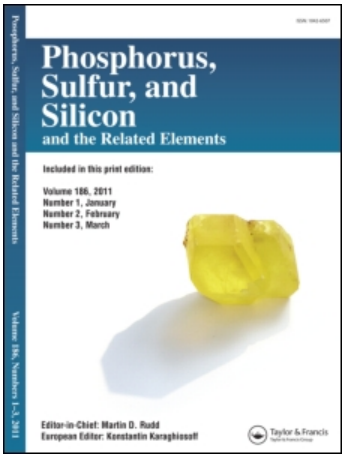



**Phosphorus, Sulfur, and Silicon and the Related Elements**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

# NEW AND EFFECTIVE SYNTHESIS OF UNSYMMETRICAL α-UREIDOALKYLPHOSPHONATES

Zai-Guo Li[a]; Qing-Min Wang[a]; Run-Qiu Huang[a]; Jun-Ran Cheng[a]; Jun-An[a]
[a] Institute and State Key Laboratory of Elemento-Organic Chemistry, Tianjin, People's Republic of China

**To cite this Article** Li, Zai-Guo , Wang, Qing-Min , Huang, Run-Qiu , Cheng, Jun-Ran and Jun-An(2000) 'NEW AND EFFECTIVE SYNTHESIS OF UNSYMMETRICAL α-UREIDOALKYLPHOSPHONATES', Phosphorus, Sulfur, and Silicon and the Related Elements, 160: 1, 51 — 59
**To link to this Article: DOI:** 10.1080/10426500008043670
**URL:** http://dx.doi.org/10.1080/10426500008043670

*Phosphorus, Sulfur and Silicon*, 2000, Vol. 160, pp. 51-59
Reprints available directly from the publisher
Photocopying permitted by license only



# NEW AND EFFECTIVE SYNTHESIS OF UNSYMMETRICAL α-UREIDOALKYLPHOSPHONATES

ZAI-GUO LI, QING-MIN WANG, RUN-QIU HUANG*, JUN-RAN CHENG and JUN-AN MA

*Institute and State Key Laboratory of Elemento-Organic Chemistry, Tianjin. 300071. People's Republic of China*

*(Received June 15, 1999; In final form November 17, 1999)*

An efficient synthesis of substituted α-ureidoalkylphosphonates **3** was reported. The method involves the conversion of α-aminoalkylphosphonates **1** to α-isocyanatoalkylphosphonates **2** by treating with triphosgene and followed by addition of substituted amine to **2**. A new kind of cyclic α- ureidoalkylphosphonates **5** was also obtained by treating **2** with o-aminobenzoic acid. followed by intramolecular cyclization of intermediate **4**.

*Keywords:* triphogene; α-Ureidoalkylphosphonate; α-aminoalkylphosphonate; o-aminobenzoic acid; α-aminocarboxylate

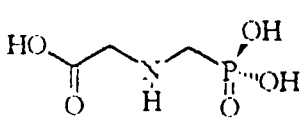


## INTRODUCTION

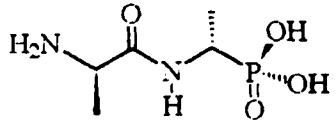
In the past two decades, α-aminoalkylphosphonates have attracted an increasing amount of attention because of their wide range of bioactivities[1-5]. Several α-aminoalkylphosphonic acid derivatives, such as the herbioide glyphosate and the antibacterial alafosfalin, are widely used commercially. Both glyphosate and alafosfalin include the sub-structure of α-aminoalkylphosphonic acids and α-aminocarboxylic acids. In order to study the effects of structure on their bioactivity, we intend to connect these two structures in a complete different way. Considering that some α-ureidoalkylphosphonates exhibit herbicidal or antiphytoviral activ-

* Corresponding Author.

ity[6,7], we decided to synthesize some novel α-ureidoalkylphosphonates with α-aminocarboxylate moiety, the title compounds **3a~3h**.

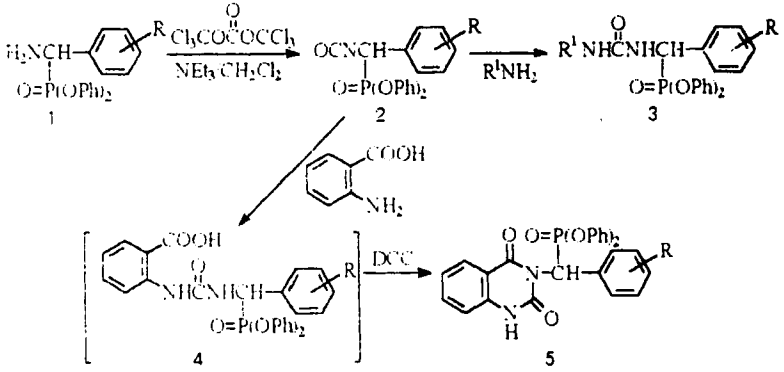


Glyphosate



Alafosfalin

The general method for synthesis of substituted α-ureidoalkylphosphonates is the three component reaction of substituted ureas, aidehydes (ketones) and trivalent phosphorus compounds [7,8]. Now we report a more convenient method for the synthesis of various unsymmetrical α-ureidoalkyl-phosphonates in this article (Scheme 1).



