

Alek Grady

Synthetic Formal Report #1 - The Synthesis of 2,3-Dibromo-3-(3-chlorophenyl)-1-(4-methoxyphenyl)-1-propanone

December 8, 2023

The bromination of 3-chloro-4'-methoxychalcone (**1**) is an alkene addition reaction. This type of reaction allows for the addition of a wide variety of substituents or proton to be attached at either end of the starting material's double bond, losing one pi bond, and gaining two sigma bonds. Alkene addition reactions can include halogen additions, hydroxylation, and others. Controlling stereochemical outcomes and creating chiral centers, which powerful tools in organic synthesis, is also possible depending on reactants and mechanism of the specific reaction¹. In the case of bromination and similar reactions, the alkene acts as a nucleophile and attacks a possible substituent. In this specific reaction, the product yields a trans vicinal dibromide. While alkene addition reactions can be used as a final step in synthesis, they can also attach groups that can be utilized in following steps, like attaching halogens to act as good leaving groups, giving way to a variety of possible pathways. This specific experiment utilized the green chemistry in situ bromination to add bromines across the chalcone's double bond, reducing danger associated with elemental bromine.

The dibromide chalcone product has several important uses. A major use of the brominated chalcone is utilizing it in following steps of a synthesis, specifically forming heterocyclic compounds², such as pyrazoles, pyrazolines, isoxazoles, and other cyclic molecules. α,β -dibromides allow for ease of attachment. The carbonyl is attacked first and, second, bromine allows for the attachment for formation of the heterocyclic group because it is a good leaving group. The resulting heterocyclic molecules have a wide variety of biological uses, including medicinal applications³. The most simple uses of the α,β -dibromides is creating three-member heterocycles. These three member rings can have anti-microbial,

antibiotic, and antibiotic properties², among others. The complexity of these heterocycles can increase, depending on the starting α,β -dibromides, leading to five and six member rings with varying stereochemistry². More specific questioning has yielded dibrominated chalcones as a starting material for quinoxaline derivatives, which have showed promise as anticancer chemicals⁵. Overall, these brominated chalcones serve best as intermediates in syntheses creating biological relevant molecules, and potentially drugs. This brominated chalcone can be utilized for creating heterocyclic systems, using the bromines as leaving groups. The chalcone general structure be utilized as a starting material of anti-cancer and anti-viral compounds³.

The balanced reaction synthesis of the brominated chalcone product goes through three major steps. The first step involves orthoperiodic acid oxidizing bromine anions from potassium bromide to water, periodic acid, and elemental bromine ($2\text{Br}^- + \text{H}_5\text{IO}_6 \rightarrow \text{Br}_2 + 2\text{H}_2\text{O} + \text{HIO}_6$). The alkene from 3-chloro-4'-methoxychalcone (**1**) nucleophilic attacks the elemental bromine to form a cyclic bromonium intermediate. The electrons from the elemental bromine bond are pushed onto the neighboring bromine, forming a bromine nucleophile. This unstable intermediate is then attacked by a bromine nucleophile. The lone pair of the bromine nucleophile attacks one of the carbons of the cyclic bromonium, and the electrons of the bond from the nucleophilic attacked carbon are pushed onto the initial addition bromine. The result is the trans vicinal dibromide product, 2,3-dibromo-3-(3-chlorophenyl)-(4-methoxyphenyl)propan-1-one (**2**). Other experimental results propose reacting the chalcone starting material with elemental bromine in acetic acid⁴. This introduces toxicity and corrosive nature of elemental bromine and is not ideal. Additionally, a similar in-situ bromination can be achieved with potassium bromide and cerium(IV) ammonium nitrate (CAN), but environmental and personal dangers also discourage its usage⁵.

