirring. Once the mixture was cooled, n-butyllithium (2.8 mL, 1.6 M, 4 mmol) was added while keeping the temperature of the mixture constant. After 45 minutes, 2,4,6-trichlorobenzaldehyde (1, 0.838 g, 4 mmol) was dissolved in tetrahydrofuran (7 mL) and added to the reaction mixture via cannula addition. Hexane was used to dilute the crude product which was then vacuum filtrated. The filtrate was concentrated via rotary evaporation and then absorbed onto silica gel for chromatography (hexanes) giving a 67% yield (0.549 g). 1H NMR (400 MHz) δ 7.34 (s, 2H), 6.64 (dd, J = 18, 12 Hz, 1H), 5.79 (dd, J = 18, 1.1 Hz, 2H) 5.74 (dd, J = 12, 1.1 Hz, 2H); 13C NMR (100 MHz) δ 134.7, 133.7, 133.0, 130.0, 128.4, 123.4.

2-Bromo-1,3,5-trichlorobenzene (3). Sulfuric acid was added drop wise to sodium nitrite with stirring. The mixture was allowed to stir for one hour and then cooled to 10 °C. Glacial acetic acid was added following the cooling. In a separate flask glacial acetic acid was added to 2,4,6-trichloroaniline. The 2,4,6-trichloroaniline mixture was added to the sodium nitrite mixture drop wise while stirring and holding the temperature at 10 °C. The mixture was allowed to stir for one hour. Copper sulfate pentahydrate was added to a mixture of sodium bromide and water. To this a mixture of sodium sulfite and water was added. The supernatant of the mixture was decanted and the crystals were washed with water. Aqueous hydrogen bromide was added to the washed copper (I) bromide crystals and cooled with ice water. To this a mixture of sodium sulfite and water was added. The supernatant of the mixture was decanted and the crystals were washed with water. Aqueous hydrogen bromide was added to the mixture of sodium bromide and water. To this a mixture of sodium sulfite and water was added. The supernatant of the mixture was decanted and the crystals were washed with water. Aqueous hydrogen bromide was added to the washed copper (I) bromide crystals and cooled with ice water. The 2,4,6-trichloroaniline mixture was added to the mixture of sodium bromide and water. The organic layers were
combined and washed with 5% aqueous sodium bicarbonate and brine. The organic layer was then dried with magnesium sulfate and concentrated by rotary evaporation followed by high vacuum. 83.4 % (2.17 g). \(^1\)H NMR (400 MHz) \(\delta 7.40 \text{ (s, 2H); }^{13}\)C NMR (100 MHz) \(\delta 136.9, 133.6, 128.4, 122.0.\)

2,4,6-Trichlorostyrene (2) via Stille coupling. Tributylvinyltin (1.3 g, 4 mmol) was added to 2-bromo-1,3,5-trichlorobenzene (3, 1.04 g, 4 mmol) and degassed with argon, followed by addition of toluene (25 mL) with degassing. The reaction was stirred. Tetrakis(triphenylphosphine)palladium(0) (0.14 g, 0.12 mmol) was then added and the reaction mixture was refluxed for 24 hours. The crude product was concentrated by rotary evaporation and absorbed onto silica gel for chromatography (hexanes). A yield could not be determined due to difficulty in separating starting material from product.

2-Bromo-1,3-dichloro-5-(trifluoromethyl)benzene (4). Copper (II) bromide (4.02 g, 18.0 mmol) and t-butyl nitrite (3.12 g, 30.3 mmol) were added to a three-neck flask under argon with acetonitrile (60 mL). In a separate flask, acetonitrile (20 mL) was added to 2,6-dichloro-4-trifluoromethylaniline (3.5 g, 15.2 mmol) under argon. The aniline mixture was added to the three-neck flask drop wise. The reaction mixture was then heated to 65 °C and stirred overnight. The reaction mixture was then cooled to room temperature and poured into a separatory funnel with water (50 mL) and ethyl ether (110 mL). The organic layer was washed with hydrochloric acid (2 x 30 mL, 3M) and dried with sodium sulfate. The product was concentrated by rotary evaporation followed by high vacuum giving an 85% yield (3.792 g). \(^1\)H NMR (300 MHz) \(\delta 7.63 \text{ (s, 2H); }^{13}\)C NMR (100 MHz) \(\delta 137.4, 131.1 \text{ (q, } J = 34 \text{ Hz), } 127.9, 125.2 \text{ (q, } J = 3.1 \text{ Hz), 122.4 \text{ (q, } J = 271 \text{ Hz).}\)

