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**Comparison of Methodologies for Synthesis of
3-(Cyclopropylethynyl)benzothiazole 1,1-Dioxide**

A Thesis Presented for the Bachelor of Science Degree in Honors Chemistry

Rachel Naramore

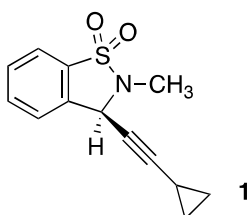
23 April 2013

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Introduction

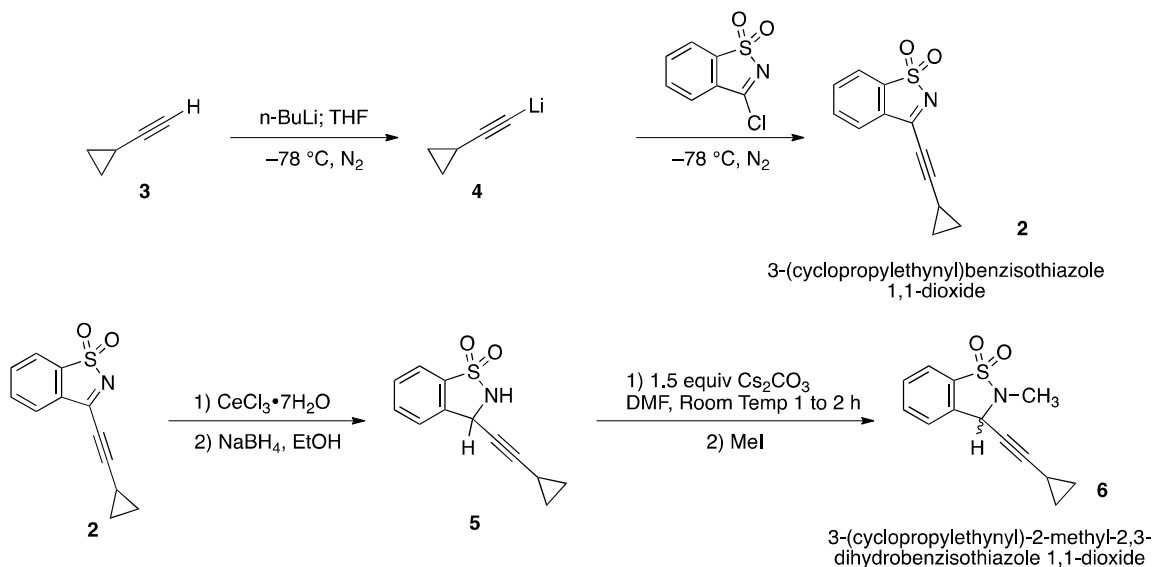
Human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome (AIDS), has infected approximately 34.0 million people around the world as of 2010, with 2.7 million new infections appearing yearly. That same year, 1.8 million people died of AIDS-related causes.¹ Thus far, three key cellular enzymatic targets for HIV drugs have been pinpointed: reverse transcriptase, protease, and integrase.² Chemical modeling using the program SYBYL 7.3 has showed that (*S*)-3-(cyclopropylethynyl)-2-methyl-2,3-dihydrobenzothiazole 1,1-dioxide (**1**) has potential to be used as a non-nucleoside reverse transcriptase inhibitor for the treatment of HIV.³



(*S*)-3-(cyclopropylethynyl)-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide

The proposed reaction scheme for the synthesis of 3-(cyclopropylethynyl)-2-methyl-2,3-dihydrobenzothiazole 1,1-dioxide (**6**) is shown below.

Scheme 1



A chiral preparatory column on HPLC can then be used to separate the racemic mixture.