SCHEME 1

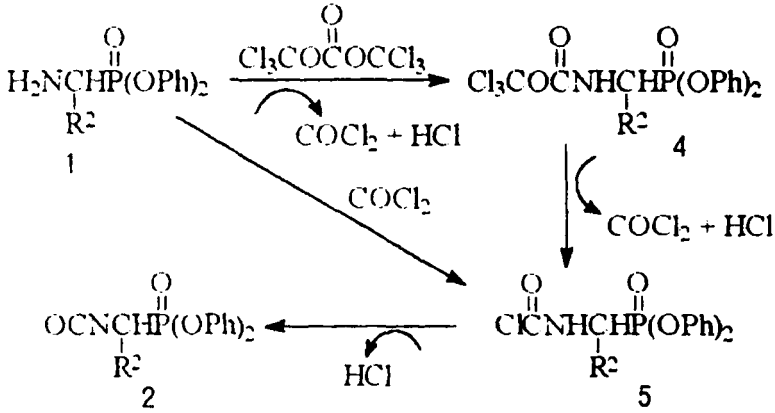
α-Aminoalkylphosphonates **1** were treated with triphosgene to give α-isocyanatoalkylphosphonates **2**, and further addition of α-aminocarboxylate hydrochloride to **2** in one pot yielded title compounds **3a~3h**. This method is also useful for the synthesis of other substituted α-ureidoalkylphosphonates, such as heterocyclic substituted α-ureidoalkylphosphonates **31~31** and 3-(α-alkylphosphonomethyl)-quinazoline-2, 4(1H,3H)-diones **5**.

## RESULT AND DISCUSSION

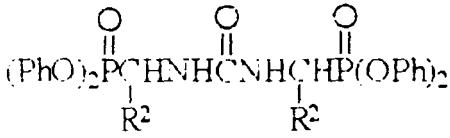
The structures and physical data of compounds **3** and **5** are listed in table I, while their $^{1}H$ NMR and $^{31}P$ NMR data are listed in table II. The specific rotations of compounds **3a~3g** are shown in table III.

We found that triphosgene can be used to convert diphenyl α-aminoalkylphosphonates **1** to diphenyl α-isocyanatoalkylphosphonates **2** under mild conditions in the presence of triethylamine. The product shows a very strong IR band at approximately 2240cm$^{-1}$, indicating the presence of the cumulative double bond of N=C=O. Compounds **2** are highly moisture sensitive. No isocyanates **2** were obtained by regular column chromatography, probably due to reactions with water and other nucleophilic species present in silica gel. Reactions with nucleophiles are best carried out in one pot without isolating the isocyanate intermediate.

α-Aminoalkylphosphonates **1** may convert to α-isocyanatoalkylphosphonates **2** through the following steps (Scheme 2).




SCHEME 2




7

TABLE I the structures and physical data of compounds **3** and **5**

| $R^1$ | R | Yield (%) | m.p. (°C) | Elemental analyses (cacld.) | | |
|---|---|---|---|---|---|---|
| | | | | C% | H% | N% |
| $(CH_3)_2CHCHCO_2CH_3$ | 2,4-$Cl_2$ | 98.6 | 48–50 | 54.94(55.23) | 4.85(4.81) | 4.70(4. |
| $(CH_3)_2CHCHCO_2CH_3$ | 2-Cl | 96.0 | -[a] | 59.00(58.82) | 5.32(5.32) | 5.28(5. |
| $H_5CH_2CHCO_2CH_3$ | 2,4-$Cl_2$ | 86.3 | 102–104 | 57.76(57.92) | 4.56(4.52) | 4.80(4. |
| $H_5CH_2CHCO_2CH_3$ | 3-$NO_2$ | 48.6 | 160–162 | 61.10(61.12) | 4.78(4.79) | 7.12(7. |
| $H_5CH_2CHCO_2CH_3$ | 2-Cl | 94.1 | 44–47 | 62.23(62 23) | 4.91(4.87) | 4.81(4. |
| $H_5CH_2CHCO_2CH_3$ | 4-Cl | 97.9 | 95–98 | 62.31(62.23) | 4.91(4.87) | 4.60(4. |
| $(CH_3)_2CHCH_2CHCO_2CH_3$ | 4-Cl | 86.0 | 105–109 | 59.34(59.51) | 5.57(5.55) | 5.15(5. |
| $O_2CCH_2$ | 2,4-$Cl_2$ | 86.1 | – | 53.60 (53.65) | 4.39(4.31) | 5.43(5. |
| nzothiazolyl | 3-$NO_2$ | 71.6 | 175–177 | 57.72(57.86) | 3.78(3.78) | 9.71(10 |
| pyryl | 2.4-$Cl_2$ | 70.2 | 98–100 | 58.10(58.41) | 4.62(4.27) | 8.34(8. |
| dimethyl-2-pyrimidyl | H | 72.6 | 120–122 | 63.79(63.93) | 5.31(5.16) | 11.56(11 |
| yridyl | 2-Cl | 78.8 | 117–119 | 56.25(56.28) | 4.39(4.36) | 10.03(10 |
| | 4-Cl | 89.6 | 175–177 | 62.51(62.62) | 3.99(3.70) | 5.21(5. |
| | 4-$CH_3$ | 92.9 | 168–170 | 67.21(67.47) | 4.85(4.85) | 5.50(5. |