1,3-Dichloro-5-(trifluoromethyl)styrene (5) via Stille coupling. Tributylvinyltin (1.268 g, 4 mmol) was added to 2-bromo-1,3-dichloro-5-(trifluoromethyl)benzene (4, 1.205 g, 4.1 mmol) and degassed with argon, followed by addition of toluene (15 mL) with degassing. The reaction was stirred. Tetrakis(triphenylphosphine)palladium(0) (0.173 g, 0.15 mmol) was then added and the reaction mixture was refluxed for one day. The crude product was concentrated by rotary evaporation and absorbed onto silica gel for chromatography (hexanes) giving a 58.3% yield (0.562 g). \(^1\)H NMR (400 MHz) \(\delta 7.58 \text{ (s, 2H), } 6.70 \text{ (dd, } J = 18, 12 \text{ Hz, 1H), 5.86 \text{ (dd, } J = 17, 1.1 \text{ Hz, 2H), 5.82 \text{ (dd, } J = 12, 1.1 \text{ Hz, 2H); }^{13}\)C NMR (100 MHz) \(\delta 138.6, 134.9, 130.6 \text{ (q, } J = 34 \text{ Hz), 130.0, 125.3 \text{ (q, } J = 3.8 \text{ Hz), 124.4, 122.6 \text{ (q, } J = 271 \text{ Hz); Calcd for } C_{9}H_{6}Cl_{2}F_{3}: C 44.85, H 2.09; Found: C 45.00, H 2.25.\)

1-(2,4,6-Trichlorophenyl)ethanol (6).

Anhydrous tetrahydrofuran (74 mL) and 1,3,5-trichlorobenzene (3.629 g, 20 mmol) were stirred at -78 °C in the presence of argon followed by drop wise addition of n-butyllithium (18 mL, 20 mmol). The reaction mixture was then stirred for one hour. A mixture of anhydrous tetrahydrofuran (2 mL) and acetaldehyde (1.762 g, 40 mmol) was added drop wise to the reaction mixture using a cold syringe. The temperature of the reaction mixture was held constant at -78 °C for one hour after the addition. The reaction was then quenched with water (40 mL) and transferred to a separatory funnel where the organic layer was extracted with ethyl acetate (100 mL) and dried with sodium sulfate. The product was concentrated via
rotary evaporation followed by high vacuum. The product was absorbed onto silica gel for chromatography (dichloromethane) giving an 81% yield (3.662 g). $^1$H NMR (300 MHz) $\delta$ 7.32 (s, 2H), 5.60–5.50 (dq, $J = 6.9$, 9.9 Hz, 1H), 2.81 (d, $J = 9.9$ Hz, 1H), 1.62 (d, $J = 6.9$ Hz, 3H); $^{13}$C NMR (75 MHz) $\delta$ 137.3, 134.4, 133.5, 129.2, 67.8, 21.3.

2,4,6-Trichlorostyrene (2) via carbinol dehydration. 1-(2,4,6-Trichlorophenyl)ethanol (6, 0.50 g, 2.2 mmol), potassium bisulfate (0.02 g, 0.15 mmol), and hydroquinone (0.01 g, 0.09 mmol) were added to a long neck condenser flask. The reaction mixture was stirred and heated to 220°C for 2 hours. The mixture was then allowed to cool to room temperature and the crude product was absorbed onto silica gel for chromatography (hexanes) giving a 47.2% yield (0.218 g).

