# การสังเคราะห์อีเธอร์ของวิลเลียมสันสำหรับปฏิบัติการเคมีอินทรีย์ระดับปริญญาตรี

# Williamson Ether Synthesis for the Undergraduate Organic Chemistry Laboratory

รัชนก เธียรวาริช* กัญญาณัฐ เรืองสกุล และ วนิดา สำแดงไพร

Ruchanok Tearavarich*, Kanyanut Reungsakul and Wanida Sumdangpai

*สาขาวิชาเคมี คณะวิศวกรรมศาสตร์ มหาวิทยาลัยเทคโนโลยีราชมงคลอีสาน วิทยาเขตขอนแก่น*

*Department of Chemistry, Faculty of Engineering, Rajamangala University of Technology Isan, Khon Kaen Campus*

วันที่รับบทความ 17 มกราคม พ.ศ. 2558

วันที่ตอบรับตีพิมพ์ 19 พฤศจิกายน พ.ศ. 2558

## บทคัดย่อ

งานวิจัยนี้ มีวัตถุประสงค์เพื่อนำเสนอวิธีการทดลองที่เป็นมิตรต่อสิ่งแวดล้อม สำหรับการเรียนเคมีอินทรีย์ระดับปริญญาตรี โดยศึกษาการสังเคราะห์อีเธอร์ของวิลเลียมสัน ระหว่างฟีนอลกับ 2-chloroacetic acid ในโซเดียมไฮดรอกไซด์ ภายใต้สภาวะที่ปราศจากตัวทำละลาย การแยกผลิตภัณฑ์ที่เกิดขึ้นจากปฏิกิริยาโดยการสกัดอยู่ในเกณฑ์ดี ปฏิกิริยาดังกล่าวเป็นวิธีที่ง่าย สะดวกและรวดเร็ว ในงานวิจัยนี้ยังได้มีการอภิปรายเกี่ยวกับปฏิกิริยา $S_N2$ สภาพความเป็นกรด ปริมาณสารสัมพันธ์และเคมีสีเขียว

**คำสำคัญ** : การสังเคราะห์อีเธอร์ของวิลเลียมสัน สภาวะปราศจากตัวทำละลาย เคมีสีเขียว

## Abstract

The aim of this work is to offer a green laboratory experiment for undergraduate organic chemistry course. Williamson ether synthesis of phenol and 2-chloroacetic acid in the presence of sodium hydroxide under solvent free condition was performed. The product was obtained in good yield by using simple extraction. This simple, mild, convenient and fast experiment provides an opportunity to discuss $S_N2$ reaction, acidity, stoichiometry and green chemistry.

**Keywords** : Williamson Ether Synthesis, Solvent free condition, Green Chemistry

***Coressponding author . E-mail** : R_Tearavarich@hotmail.com

## Introduction

The best practice to learn organic chemistry is to understand the mechanism of organic reaction pathway via laboratory exercises. Due to the limit of time for doing experiment finished within 3 hrs, we aim to present a new design for teaching laboratory including the organic reactions and organic synthesis skill within a short time. For these reasons we chose Williamson ether synthesis for undergraduate chemistry students to learn $S_N2$ reaction (Sarju, Danks and Wagner, 2004 and Smith, 2006). The reaction involve a primary alkyl halide, 2-chloroacetic acid, react with phenoxide salt under solvent free condition (Rajchakit and Netkhun, 2008 and Reungsakul and Sumdangpai, 2012). This experiment not only offers learning $S_N2$ reaction but also enriches knowledge of acidity of substances (McMurry, 2008), stoichiometry and introduce green chemistry (Cave and Raston, 2005 and Bu and *et al.,* 2006).

In this study, we report a very simple, mild, convenient and fast method for the synthesis of 2-phenoxyacetic acid (Ali and Shaharyar, 2007) under solvent free condition. The only single product was obtained in good yield. The experiment described here was carried out for the second-semester second year student in chemistry major and required 3 hours laboratory periods.

## Materials and Methods

This study was divided into 2 parts. The first part, we have investigated the optimum solvent free condition, temperature and time, for synthesis of 2-phenoxyacetic acid which was performed by senior project students. In each condition was run by only a group with 2 students. The product was identified by IR and NMR spectroscopic technique (Field, Sternhell and Kalman, 2007). The other part was performed by the second year student in chemistry major in organic chemistry laboratory course to show the efficiency solvent free method by comparison percent yield of crude product with traditional method (Williamson, 1852 and Hill and Barbaro, 2005). There were 8 groups, 2 students in each group, in the class to do the experiment. The part described here was carried out duration of two 3 hours laboratory periods. In the first period, each group performed the reaction under reflux temperature. In the second period, each group carried out the reaction under solvent free condition.