The method employed by Kafri for the synthesis of the key reagent 3-(cyclopropylethynyl)benzothiazole 1,1-dioxide (**2**) gave low yields,³ and although modifications to this synthesis by LeCroix met with early success,⁴ recent trials have also resulted in low amounts of product formation. Given the potential of **1** for treatment of HIV, as well as the usefulness of this reaction scheme for analogous compounds, attempts to increase the yield of **2** and thereby increase the production of **1** were in order. Temperature, time, molar equivalents of *n*-butyllithium, and quenching procedures were systematically varied in an attempt to increase yield of intermediate **2**. Additionally, mass spectrometry and nuclear magnetic resonance spectroscopy were used to explore potential side reactions and to measure the purity of the compound.

Human Immunodeficiency Virus

There are two major types of HIV virus, known as HIV-1 and HIV-2. HIV-2 infects less than 50,000 people and has manifested few mutations as of yet.⁵ By contrast, HIV-1 has four distinct lineages—that is, it was introduced into the human population from four separate cross-species transmission events.⁶ These lineages are known as groups M, N, O, and P.⁶ Group M, the most common group, can be further subdivided into nine clades, or mutated forms of the virus springing from a common group.⁵ About 50% of all HIV infections are in the C clade of the M group.⁵

Though there is much genetic diversity among HIV viruses, several characteristics are present in all specimens. The HIV genome consists of two identical molecules of single-stranded RNA.⁷ All HIV genomes contain the *gag* gene, which encodes the structural components of the viral matrix and core, and the *pol* gene, which encodes enzymes used in viral replication including reverse transcriptase, integrase, and protease.⁷ In addition, every HIV virus has a membrane that contains noncovalently bound glycoproteins 120 and 41 (gp120 and gp41).⁷ Each of these traits is crucial to the survival of the virus.

Although a type of white blood cell known as the T-cell is HIV's primary target, the virus usually enters the body using submucosal dendritic cells.⁸ The virus binds to a C-type lectin (a protein which binds sugar at variable rates depending on the concentration of Ca⁺²)⁹ known as DC-SIGN and is from there absorbed into an acidic

compartment within the cell, migrating with it to the lymphatic system.⁸ Once the virus has been carried to the lymphatic system, it binds to a T-cell, its primary target.⁸ The HIV virus infects T-cells through the binding of the virus' glycoprotein 120 to the cell's glycoprotein CD4. This binding induces a conformational change in the virus, exposing a region that then binds to the cell's chemokine receptors, which are molecules that bind proteins responsible for regulating inflammatory responses. This binding in turn allows fusion and endocytosis to occur.^{5,8}

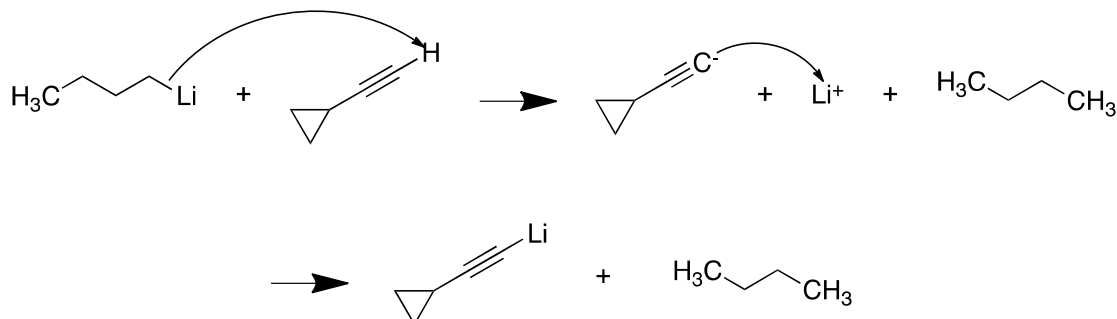
Once inside the cell, the virus uncoats and releases its reverse transcriptase complex using a mechanism that is not yet fully understood.¹⁰ Reverse transcriptase then transcribes the RNA into a double-stranded RNA/DNA hybrid.⁷ The RNA strand is then broken down, and reverse transcriptase synthesizes the complementary DNA strand to form a double-stranded DNA molecule.⁷ The reverse transcriptase docks with microtubules and forms the preintegration complex (PIC), which then enters the nucleus in a process that is also poorly understood.¹¹ Once it is within the nucleus, the virus will continue its life cycle if it is successfully integrated into the host genome in a process mediated by the viral enzyme integrase (IN).⁸ The virus will then either enter a dormant phase and replicate along with the cell as it undergoes mitosis, immediately kill the cell, or use the cell's machinery to manufacture new viruses to begin the process over again.⁸