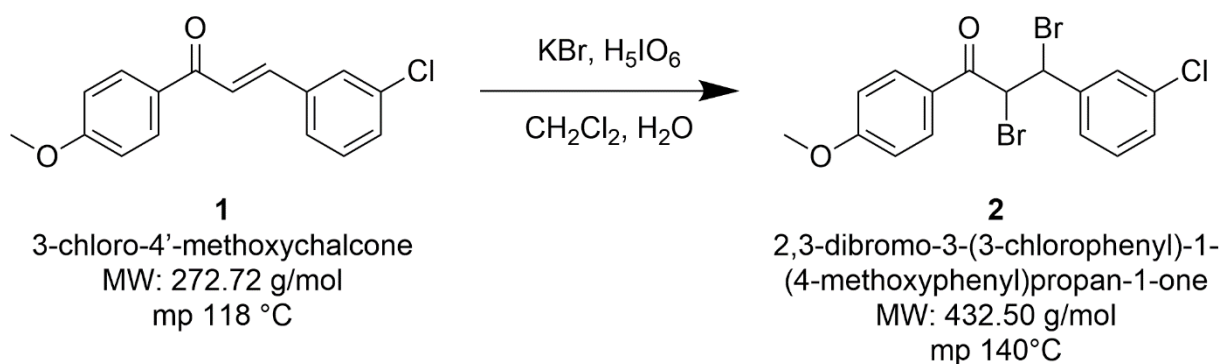


Figure 1: In-situ bromination of 3-chloro-4'-methoxychalcone

The brominated chalcone product was successfully synthesized and purified according to 400 MHz $^1\text{H-NMR}$ data. Most downfield is a doublet integrating to two at 8.085 ppm, representing hydrogen A. This aromatic hydrogen is most downfield because it is ortho to the EWG ketone. Next is a singlet integrating to one at 7.528 ppm, which is hydrogen b. Again, this aromatic hydrogen is more downfield because it is ortho to the EWG chlorine. Hydrogen C, a doublet integrating to one; H_d , a triplet integrating to one; and H_e , a doublet integrating to one, overlap to a multiplet integrating to three at 7.39 ppm. Hydrogens F is represented by a doublet integrating to two at 7.020 ppm. This aromatic hydrogen is slightly more upfield because it is ortho to the EDG ether. Two doublets integrating each to one are seen

at 5.73 and 5.587 ppm, hydrogens G and H. H_g is slightly more downfield because of the closer proximity to the EWG ketone. Finally, A singlet integrating to three representing hydrogens I is observed at 3.913 ppm. The lack of two doublets integrating to one in the 4.5-6.5 ppm region prove the chalcone was successfully brominated, and the presence of two doublets integrating each to one further upfield in the 2.0-4.1 ppm region prove product formation. The product was successfully purified by recrystallization. The only contamination was a small ethanol peak at 1.253 ppm, which was the recrystallization solvent, and no starting material was present. This small peak, in combination to the 139.7 °C expected MP, expected white, crystalline appearance indicate high purity. Overall, the brominated chalcone was successfully synthesized and purified by recrystallization.

The brominated chalcone product was successfully synthesized and purified according to ¹³C-NMR data. The starting chalcone and brominated chalcone product share many peaks but differ in several key peaks from distinct carbons. Both starting and product will produce fourteen distinct peaks, but two will differ in location, which helps confirm conversion. The ketone carbon 1 appears at 189.321 ppm, and the methoxy carbon, 13, appears at 48.645 ppm. Both these carbons appear in the starting material and final product, so they are easiest to identify first. The chalcone starting material will produce two C=C alkene peak in the 150-105 ppm range. These two peaks are notably missing in the purified ¹³C-NMR, indicating lack of starting material in final product. The brominated chalcone will produce two distinct C-Br bromide peak in the 65-30 ppm range. These peak are seen at 46.369 ppm and 55.659 ppm, proving conversion to the final product. Carbon 12 is more downfield because it is closer to the EWG ketone in relation to carbon 14. No other impurities are seen in the ¹³C-NMR, indicating high purity in the final, isolated product. All peaks present, especially the lack of alkene carbons and presence of bromide carbons, appear at expected literature values⁸. Overall, ¹³C-NMR indicates the brominated chalcone was successfully synthesized and purified by recrystallization.

The brominated chalcone product was successfully synthesized and purified according to IR data. First seen on the IR is a C-H aromatic peak at 3074.47 cm⁻¹. This is next followed by the C-H aliphatic

