Investigations in Supercritical Fluid Reaction Chemistry: Synthesis in a Non-traditional Medium

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ABSTRACT

As we move into the 21st century, the chemical industry is under increasing pressure and scrutiny to develop cleaner and "greener" technologies. Supercritical fluids (such as carbon dioxide) are emerging as environmentally attractive alternatives for a number of synthetic organic processes. Working in the supercritical medium presents a number of constraints including temperature, pressure, and solubility. We have successfully employed this medium in the Diels-Alder cycloaddition reaction. Results of our work will be presented.

INTRODUCTION

As we move forward into the next century, we must consider the environmental ramifications of the hazardous waste produced from chemical processes. Many solvents, such as methylene chloride, used for chemical synthesis and extractions are considered toxic and hazardous to the environment. Supercritical fluids are an attractive alternative because they can be easily recycled and they provide ease of product separation. A supercritical fluid is the state of matter in which a compound is subjected to conditions above its critical pressure and critical temperature but at a pressure low enough to prevent the solid from forming (Figure 1). The supercritical fluid is a hybrid state of matter consisting of properties of both liquid and gas. It has the solvating properties of a liquid and the diffusive properties of a gas. The use of supercritical carbon dioxide for synthesis and extractions is very convenient. Supercritical carbon dioxide is readily available, recyclable and has a relatively attainable critical point (31^{O} C, 74 atm).[1]

The Diels-Alder reaction[2] was chosen for further exploration in the new solvent medium. This particular reaction was chosen for a few reasons. First, it is a very useful synthetic reaction resulting in the formation of a six-member ring (scheme 1). Another reason is that the Diels-Alder reaction proceeds under neutral conditions (no acid or base required) making it a good starting point with which to perfect the methodology of the new solvent medium. Thirdly, there is precedent that the Diels-Alder reaction can be adapted to supercritical carbon dioxide.[3]

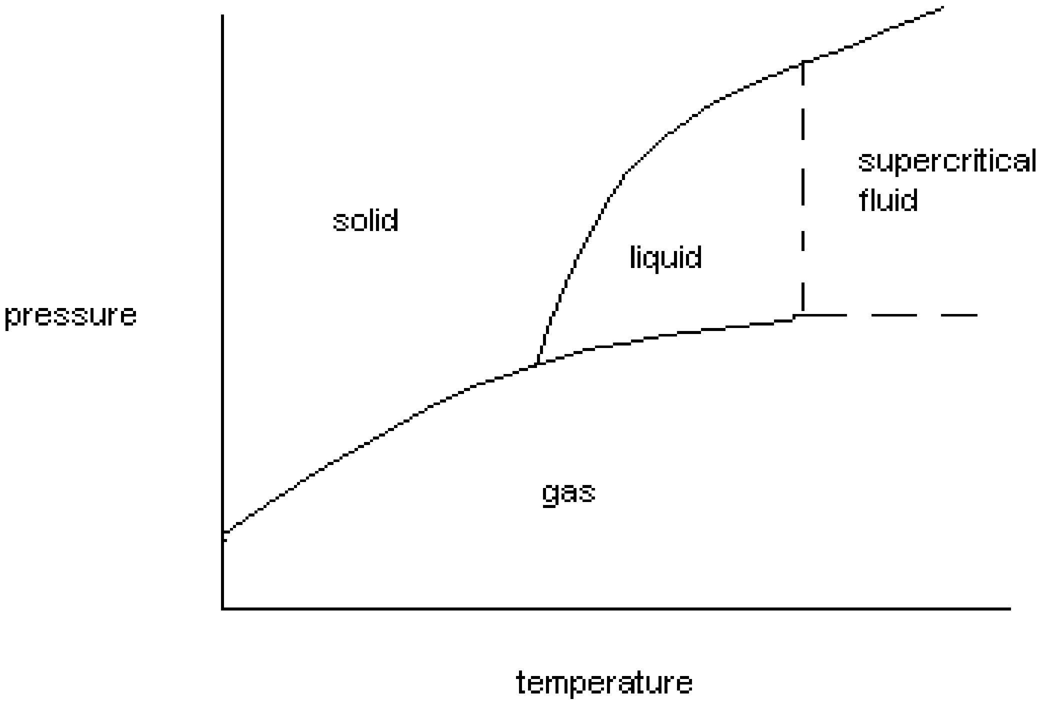
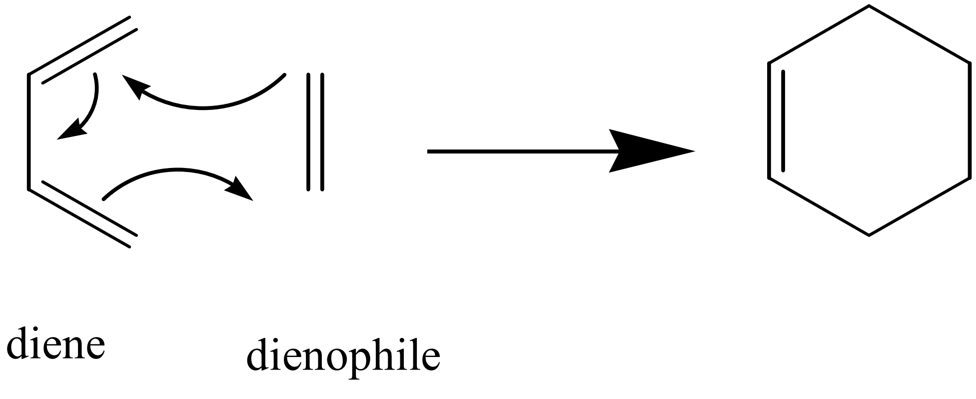