Reverse transcriptase inhibitors, as the name suggests, target reverse transcription as a means by which to interrupt the HIV replication cycle. Nucleoside reverse transcriptase inhibitors are analogous to the natural substrate of reverse transcriptase—that is, to the DNA nucleosides.¹² Like nucleosides, they are incorporated into DNA, allowing them to halt synthesis.¹² By contrast, non-nucleoside reverse transcriptase inhibitors (NNRTIs) are not necessarily analogous to natural nucleosides, and inhibit binding not by incorporation into the forming DNA, but by binding to a hydrophobic pocket on the reverse transcriptase that changes the conformation of the enzyme and interferes with its catalytic activity.¹² Computer modeling of the hydrophobic pocket has indicated that (*S*)-3-(cyclopropylethynyl)-2-methyl-2,3-dihydrobenzothiazole 1,1-dioxide (**1**) has great potential as a NNRTI.

Mechanisms

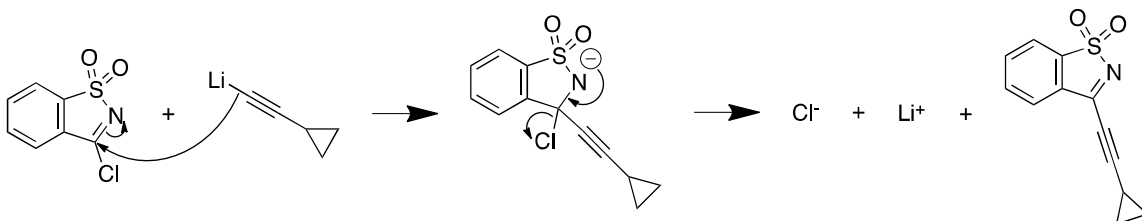
Lithiation proceeds through the mechanism as shown in Scheme 2 below.

Scheme 2



The reaction of the lithiated alkyne with saccharin *pseudo*-chloride proceeds by the mechanism drawn in Scheme 3 proposed by Riyam Kafri.³

Scheme 3



Reagents and Alternate Syntheses

Because they are strong bases, organolithium compounds will deprotonate and lithiate relatively acidic organic molecules.¹³ Lithiations are particularly favorable when the carbon to be deprotonated is stabilized by a conjugated π system, as with allylbenzene, or sp hybridization, as with ethynylcyclopropane.¹⁴ If one molar equivalent of an organolithium compound such as *n*-butyllithium is added to a terminal alkyne, the acetylenic carbon will be lithiated; if two equivalents are added, the propargylic carbon will be lithiated as well.¹⁴ If lithiation is the desired reaction, an electron-donating solvent such as THF should be used to stabilize the electron-starved lithium,¹⁴

Several relevant side-reactions are possible when organolithium compounds are used. Many organolithium compounds will react with simple ethers. For example, at 35 °C, *n*-butyllithium has a half-life of only 10 minutes in THF, with the two compounds reacting to form butane, ethylene, and the lithium enolate of acetaldehyde. The half-life

increases to 23.5 hours at 0 °C.¹⁴ Additionally *n*-butyllithium may add to the propargylic carbon as well as the terminal carbon if two molar equivalents are present.¹³ Care must be taken, therefore, to avoid the conditions under which such reactions will occur.

