VOLUME 1 ISSUE 3

Student's Journal of Chemistry

DEVELOPMENTS IN THE PREPARATION OF DIMETHYLDIOXIRANE (DMD/DMDO)

Said Nadeem

October 25, 2014

The synthesis of dimethyldioxirane (DMD/DMDO) is as complicated as its storage. It should be used within a week after its synthesis. Developments were gained in the synthetic procedure of DMD/DMDO in two steps and enough yield was obtained at moderate temperature compared to literature procedures (-78 oC). The dry ice before trap was replaced with a condenser containing chilled methanol which also resulted the condensation of DMD/DMDO back from the vacuum trap. Diethyl formylphosphonate 6 was synthesized by the oxidation of diazomethylphosphonate 5 with DMD/DMDO at different temperatures starting from -78 ºC to 0 ºC.

DEVELOPMENTS IN THE PREPARATION OF DIMETHYLDIOXIRANE (DMD/DMDO)

Said Nadeem,[a,b] Ilke Simsek,[a] Ayhan S. Demir,[a] M. R. Shah,[b]

[a] Department of Chemistry, Middle East Technical University, Ankara, 06531 Turkey, [b] International Center for Chemical and Biological Sciences, HEJ Research Institute of Chemistry, University of Karachi, Karachi-75270, Pakistan.

Corresponding author's Name: Said Nadeem

Email: said81nadeem@yahoo.com

Phone: +90-5335499880

ABSTRACT

The synthesis of dimethyldioxirane (DMD/DMDO) is as complicated as its storage. It should be used within a week after its synthesis. Developments were gained in the synthetic procedure of DMD/DMDO in two steps and enough yield was obtained at moderate temperature compared to literature procedures (-78 ºC). The dry ice before trap was replaced with a condenser containing chilled methanol which also resulted the condensation of DMD/DMDO back from the vacuum trap. Diethyl formylphosphonate **6** was synthesized by the oxidation of diazomethylphosphonate **5** with DMD/DMDO at different temperatures starting from -78 ºC to 0 ºC.

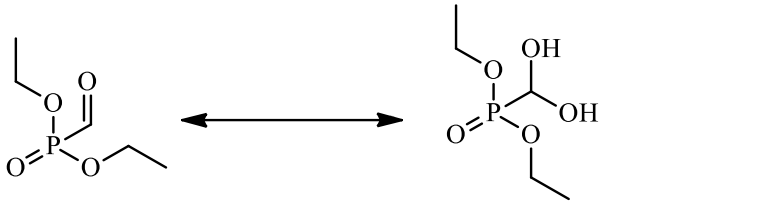
Key words: Dimethyldioxirane, ethyl formyphosphonate, oxone

INTRODUCTION

Formylphosphonate hydrate has been synthesized by the oxidation of diazomethylphosphonate with dimethyldioxirane (also called DMD or DMDO) [1]. Formylphosphonate acts as an efficient, selective formylating agent of secondary amines. β-Ketophosphonic acids derived from a range of amino acids have been prepared by the tin (II) chloride-catalysed reaction of diazomethylphosphonate with amino aldehydes and in certain cases shown to be potent inhibitors of leucineaminopeptidase [2]. R-hydroxyphosphonate derivatives are observed to be very important enzyme inhibitors because of their analogy to R-amino acids [3]. They are good inhibitors of renin [4, 5] or

human immunodeficiency virus (HIV) protease and polymerase [6]. They also show other biological activities like antiviral[7] and anticancer activities [8, 9]. Because of these important biological activities, high enantioselectivity in the synthesis of R-hydroxyphosphonates has been the goal of organic chemists. It has been also reported that proline is catalyzing asymmetric aldol reaction of R-ketophosphonates for the highly enantioselective synthesis of tertiary R-hydroxyphosphonates [10]. The first organocatalytic cross aldol reaction of ketones and diethyl formylphosphonate hydrate has been performed by using readily available L-prolinamide as the catalyst. Secondary L-hydroxyphosphonates have been synthesized in high enantioselective (up to > 99% enantiomeric excess) and good diastereoselectivity [11]. N-PMP protected L-aminopropargylphosphonates have been synthesized by using a silver(I) triflate-catalyzed one-pot three-component reaction of terminal alkynes, p-anisidine, and diethyl formylphosphonate hydrate. Good to excellent yields of the desired products are obtained with a very simple procedure [12]. α-Aminopropargylphosphonates have been synthesized for the first time in good yields and enantiomeric excesses (up to 81% ee) by using a copper(I)–pybox complex as the catalyst [13].

