Master`s Thesis
Department of Chemistry

# Alkylation of TEB Acetylide Using Tosylates

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## Abstract

Alkylated products of 3,3,4,4-tetraethoxybut-1-yne (TEB) where prepared from alkylation of the TEB acetylide with a selection of alkyl tosylates, obtained by tosylation of the corresponding tosylates, and alkyl iodides in low to moderate yields (21-66%).

Optimization of the reaction conditions where carried out through several sequental reactions, with systematic alterations to every consecutive reaction to achieve the required reaction conditions to afford the expected products.

The difference in reactivity of the alkyl tosylates and similar alkyl iodides towards the TEB acetylide is adressed.

## Selected abbreviations

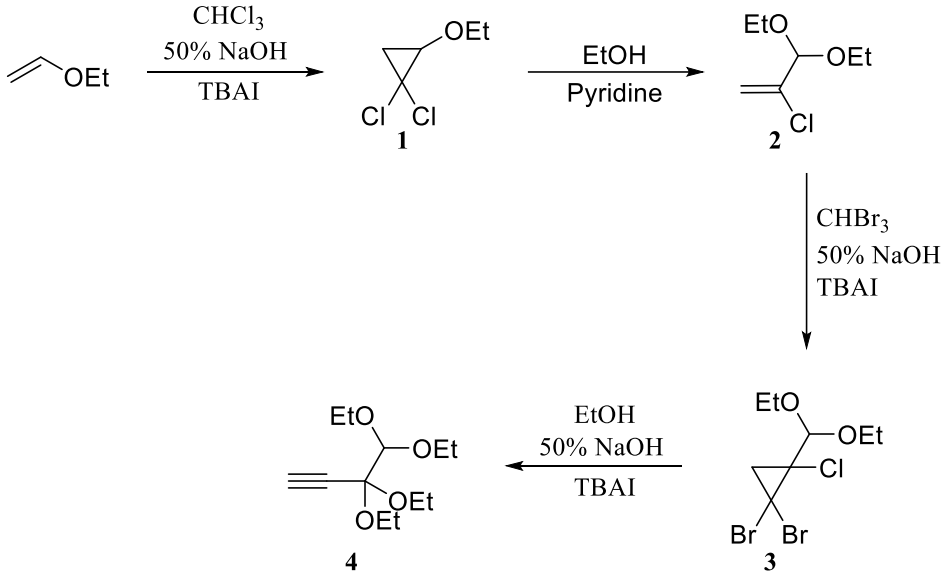
| | |
|---|---|
| aq | Aqeous |
| DCM | Dichloromethane |
| hr | Hour(s) |
| min | Minutes |
| MS | Mass spectrometry |
| rt | Room temperature |
| TBAI | Tetrabutylammonium iodide |
| TEA | Triethylamine |
| TEB | 3,3,4,4-Tetraethoxybut-1-yne |
| THF | Tetrahydrofuran |
| HRMS | High resolution mass spectrometry |

## Contents

**Part I**

# I Introduction

3,3,4,4-Tetraethoxybut-1-yne (TEB) is a highly functionalized compound, which is made in a four-step synthesis with etyl vinyl ether as the starting material. The first and third steps utilize a Maszoka-Wawrzynkiewicz cyclopropanation, while the second and last steps involve a thermal and base-induced ring opening, respectively. The synthesis is shown schematically in Scheme **1**.

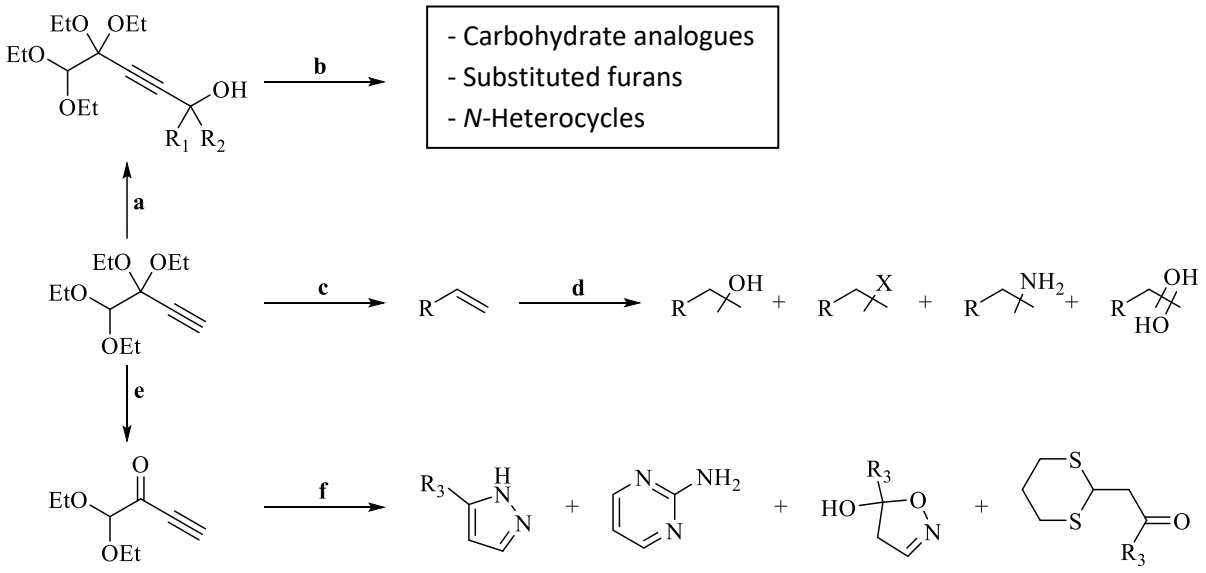



**Scheme 1**

TEB comprises of an alkyne, a ketal and an acetal moeity, making the compound an excellent starting material for a number of transformations. Most of the reactions reported so far are based on generation of the corresponding acetylide followed by chain elongations by reactions with aldehydes, ketones and epoxides.[8,21,22]

The weakly acidic acetylenic proton ($pKa \approx 25$)[14] can easily be abstracted by a strong base, such as BuLi or EtMgBr, and form the acetylide which in turn can unergo a wide

range of different chain elongations (**a**). Many of these reactions have in earlier studies been reactions between the acetylide and different aldehydes or ketones to yield propargylic alcohols in good yields, which have been converted to carbohydrate analogues, substituted furans and *N*-heterocycles (**b**).[11,22] The triple bond can be reduced to yield the corresponding alkenes (**c**) which can undergo standard olefin transformations, such as hydrogenation, hydration, amination and dihydroxylation (**d**). Furthermore, the ketal can be deketalized to form the alkynone (**e**) ,which have been reacted with different bisnucleophiles to form various heterocycles (**f**).

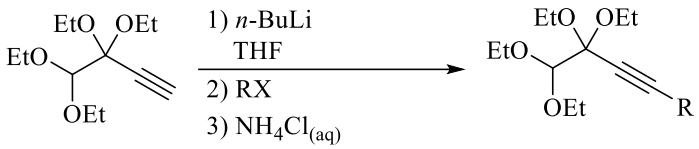



**Scheme 2**

### 1.1 Alkylation of TEB

TEB acetylide can also react with alkyl halides but this reaction has been investigated to a lesser extent. In fact, the only study carried out was done by Espeland who showed that TEB acetylide readily reacts with iodides and bromides to form the the corresponding chain-elongated alkynes in about 50% yields, except methyl iodide wich

gave 4,4,5,5-tetraethoxypent-2-yne in 76% yield.[6,7] In total four halides were tested, with the results summarized in Table 1.




**Scheme 3**

**Table 1.** Alkylation of TEB with alkyl halides.[6,7]

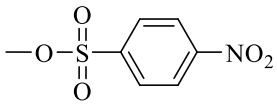
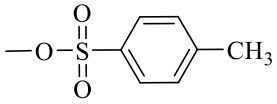
| RX | Yield (%) |
|---|---|
| Methyl iodide | 76 |
| Butyl iodide | 55 |
| Ethyl bromide | 53 |
| Prop-2-enyl bromide | 50 |

### 1.2 Alkyl tosylates as leaving group

Halides are a very common leaving group in nucleofilic substitution, but it is often more convenient to use tosylates prepared from alcohols, due to their somewhat higher stability. Sulfonic esters, such as tosylates, brosylates, nosylates, and mesylates, are powerful alkylating agents because the sulfonates are often better leaving groups than the corresponding halides[13]. Tosylates are excellent leaving groups due to resonance delocolizition of the developing negative charge on the leaving oxygen. The reactivity of the leaving groups generally correlates with their electron-attracting capacity, as with *p*-nitrobenzenesulfonate, which is which is about 10 times more more reactive than *p*-toluenesulfonate.[5] Approximate relative leaving-group abilities for $S_N1$ reactions show that the reaction rate of tosylates is $5x10^3$ times faster than bromides.[12] These rates are

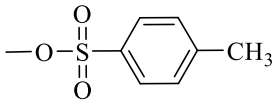
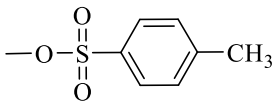
approximate and are heavily dependent on the structure of the rest of the molecule. The relative rates for some common leaving groups in $S_N1$ reactions are given in Table **2**.

**Table 2.** Relative reaction rates for some common leaving groups in $S_N1$ reactions.[5,12]

| Group | Approximate $k_x/K_{Br}$ |
|---|---|
| $-OSO_2CF_3$ (triflate) | $5 \times 10^8$ |
|  (nosylate) | $3.1 \times 10^4$ |
|  (tosylate) | $5 \times 10^3$ |
| I | 6.5 |
| Br | 1 |
| Cl | $2.5 \times 10^{-2}$ |

In $S_N2$ reactions, however, the leaving group ability of sulfonates is comparable to the halides, and the reactivity is additionally dependent on the nature of the nucleophile as well as the solvent. With a strong nucleophile, such as *p*-toluenethiolate, the tosylate reactivity is roughly half of that of the bromide, but with the weaker nucleophile, ethoxide, with a presumably looser transition state, the reactivity is higher than that of iodide, with a reaction rate 3.6 times higher than bromide.[12] A comparison of common leaving-groups with different nucleofilic substrate is given in Table **3**.