peak at 2965.85 cm^{-1} . The conjugated C=O ketone peak is observed at 1672.59 cm^{-1} . C=C aromatic peaks are then observed within peaks at 1598.45 cm^{-1} and 1464.73 cm^{-1} . The expected CH₃ umbrella peaks are seen at 1420.20 cm^{-1} and 1368.35 cm^{-1} . The two conjugated C-O ether peaks are then seen at 1254.15 cm^{-1} and 1176.80 cm^{-1} . A C-Cl aryl peak is observed at 1025.83 cm^{-1} . Finally, the C-Br aliphatic peak is observed at 567.72 cm^{-1} . This C-Br peak is the biggest indicator of product formation, as it was not present in the starting material. There are potential impurities present in the IR. First, a small peak is seen at $\sim 3200\text{ cm}^{-1}$, which could be an O-H stretch from the ethanol contamination also seen in NMR data. Second, a C-H alkane peak is seen at 2841.34 cm^{-1} , which also indicated some alkane impurity in the final, isolated product. Both of these impurity peaks are likely due to ethanol, which was utilized as a recrystallization solvent. Given the very small transmittance of the peaks, in combination with MP at expected value, and expected white crystalline appearance, the recrystallization was successful and final product was highly pure. In conclusion, according to IR data, the brominated chalcone was successfully synthesized and purified by recrystallization.

The experiment was successful. The overarching purpose was the synthesis of 2,3-Dibromo-3-(3-chlorophenyl)-1-(4-methoxyphenyl)-1-propanone from 3-chloro-4'-methoxychalcone via an in situ bromination. This goal was reached and all data obtained was within expected range. Beginning with 400 MHz ¹H-NMR, all expected peaks were present and appeared at expected ppm values. The only contamination observed in ¹H-NMR was an ethanol peak at 1.253 ppm, which was present because ethanol was utilized as the recrystallization solvent during purification. No other contaminants were observed in NMR, indicating the final, isolated product was highly pure. ¹³C-NMR also came to the same conclusion. All fourteen distinct carbon peaks were present in the data. These peaks specifically excluded two C=C alkene peaks at 65-30 ppm range, indicating that the chalcone starting material was not present. Two C-Br bromide peaks were then observed at 55.659 ppm and 46.369 ppm. These two peaks prove that 2,3-Dibromo-3-(3-chlorophenyl)-1-(4-methoxyphenyl)-1-propanone was successfully synthesized because they would not be present in the starting material. All other peaks appeared at expected literature values⁸,