It was tried to synthesize diethyl formylphosphonate (Scheme 1) by using DMD and some developments were made in the methodology of DMD synthesis.



diethyl formylphosphonate diethyl formylphosphonate hydrate

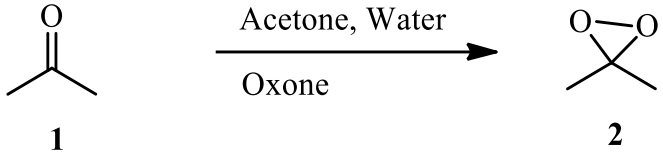
Scheme 1: *Diethyl formylphosphonate and its hydrated form*

RESULT AND DISCUSSION

Preparation of DMD/DMDO (dimethyl dioxirane)

Dimethyl dioxirane is the oxidized form of acetone and is used for selective mild oxidation. DMD cannot be stored more than a week so it is not available in the market. It is to be

prepared freshly before use and can be used in chloroform, dichloromethane and dry acetone. The general scheme of DDM synthesis is shown in scheme 2.



Scheme 2: *Synthetic scheme of DMD synthesis*

First, the literature procedure was applied for the synthesis of DMD **2** [1, 14]. The apparatus setup for DMD preparation is shown in Figure 1.

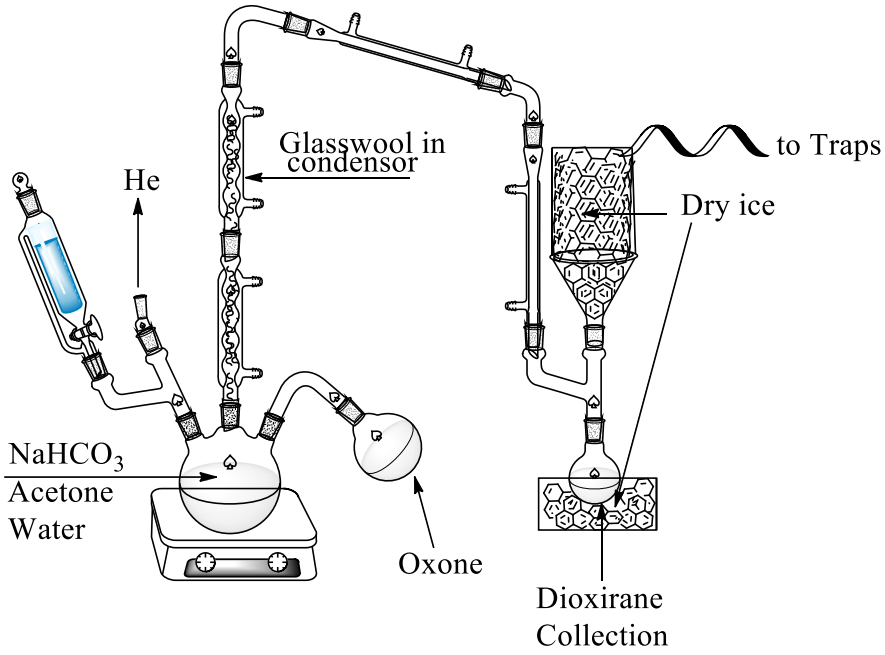


Figure 1: *Literature method of DMD preparation*

1. **Developments in the literature procedure:**

The literature procedure was followed firstly for the synthesis of DMD and was successful but there were few difficulties with this procedure. Some changes were made in the methodology which results in the development of procedure.

1.1.1st development:

In the procedure, the nitrogen or helium stream addition is omitted. The dry ice cold trap, which leads to vacuum trap is also omitted because it was breaking and instead, methanol cooled condenser (around -80 ºC) is added to condense the vapors of DMD to receiver flask, which was cooled by dry-ice/acetone. But in this method, the vacuum is developed at the lower end of methanol-cooled condenser which reduces the amount of DMD formed
The procedure with first development is shown in Figure 2.