**Table 3.** Dependence of leaving-group reactivity on the nucleofile.[12]

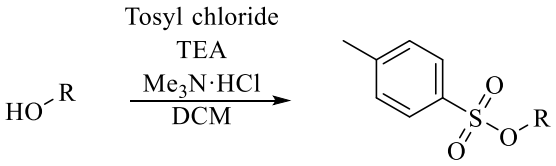
| Leaving Group (x) | Substrate and nucleophile | Temp (˚C) | $k_x/k_{Br}$ |
|---|---|---|---|
| I | $nC_3H_7X$ + *p*-$CH_3C_6H_4S^-$ | 25 | 3.5 |
| I | $C_2H_5X + C_2H_5O^-$ | 25 | 1.9 |
| Cl | $nC_3H_7X$ + *p*-$CH_3C_6H_4S^-$ | 25 | 0.0074 |
| Cl | $C_2H_5X + C_2H_5O^-$ | 40 | 0.0024 |
|  | $nC_3H_7X$ + *p*-$CH_3C_6H_4S^-$ | 25 | 0.44 |
|  | $C_2H_5X + C_2H_5O^-$ | 25 | 3.6 |

### 1.3 Tosylation of alchols

*p*-Toluenesulfonation (tosylation) of alcohols is and excellent reaction to produce alkylating agents which are versatile reagents in organic synthesis.[23] Unlike conversion of an alkohol to an alkyl halide, which might lead to a mixture of stereoisomers even from pure enantiomers, tosylation of alcohols occur with retention of configuration. They are prepared from alcohols by reactions that do not involve C-O cleavage but rather S-Cl cleavage in the sulfonyl chloride. This is in contrast to halide synthesis involving thionyl chloride or phosphorus tribromide when C-O cleavage takes place and byproduct formation may occur. Thus, tosylates are useful reagents when working with alcohols where the stereochemistry of the alcohol is crucial for the synthesis.[5]

Tosylation of alcohols is a well-studied reaction and includes a number of different methods which give varying degree of product yield depending on the structure of the alcohol. Sulfonate esters are usually prepared by reaction of an alcohol with a sulfonyl

halide in the presence of pyridine.[5] This method often requires up to 10 equivalents of pyridine and mild conditions to prevent formation of undesired side products by substitution of the formed tosylate with the chloride.[15,23] In this project a pyridine-free reaction for tosylation of alchols was applied, where the reaction is carried out under basic conditions, using $Et_3N$ and catalytic amounts of $Me_3NHCl$, to trap the HCl byproduct.[23]




**Sceme 4.** Tosylation of alchol.[23]

### 1.4 Acetylide alkylation

A commonly applied method for carbon-carbon elongation of alkynes is alkylation of a terminal alkyne with an electrophile e.g. an alkyl halide, of metallated acetylides, RC≡CM (M = Li, Na, K, MgX). These alkylations start with abstraction of the acetylenic proton with a strong base such as Grignard reagent, usually ethyl magnesium bromide, or another base such as $NaNH_2$, $KNH_2$, lithium diisopropylamide or *n*-butylithium.[3]

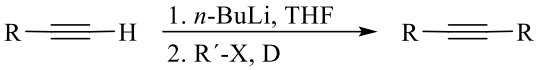
Metallation of acetylenes with alkyllithium reagents is an extremely fast reaction, even at low temperatures in the reagion of -78 °C (acetone/dry ice) and in a solvent of low polarity such as $Et_2O$.[3]

In reactions with particularly reactive alkyl halides, such as MeI, alkylation of alkynyllituim proceeds in THF at rt or below,[4] however alkylation with most primary alkyl halides have been observed to react sluggishly in $Et_2O$ or THF solvent at similar reaction conditions.[3]

Primary alkyl iodides have been shown to react with alkynyllithium compounds in THF, by heating the reaction mixture to reflux temperature, to produce the alkylated product, wheras alkyl bromides still reacted very slowly and results in inclomplete

conversion. Alkylation of lithium acetylides with alkyl bromide, is however possible in the precence of catalytic amounts of $Bu_4NI$ or NaI as an iodine source, leading to *in situ* generation of iodides by the means of a Finkelstein-like reaction, which subsequently is reacting with the lithium acetylide.[4] The results of the reactions with acetylide as shown in Scheme **5**, is given in Table **4** accuired from Buck 2001, and show good yields for most of the reactions. However the acetylides used is considerably different from that of TEB with fewer interfering groups adjecent to the acetylide.

The TEB acetylide includes four ethoxy groups in close vicinity, which possibly influencing the reactivity of TEB as nucleophile trhough steric hinderance, inductive effect of the oxygens and by oxygen complexation of $Li^+$.




**Scheme 5**

**Table 4.** Chain elongation of a selection of acetylides with diffierent alkyl halides.[4]

| Entry | R | R′-X | Additive[b] | Time (h) | Yield (%)[c] |
|---|---|---|---|---|---|
| 1 | $n$-$C_4H_9$ | $n$-$C_{10}H_{21}I$ | – | 8 | 75 |
| 2 | $n$-$C_4H_9$ | $n$-$C_{10}H_{21}Br$ | – | 18 | 50[d] |
| 3 | $n$-$C_4H_9$ | $n$-$C_{10}H_{21}Br$ | TBAI | 12 | 95 |
| 4 | $n$-$C_4H_9$ | $n$-$C_5H_{11}I$ | – | 9 | 88 |
| 5 | $n$-$C_4H_9$ | $n$-$C_7H_{15}Cl$ | TBAI | 60 | 52 |
| 6 | $n$-$C_4H_9$ | $n$-$C_7H_{15}Br$ | NaI | 15 | 90 |
| 7 | $n$-$C_4H_9$ | $THPO(CH_2)_9Br$ | NaI | 16 | 85 |
| 8 | $t$-$C_4H_9$ | $n$-$C_{10}H_{21}I$ | – | 7 | 86 |
| 9 | $t$-$C_4H_9$ | $n$-$C_{10}H_{21}Br$ | NaI | 11 | 85 |
| 10 | $t$-$C_4H_9$ | $n$-$C_7H_{15}I$ | – | 7 | 84 |
| 11 | Ph | $n$-$C_{10}H_{21}I$ | – | 12 | 99 |
| 12 | Ph | $n$-$C_5H_{11}Br$ | TBAI | 16 | 90 |
| 13 | Ph | $n$-$C_5H_{11}Br$ | NaI | 16 | 86 |
| 14 | $THPOCH_2$ | $n$-$C_{10}H_{21}I$ | – | 33 | 89 |
| 15 | $THPOCH_2$ | $n$-$C_{10}H_{21}Br$ | NaI | 40 | 83 |
| 16 | $THPO(CH_2)_2$ | $n$-$C_{10}H_{21}I$ | – | 11 | 94 |
| 17 | $THPO(CH_2)_2$ | EtI | – | 2 | 91 |
| 18 | $THPO(CH_2)_4$ | $n$-$C_{10}H_{21}I$ | – | 11 | 89 |
| 19 | $THPO(CH_2)_4$ | EtI | – | 2 | 93 |
| 20 | $THPO(CH_2)_4$ | EtBr | NaI | 8 | 92 |
| 21 | $THPO(CH_2)_4$ | $n$-$C_3H_7I$ | – | 3 | 94 |
| 22 | $THPO(CH_2)_4$ | $CH_2$=$CHCH_2CH_2Br$ | NaI | 16 | 55 |

[a] See text for details.
[b] 10 mol% TBAI or NaI added.
[c] Isolated yields of purified products.
[d] GC yield.

As tosylates are generally stable compounds and often a good alternative to iodides in many substitution reactions, it would be interesting to carry out the reaction with the often better tosylates.

As mentioned earlier, alkyl tosylates can though, in some instances, react slower than alkyl iodides in certian $S_N2$ reactions as the reaction is dependent on the nucleophile as well as the leaving group. However the alkynylation of alkyl tosylates can be performed in the precence of catalytic amounts of TBAI to induce a finkelstein-like reaction similar to the reaction with alkylbromides.[19]

## 2 The aim of the project

Chain elongations of the terminal alkyne of TEB have in earlier studies been performed by deprotonation with a strong base and reaction of the formed acetylide with carbonyl compounds.

In a recent study, alkylation of the TEB acetylide was performed with a small number of different alkyl halides under similar reaction conditions, wheras use of other leaving groups such as tosylates or mesylates have not yet been examined.

The aim of this study is to investigate the feasibility of synthesising different 1,1-diethoxyalk-3-yn-2-ones by reacting the terminal acetylide from 1,1,2,2-tetraethoxybutyne with different alkyl sulfonates. The reactivity between the alkyl sulfonates and alkyl iodides as electrophiles in the alkylation of TEB is also adressed.

**Part II Results and discussion**

# 3 Synthesis

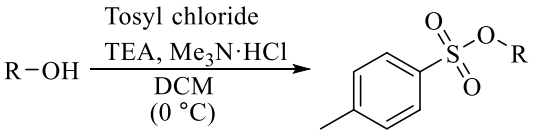
## 3.1 Synthesis of TEB

TEB was synthesised from ethyl vinyl ether following the four step synthesis published in the litterature[11,20] and outlined in Scheme **1**. The scale varied from  0.2 mol and 0.5 mol. The small scale syntheses were not fully completed due to low yield in the third step. The large scale procedure gave an over all yield of 10 % of essentially pure TEB, purified by destillation.

## 3.2 Conversion of alcohols to tosylates

Five alcohols were converted to the corresponding tosylates by a one-step synthesis, reported in the litterature,[23] using combined amine bases, TEA and catalytic $Me_3NHCl$, to trap the HCl pruduced during the reaction.

