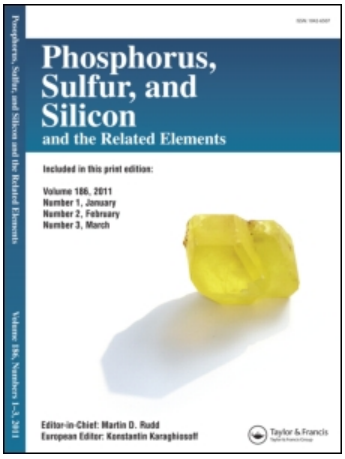


**Phosphorus, Sulfur, and Silicon and the Related Elements**
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http://www.informaworld.com/smpp/title~content=t713618290

# A CONVENIENT SYNTHESIS OF DIMETHYLPHOSPHINYL ACETIC ACID

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**To cite this Article** Chen, J. and Calvo, K. C.(1991) 'A CONVENIENT SYNTHESIS OF DIMETHYLPHOSPHINYL ACETIC ACID', Phosphorus, Sulfur, and Silicon and the Related Elements, 63: 3, 403 — 404
**To link to this Article: DOI:** 10.1080/10426509108036846
**URL:** http://dx.doi.org/10.1080/10426509108036846

*Phosphorus, Sulfur, and Silicon*, 1991, Vol. 63, pp. 403–404
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## *Communication*

# A CONVENIENT SYNTHESIS OF DIMETHYLPHOSPHINYL ACETIC ACID

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*(Received April 2, 1991; in final form July 12, 1991)*

A method is presented for preparing dimethylphosphinyl acetic acid by carboxylation of trimethylphosphine oxide α-carbanion. The product from this simple one step reaction is easily purified by extraction and ion exchange chromatography.

*Key words:* Dialkylphosphinyl acetic acids; phosphine oxide; carboxylation.

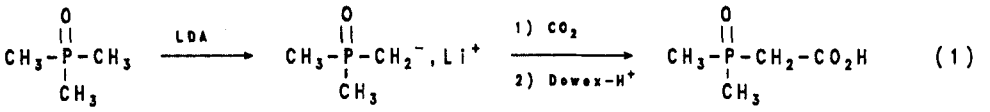


## INTRODUCTION

As part of a study into the inhibition of enzyme catalyzed Claisen condensation reactions, we required a facile synthesis of dimethylphosphinyl acetic acid. A literature review indicated that the requisite compound could be synthesized by reaction of the anion of dimethylphosphinous acid with ethyl chloroacetate,[1] by reaction of methyl dimethylphosphinite with ethyl iodo-acetate,[2] by metalation of the corresponding trimethylphosphine followed by addition of carbon dioxide and oxidation,[3] or by reaction of chlorodimethylphosphine with the sodium salt of diethylmalonate followed by oxidation, saponification and decarboxylation.[4] Although the carboxylation of the anion of diethyl methylphosphonate has been used to generate the corresponding phosphonoacetic,[5] the analogous reaction with phosphine oxides has apparently never been successfully accomplished. Indeed, it has been reported that carboxylation of a trialkylphosphine oxide anion resulted in an inseparable mixture of products.[6] In view of the difficulty in preparing the trivalent phosphorus compounds and their susceptibility to oxidation and other side reactions, we chose to investigate the reaction involving carboxylation of a phosphine oxide carbanion as a method for preparing these dialkylphosphinyl acetates. In contrast to the earlier report, we find the metalation and carboxylation reactions proceed in good yield.

## RESULTS AND DISCUSSION

We observed that although n-butyl lithium would work, lithium diisopropylamide is a more convenient base for the deprotonation of the phosphine oxide (equation 1) in that product purification is simplified. The metalation proceeds smoothly after cycling between dry ice temperature and room temperature. In contrast to the earlier literature report, we find that unreacted phosphine oxide can be removed




(1)

from the product of carboxylation by simple exhaustive Soxhlet extraction of the sodium salt. The sodium salt is then converted to the acid by use of Dowex-50 producing dimethylphosphinyl acetic acid in 60% overall yield. The acid can be crystallized. This method should be generally applicable to the carboxylation of symmetrical trialkylphosphine oxides.

## EXPERIMENTAL

*Dimethylphosphinyl acetic acid.* All steps are carried out under an inert nitrogen atmosphere. A mixture of anhydrous tetrahydrofuran (75 ml) and trimethylphosphine oxide[7] (0.49 g, 5.3 mmol) was cooled to −78°C using a dry ice/acetone bath. Lithium diisopropylamide (4 ml of 1.5 M in cyclohexane) was added slowly. After stirring for ten minutes, the mixture was allowed to warm to room temperature over the space of one hour. The mixture was then cooled to −78°C and dry carbon dioxide was bubbled into the solution. The $CO_2$ was dried by passage through concentrated sulfuric acid followed by a calcium chloride drying tube. After ten minutes of bubbling the gas through the solution, the gas addition was stopped and the mixture allowed to warm to room temperature. The solvent was removed *in vacuo*, the resulting solid dissolved in a minimum amount of water, and mixed with a slurry of Dowex-50 resin ($H^+$, 9 ml bed volume). After filtration, the pH of the filtrate was brought to about 9 by addition of 1 M NaOH. The water was removed by rotary evaporation and the resulting solid transferred to a Soxhlet extractor containing chloroform. The pure sodium dimethylphosphinylacetate was obtained after a two day extraction. The sodium salt was converted to the acid by using a Dowex-50 ($H^+$ form, 9 ml bed volume) column. After removal of water by rotary evaporation at 30°C, the residual oil crystallized and was recrystallized from acetonitrile/ethylacetate. Yield 0.43 g, 60%. mp 105–6°C (lit. 109–111°C[2]). Na form: $^1$H NMR ($D_2O$) $\delta$ 1.65 (d, $J_{HP}$ = 13.5 Hz, 6H), 2.93 (d, $J_{HP}$ = 16.3 Hz, 2H). $^{13}$C NMR ($D_2O$) $\delta$ 15.19 (d, $J_{CP}$ = 71 Hz, $CH_3$), 41.85 (d, $J_{CP}$ = 59 Hz, $CH_2$), 173.24 (s, COONa). $^{31}$P ($D_2O$) $\delta$ 50.2 (s). H form: $^1$H NMR ($D_2O$) $\delta$ 1.65 (d, $J_{HP}$ = 13.7 Hz, 6H), 3.11 (d, $J_{HP}$ = 14.6 Hz, 2H). $^{13}$C NMR ($D_2O$) $\delta$ 15.19 (d, $J_{CP}$ = 72 Hz, $CH_3$), 38.24 (d, $J_{CP}$ = 60 Hz, $CH_2$), 170.08 (d, $J_{CP}$ = 4 Hz, COOH).



## ACKNOWLEDGEMENTS

This work was supported in part by NIH grant R15-GM36071 and grant A-87-01 from the Ohio Affiliate of the American Heart Association to KCC.

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