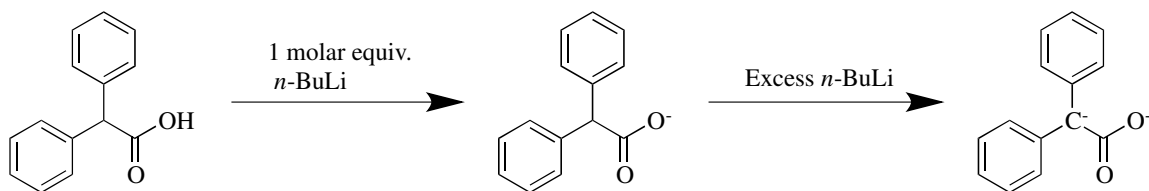
There is some variation in the literature as to optimum conditions for performing lithiations and alkylations. Most lithiations are performed in 30–45 minutes, not 4 hours as suggested by Kafri.³ Gaeta et al., for instance, report a twenty minute dropwise addition of *n*-butyllithium to the alkyne followed by ten minutes of stirring at –78 °C.¹⁵ Additionally, a paper by Abramovitch et. al., contains another potential workup method.¹⁶ The reaction described between saccharin and organolithium compounds was quenched using ice water, and the pH was lowered to approximately pH 1 with the addition of dilute aqueous HCl. The aqueous layer was then separated from the organic layer using an ether extraction. Both of these variations were incorporated into modifications of the earlier synthesis.

Procedure

Since the presence of water is known to compromise yield, the THF was obtained from a dry solvent system and distilled once more using sodium with benzophenone to produce the diphenyl ketyl anion as an indicator. Glassware used in the reaction was stored in an oven and cooled in a desiccator to minimize the presence of water. Molecular sieves were added to the ethynylcyclopropane to ensure that it had not been contaminated with water, and saccharin *pseudo*-chloride was stored in a desiccator.

Additionally, the *n*-butyllithium was titrated to standardize concentration. Approximately 600 mg of dry diphenylacetic acid were placed into a 25-mL Erlenmeyer flask and dissolved in THF. This solution was purged under nitrogen for ten minutes, and then titrated with *n*-butyllithium. The *n*-butyllithium preferentially removes the hydroxyl hydrogen. Once this reaction has gone to completion, excess *n*-butyllithium deprotonates the alpha carbon. This will turn the solution a pale-yellow color, indicating that the equivalence point has been reached. This reaction is shown in Scheme 4 below.

Scheme 4



The procedure proposed by LeCroix for synthesis of the compound 3-(cyclopropylethynyl)-1,2-benzisothiazole 1,1-dioxide (**2**) is as follows.⁴ One molar equivalent of ethynylcyclopropane (**3**) in about 10 mL THF was purged under nitrogen for 10 to 15 minutes and cooled to $-78\text{ }^{\circ}\text{C}$ using a dry ice/acetone bath. One molar equivalent of 2.5 M *n*-butyllithium in hexanes was then added to this solution, which was left to stir for four hours under nitrogen while warming to between $-40\text{ }^{\circ}\text{C}$ and $0\text{ }^{\circ}\text{C}$. Meanwhile, a solution of 1.5 molar equivalents of saccharin *pseudo*-chloride in approximately 50 mL of THF was prepared, purged for 10 to 15 minutes under nitrogen, and cooled to $-78\text{ }^{\circ}\text{C}$. The first solution was added dropwise to the second over the course of 45 minutes to 1 hour and left to stir until an hour after the beginning of the addition. This solution was then quenched using a saturated aqueous solution of ammonium chloride and allowed to warm to room temperature. The organic products were extracted from the aqueous layer in a separatory funnel using ether as the solvent, and the ether layer was dried with anhydrous magnesium sulfate. The liquid was filtered using a Buchner funnel and rotary evaporated, then placed on a high-vacuum line to remove remaining solvent. The product was purified using a column of 3:1 ether:petroleum ether and a column of 3:1 DCM:petroleum ether. If necessary, another column was run using 2:1 petroleum ether:EtOAc.