The products were easily purified by flash chromatography in reasonable yields compared to those reported in the litterature.[23]




**Scheme 6**

**Table 5.** Conversion of alcohols to tosylates.

| Alcohol | Product | R | Isolated yield (%) |
|---|---|---|---|
| **5a** | **6a** | Prop-2-enyl | 41 |
| **5b** | **6b** | 3-Methyl-3-enyl | 97 |
| **5c** | **6c** | Ethyl | 93 |
| **5d** | **6d** | Butyl | 89 |
| **5e** | **6e** | 4-Chlorobutyl | 50 |

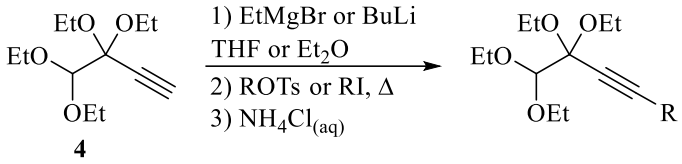
The alcohols selected for tosylation were similar to the alkyl iodides used in alkylations reported by Espeland so that the tosylates reactivity could be compared with that of the halides.

### 3.3 Alkylation of TEB

The alkylation of TEB started out relatively troublesome and were attempted several times. A number of alterations in the reaction conditions were made before any desired product were observed. The nature of the problem with the alkylation reactions was thought to be water contamination in either the solvent or the nitrogen gas used in the reactions, leading to hydrolysis of the formed TEB acetylide. None of the failed reactions due to poor reaction conditions are included in the discussion concerning the comparison of reactivity of alkyl iodides and alkyl tosylates towards TEB acetylide.

#### 3.3.1 Optimization of reaction conditions

The alkylation reactions were carried out following the procedures similar to those reported by Espeland.[6] Abstraction of the acetylenic proton on TEB **4** was performed with both BuLi and EtMgBr. The resulting TEB acetylide was then reacted with tosylates and alkyl iodides to form the alkylated product as shown in Scheme **7**.




**Scheme 7**

The first experiments where performed with allyl tosylate (**6a**), using THF, obtained from reflux, as solvent and utilizing EtMgBr and BuLi, respectively, as bases to form the corresponding acetylide from TEB. The reaction with EtMgBr was carried out at 60 °C and with BuLi at rt. As tosylate is good leaving group, it was disappointing to discover that both reactions gave no 6,6,7,7-tetraethoxyhept-1-en-4-yne (**7a**) whatsoever according to NMR data. Allylic halides and tosylates are, however, prone to undergo isomerization of the initially formed coupling products, but can be coupled with alkynylmagnesium halides in the presence of catalytic amounts of copper(I) halides.[2]

To circumvent the possible isomerization side reactions of allylic tosylates the alkylation was then then attempted with 3-methylbut-3-en-1-yl tosylate (**6b**) under equal reaction conditions, with BuLi as base, to determine if a non allylic tosylate would lead to 7,7,8,8-tetraethoxy-2-methyloct-1-en-5-yne (**7b**). Again, to our disappointment the reaction did not lead to the expected product, but gave only a mixture of the starting materials according to NMR data.

Tosylates are very good leaving groups but have been reported to have relatively poor reactivity in sertain $S_N2$ reactions[12] depending on the nature of the substituting nucleophile. As successful alkylations with a few simple alkyl iodides have been reported by Espeland,[6] the tosylates were thought to possibly have a weaker reactivty towards the TEB acetylide. Accordingly the same rection was attempted with TBAI as an iodine source at elevated temperatures to produce the corresponding alkyl iodide in situ and thus hopefully leading to a subsequent reaction with the acetylide.[19] Once again only a mixture of the starting materials were observed in the crude product, raising a suspicion that the reaction conditions required were not met.

As a result a series of parallell independent reactions, in collaboration with Espeland, where conducted, replicating the reaction condition used in the successful reactions done by Espeland as accurate as possible.

With help from Espeland, the alkylation was then carried out with butyl iodide, as this reaction earlier had been succesfully performed, accompanied by a parallell reaction with **6b**. To our discouragement none of the reactions produced any observable product when examining the crude products by TLC and NMR spectra, showing a mixture of the starting materials. It was then suspected there could be a possible water contamination in either the solvent or the applied nitrogen gas, leading to hydration of the acetylide.

Anhydrous THF used in the initial reactions were obtained by destillation of THF from sodium benzophenone ketyl over nitrogen atmosphere. Upon examination of the destillation apparatus problems with the nitrogen supply to the systemwas discovered, leading to a non inert atmosphere. THF was then obtained from a MB-SPS-800 solvent purification system based on a grubbs column to provide ultra dry solvents.

Another possible cause for the reactions to fail was an ineffective drying column, for trapping water contamination in the nitrogen gas, used to make an inert atmosphere in the reaction. It was then applied an other drying column to provide water free nitrogen gas to the reaction.

Again in collaboration with Espeland, an alkylation where attempted with methyl iodide, and a parallel reaction with **6b**, under the same reaction conditions as before, except with ultra dry THF and a new nitrogen source, utilizing BuLi as base. To our relief we could finally clearly observe formation of methylated product 4,4,5,5-tetraethoxypent-2-yne (**7f**) (33 %). However product **7b** were not observed for the parallel reaction with **6b**. Methyl iodide, as a prticularly reactive alkyl halide,[4] was the first electrophile to yield the desired product **7f** reported in entry **1** Table **7**. When performing the same reaction with methyl iodide under equal reaction conditions using nitrogen from the suspected contamiated source, the reaction gave no observable product which confirmed our suspicions of water contamination.

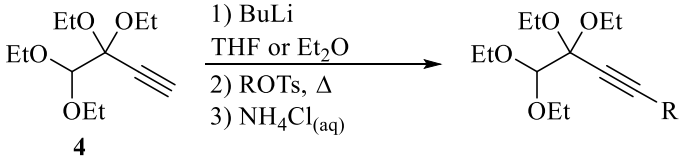
With the situation with the reaction conditions finally resolved, the alkylation with butyl iodide where again attempted, with BuLi as base and ambient reaction temperature, which had been previously successfully performed by Espeland.[7] To our suprise the reaction did not occur but gave a crude mixture of starting materials as before. Most alkyl halides have been reported react poorly with acetylides in THF at ambient temperatures[3] and requires elevated temperatures to be carried out.[4] Thus the same reaction was carried out changing the temperature to 70 °C which to our satisfaction lead to formation of 1,1,2,2-tetraethoxyoct-3-yne (**7d**) in moderate yields (66 %).

Followed by the successful alkylation with butyl iodide the reaction was performed with ethyl tosylate (**6c**) applying the same reaction conditions at elevated temperature, with added TBAI to generate the corresponding iodide *in situ*. Upon examination of the crude mixture, it was very reassuring to see formation of 1,1,2,2-tetraethoxyhex-3-yne (**7c**) using a tosylate, although the yield was as low as 21%.

With the reaction conditions adjusted, to finally give the alkylated products, alkylation of TEB were performed with a selection of alkyl tosylates and alkyl iodides with similar alkyl groups, under the same reaction conditions, to compare the reactivity of the two leaving groups.

### 3.3.2 Alkylation with tosylates

The acetylenic proton on TEB (**4**) was abstracted using BuLi, to form the acetylide. The resulting TEB acetylide was then reacted with tosylates to yield the corresponding alkylated TEB product.




**Scheme 8**

In this thesis the research was focused on alkylating substrates with different electronic differences adjacent to the tosyl leaving group and little steric hinderance. Different reaction conditions such as reaction temperature and solvent were investigated to give better yeilds of product. The reactions was also conducted with an iodine source (TBAI) as an additive to induce a Finkelstein-like reaction *in situ*.

**Table 6.** Alkylation of TEB with alkyl tosylates.

| Entry | Product | R | Base | Solvent | Reaction temperature (°C) | Additive | Reaction time (h) | Isolated yield (%) |
|---|---|---|---|---|---|---|---|---|
| **1** | **7c** | Ethyl | BuLi | THF | 70 | TBAI | 24 | 21[a] |
| **2** | **7d** | Butyl | BuLi | THF | 70 | TBAI | 24 | 33 |
| **3** | **7d** | Butyl | BuLi | THF | 70 | - | 24 | 31[b] |
| **4** | **7e** | 4-Chlorobutyl | BuLi | THF | 70 | TBAI | 24 | 45 |

**a)** Estimated yield from H-NMR spectrum due to difficulties to purify the product.

**b)** Reaction carried out without addition of TBAI.

The reactions gave moderate yields of products as some of it was lost during the purification. Product **7c** (entry **1**) was estimated from proton NMR of the attempted purified product as the starting material and the product had very similar retention times, which made them very difficult to separate from each other.

The alkylation reaction were first attempted at rt with **6b,** using BuLi as base, which resulted in a mixture of the starting materials. Thus, the alkylation with tosylates were then added TBAI as an iodine source to induce a finkelstein reaction at elevated temperature[19] giving products in moderate yields.

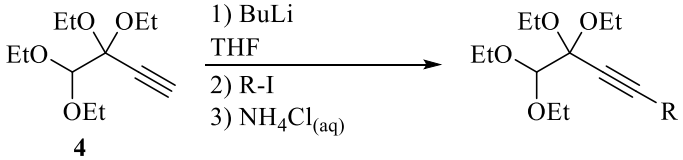
Most of the reactions were performed with an iodine source of TBAI as it initially was thought to be essential to produce the expected product. Subsequent unsuccessfull

alkylations with alkyl iodines at rt indicated that the leaving group was not the limiting factor. The alkylation reaction with butyl tosylate were then performed without TBAI at an elevated temperature, entry **3** table **6**, which also lead to formation of product without any significant difference in yield suggesting the iodine source had little to no effect on the reaction.