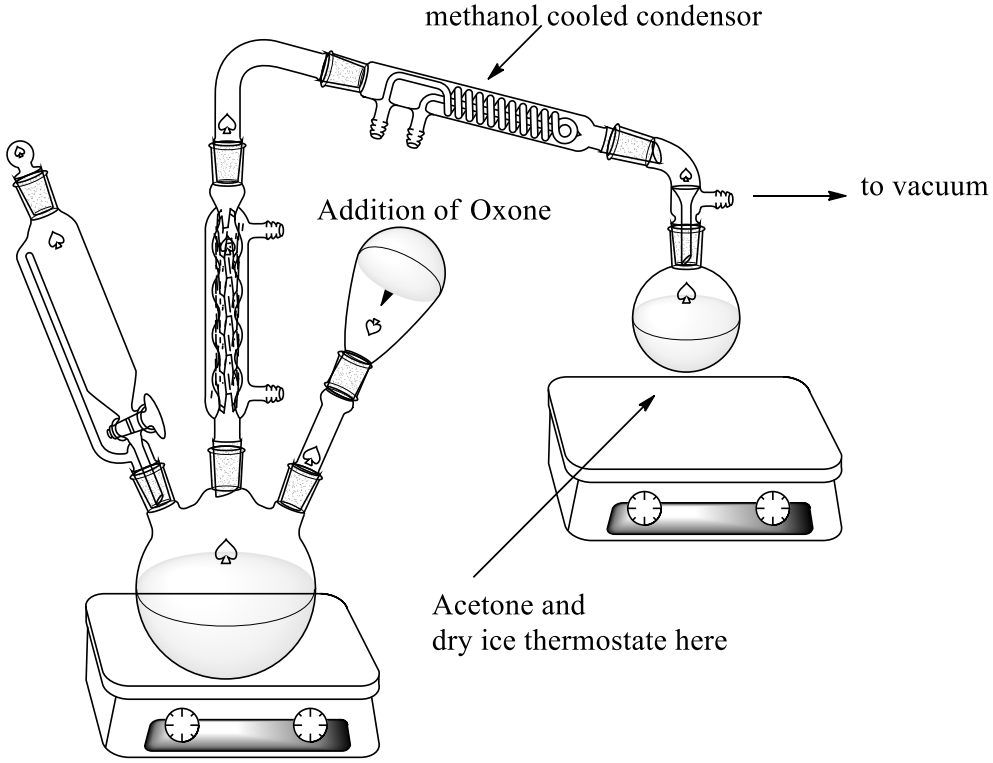


Figure 2: *first development in the procedure*

1.2.2nd development:

According to the first development, the reaction was performed while the amount of reactants were the same as described in the literature procedure [14] and 37 mL of DMD

was obtained which was much less than that of literature (reported method described earlier gives 62-76 mL). To condense more amount of DMD, the receiver flask was changed from single neck to 2-necked and another methanol-cooled condenser was introduced at the second neck of receiver flask, which was again connected to vacuum. Now the vapors remaining from first condenser has to pass through another condenser and increased the possibility of condensation. By this way, 65 mL of DMD was obtained which means increase of the product. Another development was made when the dry-ice cooled receiver was replaced with instant ice cooler and still the amount obtained of DMD was 57 mL. It means the product was decreased in amount a little but no more waiting for dry-ice.

Also the methanol temperature was increased from -80 ºC to -26 ºC, but still the amount of DMD obtained was enough (around 50 mL). So, the conditions were optimized as below:

Condensation temperature = -26 ºC rather than -80 ºC

Receiving flask temperature = 0 ºC rather than -78 ºC

Time of completion = 40 min rather than 30 min

It was observed during the experiments that fast stirring increases the amount of DMD produced per minute but the total amount obtained has decreases. Medium speed, but effective stirring (big magnet and powerful magnet stirrer) during the reaction has increases the amount of DMD obtained. After 30 min of reaction, when all the oxone is added, the amount produced per minute decreases and that time increasing the stirring speed helps to increase the DMD obtained up to 4 mL. The picture of developed reaction setup is shown in Figure 3.