Additionally, a column of 3:1 petroleum ether:ethyl acetate was run on the raw product obtained using Method 18. After all of the compounds that proved mobile in that solvent system had eluted, methanol was added at the end to remove the rest of the compounds. Each spot that eluted was set aside, rotary evaporated, and weighed. Each sample was then analyzed through mass spectrometry using DCM as the solvent. NMR spectroscopy was not determined because the high-vacuum line was unavailable to remove solvent, and because there was insufficient time to run additional columns to purify the individual spots.

Results

The variations on LeCroix's scheme and the yields obtained are listed in Table 1 below.

Table 1

Method	Deviations from Procedure	Molar Equiv. <i>n</i> -butyllithium	Yield
1	No changes to LeCroix method	1.3	22.1%
2	No changes to LeCroix method	1.2	28.6%
3	No changes to LeCroix method	1.1	38.0%
4	No changes to LeCroix method	0.8	32.2%
5	Quenched with water and 1 M HCl until pH ~1	1.2	<24.0%
6	3.5 hour lithiation, 1.25 h addition to saccharin <i>pseudo</i> -chloride, 1 h left stirring	0.9	<11.6%
7	5 hour lithiation	1.0	<36.3%
8	30 minute addition to saccharin <i>pseudo</i> -chloride, 1 h left stirring	1.3	<21.1%
9	1 h left stirring after addition to saccharin <i>pseudo</i> -chloride	1.2	9.8%
10	1 h left stirring after addition to saccharin <i>pseudo</i> -chloride	1.1	5.7%
11	Lithiated alkyne added to saccharin <i>pseudo</i> -chloride over 10 minutes	1.2	39.3%
12	30 minute lithiation at -78 °C, 1 h left stirring after addition to saccharin <i>pseudo</i> -chloride	1.2	0%
13	45 minute lithiation at -78 °C, 1 h left stirring after addition to saccharin <i>pseudo</i> -chloride	1.2	40.4%
14	4 hour lithiation at -78 °C, 1 h left stirring after addition to saccharin <i>pseudo</i> -chloride	1.0	41.3%
15	2 h lithiation at -78 °C, 10 minute addition to saccharin <i>pseudo</i> -chloride, 1 h left stirring	1.0	<42.5%
16	Warmed to 0 °C	1.0	<20.5%
17	Warmed to 10 °C	1.0	<20.2%
18	2.5 hour lithiation at -78 °C, 1 h addition to saccharin <i>pseudo</i> -chloride, 1 h left stirring	1.0	<41.7%

Note: a < indicates that the product was never completely pure even after two and sometimes three chromatographic columns had been run, and that the yield is based on the purest form the compound attained.

The mass of the eluents from the column of the raw product from method 18 as well as their mass peaks appear in Table 2. Note that the *m/z* ratio will be one greater than the mass of the molecule. The column labeled "Approximate Millimoles" indicates the

approximate amounts of product in each major peak. Since presence of other peaks indicates that a small amount of impurities remained, these relative amounts are more suited for a qualitative comparison than a quantitative analysis.

Table 2

Eluent	Approximate Mass (mg)	Approximate Millimoles	Major Peaks	Other Peaks
1	7.0	0.03-0.06	274, 149, 111, 177, 205, 232	163, 113, 143, 219, 243, 371, 345, 305
2	27.5	0.09	290	273, 231, 332, 111
3	84.6	0.28	298	268, 184, 240, 111
4	10.4	0.05-0.06	167, 201, 212	254, 232, 260, 184, 111, 139, 298, 285, 243, 111, 139
5	661.3	2.86	232	292, 103, 274
6	116.6	0.44	268	184, 232, 111, 144, 131, 199
7	71.8	0.27–0.39	184, 268	226, 232, 103, 111, 131, 210
8 (methanol)	636.0	3.0-3.5	211, 183	116