1-[2,6-Dichloro-4-(trifluoromethyl)phenyl]ethanol (7). Anhydrous toluene and 2-bromo-1,3-dichloro-5-(trifluoromethyl)benzene (3.65 g, 12.4 mmol) were mixed in the presence of argon and cooled to -78°C followed by drop wise addition of n-butyllithium (13.8 mL, 12.4 mmol) over 30 minutes. The reaction mixture was then stirred for one hour. A mixture of acetaldehyde (1.256 g, 28.52 mmol) and anhydrous toluene (4 mL) was added drop wise to the reaction mixture via a cold syringe. The reaction mixture was held constant at -78°C for one hour and allowed to stir. The mixture was then quenched with water and transferred to a separatory funnel. The organic layer was extracted, dried, and concentrated via rotary evaporation followed by high vacuum. The product was absorbed onto silica gel for chromatography (dichloromethane) giving a 78% yield (2.48 g). $^1$H NMR (300 MHz) $\delta$ 7.56 (s, 2H), 5.67–5.57 (dq, $J = 6.9$, 9.9 Hz, 1H), 2.85 (d, $J = 9.9$ Hz, 1H), 1.66 (d, $J = 6.9$ Hz, 3H); $^{13}$C NMR (75 MHz) $\delta$ 142.5, 134.6, 131.2 (q, $J = 33.8$ Hz), 126.3 (q, $J = 3.4$ Hz), 122.4 (q, $J = 271$ Hz), 68.1, 21.0. Calcd for C$_9$H$_7$Cl$_2$F$_3$: C 41.73, H 2.72; Found: C 41.49, H 2.83.

1,3-Dichloro-5-(trifluoromethyl)styrene (5) via carbinol dehydration. 1-[2,6-Dichloro-4-(trifluoromethyl)phenyl]ethanol (7, 1.235 g, 4.78 mmol), potassium bisulfate (0.099 g, 0.73 mmol), and hydroquinone (0.05 g, 0.45 mmol) were added to a long neck condenser flask. The mixture was stirred at 220°C for 3 hours. The reaction mixture was then allowed to cool to room temperature and extracted with ethyl ether. The organic layer was washed with 5% sodium hydroxide, dried with sodium sulfate, and concentrated via rotary evaporation followed by high vacuum. The crude product was absorbed onto silica gel for chromatography (hexanes) giving a 16% yield (0.148 g). The starting alcohol (0.418 g) and ether diastereomers (0.263 g) were retrieved with dichloromethane.

1,3,5-Trichloro-2-iodobenzene (8). 2,4,6-Trichloroaniline (1.477 g, 7.52 mmol) was dissolved in hydrochloric acid (4 mL, 18 M). A solution of sodium nitrite (0.613 g, 8.88 mmol) and water (3 mL) was added drop wise to the reaction mixture. After stirring for 20 minutes the mixture was added drop wise to a solution of potassium iodide (12 g, 73 mmol) and water (15 mL). After stirring overnight the crude product was extracted with dichloromethane (3 x 25 mL) in a separatory funnel. The combined extracts were washed once with 10% sodium hydroxide (25 mL), once with 5% sodium bicarbonate (25 mL), once with 5% sodium bisulfate (25 mL), and once with water (25 mL). The organic layer was dried with magnesium sulfate and concentrated via rotary evaporation. The product was
then absorbed onto silica gel for chromatography (hexanes) giving a 67.4% yield (1.55 g). 1H NMR (400 MHz) δ 7.38 (s, 2H); 13C NMR (100 MHz) δ 141.3, 135.2, 127.3, 101.8.

