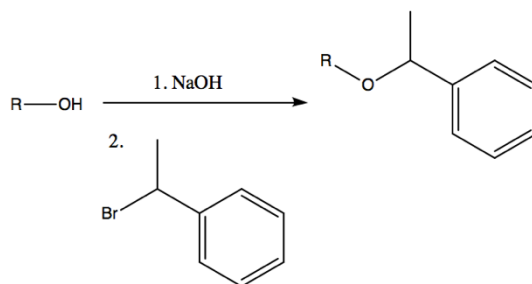


## OPTIMIZATION OF ALCOHOL REAGENT IN WILLIAMSON ETHER SYNTHESIS TO FORM SPECIFIC ASYMMETRIC ETHER

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Resubmitted March 16, 2020**Introduction:**

Williamson ether synthesis occurs when an alkoxide is reacted with an alkyl halide, such that the negatively charged oxygen attacks the carbon that is bonded to the halide, and the halide leaves.



This forms an asymmetrical ether molecule, which can be useful in synthesizing several other materials. This project was developed to optimize a reaction to be used in teaching labs for Organic Chemistry II. The reaction involves combining an alcohol substrate with an alkyl halide, commonly 1-bromoethyl benzene. The alcohol substrate, in this reaction, is used as both a reagent and solvent. The resulting product is an asymmetric ether, consisting of the original alcohol's carbon chain on one side, and the 1-bromoethyl benzene's carbon structure on the other.

It is unknown which alcohol yields the most selective products in this reaction. In this project, various alcohol reagents were tested to observe selectivity and percent yield of the target product. Selectivity was determined using  $^1\text{H}$  NMR.

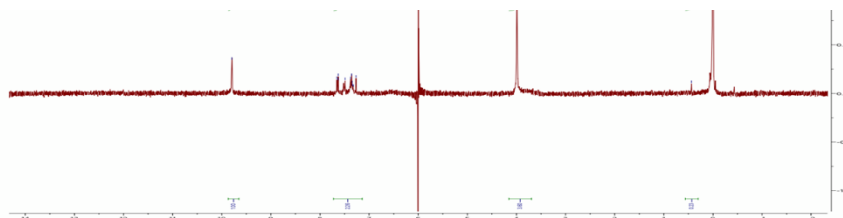
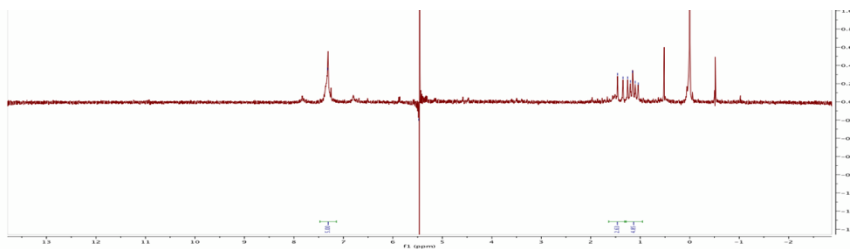
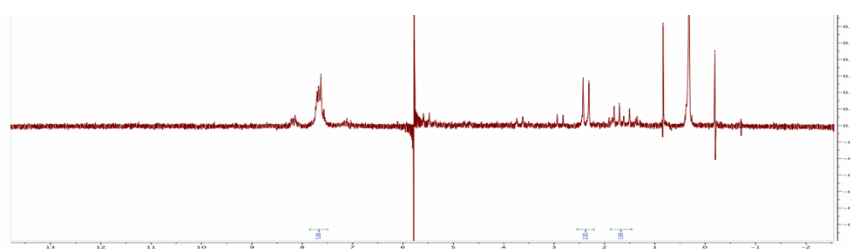
**Results & Discussion:***Analysis Figures:*Figure 1.  $^1\text{H}$  NMR of product from isopropanol 9:1 reaction (SPL-I-9)

Figure 2.  $^1\text{H}$  NMR of product from n-butanol 9:1 reaction (SPL-I-11)Figure 3.  $^1\text{H}$  NMR of product from ethanol 1:2 reaction (SPL-I-17)*Discussion:*

The primary challenge of performing this study was selecting alcohol reagents which would allow a reaction to occur. For the trials from SPL-I-13 and SPL-I-17, it is likely that no reaction occurred, since there is no NMR peak in the 4-5 ppm region, where an ether would be indicated. The identity of the products is unknown, due to the presence of peaks that are inconclusive, but it is clear that the target product was not formed. NMR was a helpful analysis tool to observe the result and purity of a reaction product, but IR may have also been helpful to further assess the composition of the product, if the expected one did not form.

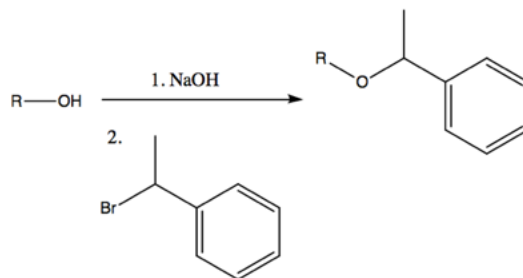
One noticeable trend was a white solid that formed on the walls of the pressure vial after the addition of the alkyl halide.

