

# Dimethyl sulfoxide as a solvent in the Williamson ether synthesis<sup>1</sup>

RUSSEL G. SMITH, ALAN VANTERPOOL, AND H. JEAN KULAK<sup>2</sup>

Research Department, Canadian Chemical Company, P.O. Box 99, Edmonton, Alberta

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Using the conventional Williamson ether synthesis, *n*-butyl ether was prepared from sodium hydroxide, *n*-butyl alcohol, and *n*-butyl chloride using excess of the alcohol as solvent in 61% yield after 14 h reaction time. However, when the excess alcohol was replaced by dimethyl sulfoxide, the yield of ether rose to 95% with 9.5 h reaction time. Other primary alkyl chlorides exhibited similar behavior to *n*-butyl chloride, but secondary alkyl chlorides and primary alkyl bromides gave little etherification, elimination being the major reaction. Unreactive halides, such as vinyl chloride, phenyl bromide, and 2,4-dinitrobromobenzene, were not etherified in dimethyl sulfoxide. The reaction products obtained from aliphatic dichlorides depended upon the relative positions of the chlorine atoms. Secondary alcohols reacted to give ethers, but tertiary alcohols were very unreactive. Polyols generally gave high yields of ethers, the major product being that in which all but one of the hydroxyl groups became etherified. Under forcing conditions, however, completely etherified polyols could be obtained.

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## Introduction

It has been shown by Cram and co-workers (1) that dimethyl sulfoxide (DMSO) is a useful solvent for the Williamson reaction (2). Working with phenyl bromide and potassium *t*-butoxide these authors obtained a greatly enhanced rate and a better overall yield of *t*-butyl phenyl ether in DMSO as compared to the conventional synthesis in *t*-butyl alcohol.

Later, workers studied the mechanism of the rate enhancement in greater detail and extended the application of the reaction in DMSO. Thus, ethers have been prepared from alkoxides and alkyl sulfonate esters (3, 4), from carbohydrates and dimethyl sulfate or methyl iodide (5, 6), from phenoxides and butyl halides (7), from methoxide and benzyl chlorides (8), from diphenoxides and dihaloaromatic compounds (9), and from methoxide and phenolates with poly[3,3-bis(chloromethyl)oxacyclobutane] (10). Zimmerman and Dathe (11) have shown polyol ethers can be obtained by reaction of the sodium alkoxide formed from the polyol and sodium hydroxide with alkyl chlorides.

The rate enhancement which occurs on transfer of a nucleophilic reaction from a protic solvent such as *t*-butanol to a dipolar aprotic solvent such as DMSO has been discussed in a review article by Parker (12). The rate enhancement is explained on the basis of the much

greater solvation of anions in protic solvents along with the much greater solvation of polarized charged transition states in dipolar aprotic solvents. Consequently, for nucleophilic reactions the activation energy is less in dipolar aprotic solvents than in protic solvents. Rate enhancements by factors as large as  $1 \times 10^{10}$  have been observed for some nucleophilic reactions on transfer from protic solvents to dipolar aprotic solvents.

The use of sodium hydroxide to form alkoxides and subsequent reaction with alkyl chlorides as reported by Zimmerman and Dathe (11) is of interest since it is considerably less expensive than the conventional use of sodium metal and alkyl bromides. The purpose of the work reported here was to determine the limitations and advantages of this method of ether synthesis.

## Experimental

In a typical preparation the hydroxyl containing compound, a stoichiometric excess of sodium hydroxide and DMSO (ca. 300 ml per mole of hydroxylic compound) was mixed and heated, with stirring. The temperature chosen was 5–10 °C below that at which discoloration occurred (usually 90–110 °C). When the precipitate had changed in physical appearance from a slimy to a granular form, the halide (in stoichiometric equivalence with caustic) was slowly added at such a rate that the temperature could be maintained at ca. 100 °C. Stirring and heating were maintained for 2–3 h after the addition was complete. The mixture was then cooled, and sufficient water added to dissolve the precipitated solids. The liquid layers were extracted with ethyl ether, the extracts combined, dried (sodium sulfate), and the ether removed by distillation. The residue was vacuum flashed, and the distillate analyzed by hydroxyl value and gas chromatography. Peak assignment, where possible, was made

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<sup>2</sup>Present address: 656 Thurber Drive, Columbus, Ohio 43215, U.S.A.