Discussion and Conclusions

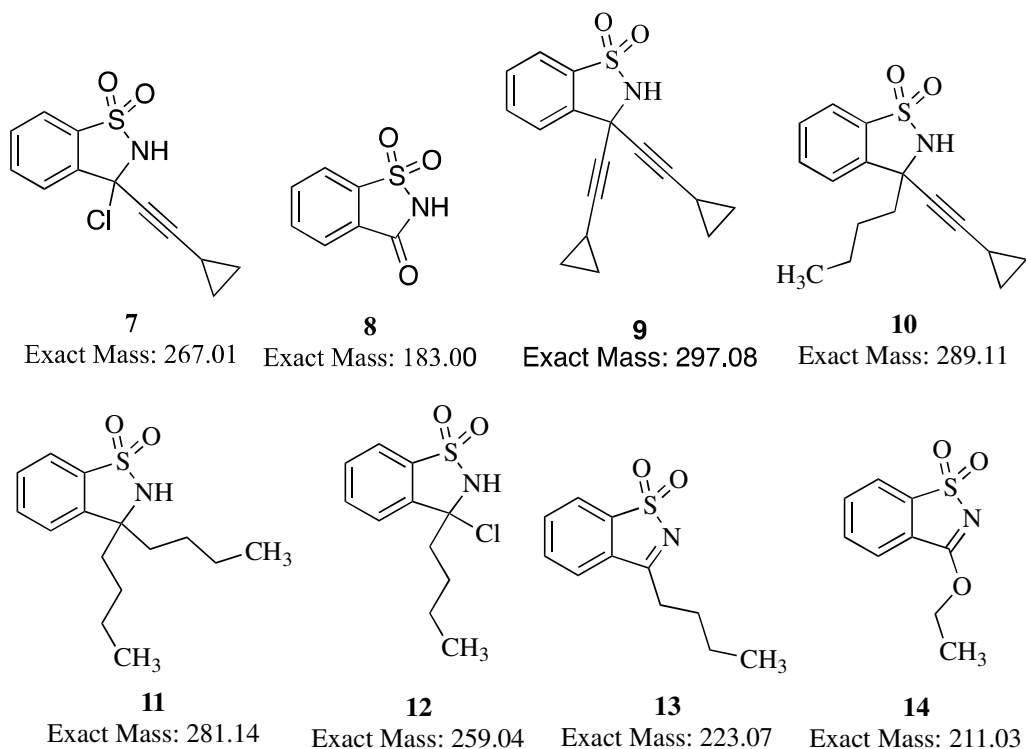
Methods 1 through 4 simply varied the relative amount of *n*-butyllithium added. This confirmed what Kafri had found in her dissertation—that although two molar equivalents are required to lithiate saccharin, only one molar equivalent *n*-butyllithium should be added to lithiate saccharin *pseudo*-chloride. Method 5 was tried because the paper on which Kafri’s method was based utilized this method instead of the one used by Kafri and LeCroix.¹⁶ Method 6 used decreased time for the lithiation step so that a comparison could be made with the four-hour lithiation time to test whether the longer time resulted in greater by-product formation. On the other hand, method 7 tested whether four hours was too short of a period of time for the reaction to go to completion. Methods 6, 8, 9, and 10 were utilized to test whether the alkylation step had enough time to go to completion, and methods 11 and 15 tested whether the rate of addition made a significant difference in reaction time as proposed by LeCroix.⁴

A clearer strategy by which to proceed presented itself when it was discovered that previous schemes had called for lithiation over much shorter periods of time than the four hours recommended by Kafri and LeCroix.¹⁵ This discovery was utilized for methods 12, 13, 15, and 18, in which the lithiation was conducted under shorter time spans. The shorter reaction times did not allow solution to warm up to anywhere near 0 °C, so it was unclear whether to the shorter time or the lower temperatures were responsible for the higher yields. For this reason, a reaction was conducted using method 14, in which the reaction was kept at -78 °C for four hours, to determine whether time or temperature was responsible for the improvement in product formation.