Entry	Alcohol	Ratio	Product appearance <sup>a</sup>
SPL-I-9	Isopropanol	9:1	Clear, some white powder
SPL-I-11	n-Butanol	9:1	Light yellow, translucent, large amount of white powder
SPL-I-17	Ethanol	1:2	Clear, large amount of white powder

<sup>a</sup> Product appearance immediately after second reaction block set, before being dissolved in 10 mL ice

This white powder is likely partially NaOH excess, but the white solid is more abundant than the original pellet, so another compound must be involved. This may be NaBr, but further testing would be required. The isopropanol trial, SPL-I-11, resulted in an emulsified product, which did not separate with brine addition. This product eventually separated after two weeks.

Table 1. Alcohol trials, amounts, and yields



Entry	Alcohol reagent	Solvent	ROH:RX (mL)	% yield	Product formation?	Pure product? <sup>b</sup>
SPL-I-11	Isopropanol	Isopropanol	9:1		No	No
SPL-I-13	n-Butanol	n-Butanol	9:1		No	No
SPL-I-17	EtOH	EtOH	1:2		No	No
KEP-I-9	MeOH	MeOH	9:1	33.3%	Yes	Yes
KEP-I-11	s-Butanol	s-Butanol	9:1	381.4% <sup>a</sup>	Yes	No
KEP-I-13	EtOH	THF	4.3:1	107.2% <sup>a</sup>	Yes	No
KEP-I-15	EtOH	THF	2.1:1		Yes	No
WKW-I-21	n-Propanol	n-Propanol	9:1	439.0% <sup>a</sup>	Yes	No
WKW-I-23	t-Butanol	t-Butanol	9:1	465.0% <sup>a</sup>	Yes	No

<sup>a</sup> High yields likely due to impurities in the final product

<sup>b</sup> Purity determined by <sup>1</sup>H NMR

The alcohols chosen were primarily those with small carbon chains, so they would have more ability to react with the NaOH initially. The smaller alcohols (i.e. methanol and ethanol) did appear to react more successfully. Miscibility in water seems to be a reason for this success, because this allows the organic layer to only contain the target product in the end. However, more study needs to be done on using larger alcohol substrates.

#### Conclusions:

This project resulted in providing more options for alcohol substrates and solvents to be used in this pedagogical experiment, but none of the trials seemed to be as optimal as the standard EtOH 9:1 reaction. More testing should be done on various alcohol reagents, especially larger alcohols, such as phenol or n-hexanol. Reagents with alkenes may also be a future area of study. IR spectroscopy would also be a helpful method for inconclusive NMR results, because it may allow the researcher to further observe the actual product and hypothesize its structure.

#### Experimental:

##### General methods:

The workup and synthesis procedures were performed under fume hoods to prevent spread of fumes. The alkyl halide, specifically, released gasses that could be eye irritants. A reaction block set was set to 1130 rpm at 75°C. The reactants were commercial and used in their received states, without being purified. A 60 MHz Anasazi NMR instrument was used to obtain all NMR spectra.

##### General procedure:

An NaOH pellet, magnetic stir bar, and alcohol substrate were added to pressure vial. The vial was placed in the reaction block set for 15 min. The vial was then removed, and cooled approximately to

room temperature. The 1-bromoethyl benzene was added to the mixture. The vial was reinserted in the reaction block set for 30 min, then removed and cooled to room temperature again. The solution was poured over about 10 mL of ice, then swirled to fully dissolve. The mixture was poured into a separatory funnel, and the organic layer was separated from the aqueous layer. This final organic layer, the product, was analyzed via NMR.

*SPL-I-11:*

Isopropanol (9 mL, 115.88 mmol) was used as the alcohol substrate and solvent. The unseparated product after swirling in ice was emulsified, so brine was added. The product remained emulsified and was allowed to settle for two weeks. Once a separation had clearly formed, the aqueous layer was drained off. The final product was not weighed, and was a clear liquid.  $^1\text{H}$  NMR (60 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.83 (s, 1.00H), 7.48 (q, 2.26H), 3.94 (s, 3.60H), 0.47 (s, 0.23H)

*SPL-I-13:*

n-Butanol (9 mL, 98.51 mmol) was used as the alcohol substrate and solvent. The organic layer remaining from the separation was not weighed, and was light brown and translucent. The organic layer was processed via  $^1\text{H}$  NMR (60 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.42 (t, 5.00H), 1.35 (m, 4.85H)

*SPL-I-17:*

Ethanol (1 mL, 17.13 mmol) was used as the alcohol substrate and solvent. The remaining product from the separation was not weighed, and was a clear liquid. The organic layer was processed via  $^1\text{H}$  NMR (60 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.75 (t, 5.00), 2.44 (d, 2.02H), 1.70 (m, 1.69H)

**References:**

- (1) Esteb, J. J.; Magers, J. R.; McNulty, L.; Morgan, P.; Wilson, A. M. A Simple  $\text{S}_\text{N}2$  Reaction for the Undergraduate Organic Laboratory. *J. Chem. Educ.* **2009**, *86* (7), 850.  
<https://doi.org/10.1021/ed086p850>.