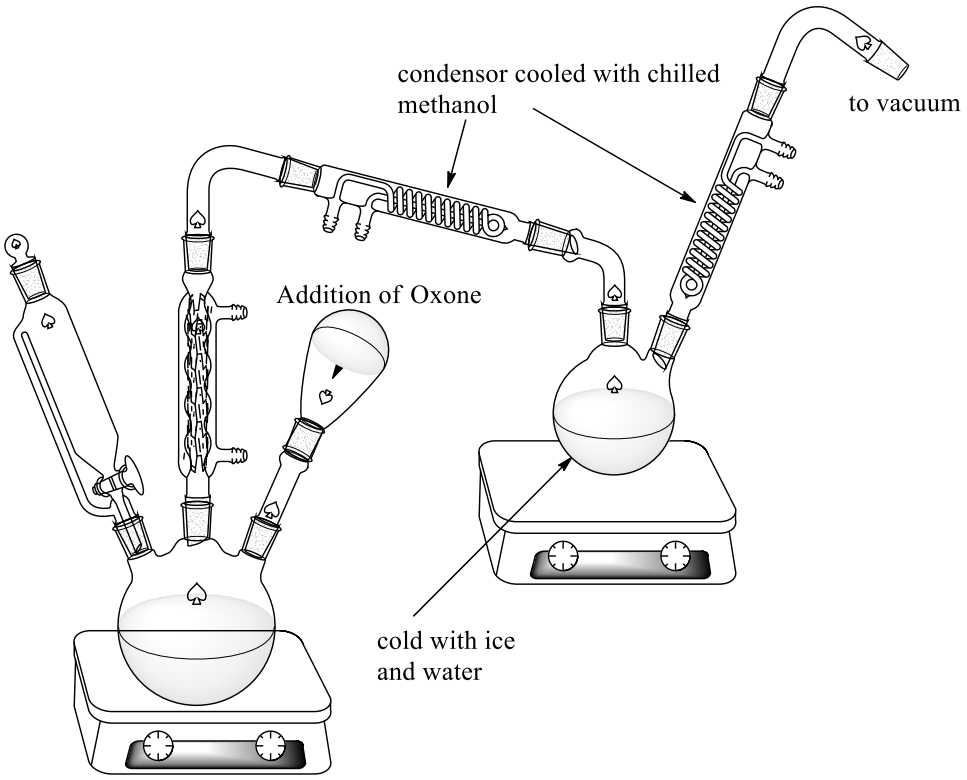
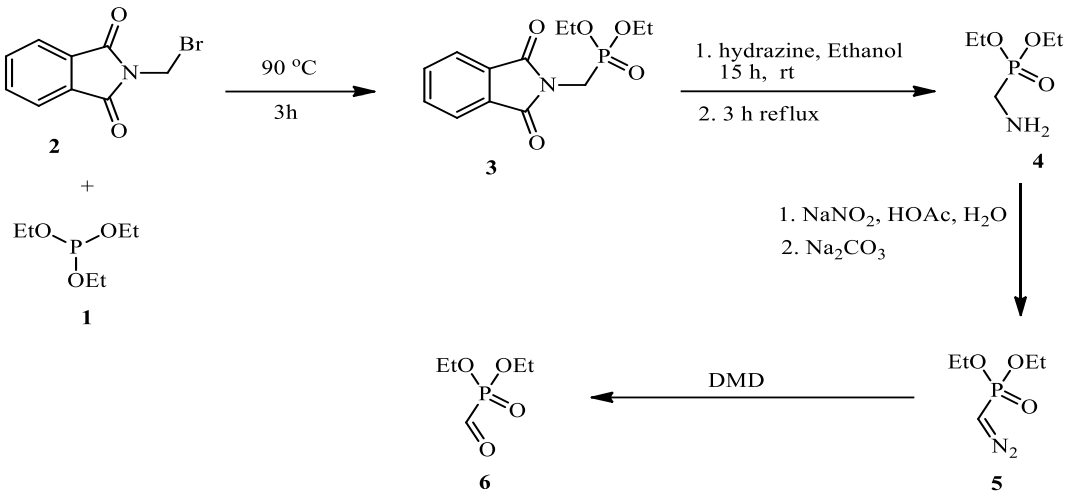


Figure 3: *second development in methodology*

2. Synthesis of formylphosphonate:

Diethyl formylphosphonate was synthesized in 4 different steps as shown in scheme 2. First, triethyl phosphite **1** was reacted without any solvent with N-bromomethylphthalimide **2** at the temperature 90 ºC for 3 h to get phosphonate **3** as shown in scheme 3. Compound **2** was used to get one carbon with the phosphonate group which would be converted to aldehyde.