Methods 16 and 17 were utilized to determine whether the issue was one of kinetic vs. thermodynamic control. It was hypothesized that the contaminants observed were kinetic products favored at cold temperatures. To test this, temperatures were increased to allow for the formation of the thermodynamic product. Yields obtained for these methods as compared to methods in which the lithiation was conducted at -78 °C for the duration of the reaction indicate that the desired product is obtained when the reaction is under kinetic control.

Various products were observed on mass spectra. Compounds 7-10 in Figure 1 correspond to the peaks recorded in Table 2, while compounds 11-14 correspond to peaks observed in other trials but not in the mass spectra corresponding of the various elutions obtained using method 18.

Figure 1



For method 18, a rough estimate for the number of moles of each byproduct was determined by assuming that the major peak was the only substance present. In the case of multiple major peaks, a range was generated by assuming that the lowest and the highest molecular weight compounds were the only compounds present. This approximation is very loose, but gives a sense of the abundance of products relative to one another.

The most prevalent structures found were in elution 7 with peaks at 211 and 183. Their identity is unknown, but mass spectrometry revealed that both were present in the saccharin *pseudo*-chloride starting material. The second most prevalent was the desired product **2**. Next came the mono-alkylated form in which the chloro group remained bonded to the heterocycle **7**. The presence of **7** indicates either that the reaction was not conducted at a high enough temperature, that not enough time was allowed for the alkylation, or a combination of the two.

The next most prevalent byproducts were saccharin (**8**) and the bis-alkylated form **9**. The presence of the bis-alkylated form indicates either that the reaction was conducted at too high of a temperature, that the reaction was left to run for too long, that the lithiated

alkyne was added to the saccharin *pseudo*-chloride too quickly, or that there was too much lithiated alkyne present in relation to the saccharin *pseudo*-chloride. Since the presence of **7** indicates the exact opposite of former two possibilities, the latter two possibilities are more likely.

The presence of saccharin and the unknown contaminants with *m/z* peaks at 211 and 183 indicates that the amount of saccharin *pseudo*-chloride calculated to be present is incorrect. Mass spectrometry of the saccharin *pseudo*-chloride used indicates the presence of saccharin contaminants, so the origin of the saccharin observed in the mass spectrum of the raw product is almost certainly the saccharin *pseudo*-chloride starting material. Since the starting material is contaminated, the calculated amount of saccharin *pseudo*-chloride is likely greater than the actual amount. While saccharin does react with lithiated alkynes, it is less reactive than *pseudo*-saccharin chloride.³ The disparity between the calculated and actual amount of saccharin *pseudo*-chloride likely contributes to the formation of **9**.

An extremely small amount of compound **11** was formed. This indicates that there was a slight excess of *n*-butyllithium, so that it was left in solution to add to saccharin *pseudo*-chloride. It is possible, then, that the concentration used in calculating the amount of *n*-butyllithium present is slightly off, but the fact that the amount is so small indicates that the difference between actual and calculated amounts of *n*-butyllithium is not a significant concern.

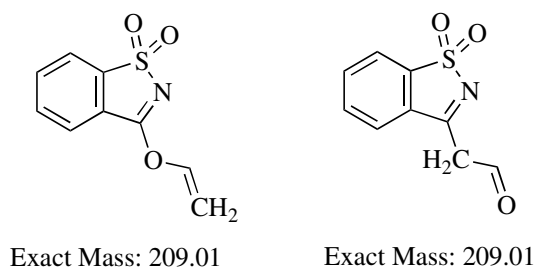
The rest of the compounds indicated by the mass peaks are present in vanishingly small amounts and are not significant contributors to yield. The peak at 177 is most likely a dimer of ethyl acetate, and many of the small molecular weight compounds probably come from the petroleum ether.