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Infared (IR) spectra were recorded as KBr disks with a Perkin Elmer Spectrum One spectrophotometer. $^1H$ and $^{13}C$ NMR spectra were obtained using a Varian Mercury Plus 400 spectrometer. Chemical shifts were recorded on $\delta$ (ppm) scale using $CDCl_3$ as the solvents. The internal standard was referenced from the residue of these solvents. $^1H$ NMR data were listed in order of the number of protons, multiplicity [singlet (s), broad singlet (brs), doublet (d), triplet (t), quartet (q), and multiplet (m)], coupling constants (*J*) in Hz and assignment of nuclei concerned. Thin layer chromatography (TLC) was carried out on MERCK silica gel 60 $F_{254}$ TLC aluminium sheets.

**Reflux condition**

A mixture of phenol (0.63 g, 6.7 mmol), sodium hydroxide (0.77 g, 19.3 mmol) and 2-chloroacetic acid (0.50 g, 5.3 mmol), in ethanol (20 ml), was heated at reflux temperature for an hour. Then the reaction mixture was concentrated under reduced pressure. The mixture was acidified with 10% HCl and then extracted with $CH_2Cl_2$ (2x10 ml). The combined $CH_2Cl_2$ layer was washed with 10% $NaHCO_3$ (2x10 ml). The aqueous layer was acidified with 10% HCl and then extracted with $CH_2Cl_2$ (2x10 ml). The combined organic layer was dried over anh.$MgSO_4$ and evaporated to dryness to give 2-phenoxyacetic acid as white solid. The collected crude solid was recrystallized from water to give 2-phenoxyacetic acid (0.66 g, 81%).

**Solvent free condition**

The mixture of phenol (6 mmol) and sodium hydroxide (18 mmol) was grinded in a mortar. Water was added dropwise (10-15 drops) to the mixture and 2-chloroacetic acid (5 mmol) was then added. The reaction mixture was heated in an oven for 1 hour at various temperatures (60, 90 and 120 $^{\circ}$C). After that the reaction mixture was cooled to room temperature. The mixture was acidified with 10% HCl and then extracted with $CH_2Cl_2$ (2x10 ml). The combined $CH_2Cl_2$ layer was washed with 10% $NaHCO_3$ (2x10 ml). The aqueous layer was acidified with 10% HCl and then extracted with $CH_2Cl_2$ (2x10 ml). The combined organic layer was dried over anh.$MgSO_4$ and evaporated to dryness to give 2-phenoxyacetic acid as white solid. The collected crude solid was recrystallized from water to give 2-phenoxyacetic acid.

The above experimental was repeated by heating the reaction mixture in an oven for 30 minutes at 60 $^{\circ}$C. The reaction was expected to give the same yield with shorter time.

**2-phenoxyacetic acid**

mp 97.8-98.2 $^{\circ}$C; IR (KBr) $\nu_{max}$ 3012, 2950, 1701, 1698, 1595, 1499, 1223, 751 and 787 $cm^{-1}$; $^{1}$H NMR ($CDCl_3$): $\delta$ 7.31 (2H, t, *J* = 7.6 Hz, 3- and 5-Ar*H*), 7.02 (1H, t, *J* = 7.6 Hz, 4-Ar*H*), 6.93 (2H, d, *J* = 8.4 Hz, 2- and 6-Ar*H*) and 4.68 (2H, s, $CH_2$); $^{13}$C NMR ($CDCl_3$): $\delta$ 64.8, 114.6, 122.1, 129.7, 144.6, 157.3 and 173.2 ppm.

## Results and Discussion

Since green chemistry has gained to be interested, organic reaction carrying out in the absence of conventional organic solvents receive more attention. We have investigated the solvent free condition of the Williamson ether reaction. Therefore, we examined various conditions for a simple grinding experiment of 2 equivalents of sodium hydroxide with 1 equivalent of phenol and 1 equivalent of 2-chloroacetic acid. All examined reactions were carried at 6-7 mmol scale and the results were shown in Table 1.

*Table 1.* Percent yield of 2-phenoxyacetic acid obtained from various conditions

| Entry | Temp (°C) | Time (min) | %yield |
|---|---|---|---|
| 1 | 120 | 60 | 61 |
| 2 | 90 | 60 | 78 |
| 3 | 60 | 60 | 78 |
| 4 | 60 | 30 | 83 |

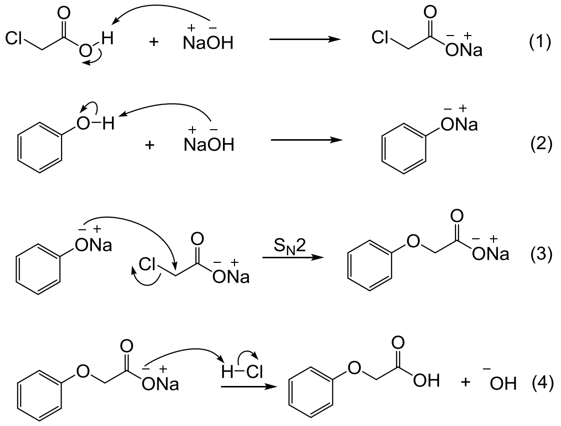
As shown in entry 1-3, the reaction was heated in an oven for 1 hour at 60 °C gave the highest yield. Therefore, we tried to carry out the reaction at 60 °C by reducing time to 30 minutes to find for better time.