FIGURE 1. PHASE DIAGRAM SHOWING THE SUPERCRITICAL FLUID REGION

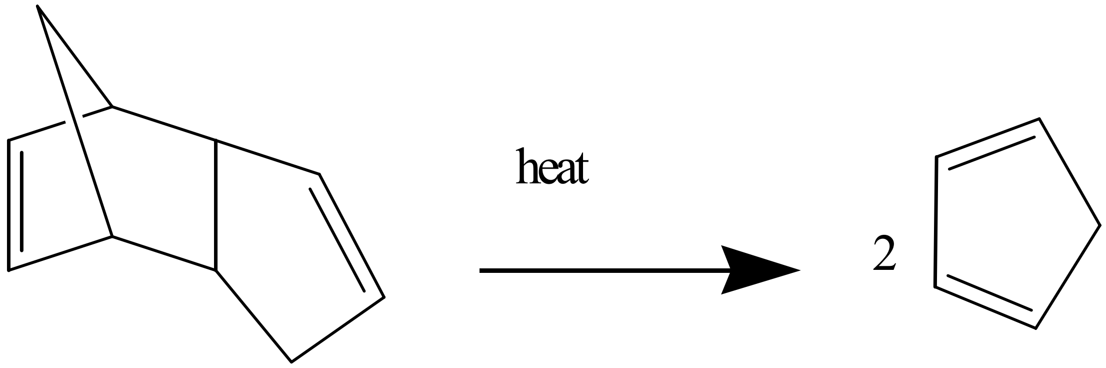


SCHEME 1. BASIC DIELS-ALDER REACTION

RESULTS AND DISCUSSION

The initial stages of my research involved the screening of numerous Diels-Alder reactions. Three reactions were selected and conducted under traditional solvents. The purpose of this process was to find a reaction that could be reliably reproduced and provide pure product with good yield. It was also necessary to find a reaction that could be adapted to the limitations of the supercritical fluid instrument. For example, once the pressurization is started, the vessel can not be opened. Another limitation is that the diameter of the vessel is not very large resulting in difficulties when adding reagents.