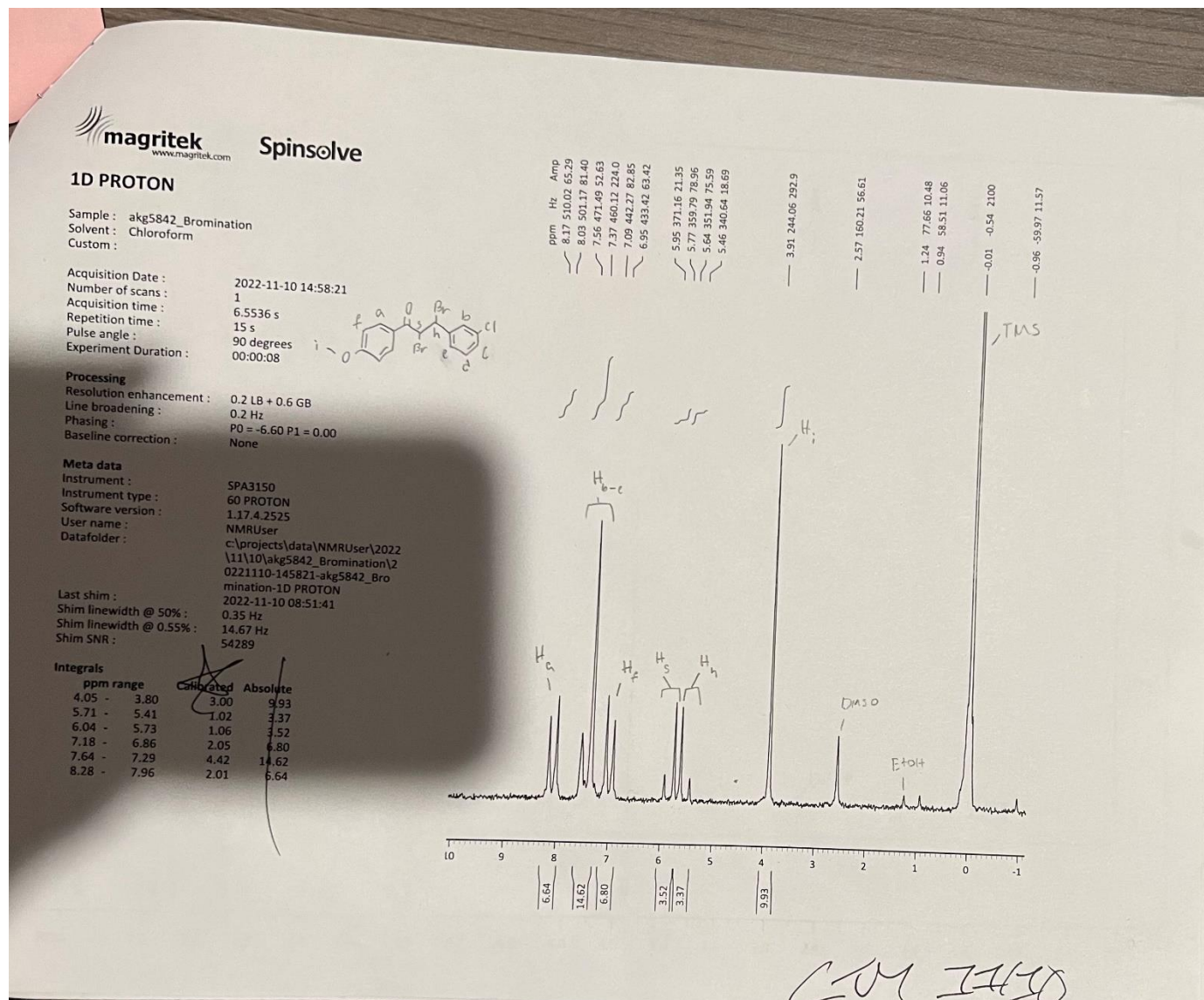
and no other distinct peaks were observed in ^{13}C -NMR, indicating high purity. IR data reinforced this. Trans C=C peaks were not observed in the final data, proving that the starting material had been converted to the brominated chalcone product. Additionally, a C-Br aliphatic peak is seen at 567.72 cm^{-1} . The presence of this C-Br peak proves that the brominated chalcone was synthesized. Minimal impurities were seen in IR, specifically an O-H stretch at approximately 3200 cm^{-1} and C-H alkane at 2841.34 cm^{-1} . Both of these impurity peaks are likely due to the ethanol contamination that was also seen in NMR data. All other peaks expected were seen in the IR of the final, isolated product⁸. The physical appearance of the final product was a white, crystalline solid. This also matches the expected physical appearance. Additionally, the melting point of the final isolated product was 139.7 C , which was extremely close to the expected 140 C . Pure yield of the product, 0.462g , was 58% and percent recovery was 69% . This pure yield remain the only source of error. Possible improvements include running the in situ bromination for longer, so more starting material can be converted to product and Considering all of this data, 2,3-Dibromo-3-(3-chlorophenyl)-1-(4-methoxyphenyl)-1-propanone was successfully synthesized via in situ bromination from 3-chloro-4'-methoxychalcone, and subsequently purified by recrystallization in ethanol.