The alkylation is thought to undergo a $S_N2$ reaction as the applied alkyl tosylates make substantially unstable corresponding carbocations. Even though tosylate is regarded a particularly good leaving group, the reaction rate is markedly dependant on the nucleophile in a $S_N2$ reaction.[12,18] Tosylates are classified as hard electrophiles and seem to react faster with other hard nucleophiles than with soft ones.[18] A lithium acetylide is a good nucleophile and is classified as a hard nucleophile and TEB was expected to react readily react with tosylates but seem to substitute the tosylate at a slower rate than iodides. The ethoxy groups in vicinity to the acetylide is thought to modify the reactivity of the acetylitde,[8] lowering the electron density of the acetylide and weaken its nucleophilic properties. The withdraw of electron density from the acetylide possybly making it a softer nucleophile which have lower reactivity towards hard tosylates.

### 3.3.3 Alkylation with alkyl iodides

Alkylation of TEB were also performed using alkyl iodides as the alkylating agent to compare the reactivity of tosylates with alkyl iodides, and the reaction were executed under similar conditions as with the tosylates except addition of TBAI.




**Scheme 9**

**Table 7.** Alkylation of TEB with alkyl iodides.

| Entry | Product | R | Base | Solvent | Rection temperature (°C) | Reaction time (h) | Isolated yield (%) |
|---|---|---|---|---|---|---|---|
| **1** | **7f** | Methyl | BuLi | THF | rt | 24 | 33 |
| **2** | **7c** | Ethyl | BuLi | THF | 70 | 24 | 51 |
| **3** | **7d** | Butyl | BuLi | THF | 70 | 24 | 66 |

The reactions gave moderate yields of product as some of the product were lost in the purification by flash chromatography, espesially affecting the yield of product **7c** as it was difficult to separate from the starting material.

Alkylation of TEB with alkyl iodides have been reported to be successfully performed in earlier studies and were thus used as a reference to optimize the reaction conditions for the alkylations and to compare with the reactivity of the tosylates.

As a very reactive alkylhalide, methyl iodide was the only electrophile to yield any observable product at ambient temperatures, though yielding considerably lower amount of product due to the low reaction temperature compared to the other reactions.

Using butyl iodide as the electrophile at equal reaction conditions produced no desired product. This conflicts with earlier studies done by Espeland, where butyl iodide were used to alkylate TEB under the same reation conditions at rt. Most alkyl halides have been reported to react poorly with acetylides at rt and requires therefore elevated temperatures.[4] Therefore the temperature after addition of the electrophile was raised to induce the reaction to finaly yield product **7d** in moderate yield indicating that less reactive iodides react sluggishly with TEB acetylide at low temperatures.

The reaction rate was estimated for a selection of the successful reactions with aliquot $^{1}$H-NMR samples to observe differences in reactivity between alkylation with alkyl-tosylates and halides, and the estimated conversion of TEB is given in Figure **1**. The

reactions were carried out under equal conditions except an additive of TBAI for the alkyl tosyaltes.

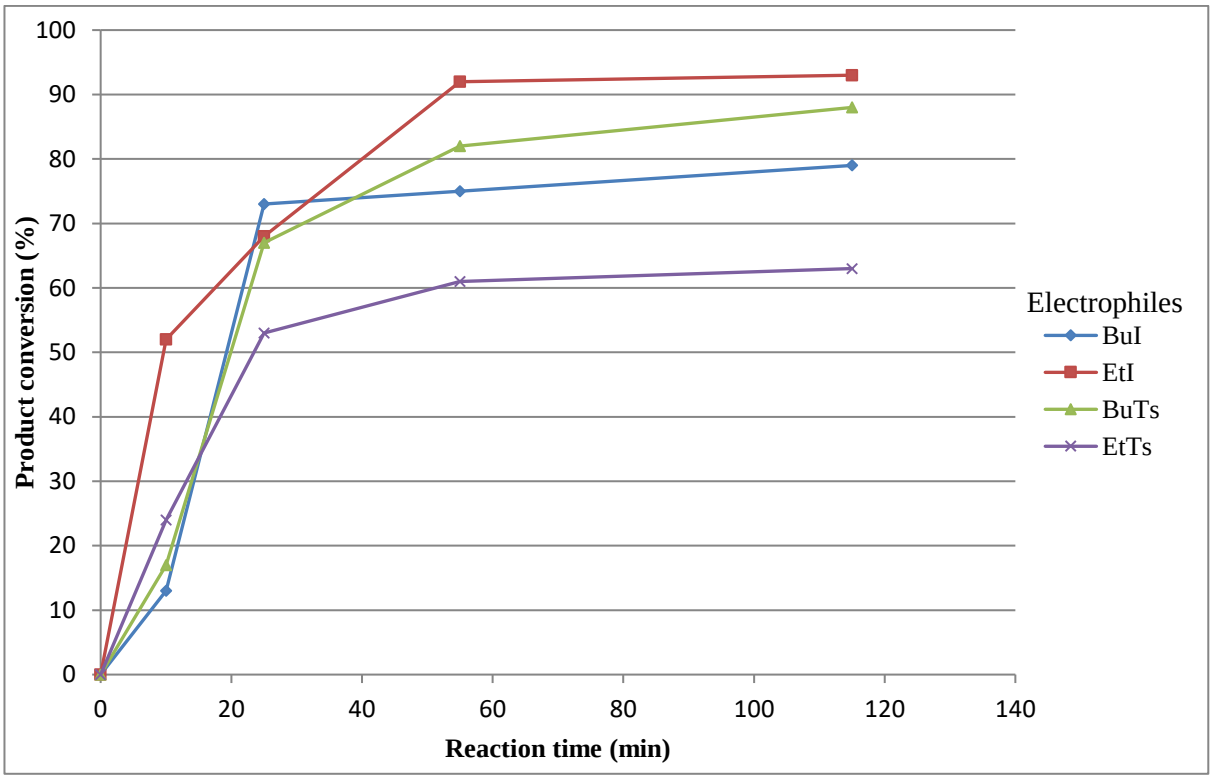



**Figure 1**: Conversion to product over time.

These estimations show a significant difference in reaction time for the ethylated product, with the alkyl halide displaying a significant faster reaction time than the tosylate. With the larger alkyl group the reaction time seems to be on par with each other. The calculation of conversion from $^{1}$H-NMR spectrum are, however, not absolutely reliable due to possible differences in relaxation times for the protons in TEB and the alkylated product leading to variation in the peak intensity in the $^{1}$H-NMR spectrum. Several prosesses, both intramolecular and inermolecular processes contribute to the relaxation of the spin relaxation,[17] and alterations in the molecule might affect the relaxation time considerable. The methine proton were used for the estimations due to its remoteness to the site of alkylation and possibly avoiding to much alteration in its relaxation time. It is also a well suited to use as verification for

possible formation of product as its chemical shift is slightly displaced as the result of the chain elongation as shown in Fig **2**.

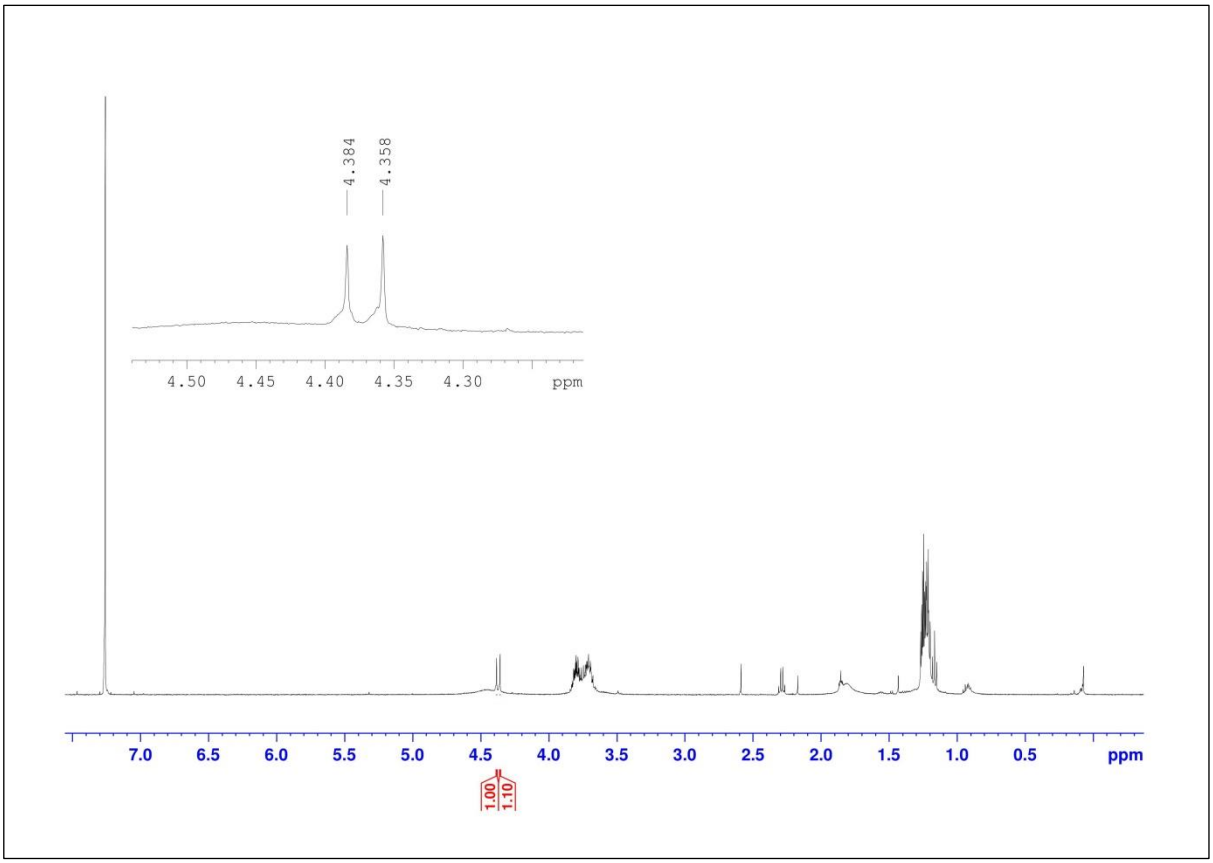



**Figure 2**. Example of shift in methine proton in $^{1}$H-NMR spectrum. Alkylation of TEB acetylide with EtI after 10 min.