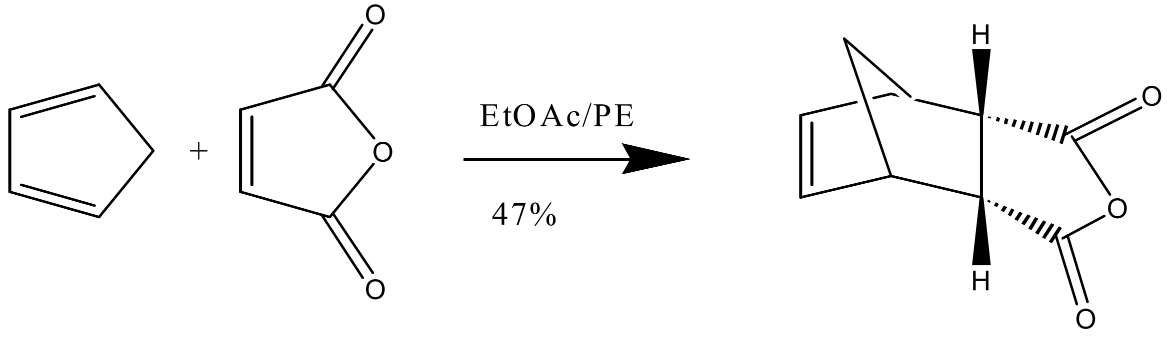
The first reaction investigated was the synthesis of cis-norbornene-5,6-endo-dicarboxylic acid (SCHEME 3).[4] Before this reaction may be attempted, dicyclopentadiene must be "cracked" (distilled) to give cyclopentadiene (scheme 2). The reason is that cyclopentadiene is not stable at room temperature. It can react to reform dicyclopentadiene. The monomer must then be kept cold in order to prevent it from reforming the dimer. The product of this reaction is a white solid. This reaction is attractive because it requires only 30 minutes of gentle heating (40-43^{O} C) in order to react.



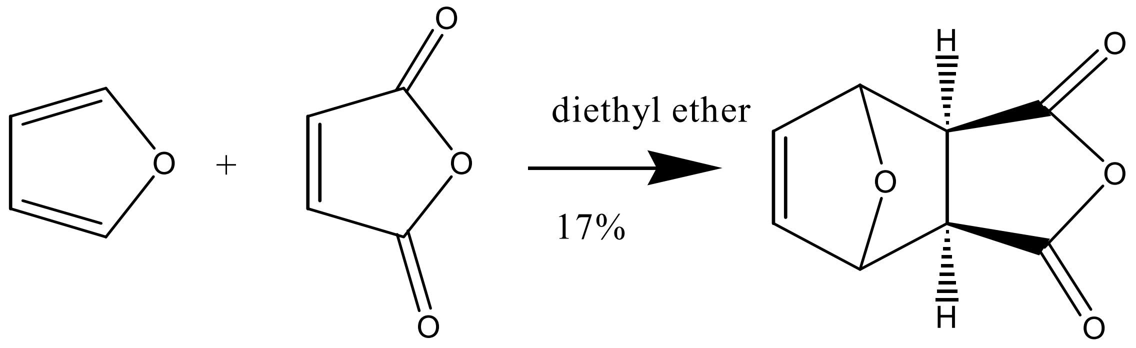
SCHEME 2. CRACKING OF DICYCLOPENTADIENE

The second reaction examined was the synthesis of exo-3,6-epoxy-1,2,3,6-tetrahydrophthalic anhydride (SCHEME 4).[5]

This reaction is unique in that it produces the exo product and not the endo isomer. This is confirmed by melting point since both have considerably different melting points (81^{O} C for the endo and 114^{O}C for the exo). The reaction proceeds at room temperature and requires a couple of hours of stirring to react.