TABLE I  
Effect of solvent on the yield of *n*-butyl ether prepared from *n*-butyl alcohol and *n*-butyl chloride

| Solvent                 | Reaction time (h)      |                     | Products obtained            |                              |
|-------------------------|------------------------|---------------------|------------------------------|------------------------------|
|                         | For alkoxide formation | For ether formation | % Alcohol converted to ether | % Halide converted to olefin |
| <i>n</i> -Butyl alcohol | 4.0                    | 10.0                | 61*                          | 0                            |
| DMSO                    | 2.5                    | 3.5                 | 62†                          | 19                           |
| DMSO                    | 7.0                    | 2.5                 | 95                           | ‡                            |

\*Percent *n*-C<sub>4</sub>H<sub>9</sub>Cl converted to ether.

†Thirty-seven percent of the alcohol was recovered unchanged.

‡Not determined.

using known compounds. When these were not available, the assignment was chosen so as to agree with the determined hydroxyl value.

Volatile by-products were trapped in a dry ice - acetone bath and analyzed by mass spectrometry.

### Results and Discussion

In general, it proved difficult to prepare alkoxides at practical synthetic levels in DMSO since both sodium hydroxide and the alkoxides studied had very limited solubility in DMSO. Consequently, long reaction times and high temperatures were necessary for the alkoxide production stage of the synthesis. Once the alkoxide had been formed, reaction with alkyl chlorides was rapid and ethers could be obtained in good yields. When *n*-butyl ether was prepared (Table I), it was obtained in 95% yield after a total of 9.5 h reaction time of which 7.0 h were required for alkoxide formation. This result compares favorably with a 61% yield obtained after 14 h reaction time, when *n*-butyl alcohol was used as the solvent instead of DMSO. When a reaction time of only 2.5 h for alkoxide formation in DMSO was allowed, the yield of the ether was only 62%.

In the synthesis of *n*-butyl ether in DMSO, a portion of the excess *n*-butyl chloride employed was converted to 1-butene. This elimination reaction did not occur in *n*-butyl alcohol solvent or when aqueous DMSO was employed. If stoichiometrically equivalent quantities of *n*-butyl alcohol, sodium hydroxide, and *n*-butyl chloride were used in the synthesis, a low yield of *n*-butyl ether was obtained due to this competing elimination. However, good yields of *n*-butyl ether could be obtained if a 1.5 fold

excess of sodium hydroxide and *n*-butyl chloride was used over the *n*-butyl alcohol.

The synthesis gives good results when other primary alcohols and other primary chlorides are used. Thus, *n*-dodecyl ether was prepared (Table II) in 54% yield from *n*-dodecyl alcohol and *n*-dodecyl chloride.

A series of halides was reacted with *n*-butyl alcohol to determine the limitations to the type of halide which could be used in the synthesis. With isopropyl chloride (Table II), *t*-butyl chloride, and *n*-butyl bromide, the elimination reaction was sufficiently pronounced that little, if any, etherification occurred. On the other hand, vinyl chloride, 2,4-dinitrobromobenzene, and phenyl bromide failed to react at all (unreported experiments). This result is in contrast to the work of Cram *et al.* (1) where however, rigorously anhydrous conditions were employed.

Secondary alcohols, e.g., isopropyl alcohol, cyclohexyl alcohol, were found to be less reactive than *n*-butyl alcohol, while *t*-butyl alcohol was very unreactive (cf. Cram *et al.* (1)) (Table II). This lack of reactivity probably relates more to a difficulty in forming the alkoxide than to a difficulty in reacting the alkoxide with the halide. With phenol the reaction was particularly satisfactory since sodium phenoxide formed easily and was soluble in DMSO.

The reaction products obtained from aliphatic dichlorides depended on their structure. Thus, the *vicinal* dihalides studied (Table III) gave no ethers. Instead, appreciable amounts of acetylenes were formed, together with minor amounts of vinyl chlorides. With 1,3-dichloropropane