When comparing alkyl tosylates and alkyl iodides reactivity toward TEB with respect to isolated yileds, the alkylation with iodides gave generally better yields of product, both for the ethyl iodides (51 %) and butyl iodides (66 %), compared to alkylation with the corresponding tosylates, ethyl tosylate (21 %) and butyl tosylate (33 %). The reactivty of the tosylates thus seem to be worse with the TEB acetylide, which was somewhat unexpected as tosylates often act as better leaving groups than halides. Tosylates are also regarded as hard electrophiles which usually readily react with other hard nucleophiles, like an acetylide ion.[9,18] A possibility for this observation may be a result of the ethoxy groups, close to the TEB acetylide, most likely altering its

reactivity. As the reactions where followed over time, representet graphically in Figure **1**, the reaction rate of the ethyl iodide show a notable faster initial reaction rate, consuming over 50% of TEB within the first 10 minutes, compared to about 25% for the tosylate. However no such difference was observed between the butyl tosylate and the butyl iodide indicating that tosylates may be a viable option for future alkylation of the TEB acetylide.

# 4 Summary


### Optimization of reaction conditions

Initially unsuccessfull alkylation reactions of 3,3,4,4-tetraethoxybut-1-yne (TEB) with a selection of tosylates and iodides where improved by attempting a series of reactions, with help from Espeland. By altering the reaction conditions systematically at each subsequent reaction the limiting reaction conditions of water contamination in the applied nitrogen gas and in the solvent used, as well as limiting reaction temperature, where thus found and corrected, leading to successfull alkylation with both alkyl tosylates and butyl iodides in moderate yields (21-66%).

### Tosylation of alcohols

Five different tosylates were successfully produced from the corresponding alcohols, which included allyl alcohol **5a**, 3-methylbut-3-enol **5b**, ethanol **5c**, butanol **5d** and 4-chlorobutanol, yielding essentially pure products in moderate to excellent yields (41-97%).

### Alkylation of 3,3,4,4-tetraethoxybut-1-yne (TEB)

The alkylation reaction of 3,3,4,4-tetraethoxybut-1-yne (TEB) where successfully performed with a selection of electrophiles consisting of ethyl tosylate **6c**, butyl tosylate **6d** and 4-chlorobutyl tosylate **6e** and alkyliodides, as well as methyl-, ethyl- and butyl iodide. The reactivity of the different alkyl iodides and tosylates towards the TEB acetylide were also adressed.

# 5 Further research

As the alkylation reactions of TEB with tosylates did not lead to expected amounts of product, it would be interesting to compare reactivity of the tosylates with other metallated acetylides. As the attached ethoxy groups may lead to reduced reactivity of the TEB acetylide as a nucleophile, acetylides with fewer possible interactions from functional groups in close vicinity to the acetylide may show a better reactivity towards alkyl tosylates than TEB.

Using MeMgBr as a base in the alkylation reaction were not performed at satisfactory reaction conditions, and it would be interessting to examine if the the alkylation reaction with tosylates are possible with a counter ion of $MgBr^+$, with different basicity and reactivity compared to the lithium acetylide.

**Part III Experimental**

# 6 General

## 6.1 Chemicals and reagents

All chemicals were purchased from Sigma-Aldrich Chemical Company (Oslo, Norway) with the exception of absolute ethanol, which was obtained from Arcus (Oslo, Norway) and stored over molecular sieves (4 Å). The chemicals were used without further purification. Anhydrous THF was prepared by destillation from sodium benzophenone ketyl over nitrogen atmosphere and from MB-SPS-800 solvent purification system based on a grubbs column to provide ultra dry solvents.

## 6.2 Experimental equipment

IR spectra were recorded on a Nicolet Protege 460 FT-IR spectrophotometer equipped with an attenuated total reflectance (ATR) attachement. Samples were analysed neat on a ZnSe crystal and the absorbtion frequencies are given in wave numbers ($cm^{-1}$). Intensities are not reported as the ATR technique renders them inaccurate.

NMR spectra were recorded on a Bruker Biospin AV500 (500 MHz for $^{1}H$, 125 MHz for $^{13}C$). Coupling constants (*J*) are given in Hz and the multiplicity is reported as a singlet (s), doublet (d), triplet (t) and multiplet (m). The chemical shifts are reported in ppm using the residual $CHCl_3$ peak (7.26 ppm) as the internal reference for $^{1}H$ spectra and the central peak of the $CDCl_3$ triplet (77.16 ppm) for $^{13}C$ spectra.

Thin-layer chromatography (TLC) was carried out with silica gel (60 $F_{254}$) an aluminium sheets with solvent systems consisting of various mixtures of isomeric hexanes and ethyl acetate. Flash chromatography was preformed with silica gel (230-400 mesh) and the same mobile phase for the TLC analyses. The eluent composition is given in each case. Staining was acheived with either exposure to UV light (254 nm) or a 20 wt% solution of phosphomolybdic acid (PMA) in ethanol.

# 7 Experimental procedures

## 7.1 Synthesis of TEB

### 1,1-Dichloro-2-ethoxycyclopropane (1)

A 1000 mL, three-necked, roundbottomed flask, equipped with a dropping funnel, condenser and a mechanical stirrer, was charged with ethyl vinyl ether (48.0 mL, 36.1 g, 0.5 mol), chloroform (160 mL, 238.72 g, 2.0 mol) and TBAI (0.80 g, 2.19 mmol) and placed in a water/ice bath under moderate stirring. The resulting mixture was cooled for 15 min before a 50% aqueous solution of sodium hydroxide (120 g, 1.5 mol) was added over 45 min under vigorous stirring. After complete addition the reaction mixture was left stirring for 2 hr at 0 °C (ice/water), after which the mixture was allowed to slowly reach rt and stirred for an additional 22 hr. The reaction was then quenched with a aqueous solution of 6 M hydrochloric acid (150 mL) and the hydrolysate was transferred to a separatory funnel. The reaction flask was washed with water (3 x 40 mL), which was added to the funnel and the phases separated. The aqueous phase was then extracted with DCM (3 x 100 mL), and the organic phases combined, dried ($MgSO_4$), filtered and concentrated on a rotary evaporator to yield **1** (65.60 g, 84 %) as an essentially pure pruduct based on NMR data which are in accordance with previously reported litterature.[11]

### 2-Chloro-3,3-diethoxyprop-1-ene (2)

A 1000 mL, single-necked rondbottomed flask equipped with a magnetic stirrer, condenser and drying tube, was charged with **1** (71.20 g, 0.46 mol), ethanol (328 mL, 258.79 g, 5.62 mol) and pyridine (48 mL, 46.9 g, 0.6 mol). The reaction mixture was set to reflux at 90 ° C at moderate stirring for 48 hr, before being concentrated *in vacuo*, and then transferred to a separatory funnel. The roundbottomed flask was washed with water (2 x 100 mL) and DCM (100 x mL) which was also transferred to the separatory funnel. The phases were separated and the aqueous phase was extracted with DCM (2 x 100 mL). The organic phases combined and washed with aqueous 0.7 M solution of

copper sulfate (3 x 100 mL) and dried ($MgSO_4$). The organic phase was then filtered through a plug of aluminum oxide and concentrated *in vacuo* to yield **2** (37.97 g, 50 %) as an essentially pure product based on NMR data which are in accordance with previosly reported litterature.[11]

**1,1-Dibromo-2-chloro-2-diethoxymethylcyclopropane (3)**

A 1000 mL, three-necked, round-bottomed flask, equipped with a condenser, drying tube, dropping funnel and a mechanical stirrer, was charged with **2** (52.13 g, 0.26 mol), bromoform (108 mL, 312.12 g, 1.24 mol) and TBAI (0.95 g, 2.57 mmol). The resulting mixture was cooled to 0 °C (ice/water) over 15 min under gentle stirring, after which a 50 % aqueous solution of NaOH (166 mL, 82.95 g, 2.07 mol) was added over 40 min under vigorous stirring. The reaction mixture was then left stirring over 2 hr as the ice/water bath melted, and then at rt for 22 hr. A 6 M aqueous solution of hydrochloric acid was added dropwise until reaching pH 5, and the resulting mixture was transferred to a seporatory funnel, the phases separated, and the aqueous phase extracted with DCM (3 x 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to produce a black, tarry crude. The crude product was destilled under vacuum (82-84 ° C) to give an essentially pure product **3** (22.22 g, 20.9 %) based on NMR data, which are in accordance with previosly reported litterature.[20]

**3,3,4,4-Tetraethoxybut-1-yne (4)**

A 250 mL, three-necked round-bottomed flask, equipped with a condenser, drying tube, dropping funnel and a mechanical stirrer, was charged with **3** (22.21 g, 0.07 mol), absolute ethanol (23 mL, 18.15 g, 0.39 mol), TBAI (0.22 g, 0.59 mmol) and DCM (92.5 mL). The reaction mixture was cooled to 0 °C (ice/water) over 15 min, before 50 % aqueous solution of NaOH (21.2 g, 0.27 mol) was added dropwise over 20 min under vigorous stirring. The reaction mixture was then stirred for 2 hr at 0 °C (ice/water) before the water bath was allowed to melt and the reaction mixture stirred for an additional 22 hr. An aqueous solution of 3 M hydrochloric acid (75 mL) was added, the phases separated, and the aqueous phase extracted with DCM (3 x 75 mL).