References

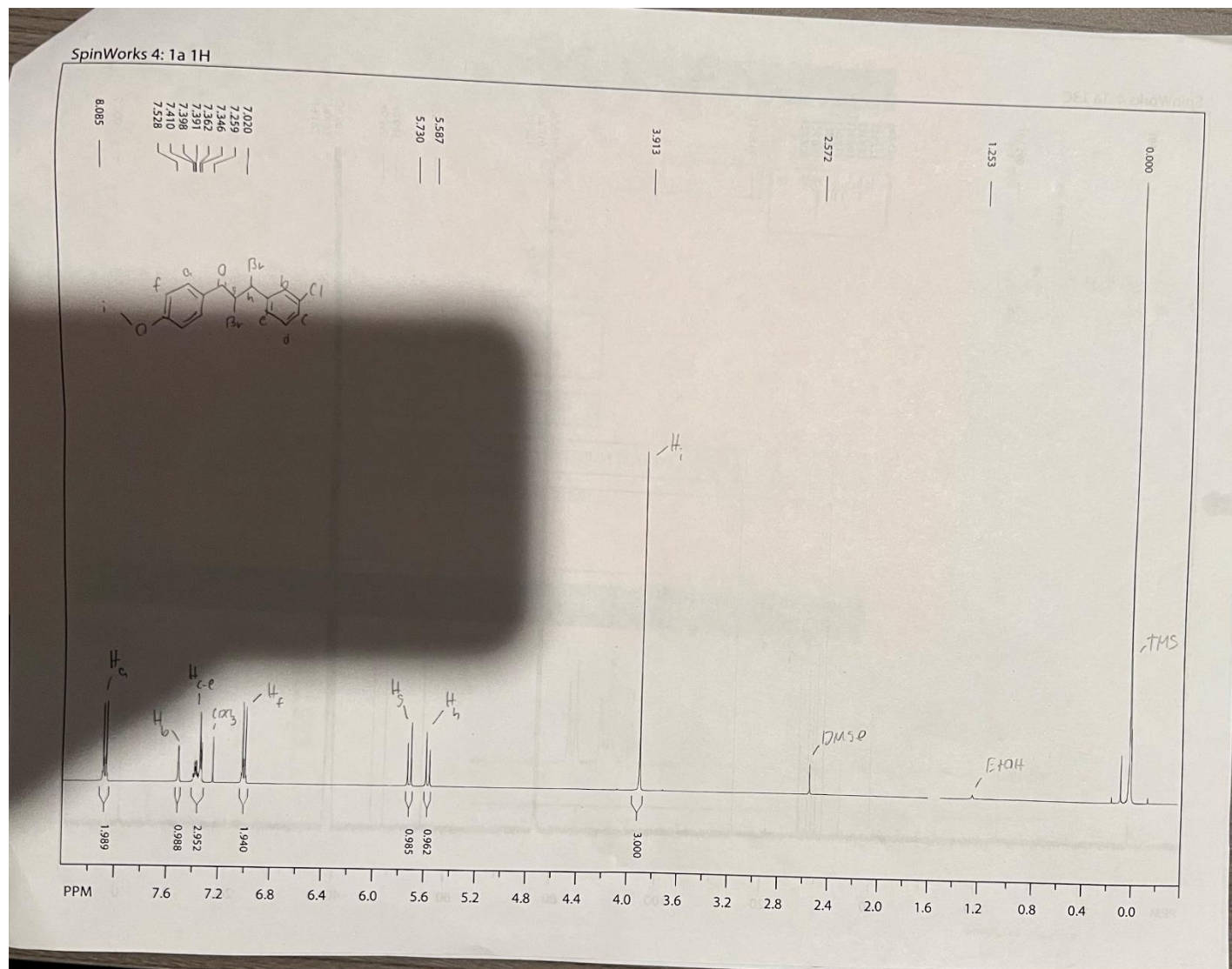
- 1) Bock, J.; Guria, S.; Wedek, V.; Hennecke, U. Enantioselective Dihalogenation of Alkenes. *Chem. Eur. J.*, **2020**, *27*, 14, 4517-4530
- 2) Kamal, R.; Kumar, Ravinder; Kumar, Vipin; Bhardwaj, Vikas. Synthetic Utilization of α,β -Dibromide In Heterocyclic Chemistry and Stereoselective Debromination. *ChemistrySelect*, **2019**, *4*, 39, 11578-11603
- 3) Stephens, C.E.; Arafa, R.K. 3,5-Diarylisoxazoles: Individulized Three-Step Synthesis and Isomer Determination Using ^{13}C NMR or Mass Spectroscopy. *J. Chem. Educ.*, **2006**, *83*, 9, 1336-1340
- 4) Khazaei, A.; Zolfigol, M.A.; Kolvari, E.; Koukabi, N.; Soltani, H.; Komaki, F. Electrophilic Bromination of Alkenes, Alkynes, and Aromatic Amines with Potassium Bromide/Orthoperiodic Acid under Mild Conditions. *Synth. Commun.*, **2009**, *21*, 3672-3676
- 5) Popat, K. H.; Nimavat, K. S.; Thaker, K. M.; Joshi, H. S. Synthesis of some quinoxaline derivatives containing halogen atoms starting from carbonyl compounds and evaluation of their biological activity. *J. Chemtracks*, **2003**, *15*, 2, 443-446
- 6) Nair, V.; Panicker, S.B.; Augustine, A.; George, T.G.; Thomas, S.; Vairamani, M. An efficient bromination of alkenes using cerium(IV) ammonium nitrate (CAN) and potassium bromide. *Tetrahedron*, **2001**, *57*, 34, 7417-7422
- 7) Dykstra, S.A.; Schmid, K.M.; Beiswenger, K.M.; Bischof, A.M.; Mahon, C.T.; Rose, H.C. *Lab Guide For Chemistry 213W Introductory Organic Chemistry Laboratory, 2022-2023*; Macmillan Learning Curriculum Solutions: Plymouth, MI; 2022
- 8) Dykstra, S.; Williams, R.; Mahon, C. *Synthesis Project 2, Step 1: Bromination of 3-chloro-4'-methoxychalcone*, 2022; Pennsylvania State University: State College. PA; 2022