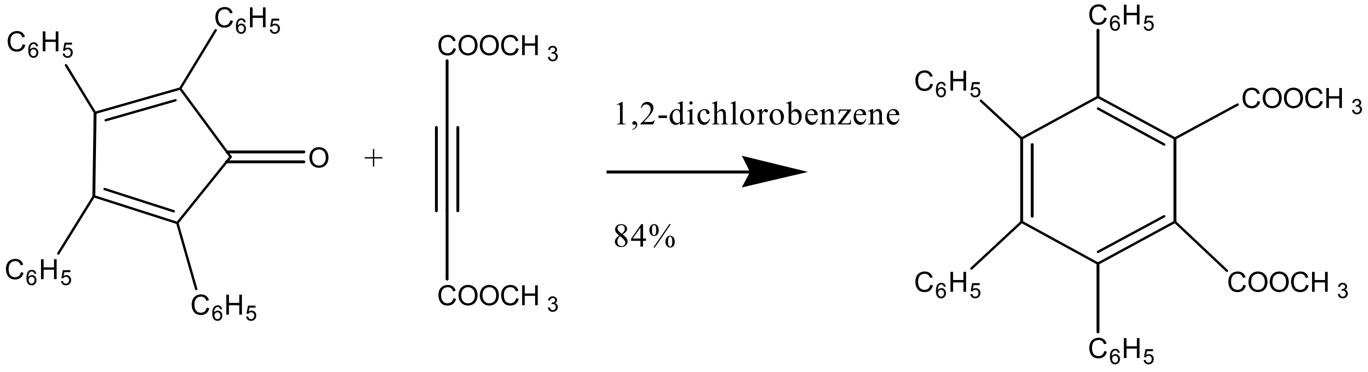


SCHEME 3. SYNTHESIS OF CIS-NORBORNENE-5,6-DICARBOXYLIC ANHYDRIDE

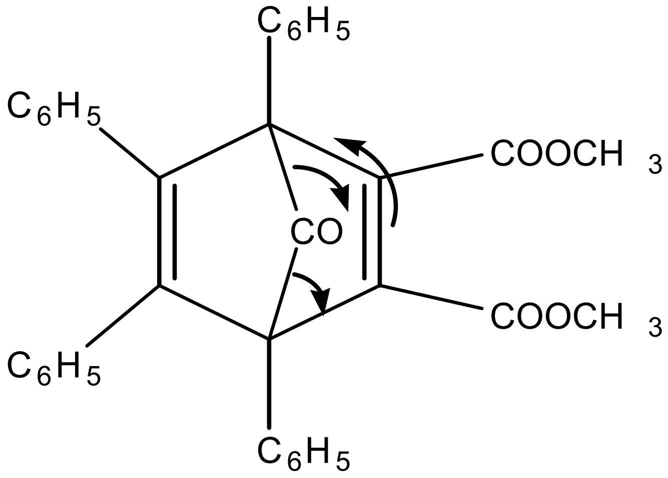


SCHEME 4. SYNTHESIS OF EXO-3,6-EPOXY-1,2,3,6TETRAHYDRO-PHTHALIC ANHYDRIDE

The third reaction explored was the synthesis of dimethyl tetraphenylphthalate (SCHEME 5).[6] This reaction features an intermediate which is shown below (SCHEME 6). The product is a white solid that requires approximately 2 hours of heating at 180^{O} C to form. This particular reaction was chosen for adaptation to supercritical carbon dioxide because it does not have any reactants that must be kept cold prior to use thereby reducing the chance for side reactions. Another point that should be noted is that the traditional solvent used in this reaction is a toxic irritant and cancer suspect agent. By performing this synthesis in supercritical carbon dioxide, one can eliminate the use of a very harmful solvent.



SCHEME 5. SYNTHESIS OF DIMETHYLTETRAPHENYLPHTHALATE



SCHEME 6. INTERMEDIATE FOR SCHEME 5

The next part of the research involved adapting the reaction from scheme 5 to supercritical carbon dioxide. Numerous problems were encountered during this process. The first problem dealt with the reaction vessel itself, which has a small diameter and a fixed volume of 50 mL. A unique aspect of working with a supercritical fluid is that the solvent fills the entire vessel whether or not that volume of solvent is necessary. Glass beads were used to occupy some of the excess volume and to increase the concentration of starting materials in the supercritical carbon dioxide. Small (4 mL) vials were used to hold the reagents because they had a diameter narrow enough to be placed within the vessel.

The next problem to be addressed was the need to separate the reactants prior to pressurization to ensure that they did not react in the absence of solvent. This was accomplished by placing each reagent in its own 4 mL vial. Early TLC analysis revealed that very little product was forming and that mostly unreacted starting materials remained indicating poor mixing. Trials were conducted with the vials uncapped and stacked on top of each other, separated by a third empty vial. Other attempts were made with 2 vials stacked with a mesh screen separating them. None of these arrangements seemed to solve the problem of reducing large portions of unreacted starting material. The final decision was to sprinkle the solid reagent onto the glass beads (making it more solvent accessible) and to place a vial containing the liquid reagent on top. This setup improved yield while ensuring that each reagent was kept separate.

Another problem encountered was that some starting material was expelled out the top of the vessel upon initial pressurization. The vessel is designed as a flow-through cell so that gas is pumped in the bottom and out the top upon depressurization. Placing a 5 μ metal frit covering the outlet valve of the vessel alleviated this problem. All trials with the exception of the first two were conducted using the metal frit.