The combined organicextracts were dried ($MgSO_4$), filtered, and concentrated *in vacou*. The crude product was then purified by silica gel column chromatography (hexane/ethyl acetate, 9:1) to yield an essentially pure product **4** (2.46 g, 16 %) based on NMR data, which are in accordance with previosly reported litterature.[20]

### 7.2 Tosylation of alcohols

#### General procedure

A three-necked round-bottomed flask, equipped with a condenser, dropping funnel and a magnetic stirrer, was charged with alcohol (1.00 eq), TEA (1.50 eq), $Me_3N{\cdot}HCl$ (0.1 eq) and DCM and cooled to 0°C (ice/water) over 15 min. *p*-Toluensulfonyl chloride (1.2 eq), dissolved in DCM, was then added over a period of 25 to 90 min, and the solution left stirring for 2.5 to 3.5 hr at 0°C. The mixture was then quenced with water, and transferred to a seporatory funnel, the phases were separated and the aqueous phase extracted with DCM (3 x 50 mL). The organic phases were combined, washed first with water (50 mL), then with saturated $NaCl_{(aq)}$ solution (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacou*. The resulting crude products were purified by flash chromatography (hexane:ethyl acetate, 9:1) to yield the essentially pure pruducts.

#### Allyl 4-methylbenzenesulfonate (6a)

A mixture of allyl alcohol (0.85 g, 14.7 mmol), TEA and $Me_3NHCl$ dissolved in DCM (20 mL) were added *p*-toluenesulfonate cholride, dissolved in DCM (25 mL), over 25 min, stirred for 2.5 hours at 0 °C and quenched with water (30 mL). Work up and purification yielded the essentially pure title product product as a colorless oil **6a** (1.28 g, 41 %) based on $^1$H-NMR and $^{13}$C-NMR data which are in accordance with previosly reported litterature.[1]

**3-Methylbut-3-en-1-yl 4-methylbenzenesulfonate (6b)**

A mixture of 3-methylbut-3-enol (2.56 g, 29.7 mmol), TEA and $Me_3NHCl$ solved in DCM (40 mL) were added *p*-toluenesulfonate chloride, dissolved in DCM (70 mL), over 90 min, stirred for 3.5 hours at 0 °C and quenched with water (100 mL). Work up and purification yielded the essentially pure title product as a colorless oil **6b** (6.67 g, 93 %) based on $^{1}$H-NMR, $^{13}$C-NMR and MS data which are in accordance with previosly reported litterature.[10]

**Ethyl 4-methylbenzenesulfonate (6c)**

A mixture of ethanol (0.925 g, 20.08 mmol), TEA and $Me_3NHCl$ dissolved in DCM (30 mL) were added *p*-toluenesulfonate chloride, solved in DCM (60 mL), over 40 min, stirred for 3.5 hours at 0 °C and quenched with water (75 mL). Work up and purification yielded the essentially pure title product as a colorless oil **6c** (3.759 g, 93 %) based on $^{1}$H-NMR and $^{13}$C-NMR data which are in accordance with previosly reported litterature.[1]

**Butyl 4-methylbenzenesulfonate (6d)**

A mixture of butanol (0.733 g, 9.89 mmol), TEA, $Me_3NHCl$ dissolved in DCM (20 mL) were added *p*-toluenesulfonate chloride, dissolved in DCM (30 mL), over 50 min, stirred for 3.5 hours at 0 °C and quenched with water (50 mL). Work up and purification yielded the essentially pure title product as a colorless oil **6d** (2.02 g, 89 %) based on $^{1}$H-NMR and $^{13}$C-NMR data which are in accordance with previosly reported litterature.[1]

**4-Chlorobutyl 4-methylbenzenesulfonate (6e)**

A mixture of 4-chlorobutan-1-ol (2.175 g, 20.03 mmol), TEA, $Me_3NHCl$ dissolved in DCM (40 mL) were added *p*-toluenesulfonate chloride, dissolved in DCM (60 mL), over 60 min, stirred for 3.5 hours at 0 °C and quenched with water (75 mL). Work up and purification yielded the essentially pure title product as a colorless oil **6e** (2.638 g,

50 %) based on $^{1}$H-NMR, $^{13}$C-NMR and MS data which are in accordance with previosly reported litterature.[16]

### 7.3 Alkylation of TEB

**General procedures**

Method A:

A two-necked round-bottomed flask, equipped with a condenser, drying tube, magnetic stirrer and septum, was charged with anhydrous THF and **4** (2.00 mmol) under $N_2$ atmosphere. The reaction mixture was heated to reflux (60 °C) followed by dropwise addition of 3 M EtMgBr (1.1 eq) with a syringe over 10 min before refluxing for an additional hr. It was then cooled to rt and the alkyl tosylate (1.1 eq), was added dropwise via a syringe over 10 min followed by heating to reflux for 2 hr. The reaction was then cooled to 0 °C (ice/water), quenched with saturated aqueous solution of $NH_4Cl$ (20 mL), and transferred to a seporatory funnel, the phases was separated, and the water phase extracted with $Et_2O$ (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacou*. The crude products were purified by flash chromatography (hexane:ethyl acetate, 9:1).

Method B:

A two-necked round-bottomed flask, equipped with a condenser, drying tube, magnetic stirrer and septum, was charged with anhydrous $Et_2O$ or THF (5-12 mL) and **4** (0.50 – 1.00 mmol) under $N_2$ atmosphere. The reaction mixture was cooled to -78 °C (acetone/dry ice) followed by dropwise addition of 2.5 M *n*-BuLi (1.0 – 1.2 eq) over 5 to 20 min. It was then stirred at -78 °C for 10 to 30 min before warming to 0 °C (ice/water) followed by addition of the electrophile, alkyl iodide or alkyl tosylate (1.0-1.5 eq) over 1 to 10 min. The reaction was left stirring for 24 hr and reached rt as ice bath melted. Work up and purification performed as described in method A.

Method C:

A two-necked round-bottomed flask, equipped with a condenser, drying tube, magnetic stirrer and septum, was charged with anhydrous THF and **4** (0.50 – 1.00 mmol) under $N_2$ atmosphere and cooled to -78 °C (acetone/dry ice) followed by addition of *n*-BuLi (1.0 – 1.2 eq) over 5 to 10 min and stirred at -78 °C for 10 to 30 min. The mixture was then warmed to 0 °C (ice/water) before addition of the electrophile, alkyl iodide or alkyl tosylate (1.00 – 1.5 eq). When using alkyl tosylates TBAI (0.1 eq) was addded as a slurry in THF (3 mL) right after addition of the tosylate. The reaction mixture was then warmed 70 °C for 24 hr. Work up and purification were performed as described in method A.

*Alkylation with tosyates*

**6,6,7,7-Tetraethoxyhept-1-en-4-yne (7a)**

Method A: A solution of **4** (0.51 g, 2.19 mmol) dissolved in THF (5.6 mL) was added EtMgBr and **6a**. The reaction mixture was worked up as described in the general description yielding the staring material **4** as an essentially pure product based on $^1$H-NMR data.

Method B: A solution of **4** (0.46 g, 2.00 mmol) dissolved in THF (12 mL) cooled to -78 °C was added 2.5 M BuLi (0.96 mL, 2.4 mmol) over 20 min and stirred for 15 min at -78 °C followed by addition of **6a** (0.63 g, 2.96 mmol) over 10 min. The reaction was worked up as described in the geneal description to yield a mixture of **4** and **6a**, based on $^1$H-NMR data.

**7,7,8,8-Tetraethoxy-2-methyloct-1-en-5-yne (7b)**

Method B: A solution of **4** (0.12 g, 0.52 mmol) dissolved in $Et_2O$ (10 mL) cooled to -78 °C was added 2.5 M BuLi (0.22 mL, 0.6 mmol) over 10 min and stirred for 10 min at -

78 °C followed by addition of **6b** (0.14 g, 0.57 mmol) over 5 min. The reaction mixture was worked up as described in the general description to yield a mixture of **4** and **6b**, based on $^{1}$H-NMR data.

Method C: A solution of **4** (0.231 g, 1.00 mmol) dissolved in THF (10 mL) cooled to -78 0 °C was added 2.5 M BuLi (0.44 mL, 1.1 mmol) over 10 min and stirred for 30 min at -78 °C followed by addition of **6b** (0.241 g, 1.00 mmol) over 10 min and heated to 70 °C for 24 hr. The reaction mixture was worked up as described in the general description to yield a mixture of **4** and **6b**, based on $^{1}$H-NMR data.

**1,1,2,2-Tetraethoxyhex-3-yne (7c)**

Method C: A solution of **4** (0.233 g, 1.01 mmol) dissolved in THF (10 mL) cooled to -78 °C was added 2.5 M BuLi (0.46 mL, 1.2 mmol) over 5 min, stirred for additionally 30 min at -78 °C before addition of **6c** (0.304 g, 1.52 mmol) over 2 min followed by TBAI as a suspension in THF, and heated to 70 °C for 24 hr. The reaction mixture was worked up as described in the general description to yield **7c** as a slightly yellow oil (0.056 g, 21 %) as a slightly yellow oil, based on $^{1}$H-NMR and $^{13}$C-NMR data which are in accordance with previosly reported litterature.[6]

**1,1,2,2-Tetraethoxyoct-3-yne (7d)**

Method C: A solution of **4** (0.229 g, 0.99 mmol) dissolved in THF (10 mL) cooled to -78 °C was added 2.5 M BuLi (0.46 mL, 1.2 mmol) over 5 min, stirred for additionally 30 min at -78 °C before addition of **6d** (0.345 g, 1.51 mmol) over 1 min followed by addition of TBAI as a suspention in THF, and heated to 70 °C for 24 hr. The reaction mixture was worked up as described in the general description to yield **7d** as a slightly yellow oil (0.094 g, 33 %) based on $^{1}$H-NMR and $^{13}$C-NMR data.[7]

The alkylation were also carried out without adding TBAI. The reaction was performed under equal reaction conditions with **4** (0.230 g, 1.00 mmol) dissolved in THF (10 mL) yielding **7d** as a slightly yellow oil (0. 89 g, 31 %)**,** based on $^{1}$H-NMR and $^{13}$C-NMR data.[7]

**8-Chloro-1,1,2,2-tetraethoxyoct-3-yne (7e)**

Method C: A solution of **4** (0.230 g, 1.00 mmol) dissolved in THF (10 mL) cooled to -78 °C was added 2.5 M BuLi (0.46 mL, 1.2 mmol) over 5 min, stirred for additionally 30 min at -78 °C before addition of **6e** (0.390 g, 1.48 mmol) over 1 min followed by addition of TBAI as a suspention in THF, and heated to 70 °C for 24 hr. The reaction mixture was worked up as described in the general description to yield **7e** as a slightly yellow oil (0.145 g, 45 %), based on $^{1}$H-NMR, $^{13}$C-NMR and HRMS.