Spectral Data

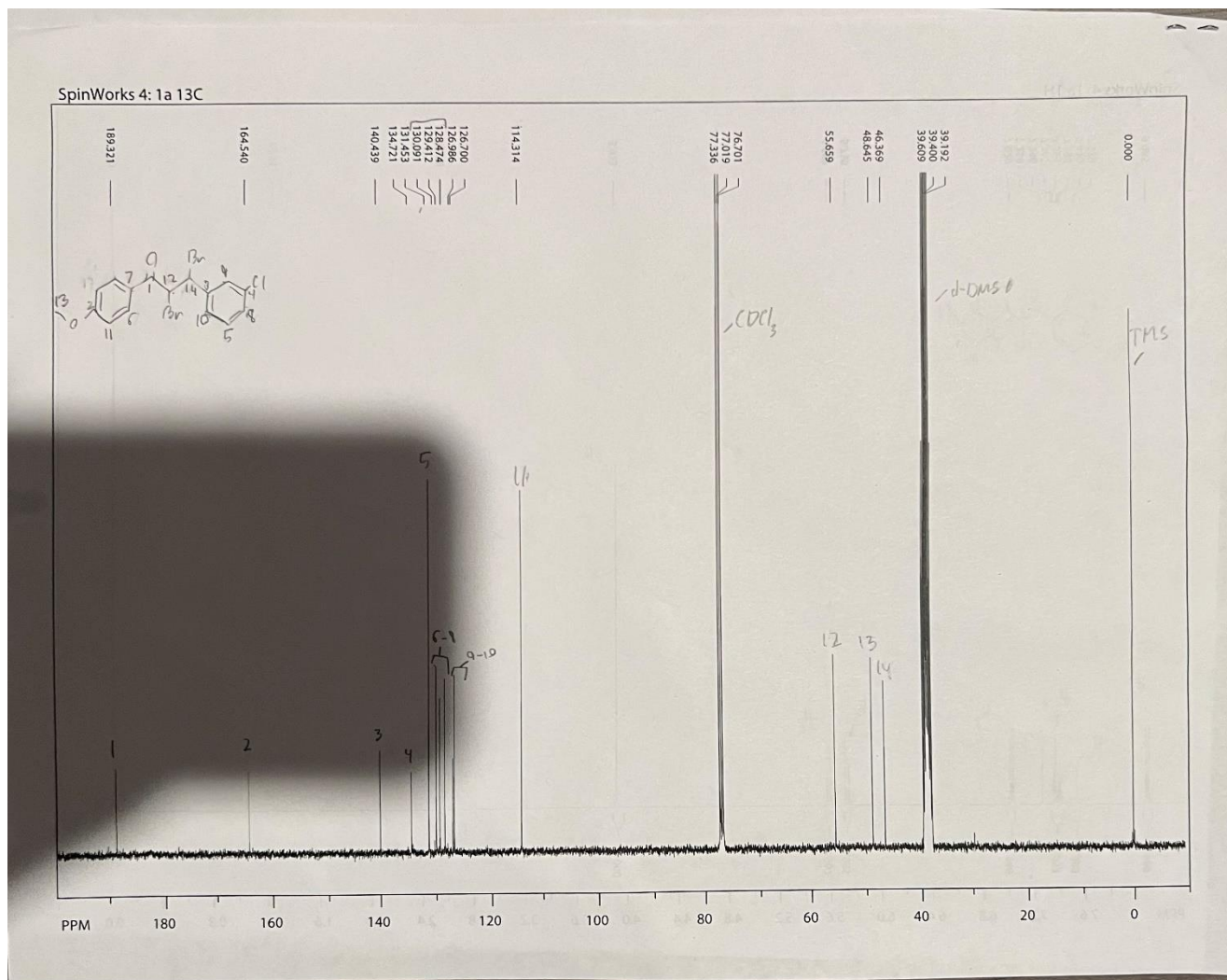
- Proton NMR (60 MHz), annotated



- Proton NMR (400 MHz), annotated



- Carbon-13 NMR (100 MHz), annotated



- IR, annotated