Scheme 3: *Synthetic preparation of Formylphosphonate*

Ethyl bromide was formed as side product which was distilled at 105 ºC. The compound **3** was obtained in pure crystal form from 1:2 ratio of diethyl ether and hexane. In the next step, compound **3** was converted to methylamine phosphonate **4** by stirring in ethanol in the presence of hydrazine for 15 h followed by 3 h reflux.

The compound **4** was confirmed on TLC and also from the color changed on the TLC after 24 h to dark red and gave positive test with ninhydrin.

The reactant **3** was soluble in ethanol and at the start after addition of the reactant in ethanol, it become clear solution but after stirring overnight at room temperature, white precipitate were formed which was the indication of some reaction. The white precipitates were washed with ethanol and dried. The main product is in the form of colorless viscous liquid.

The amine **4** was forwarded to diazotization in the next step. Sodium nitrite was added to **4** in the presence of acetic acid at 0 ºC and stirred for 10 minutes and followed by the addition of sodium carbonate in parts. Diazo- compound **5** was extracted from aqueous solution dichloromethane, dried with sodium sulphate and evaporated. Compound **5** was obtained as yellowish liquid.

An alternate procedure was also tried without the isolation of amine **4** and converted in one step to diazo- compound **5**. But there the disadvantage was the purity. If **4** is isolated and purified with methanol and diethyl ether, **5** can be obtained pure in diazotization step. Another option for purification of **5** is to distill at 0.1 atm at 56 ºC.

A care is required during the evaporation of solvent from the product diazo- compound **5**. At 32 ºC, the compound is also going to the condenser in the rotary evaporator if the vacuum is good enough and trap is ice cold. Also the compound was purified in the next batch on silica gel column chromatography by using eluent hexane with 10-30% ethyl acetate. The compound stay longer in the column and come slowly so the polarity should not be increased more than 30% in a sudden. After the diazotization step, be careful about the color in solvent-solvent extraction step. The color of $NaNO_2$ aqueous layer and the diazo-compound diethyl (diazomethyl) phosphonate **5** in dichloromethane layer are both light yellow but still the layers can be seen.

Synthesis of formylphosphonate

Formylphosphonate **6** was synthesized from diazo- compound **5** with DMD. In literature procedures, the DMD is prepared first and then dried with Na_2SO_4 and to be used within a week. Some authors are adding water and then extracting by chloroform for better results. In our case, dry DMD was not required because the product aldehyde is to be in the form of hydrate. It was decided to put the diazo- compound at the receiving flask and do the reaction in situ. Interestingly, it was a good idea and the reaction resulted in 100% conversion to aldehyde.

The proton NMR showed the peaks related to the ethyl group at 1.34 ppm ($-CH_3$) in the form of a triplet and 4.21 ppm ($-CH_2-$) in the form of multiplet as they neighbors phosphorus which also split the peaks further. As the target product can be obtained in the hydrated form and not the aldehyde form, the aldehyde peak was not observed but the peak of P-CH- proton was observed at 5.09 ppm in the form of a doublet which was split by phosphorus with coupling constant of 12 Hz.

The final developed procedure for the synthesis of formylphosphonate is given in detail in below:

80 mL distilled water, 50 mL acetone, 96 g $NaHCO_3$, and a magnetic stirrer were transferred into a 2 L 3-necked round bottomed *flask 1*. Neck-1 of *flask 1* was connected with a rubber pipe to 250 mL round bottomed *flask 2* containing 180 g oxone. Neck-3 was connected to pressure equalizing funnel containing 60 mL water and 60 mL acetone. Neck-2 was connected with a *condenser 1* (charged with glass wool). *Condenser 1* was connected with *condenser 2* (cooled with methanol at different temperatures (-80 ºC to -26 ºC). *Condenser 2* was connected with a receiving 2-necked round bottomed 100 mL *flask 3* containing 1mL of diazo- compound **5** and a magnet. *Flask 3* was further connected with methanol cooled (same as *condenser 2*) *condenser 3*. *Flask 3* was put in a thermostat which was kept at different temperatures (-78 ºC to 0 ºC). *Condenser 3* was connected to tape water vacuum line. Stirring was started in both *flask 1* and *flask 3*. Oxone was added in portions from *flask 2* to *flask 1* and the addition was finished in 40 min with continuous vacuum and stirring. After completion, the *flask 3* was disconnected form the assembly and both the necks were closed with rubber septum. The reaction mixture was stirred for 20 h at room temperature starting from 0 ºC. The remaining DMD and acetone formed was evaporated by the help of rotary evaporator not more than 30 ºC. The product formylphosphonate **6** formed was stored at -20 ºC.