2,4,6-Trichlorophenylacetylene (9). 1,3,5-Trichloro-2-iodobenzene (8, 0.925 g, 3.01 mmol), triethylamine (10.7 mL), and dichlorobistriphenylphosphine palladium (II) (1.6 mg, 0.023 mmol) were added together in a specialized tube for pressurized reactions and stirred for 10 minutes. Copper (I) iodide (0.1 g, 0.53 mmol) and trimethylsilylacetylene (0.5 mL, 3.6 mmol) were added in the presence of argon. The tube was sealed and then heated to 110 °C for 24 hours. The solid obtained underwent vacuum filtration with hexanes. The extractions were washed with water and brine. The organic layer was dried with magnesium sulfate and concentrated via rotary evaporation. The reaction was completed by deprotection. Methanol (50 mL) and potassium carbonate (0.5 g, 3.62 mmol) were added to the product and mixed for one hour. The crude product was then extracted with dichloromethane and washed with water. Product was dried with magnesium sulfate and concentrated via rotary evaporation. The product was then absorbed onto silica gel for chromatography (hexanes) giving a 77% yield (0.475 g). 1H NMR (400 MHz) δ 7.58 (s, 2H); 13C NMR (75 MHz) δ 141.7, 132.4 (q, J = 34 Hz), 123.7 (q, J = 34 Hz), 122.5 (q, J = 271 Hz), 108.7.

1,3-Dichloro-5-(trifluoromethyl)phenylacetylene (11). The procedure described above for compound (9) was employed to scale with the following differences: 1,3-dichloro-2-iodo-5-(trifluoromethyl)benzene (1.50 g, 4.4 mmol), triethylamine (12 mL), and dichlorobistriphenylphosphine palladium (II) (30 mg, 0.43 mmol) were added together and stirred for 10 minutes. Copper (I) iodide (20 mg, 0.11 mmol) and trimethylsilylacetylene (0.71 mL, 5.1 mmol) were used giving a 47% yield (0.490 g). 1H NMR (400 MHz) δ 7.60 (s, 2H), 3.82 (s, 1H); 13C NMR (100 MHz) δ 138.3, 134.8, 127.7, 120.9, 88.7, 76.6.
General 1,3-Dipolar Cycloaddition Reaction for Isoxazolines (4,5-dihydroisoxazoles)

Substituted styrene (0.25-4.1 equiv) was dissolved in dichloromethane (6 mL). Oxime (1 equiv) was added with stirring. Bleach (1 equiv) and water (by volume) were mixed and placed in a syringe. A syringe pump was used to slowly add the bleach solution overnight. The reaction mixture was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (3 x 25 mL), and the organic layers were combined and dried over sodium sulfate, filtered, and concentrated via rotary evaporation. The crude material was purified by silica gel flash chromatography (25:1 hexanes:ethyl acetate) to provide the purified isoxazoline.

3-Isopropyl-5-(2,4,6-trichlorophenyl)-4,5-dihydroisoxazole (12A): 2-methylpropanal oxime (0.118 g, 1.36 mmol) styrene (0.280 g, 1.36 mmol). 0.11 g, 28% yield. IH NMR (400 MHz) δ 7.35 (s, 2H), 6.18 (dd, J = 11, 11 Hz, 1H), 3.27 (dd, J = 17, 11 Hz, 1H), 3.20 (dd, J = 17, 11 Hz, 1H), 2.83 (sept, J = 7.0 Hz, 1H), 1.23 (d, J = 7.0 Hz, 6H); 13C NMR (100 MHz) δ 162.7, 136.0, 134.7, 132.9, 129.2, 77.1, 40.2, 27.9, 20.3, 20.2; Calcd for C13H12ClNO: C 49.26, H 4.13, N 4.79; Found: C 49.05, H 4.12, N 4.70

3-Isobutyl-5-(2,4,6-trichlorophenyl)-4,5-dihydroisoxazole (12B): 3-methylbutanal oxime (0.07 g, 0.7 mmol) styrene (0.142 g, 0.68 mmol). 0.056 g, 27% yield. IH NMR (400 MHz) δ 7.35 (s, 2H), 6.17 (dd, J = 12, 11 Hz, 1H), 3.26-3.22 (m, 1H), 3.19-3.14 (m, 1H), 2.31 (d, J = 7.0 Hz, 2H), 2.00-1.90 (m, 1H), 1.02 (d, J = 5.5 Hz, 6H); 13C NMR (100 MHz) δ 157.5, 136.0, 134.6, 132.6, 129.2, 77.2, 42.6, 36.5, 26.2, 22.6, 22.5; Calcd for C13H14Cl3NO: C 50.92, H 4.60, N 4.57; Found: C 51.21, H 4.51, N 4.57