Among various condition studied, Williamson ether synthesis of phenol and 2-chloroacetic acid in the presence of sodium hydroxide under solvent free at 60 °C for 30 minutes was the optimum condition because the yield of 2-phenoxyacetic acid was obtained the highest yield in shortest time.

The optimum solvent free condition of synthetic of 2-phenoxyacetic acid was performed by the second year student in chemistry major in organic chemistry laboratory cause. The result of the obtained product was compared to those from under reflux. Each group typically achieved yields between 75-95% in both methods. The range in yields for both methods was due to varying student extraction abilities and their removal of the solvent from crude product. Among the obtained results from solvent free condition and under reflux. It illustrates that the solvent free condition could be used as alternative condition for preparing of 2-phenoxy acetic acid.

Solvent free experiment presents three major advantages compared to traditional experiment. Firstly, faster due to shorter of the reaction time and skip of removing of the solvent before working up. Secondly, more convenient cause glasswares were not necessary and third, this experiment represented in the green direction because the solvent free reaction avoided to use hazardous and toxic solvent and minimized generation of waste.

Formation of 2-phenoxyacetic acid could be explained by reaction mechanism as shown in Scheme I. The acid-base reaction was first occurred. Sodium 2-chloroacetate and sodium phenoxide were generated from the reaction between 2-chloroacetic acid and phenol with sodium hydroxide, respectively (eq 1 and eq 2). The phenoxide salt reacted with sodium 2-chloroacetate *via* $S_N2$ mechanism (eq 3). Then the obtained adduct was acidified with HCl to give 2-phenoxyacetic acid (eq 4).



**Scheme I**

## Conclusion

The propose of this work is to offer an alternative laboratory experiment for undergraduate organic chemistry course. Williamson ether synthesis of 2-phenoxy acetic acid under solvent free condition gave similar high yield compared to the traditional method. We had found that solvent free experiment present more advantages than traditional experiment such as faster, convenient and green direction.

We would like to conclude that this laboratory experiment was suitable for second semester second year undergraduate organic chemistry laboratory course. We wish to offer this laboratory experiment for undergraduate organic chemistry course to use instead the traditional method.

### Acknowledgements

Grateful thanks are extended to Rajamangala University of Technology Isan, Khon Kaen Campus, Khon Kaen, Thailand for Financial support.

## References

Ali, M.A. and Shaharyar, M. (2007). Discovery of novel phenoxyacetic acid derivatives as antimycobacterial agents. *Bioog. Med. Chem.*, *15*, 1896-1902.

Bu, X., Jing, H., Wang, L., Chang, T., Jin, L. and Liang, Y. (2006). Organic base catalyzed *O*-alkylation of phenols under solvent-free condition. *J. Mol. Cata. A. Chem.*, *259*, 121-124.

Cave, G.W.V. and Raston, C.L. 2005. Green chemistry laboratory: Benign synthesis of 4,6-diphenyl[2,2′]bipyridine via sequential solventless aldol and Michael addition reactions. *J. Chem. Educ.*, *82*, 468-469.

Field, L.D. Sternhell, S. and Kalman, R.J. (2007). *Organic Structures from Spectra*. 4th ed., John Wiley & Sons. Ltd., Singapore.

Hill, R.K. and Barbaro, J. (2005). *Experiment in Organic Chemistry*. 3rd ed., Contemporary Publishing Company. 1-5.

McMurry, J. (2008). *Organic chemistry*. 6th ed., Thomson-Brooks/Cole, Belmont, CA., USA. 755-757.

Rajchakit, U. and Netkhun, P. (2008). *Preparation of aryloxyacetic acid under solventless condition*. Senior project, Faculty of Science, Khon Kaen University.

Reungsakul, K. and Sumdangpai W. (2012). *Williamson ether synthesis of 2-phenoxyacetic acid under solvent free condition.* Senior project, Faculty of Engineering, Rajamangala University of Technology Isan, Khon Kaen Campus.

Sarju, J., Danks, T. N. and Wagner, G. (2004). Rapid microwave-assisted synthesis of phenyl ethers under mildly basic and nonaqueous conditions. *Tetrahedron Lett., 45*, 7675-7677.

Smith, J. G. (2006). *Organic chemistry*. McGraw-Hill, New York, USA. 311-313.

Williamson, A.W. (1852). On Etherification. *J. Chem. Soc. 4*, 229-239.