After the establishment of the procedure, the next step was to modify conditions in an effort to maximize yield. Many trials were run with the following conditions varied one at a time: pressure, reaction time, and amount of dienophile (TABLE 1). The one parameter which has not been addressed as of yet is temperature. Under traditional solvent, the reaction was conducted at 180^{O} C. A problem with the software of the supercritical fluid instrument only allows set temperatures up to 150^{O} C. All trials up to this point have been run at this temperature.

Trial	**Time (hours)**	**Pressure (psi)**	**Equivalence**	**% yield**	**% conversion**
1	**5**	**7289**	**5.646**	**31**	
2	**5**	**7487**	**1.563**	**44**	
3	**2**	**7482**	**1.563**	*****	
4	**5**	**7489**	**1.563**	**58**	
5	**5**	**5299**	**1.563**	**22**	**34**
6	**5**	**4940**	**1.563**	**22**	**25**
7	**5**	**7511**	**5.646**	**78****	

*Most of starting material remained, unable to isolate product.
**^{1}H NMR analysis revealed presence of starting material

TABLE 1. CONDITIONS AND YIELDS FOR SUPERCRITICAL CARBON DIOXIDE

CONCLUSIONS

We have observed the successful implementation of the dimethyl tetraphenylphthalate Diels-Alder reaction in supercritical carbon dioxide. Further research will be performed to optimize the yield for this reaction. It is proposed that the reaction does not go to completion because not all of the starting material is going into solution. The recent acquisition of a new vessel will allow the reaction to be mixed to uniformly distribute the starting materials throughout the vessel. The new vessel will also allow access to a higher temperature. Future plans include the investigation of other Diels-Alder reactions to see if they can also be successfully adapted to the new solvent medium.

EXPERIMENTAL

Diels-Alder reactions were done on a typical scale producing 1 g of product. Supercritical fluid reactions were conducted in an SFT-1000 from Supercritical Fluid Technologies, Inc., Newark, DE. The reaction vessel routinely used was the 50 mL stainless steel vessel (rated to 10000 psi and 200^{O} C). The vessel has an outer diameter of 1/4 in, inner diameter of 7/8 in, wall thickness of 1/4 in and a length of 8 3/4 in.

Reactions were pressurized by initially setting the pressure and temperature to 2000 psi and 40^{O}C, respectively. The pressure and temperature were slowly increased in increments of 250 psi and 20^{O} until the desired conditions were reached. All of this was done in static mode, which means that the outlet valve is closed preventing any gas from escaping. Depressurization of the reactions was done in the following manner. The pressure and temperature settings were changed to 0 psi and 20^{O}C while switching the instrument to dynamic mode, which means that the outlet valve is opened allowing gas to escape slowly.

Organic chemicals were purchased from the Aldrich Chemical Company. Bone dry carbon dioxide with dip tube was purchased from Tech AIR, Inc. Ice baths were used for the storage of cyclopentadiene. Reaction mixtures were checked by TLC before extractions. R_f values refer to TLC on Analtech (2.5 x 10 cm, 250 μm) analytical plates coated with silica gel GF. Developed plates were observed under a short wave UV lamp and then sprayed with 5% ceric ammonium nitrate in 20% sulfuric acid and heated on a hot plate to char.

Column chromatography was conducted with TLC-mesh silica gel (Aldrich # 28,850-0), following the procedure described by Taber.[7] The solvent mixtures used for chromatography are volume/volume mixtures. Samples were concentrated by rotary evaporation followed by concentration in vacuo to remove last traces of solvent. Melting points were uncorrected.

The infrared (IR) spectra were determined on a Perkin-Elmer Spectrum One FT-IR Spectrophotometer as solutions in CH_2Cl_2. IR results were reported in reciprocal centimeters (cm^{-1}).

Low resolution mass spectra were obtained on an HP5973 mass spectrometer. High resolution mass spectra were obtained on a PerSeptive Biosystems Electrospray Time of Flight MS. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker 500 spectrometer as solutions in $CDCl_3$. Chemical shifts are reported in δ units downfield from the internal reference tetramethylsilane (TMS). The couplings (J) are reported in Hertz (Hz). When possible, the attached proton test (APT) was performed to edit the ^{13}C spectra. This test gives positive signals (u) for carbons with an odd number of protons attached (primary or tertiary) and negative signals (d) for carbons with an even number of protons attached (quaternary or secondary).