3-tert-Butyl-5-(2,4,6-trichlorophenyl)-4,5-dihydroisoxazole (12C): mp 59-60 °C, 2,2-dimethylpropanal oxime (0.082 g, 0.81 mmol) styrene (0.167 g, 0.81 mmol). 0.17 g, 69% yield. IH NMR (400 MHz) δ 7.35 (s, 2H), 6.18 (dd, J = 12, 11 Hz, 1H), 3.22 (dd, J = 17, 12 Hz, 1H), 3.22 (dd, J = 17, 11 Hz, 1H), 1.26 (s, 9H); 13C NMR (100 MHz) δ 165.0, 136.0, 134.6, 132.9, 129.1, 77.5, 39.7, 33.2, 28.3; Calcd for C13H14Cl3NO: C 50.92, H 4.60, N 4.57; Found: C 50.60, H 4.51, N 4.53

3-(1-Ethylpropyl)-5-(2,4,6-trichlorophenyl)-4,5-dihydroisoxazole (12D): 2-ethylbutanal oxime (0.115 g, 1 mmol) styrene (0.228 g, 1.1 mmol). 0.155 g, 48% yield. IH NMR (400 MHz) δ 7.34 (s, 2H), 6.13 (dd, J = 12, 12 Hz, 1H), 3.21-3.17 (m, 1H), 3.14-3.09 (m, 1H), 2.51-2.42 (m, 1H), 1.66-1.44 (m, 4H), 1.00-0.94 (m, 6H); 13C NMR (100 MHz) δ 160.8, 135.9, 134.6, 132.5, 129.0, 77.0, 41.7, 39.5, 25.4, 25.2, 11.7; Calcd for C14H16ClNO: C 52.44, H 5.03, N 4.37; Found: C 52.45, H 4.91, N 4.36

5-[(2,6-Dichloro-4-(trifluoromethyl)phenyl]-3-isopropyl-4,5-dihydroisoxazole (13A): 2-methylpropanal oxime (0.092 g, 1.05 mmol) styrene (0.381 g, 1.58 mmol). 0.202 g, 59% yield. IH NMR (300 MHz) δ 7.59 (s, 2H), 6.25 (dd, J = 12, 11 Hz, 1H), 3.31 (dd, J = 17, 12 Hz, 1H), 3.22 (dd, J = 17, 11 Hz, 1H), 2.84 (sept, J = 6.9 Hz, 1H), 1.24 (d, J = 6.9 Hz, 6H); 13C NMR (100 MHz) δ 162.3, 138.1, 136.2, 132.0 (q, J = 34.4 Hz), 126.1 (q, J = 3.8 Hz), 122.3 (q, J = 272 Hz), 77.1, 40.3, 27.8, 20.3, 20.1; Calcd for C13H14Cl3F3NO: C 47.87, H 3.71, N 4.29; Found: C 48.12, H 3.68, N 4.30

5-[(2,6-Dichloro-4-(trifluoromethyl)phenyl]-3-isopropyl-4,5-
dihydroisoxazole (13B): mp 39-41 °C. 3-methylbutanal oxime (0.085 g, 0.85 mmol) styrene (0.289 g, 1.2 mmol). 0.164 g, 57% yield. $^1$H NMR (300 MHz) δ 7.59 (s, 2H), 6.25 (dd, J = 12, 12 Hz, 1H), 3.32-3.25 (m, 1H), 2.33 (d, J = 7.1 Hz, 2H), 2.03-1.89 (m, 1H) 1.03 (d, J = 6.6 Hz, 6H); $^{13}$C NMR (75 MHz) δ 157.5, 137.9, 136.2, 132.0 (q, J = 33.8 Hz), 126.1 (q, J = 3.4 Hz), 122.3 (q, J = 271 Hz), 77.2, 42.7, 36.4, 26.2, 22.54, 22.48; Calcd for C$_{14}$H$_{14}$Cl$_2$F$_3$NO: C 49.43, H 4.15, N 4.12; Found: C 49.43, H 4.09, N 4.22;