CONCLUSİON

In conclusion, the complicated synthetic procedure was modified in separated steps while every step resulted mild conditions and better yield at moderate temperature (0 ºC and 26 ºC) compared to literature procedures (-78 ºC). The dry ice before trap was replaced with a condenser containing chilled methanol which also resulted the condensation of DMD/DMDO back from the vacuum trap. After successful synthesşs of DMD/DMDO, Diethyl formylphosphonate **6** was synthesized by the oxidation of diazomethylphosphonate **5** with the help of DMD/DMDO at different temperatures starting from -78 ºC to 0 ºC. **6** was obtained in a good yield and was characterized by ^{1}HNMR.

ACKNOWLEDGEMENT

We are thankful to the TUBITAK (The Scientific and Technological Research Council of Turkey) for financial support (Program# 2216) and Chemistry department of Middle East Technical University, Ankara, Turkey.

REFERENCES

1. Hamilton, R., et al., *The Reaction of Dimethyl Dioxirane with Diazomethylphosphonates - the First Synthesis of a Formylphosphonate Hydrate.* Journal of the Chemical Society-Chemical Communications, 1994(1): p. 37-38.
2. Hamilton, R., et al., *Reactions of diazomethylphosphonate: The first synthesis of a formylphosphonate hydrate.* Phosphorus Sulfur and Silicon and the Related Elements, 1996. **109**(1-4): p. 441-444.
3. Kolodiazhnyi, O.I., *Asymmetric synthesis of hydroxyphosphonates.* Tetrahedron-Asymmetry, 2005. **16**(20): p. 3295-3340.
4. Dellaria, J.F., et al., *New Inhibitors of Renin That Contain Novel Phosphostatine Leu-Val Replacements.* Journal of Medicinal Chemistry, 1990. **33**(2): p. 534-542.
5. Tao, M., et al., *Novel peptidyl phosphorus derivatives as inhibitors of human calpain I.* Journal of Medicinal Chemistry, 1998. **41**(20): p. 3912-3916.
6. Stowasser, B., et al., *New Hybrid Transition-State Analog Inhibitors of Hiv Protease with Peripheral C2-Symmetry.* Tetrahedron Letters, 1992. **33**(44): p. 6625-6628.
7. Snoeck, R., et al., *Antivaccinia Activities of Acyclic Nucleoside Phosphonate Derivatives in Epithelial Cells and Organotypic Cultures.* Antimicrobial Agents and Chemotherapy, 2002. **46**: p. 3356-3361.
8. Peters, M.L., M. Leonard, and A.A. Licata, *Role of alendronate and risedronate in preventing and treating osteoporosis.* Cleveland Clinic Journal of Medicine, 2001. **68**(11): p. 945-951.
9. Leder, B.Z. and H.M. Kronenberg, *Gastroenterologists and choosing the right bisphosphonate.* Gastroenterology, 2000. **119**(3): p. 866-869.
10. Samanta, S. and C.G. Zhao, *Organocatalytic enantioselective synthesis of alpha-hydroxy phosphonates.* Journal of the American Chemical Society, 2006. **128**(23): p. 7442-7443.
11. Dodda, R. and C.G. Zhao, *Organocatalytic highly enantioselective synthesis of secondary alpha-hydroxyphosphonates.* Organic Letters, 2006. **8**(21): p. 4911-4914.
12. Dodda, R. and C.G. Zhao, *Silver(I) triflate-catalyzed direct synthesis of N-PMP protected alpha-aminopropargylphosphonates from terminal alkynes.* Organic Letters, 2007. **9**(1): p. 165-167.
13. Dodda, R. and C.G. Zhao, *Enantioselective synthesis of alpha-aminopropargylphosphonates.* Tetrahedron Letters, 2007. **48**(25): p. 4339-4342.
14. Murray, R.W. and M. Singh, Organic Syntheses, Coll., 1998. **9**: p. 5.