TABLE II  
Ethers from monohydric compounds

| Hydroxylic compound*                         | Halide                                       | Moles halide per mole alcohol | Reaction time (h)      |                     | Products obtained            |                               |                              |                             |
|--|--|-------------------------------|------------------------|---------------------|------------------------------|-------------------------------|------------------------------|-----------------------------|
|  |  |                               | For alkoxide formation | For ether formation | % alcohol converted to ether | % unreacted alcohol recovered | % halide converted to olefin | % unreacted halide detected |
| <i>n</i> -C <sub>4</sub> H <sub>9</sub> OH   | <i>n</i> -C <sub>4</sub> H <sub>9</sub> Cl   | 1.5                           | 3.0                    | 3.5                 | 62                           | 37                            | 19                           | 23                          |
| <i>n</i> -C <sub>4</sub> H <sub>9</sub> OH   | <i>i</i> -C <sub>3</sub> H <sub>7</sub> Cl   | 1.5                           | 2.5                    | 3.5                 | 0                            | †                             | 79                           | †                           |
| <i>n</i> -C <sub>4</sub> H <sub>9</sub> OH   | C <sub>6</sub> H <sub>5</sub> Br             | 1.2                           | 3.0                    | 10.0                | 11                           | 61                            | 0                            | 53                          |
| <i>n</i> -C <sub>12</sub> H <sub>25</sub> OH | <i>n</i> -C <sub>12</sub> H <sub>25</sub> Cl | 2.0                           | 2.5                    | 5.0                 | 54                           | †                             | †                            | †                           |
| <i>i</i> -C <sub>3</sub> H <sub>7</sub> OH   | <i>n</i> -C <sub>4</sub> H <sub>9</sub> Cl   | 1.5                           | 5.0                    | 3.0                 | 55                           | †                             | 32                           | 3                           |
| C <sub>6</sub> H <sub>11</sub> OH            | <i>n</i> -C <sub>4</sub> H <sub>9</sub> Cl   | 1.5                           | 4.0                    | 3.0                 | 49                           | †                             | †                            | 0                           |
| <i>i</i> -C <sub>4</sub> H <sub>9</sub> OH   | <i>n</i> -C <sub>4</sub> H <sub>9</sub> Cl   | 1.5                           | 6.0                    | 4.0                 | 13                           | †                             | 43                           | 6                           |
| <i>i</i> -C <sub>4</sub> H <sub>9</sub> OH   | C <sub>6</sub> H <sub>5</sub> Br             | 1.0                           | 6.0                    | 8.0                 | 0                            | †                             | 0                            | †                           |
| C <sub>6</sub> H <sub>5</sub> OH             | <i>n</i> -C <sub>4</sub> H <sub>9</sub> Cl   | 1.5                           | 1.0                    | 3.5                 | 100                          | 0                             | †                            | †                           |

\*One to five moles NaOH employed per mole of alcohol.  
†Not determined.

TABLE III  
Products obtained from the reaction of aliphatic dihalides with *n*-butyl alcohol

| Dihalide             | Reaction time (h)      |                     | % unreacted alcohol detected | % unreacted dihalide detected | Other products identified (% based on dihalide)  |
|----------------------|------------------------|---------------------|------------------------------|-------------------------------|--|
|                      | For butoxide formation | For ether formation |                              |                               |  |
| 1,2-Dichloroethane*  | 3.5                    | 3.5                 | 80                           | 0                             | Acetylene 30<br>Vinyl chloride 2   |
| 1,2-Dichloropropane† | 3.5                    | 5.0                 | 74                           | 24                            | Methylacetylene 36<br>2-Chloropropene 4  |
| 1,3-Dichloropropane† | 4.0                    | 5.0                 | 54                           | 35                            | Allyl chloride 7<br>Allyl ether 4<br>Butyl allyl ether 35<br>γ-Hydroxypropyl                 |
| 1,4-Dichlorobutane*  | 5.5                    | 6.5                 | 63                           | 8                             | Butyl ether 7<br>1,3-Butadiene 42<br>δ-Chlorobutyl<br>Butyl ether 6<br>1,4-Dibutoxybutane 16 |

\*Used 1.0 mole NaOH and 0.5 mole of halide per mole of alcohol.  
†Used 1.1 moles NaOH and 1.1 moles of halide per mole of alcohol.

TABLE IV  
*n*-Butyl ethers of selected polyhydric alcohols made from *n*-butyl chloride

| Polyol                                  | Reaction temperature for salt formation (°C) | Reaction time (h)      |                     | Monoether (%) | Conversion of polyol to |              |                |
|---|--|------------------------|---------------------|---------------|-------------------------|--------------|----------------|
|   |  | For alkoxide formation | For ether formation |               | Diether (%)             | Triether (%) | Tetraether (%) |
| 1,2-Dihydroxyethane*                    | 100  | 3.0                    | 4.5                 | 22            | 66                      | —            | —              |
| 1,2-Dihydroxypropane†                   | 110  | 1.0                    | 2.0                 | 55‡           | 27                      | —            | —              |
| 1,2,3-Trihydroxypropane*                | 140  | 4.5                    | 4.5                 | 0             | 41‡                     | 24           | —              |
| 2,2-bis(Hydroxymethyl)-propane†         | 100  | 1.0                    | 2.0                 | 41            | 36                      | —            | —              |
| 2,2-bis(Hydroxymethyl)-butanol-1*       | 95   | 3.0                    | 5.0                 | 0             | 74                      | 16           | —              |
| 2,2-bis(Hydroxymethyl)-propanediol-1,3* | 95   | 3.0                    | 8.0                 | 0             | 4                       | 71           | 20             |

\*Used 1.1 moles NaOH and 1.1 moles *n*-butyl chloride per mole of hydroxyl group.