$^{1}$H NMR: (500 MHz, $CDCl_3$) δ 4.35 (s, 1H), 3.83-3.73 (m, 4H), 3.72-3.65 (m, 4H), 3.56 (t, *J*=7 Hz, 2H), 2.33 (t, *J*=7 Hz, 2H), 1.94-1.89 (m, 2H), 1.73-1.67 (m, 2H), 1.25-1.19 (m, 12H).

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 104.1, 98.9, 87.0, 75.8, 64.9, 59.5, 44.7, 31.7, 25.7, 18.3, 15.5, 15.4.

HRMS Calcd for $C_{16}H_{29}ClO_4Na$ [M+$Na^+$] 343.16521, found 343.16547.

*Alkylation with alkyl iodides*

**4,4,5,5-Tetraethoxypent-2-yne (7f)**

Method B: A solution of **4** (0.237 g, 1.03 mmol) dissolved in THF (10 mL) cooled to -78 °C was added 2.5 M BuLi (0.45 mL, 1.1 mmol) over 2 min, stirred for 30 min at -78 °C before addition of MeI (0.241 g, 1.70 mmol) over 5 min. The reaction mixture was worked up as described in the general description to yield **7f** as a slightly yellow oil (0.084 g, 33 %), based on $^{1}$H-NMR and $^{13}$C-NMR data which are in accordance with previosly reported litterature.[6]

**1,1,2,2-tetraethoxyhex-3-yne (7c)**

Method C: A solution of **4** (0.231 g, 1.00 mmol) dissolved in THF (10 mL) cooled to -78 °C was added 2.5 M BuLi (0.46 mL, 1.2 mmol) over 5 min, stirred for additionally 30 min at -78 °C before addition of EtI (0.237 g, 1.52 mmol) over 1 min and heated to 70 °C for 24 h. The reaction mixture was worked up as described in the general

description to yield **7c** as a slightly yellow oil (0.131 g, 51 %) based on $^{1}$H-NMR and $^{13}$C-NMR data which are in accordance with previosly reported litterature.[6]

**1,1,2,2-Tetraethoxyoct-3-yne (7d)**

Method B: A solution of **4** (0.118 g, 0.51 mmol) dissolved in THF (5 mL) cooled to -78 °C was added 2.5 M BuLi (0.23 mL, 0.6 mmol) over 5 min, stirred for 30 min at -78 °C before addition of BuI (0.144 g, 0.78 mmol) over 1 min. The reaction mixture was worked up as described in the general description to yield a mixture of **4** and butyl iodide based on $^{1}$H-NMR data.

Method C: A solution of **4** (0.230 g, 1.00 mmol) dissolved in THF (10 mL) cooled to -78 °C was added BuLi (0.46 mL, 1.2 mmol) over 5 min, stirred for additionally 30 min at -78 °C before addition of BuI (0.276 g, 1.5 mmol) over 1 min and heated to 70 °C for 24 h. The reaction mixture was worked up as described in the general description to yield **7d** as a slightly yellow oil (0.185 g, 66 %) based on $^{1}$H-NMR and $^{13}$C-NMR data.[7]

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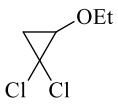
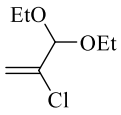
# Part IV Appendix

## Structures




**1**

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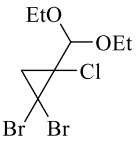


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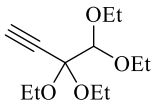


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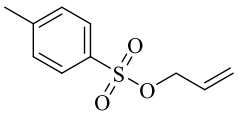


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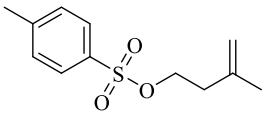


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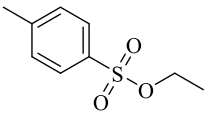


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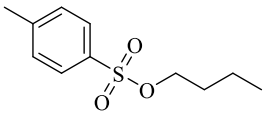


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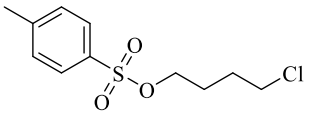


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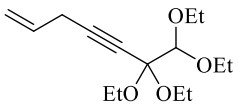


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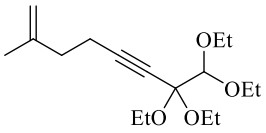


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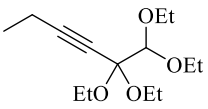


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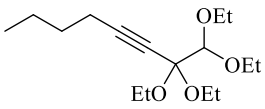


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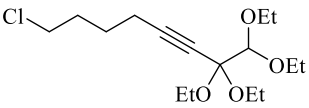


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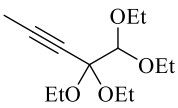
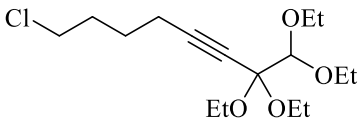