Cis-norbornene-5,6-endo-dicarboxylic anhydride. Dicyclopentadiene (15 mL) was heated for 35 minutes under reflux to produce cyclopentadiene, which was kept in an ice water bath in order to prevent the monomer from reforming the dimer. Maleic anhydride (0.400 g, 4.08 mmol) was dissolved in ethyl acetate (1.6 mL) and petroleum ether (1.6 mL). Cyclopentadiene (0.40 mL, 6.06 mmol) was added. Upon reacting, the solution became a cloudy white and a solid formed which was collected by vacuum filtration. Recrystallization of the product from petroleum ether gave 0.471 g of a white solid (47% yield). A melting point of 160-162^O C was observed (literature melting point = 164^O C). R_f = 0.51 (40% EtOAc/ petroleum ether). 1H NMR (δ): 6.31-6.30 (m, 2H), 3.60-3.59 (m, 2H), 3.52-3.49 (m, 2H), 1.80-1.77 (m, 1H), 1.60-1.56 (m, 1H); 13C NMR (δ): 171.8 (d), 135.9 (u), 53.1 (d), 47.5 (u), 46.5 (u); IR (cm^{-1}): 3058, 2982, 1855, 1774, 1228, 1089, 906.

Exo-3,6-epoxy-1,2,3,6-tetrahydrophthalic anhydride. Maleic anhydride (1.20 g, 12.23 mmol) was dissolved in diethyl ether (10 mL) with gentle warming for 37 minutes. Additional diethyl ether was then added to replace any that had previously evaporated. The solution was cooled to room temperature. Furan (1.00 mL, 13.75 mmol) was added neat. The solution was stirred overnight. White crystals formed and were collected by vacuum filtration. Recrystallization from hexane/ethyl acetate gave 0.354 g of a white solid (17% yield). A melting point of 114^O C was measured which matches the literature value for the exo isomer. 1H NMR (δ): 6.66 (m, 2H), 5.54 (m, 2H), 3.27 (m, 2H); IR (cm^{-1}): 3055, 2988, 2306, 1860, 1786, 1422, 1264, 1233.

Dimethyl tetraphenylphthalate. Tetraphenylcyclopentadienone (2.004 g, 5.21 mmol) was dissolved in 1,2-dichlorobenzene (10 mL, 0.5 M) and dimethyl acetylenedicarboxylate (1 mL, 8.13 mmol) was added. The solution was heated at 180-185^O C for 1 hour and 40 minutes during which a color change from dark purple to dark tan was observed. The solution was then cooled to 100^O C. Ethanol (15 mL) was slowly added, with stirring. Light brown crystals formed and were collected by vacuum filtration and rinsed with methanol. Recrystallization from 95% ethanol gave 2.064 g of a white solid (84% yield). A melting point of 256-258^O C was observed for the crude product (literature melting point = 258^{O}C). The percent yield was 84. R_f = 0.66 (40% EtOAc/petroleum ether). ^{1}H NMR (δ): 7.06-7.04 (m, 6H), 6.98-6.96 (m, 4H), 6.80-6.79 (m, 6H), 6.64-6.63 (m, 4H), 3.42 (s, 6H). ^{13}C NMR (δ): 169.1, 143.7, 139.7, 139.1, 139.0, 132.6, 131.3, 130.1, 127.8, 127.3, 127.2, 126.4, 52.7; IR (cm^{-1}): 3026, 1727, 1497, 1443, 1343, 1276, 1260, 1172, 1066

Dimethyl Tetraphenylphthalate. Glass beads (30 mL) were placed in a 50 mL Thar vessel. Tetraphenylcyclopentadienone (0.515 g, 1.340 mmol) was poured onto the glass beads. Dimethyl acetylene dicarboxylate (0.25 mL, 2.034 mmol) was placed into a 4 mL cylindrical vial and put on top of the other reagent. The vessel was pressurized to 7500 psi with liquid CO_2 and heated to 150^{O} C (well above the critical point) for 5 hours. The vessel was then depressurized slowly and the crude product rinsed out with ethyl acetate (100 mL). The crude product was chromatographed on silica gel (50 g). Elution with 8% EtOAc and concentration gave 0.486 g of a white, crystalline solid; TLC R_f = 0.29 (10% EtOAc/petroleum ether) ^{1}H NMR and ^{13}C NMR were consistent with the spectra of the conventional solvent product.

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