In reactions in which 1.1 or more molar equivalents of *n*-butyllithium were used, compounds **12**, **13**, and **14** appeared on mass spectra. Excess *n*-butyllithium competed with ethynylcyclopropyl lithium in the alkylation reaction of saccharin *pseudo*-chloride. Thus, an excess of *n*-butyllithium should result in an overall reduction of yield. Although this trend held true for methods 1, 2, and 3, the reverse trend held true for methods 9 and 10. This makes little sense, as it seems that additional time would allow for more addition of the butyl group. Regardless, the yields are quite small in methods 9 and 10.

Compound **15** ($m/z = 212$) also appeared in most mass spectra. The origin of this byproduct is unknown. It was thought that it might be due to a reaction of potential ethanol contaminants in ether with saccharin *pseudo*-chloride, but when saccharin *pseudo*-chloride was placed in a vial of diethyl ether, compound **15** was not observed in the mass spectrum.

There is no indication that the *n*-butyllithium and THF underwent degradation of the kind described in the introduction. If the acetaldehyde enolate were forming, it would be expected to compete with ethynylcyclopropyl lithium in the reaction, and one or both of the compounds in Figure 2 would be present. Since the half-life of *n*-butyllithium even at temperatures as high as 0 °C is 23.5 h,¹⁷ it is unlikely that *n*-butyllithium decayed enough for this to occur in significant amounts using any of the methods described here, with the possible exception of method 17, depending on the half-life of *n*-butyllithium at 10 °C.

Figure 2



One potential means by which to speed up the lithiation step that was not explored here is the use of *tert*-butyllithium instead of *n*-butyllithium. Carbon-lithium bonds tend to have a strong covalent character, which in turn leads to their complexation in solution. Less branched organolithium reagents, such as *n*-butyllithium, tend to form stronger complexes than more branched organolithium reagents, such as *tert*-butyllithium. Because these complexes are stronger, the time to lithiate is longer. However, it is possible that the use of *tert*-butyllithium would decrease yield, since this complexation increases the bond polarity between lithium and carbon, which in turn lowers the activation energy for lithiation reactions. Additionally, although both *n*-butyllithium and *tert*-butyllithium are violently reactive with the moisture in the air, *tert*-butyllithium is more so, creating a greater safety concern than does *n*-butyllithium.¹⁸ Finally,

tert-butyllithium degrades more quickly than does *n*-butyllithium, with a half-life of a little over five and a half hours in THF even as cold as $-40\text{ }^{\circ}\text{C}$.¹⁷

The most likely source of procedural error for this reaction stems from the fact that it must be performed under completely dry conditions. Although the reactions were conducted under nitrogen in septum-sealed flasks, it was still difficult to keep every bit of moisture from the atmosphere out of the reaction. Since water reacts with *n*-butyllithium, the presence of moisture would be problematic.

Another limitation to this study involves the number of molar equivalents of *n*-butyllithium. Because it was initially thought that the *n*-butyllithium sent by the company was 2.5 M, many of the trials were conducted with more or less than one equivalent of *n*-butyllithium. Thus, an additional variable was inadvertently introduced for several of the trials. It is thus more difficult to draw direct correlation with any one variable.

The temperature at which the lithiation takes place appears to be the most important factor in obtaining a higher yield. For the methods in which the temperature was kept around $-78\text{ }^{\circ}\text{C}$ for the duration of the reaction, yields remained above 40%; for those in which the reaction was allowed to warm to above $-40\text{ }^{\circ}\text{C}$, on the other hand, the maximum yield obtained was 39%. Synthesis of 3-(cyclopropylethynyl)benzothiazole 1,1-dioxide should be conducted over two to four hours and should be kept near $-78\text{ }^{\circ}\text{C}$ for the duration of the reaction. In addition, the lithiated alkyne should be added slowly to the saccharin *pseudo*-chloride over the course of 45 minutes or more, as rapid addition seems to have a more deleterious effect on yield than the heating of the lithiated alkyne when it is removed from the dry-ice/acetone bath. Taking these steps will maximize yield.

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