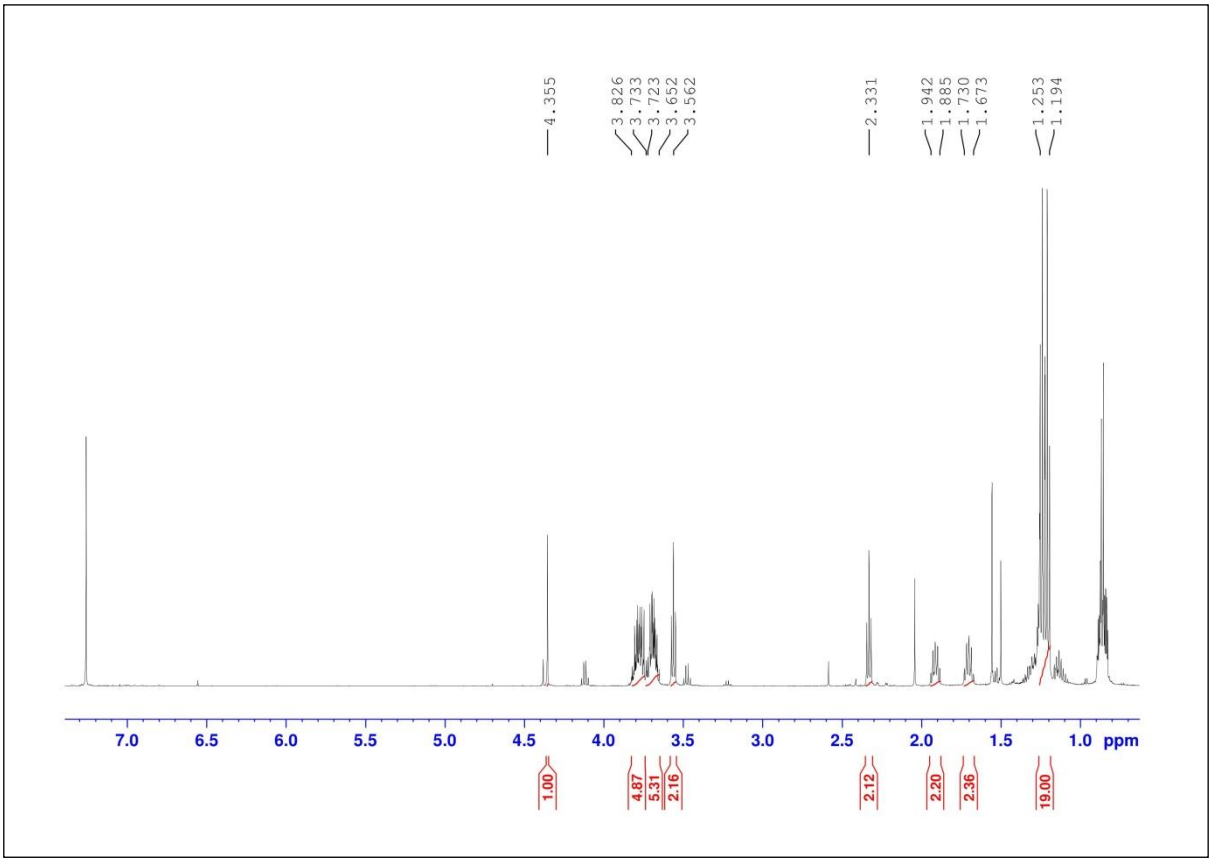

**7f**

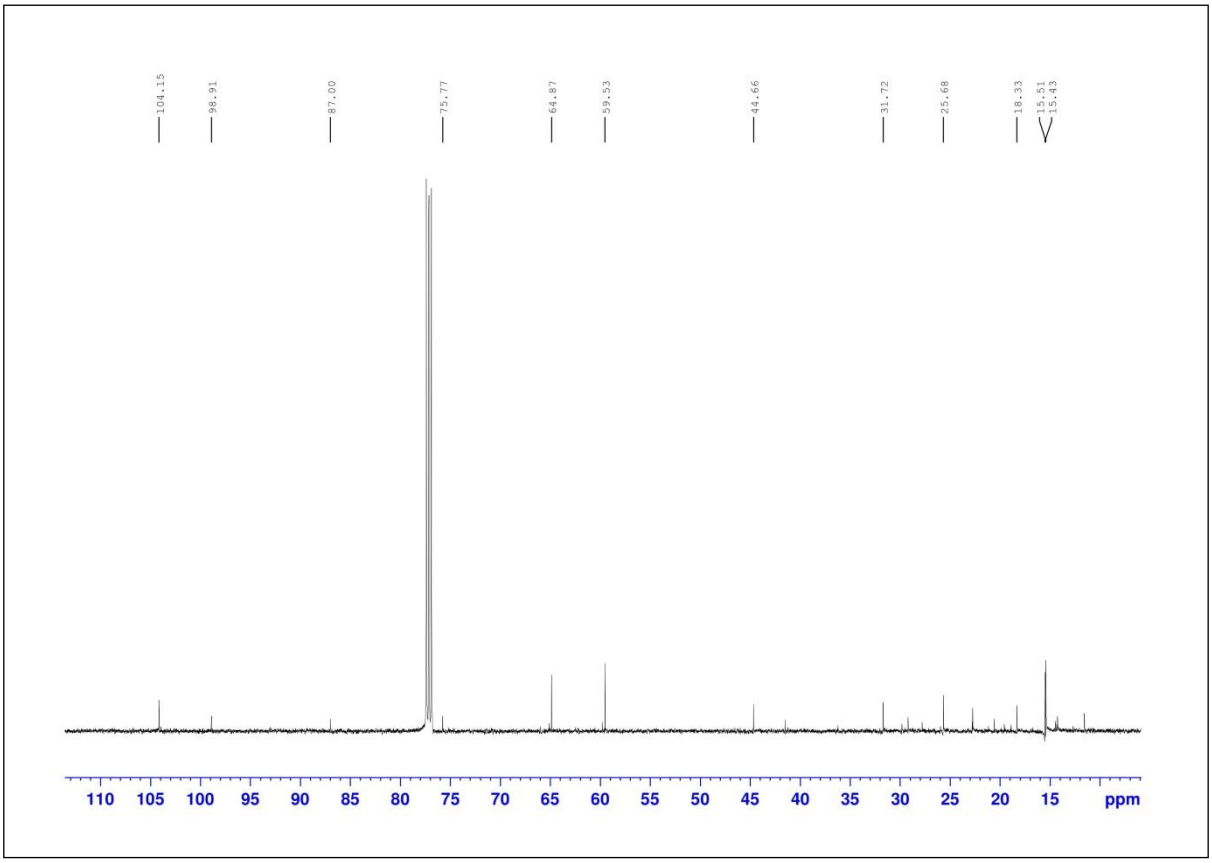
## Spectra of new compounds

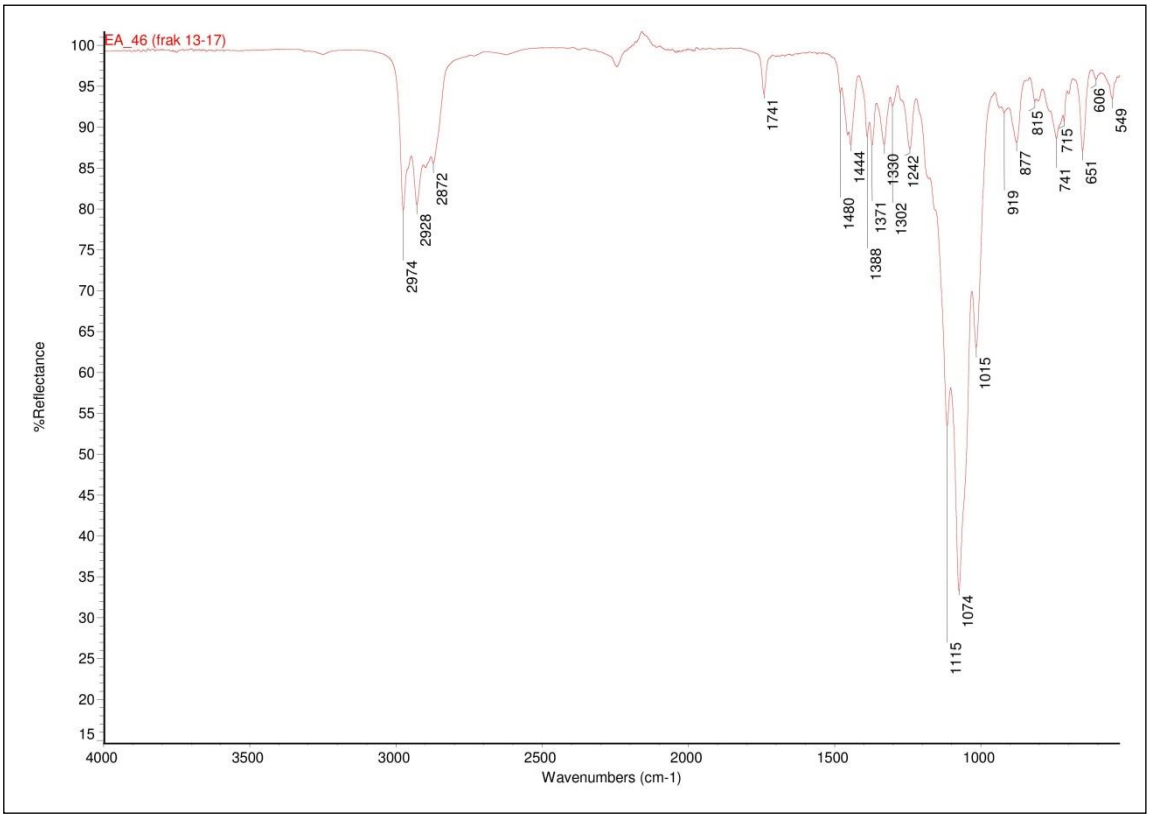


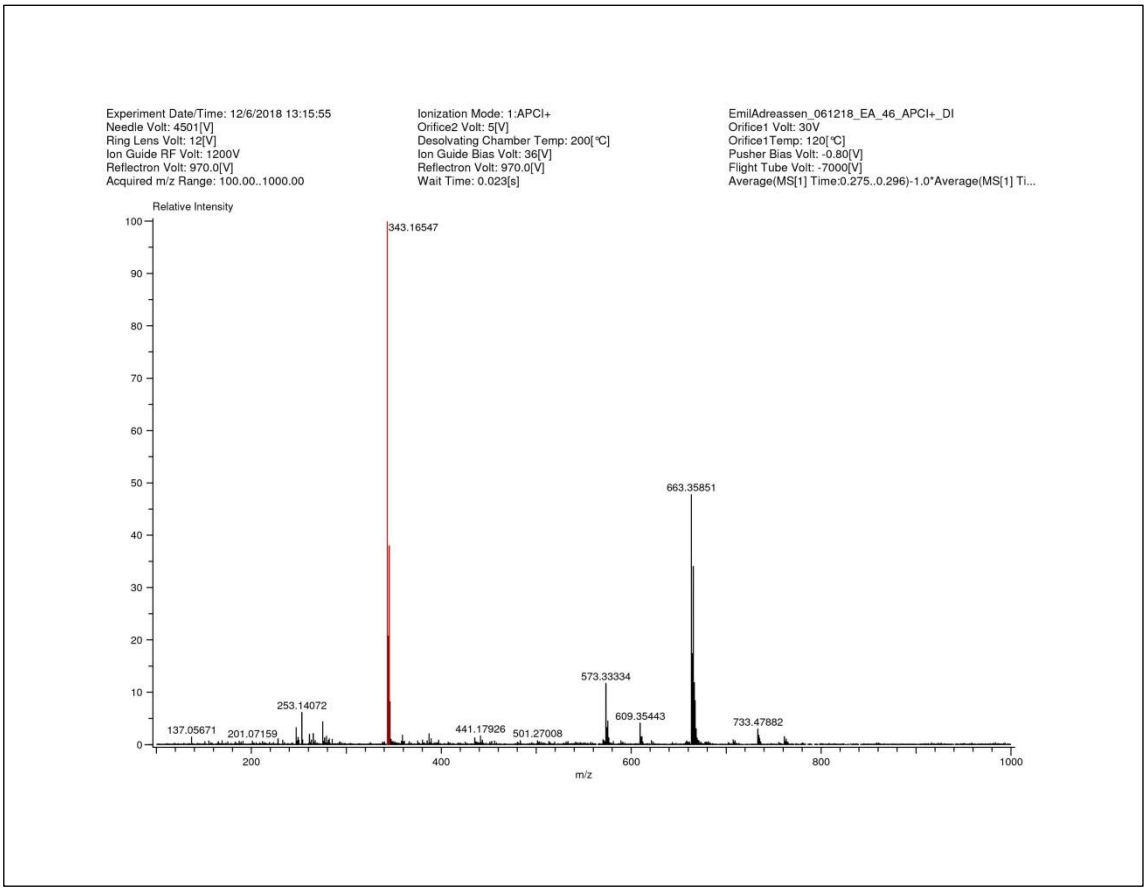

**7e**

8-chloro-1,1,2,2-tetraethoxyoct-3-yne




104.15
98.91
87.00
75.77
64.87
59.53
44.66
31.72
25.68
18.33
15.51
15.43
110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 ppm


EA_46 (frak 13-17)
%Reflectance
Wavenumbers (cm-1)
2974
2928
2872
1741
1480
1444
1388
1371
1330
1302
1242
1115
1074
1015
919
877
815
741
715
651
606
549


Experiment Date/Time: 12/6/2018 13:15:55
Needle Volt: 4501[V]
Ring Lens Volt: 12[V]
Ion Guide RF Volt: 1200V
Reflectron Volt: 970.0[V]
Acquired m/z Range: 100.00..1000.00
Ionization Mode: 1:APCI+
Orifice2 Volt: 5[V]
Desolvating Chamber Temp: 200[°C]
Ion Guide Bias Volt: 36[V]
Reflectron Volt: 970.0[V]
Wait Time: 0.023[s]
EmilAdreassen_061218_EA_46_APCI+_DI
Orifice1 Volt: 30V
Orifice1Temp: 120[°C]
Pusher Bias Volt: -0.80[V]
Flight Tube Volt: -7000[V]
Average(MS[1] Time:0.275..0.296)-1.0*Average(MS[1] Ti...
Relative Intensity
m/z
343.16547
663.35851
573.33334
609.35443
733.47882
253.14072
137.05671
201.07159
441.17926
501.27008