†Used 1.5 moles NaOH and 1.5 moles *n*-butyl chloride per mole of hydroxyl group.

‡Combines total of the two possible isomers.

TABLE V  
 Selectivity in the preparation of ethers of pentaerythritol\*

| Ether desired           | Moles NaOH used per mole pentaerythritol | Moles alkyl chloride used per mole pentaerythritol | Reaction time (h)      |                     | % Pentaerythritol converted to |         |          |            |
|-------------------------|--|--|------------------------|---------------------|--------------------------------|---------|----------|------------|
|                         |  |  | For alkoxide formation | For ether formation | Monoether                      | Diether | Triether | Tetraether |
| di- <i>n</i> -Butyl     | 3.0                                      | 3.0  | 0.5                    | 10.0                | 10                             | 32      | 23       | 0          |
| tri- <i>n</i> -Butyl†   | 8.0                                      | 8.0  | 0.5                    | 5.0                 | 0                              | 4       | 88       | 6          |
| tetra- <i>n</i> -Butyl‡ | 8.0                                      | 8.0  | 3.0                    | 8.0                 | 0                              | 0       | 20       | 68         |
| di-Allyl                | 3.0                                      | 3.0  | 0.5                    | 3.5                 | 0                              | 42      | 31       | 2          |
| tri-Allyl               | 3.6                                      | 3.6  | 0.5                    | 4.5                 | 0                              | 26      | 56       | 5          |
| tetra-Allyl             | 8.0                                      | 8.0  | 1.5                    | 4.0                 | 0                              | 0       | 11       | 79         |

\*Of the various reaction conditions examined, those shown gave the highest selectivity to the desired ether.

†Solvent was 66% aq. DMSO.

‡The mixed pentaerythritol alkoxides were isolated and dried before proceeding to ether formation.

there was a substantial amount of elimination to give allyl chloride, much of which reacted to form a mixture of ethers. However, there was also an appreciable degree of hydrolysis of the halides resulting, after subsequent reaction, in allyl ether and  $\gamma$ -hydroxypropyl butyl ether. 1,4-Dichlorobutane on the other hand, gave 1,3-butadiene as the major product with minor amounts of 1,4-dibutoxybutane and  $\delta$ -chlorobutyl butyl ether. All these aliphatic dichlorides, however, were considerably less reactive than *n*-butyl chloride, as shown by the amount of unreacted *n*-butyl alcohol detected in the reaction product.

The reaction of several polyols with *n*-butyl chloride demonstrated (Table IV) that they were more reactive than the monohydric alcohols examined. This was to be expected on the basis of their higher acidity (13). However, mixtures of products were invariably obtained. Thus, ethylene glycol gave 22% monoether and 66% diether. With 1,2-propylene glycol, 27% of the fully etherified material was obtained along with 55% of the monoether. There were two monoethers formed, however; one, presumably 1-butoxy-2-hydroxypropane, to a much greater extent than the other (49% vs. 6%). With glycerol, no monoether was formed, only a mixture of diethers (34% of one isomer and 7% of the other) and the triether (24%). Trimethylolpropane and pentaerythritol also formed ethers in high conversion. The major product was that in which all but one of the hydroxyl groups had been etherified. *n*-Octyl chloride reacted with pentaerythritol in a similar manner to *n*-butyl chloride, while benzyl and methallyl chlorides gave results more similar to allyl chloride.

An appreciation of the selectivity of the reaction system, using pentaerythritol as an example can be gained from Table V. With either butyl or allyl chloride, no conditions were found which gave any appreciable amount of monoether. Diethers were obtained in modest conversions by using short reaction times for alkoxide formation and by reducing the moles of base and halide per mole of pentaerythritol. High conversion to tri-ether resulted when additional water was added to the solvent or by control of the stoichiometry. Tetra-ethers

resulted when a large excess of alkyl chloride was employed with or without concomitant removal of water from the system. Previously it had not been found possible to make pentaerythritol tetraether in one step (14). The reaction using *n*-butyl chloride in DMSO resulted in production of 1-butene, *n*-butyl alcohol, and *n*-butyl ether by-products, but these were absent when the solvent was aqueous DMSO.

Polyallyl ethers of several other polyols were prepared. The mixed products were analyzed by determining hydroxyl number and iodine number. For materials, such as, sucrose, sorbitol, and inositol, which contain both primary and secondary hydroxyl groups, there was a low conversion (i.e., 10 to 30%) to highly etherified products. In each case, there was on an average, less than one free hydroxyl group remaining. Glucose was resinified by the highly alkaline reaction medium.

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