3-tert-Butyl-5-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4,5-dihydroisoxazole (13C): mp 90-91 °C, 2,2-dimethylpropanal oxime (0.142 g, 1.4 mmol) styrene (0.362 g, 1.5 mmol). 0.230 g, 49% yield. $^1$H NMR (400 MHz) δ 7.59 (s, 2H), 6.25 (dd, J = 12, 11 Hz, 1H), 3.36 (dd, J = 17, 12 Hz, 1H), 3.25-3.20 (m, 1H), 1.28 (s, 9H); $^{13}$C NMR (75 MHz) δ 165.0, 138.2, 136.2, 132.0 (q, J = 33.8 Hz), 126.2 (q, J = 4.0 Hz), 122.3 (q, J = 271 Hz), 77.5, 39.9, 33.2, 28.3; Calcd for C$_{14}$H$_{14}$Cl$_2$F$_3$NO: C 49.43, H 4.15, N 4.12; Found: C 49.43, H 4.09, N 4.22;

5-[2,6-Dichloro-4-(trifluoromethyl)phenyl]-3-(1-ethylpropyl)-4,5-dihydroisoxazole (13D): 2-ethylbutanal oxime (0.098 g, 0.85 mmol) styrene (0.362 g, 1.5 mmol). 0.230 g, 49% yield. $^1$H NMR (400 MHz) δ 7.59 (s, 2H), 6.21 (dd, J = 12, 12 Hz, 1H), 3.25 (dd, J = 17, 11 Hz, 1H), 1.28 (s, 9H) $^{13}$C NMR (75 MHz) δ 169.2, 163.2, 136.9, 136.3, 128.4, 126.1, 104.6, 26.7, 21.6; Calcd for C$_{14}$H$_{14}$Cl$_2$F$_3$NO: C 49.43, H 4.15, N 4.12; Found: C 49.43, H 4.07, N 4.16;

3-Isopropyl-5-(2,4,6-trichlorophenyl)isoxazole (14A): 2-methylpropanal oxime (0.041 g, 0.47 mmol) phenylacetylene (0.297 g, 1.44 mmol). 0.072 g, 52% yield. $^1$H NMR (400 MHz) δ 7.44 (s, 2H), 6.34 (s, 1H), 3.15 (sept, J = 7.0 Hz, 1H), 1.37 (d, J = 7.0 Hz, 6H); $^{13}$C NMR (100 MHz) δ 169.2, 163.2, 136.9, 136.3, 128.4, 126.1, 104.6, 26.7, 21.6; Calcd for C$_{12}$H$_{10}$Cl$_3$NO: C 49.60, H 3.47, N 4.82; Found: C 49.75, H 3.51, N 4.94;

3-Isopropyl-5-(2,4,6-trichlorophenyl)isoxazole (14B): 3-methylbutanal oxime (0.047 g, 0.47 mmol) phenylacetylene (0.381 g, 1.85 mmol). 0.035 g, 25% yield. $^1$H NMR (400 MHz) δ 7.45 (s, 2H), 6.30 (s, 1H), 3.15 (sept, J = 7.0 Hz, 1H), 1.37 (d, J = 7.0 Hz, 6H); $^{13}$C NMR (100 MHz) δ 169.2, 163.2, 136.9, 136.3, 128.4, 126.1, 104.6, 26.7, 21.6; Calcd for C$_{12}$H$_{10}$Cl$_3$NO: C 49.60, H 3.47, N 4.82; Found: C 49.75, H 3.51, N 4.94;

3-Isobutyl-5-(2,4,6-trichlorophenyl)isoxazole (14C): 2,2-dimethylpropanal oxime (0.062 g, 0.58 mmol) phenylacetylene (0.381 g, 1.85 mmol). 0.035 g, 25% yield. $^1$H NMR (400 MHz) δ 7.45 (s, 2H), 6.30 (s, 1H), 2.65 (d, J = 7.3 Hz, 2H), 2.10-2.00 (m, 1H), 1.01 (d, J = 6.6 Hz, 6H); $^{13}$C NMR (100 MHz) δ 163.2, 163.0, 136.9, 136.3, 128.3, 126.0, 106.4, 34.9, 28.0, 22.3;

3-tert-Butyl-5-(2,4,6-trichlorophenyl)isoxazole (14D): 2,2-dimethylpropanal oxime (0.062 g, 0.58 mmol) phenylacetylene (0.381 g, 1.85 mmol). 0.035 g, 25% yield. $^1$H NMR (400 MHz) δ 7.45 (s, 2H), 6.30 (s, 1H), 2.65 (d, J = 7.3 Hz, 2H), 2.10-2.00 (m, 1H), 1.01 (d, J = 6.6 Hz, 6H); $^{13}$C NMR (100 MHz) δ 163.2, 163.0, 136.9, 136.3, 128.3, 126.0, 106.4, 34.9, 28.0, 22.3;
mmol) phenylacetylene (0.475 g, 2.3 mmol). 0.094 g, 50% yield. $^1$H NMR (400 MHz) δ 7.44 (s, 2H), 6.36 (s, 1H), 1.40 (s, 9H); $^{13}$C NMR (100 MHz) δ 172.0, 163.1, 136.8, 136.3, 128.4, 126.0, 104.3, 32.2, 29.5; Calcd for C$_{13}$H$_{12}$Cl$_{13}$NO: C 51.26, H 3.97, N 4.60; Found: C 50.98, H 3.79, N 4.48

3-(1-Ethylpropyl)-5-(2,4,6-trichlorophenyl)isoxazole (14D): 2-ethylbutanal oxime (0.07 g, 0.61 mmol) phenylacetylene (0.294 g, 1.43 mmol). 0.127 g, 67% yield. $^1$H NMR (400 MHz) δ 7.45 (s, 2H), 6.28 (s, 1H), 2.79-2.72 (m, 1H), 1.82-1.71 (m, 2H), 1.69-1.59 (m, 2H), 0.91 (t, $J = 7.5$ Hz, 6H); $^{13}$C NMR (75 MHz) δ 167.1, 163.3, 136.9, 136.3, 128.4, 126.2, 104.5, 40.6, 27.3, 11.7; Calcd for C$_{14}$H$_{14}$Cl$_3$NO: C 52.77, H 4.43, N 4.40; Found: C 52.74, H 4.22, N 4.47;

5-[2,6-Dichloro-4-(trifluoromethyl)phenyl]-3-isopropylisoxazole (15A): 2-methylpropanal oxime (0.078 g, 0.9 mmol) phenylacetylene (0.239 g, 1 mmol). 0.015 g, 53% yield. mp 47-48 °C $^1$H NMR (300 MHz) δ 7.68 (s, 2H), 6.38 (s, 1H), 3.17 (sept, $J = 7.1$ Hz, 1H), 1.37 (d, $J = 7.1$ Hz, 6H); $^{13}$C NMR (75 MHz) δ 169.3, 162.8, 136.7, 133.8 (q, $J = 34$ Hz), 131.0, 125.3 (q, $J = 3.2$ Hz), 122.2 (q, $J = 270$ Hz), 104.8, 26.7, 21.6;

5-[2,6-Dichloro-4-(trifluoromethyl)phenyl]-3-isopropylisoxazole (15B): 2-methylpropanal oxime (0.065 g, 0.33 mmol) phenylacetylene (0.277 g, 2.3 mmol). 0.065 g, 61% yield. $^1$H NMR (400 MHz) δ 7.68 (s, 2H), 6.42 (s, 1H), 1.42 (s, 9H); $^{13}$C NMR (75 MHz) δ 172.1, 162.6, 136.7, 136.3, 128.4, 126.2, 104.5, 40.6, 27.3, 11.7; Calcd for C$_{14}$H$_{14}$Cl$_3$F$_3$NO: C 49.73, H 3.58, N 4.14; Found: C 49.65, H 3.46, N 3.91.

References

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