liquid.

TABLE II $^{1}H$ NMR and $^{31}P$ NMR data of compounds **3** and **5**

| *P (ppm)* | *$^{1}H$ NMR (δ, ppm)* |
|---|---|
| 19.23<br>19.34 | 0.82(m, 6H, CH($C\underline{H}_3$)$_2$); 1.98(m, 1H, C$\underline{H}$(CH$_3$)$_2$); 3.61(d, 3H, OC$\underline{H}_3$); 4.09(m, 1H, C$\underline{H}$CO$_2$CH$_3$); 6.10(m, 1H, N$\underline{H}$); 6.64(d<br>C$\underline{H}$P); 6.90–7.77(m, 13H, H$_{arom}$) |
| 14.57<br>14.85 | 0.47(t, 3H, CH$_3$CHC$\underline{H}_3$); 0.68(dd, 3H, C$\underline{H}_3$CHCH$_3$); 1.76(m, 1H, C$\underline{H}$(CH$_3$)$_2$); 3.50(d, 3H, OC$\underline{H}_3$); 4.35(m, CHC$\underline{H}$NH); 5.9<br>1H, N$\underline{H}$); 6.52(dd, 1H, C$\underline{H}$P); 6.79–7.58(m, 14H, H$_{arom}$) |
| 13.03<br>14.28 | 2.78(m, 2H, C$\underline{H}_2$); 3.53(d, 3H, OC$\underline{H}_3$); 4.65(dm, 1H, C$\underline{H}$CO$_2$CH$_3$); 5.76(dd, 1H, N$\underline{H}$); 6.29(dd, 1H, C$\underline{H}$P); 6.79–7.38(m, 18<br>H$_{arom}$) |
| 13.63 | 2.83(m, 2H, C$\underline{H}_2$CH); 3.50(s, 3H, OC$\underline{H}_3$); 4.64(m, 1H, C$\underline{H}$CO$_2$CH$_3$); 5.73(br, 1H, N$\underline{H}$); 5.85(dd, 1H, C$\underline{H}$P); 6.92–8.33(m, 1<br>H$_{arom}$ |
| 14.59<br>14.82 | 2.65(m, 2H, C$\underline{H}_2$); 3.48(s, 3H, OC$\underline{H}_3$); 4.58(dm, 1H, C$\underline{H}$CO$_2$CH$_3$); 5.85(d, 1H, N$\underline{H}$); 6.40(dd, 1H, C$\underline{H}$P); 6.63–7.40(m, 24H<br>H$_{arom}$) |
| 14.79<br>15.04 | 2.84(m, 2H, C$\underline{H}_2$CH); 3.51(s, 3H, OC$\underline{H}_3$); 4.68(m, 1H, C$\underline{H}$CO$_2$CH$_3$); 5.81(br, 1H, N$\underline{H}$); 5.74(dd, 1H, C$\underline{H}$P); 6.73–7.33(m, 1<br>H$_{arom}$) |
| 15.04<br>15.25 | 0.70(m, 6H, CH($C\underline{H}_3$)$_2$); 1.00(m, 1H, C$\underline{H}$(CH$_3$)$_2$); 1.33(m, 2H, C$\underline{H}_2$); 3.60(d, 3H, OC$\underline{H}_3$); 4.33(br, 1H, C$\underline{H}$CO$_2$CH$_3$); 5.79(r<br>C$\underline{H}$P&N$\underline{H}$); 6.75–7.38(m, 14H, H$_{arom}$) |
| 15.33 | 1.18(t, 3H, C$\underline{H}_3$CH$_2$O); 3.67(d, 2H, C$\underline{H}_2$NH); 4.07(q, 2H, CH$_3$C$\underline{H}_2$O); 5.77(t, 1H, CH$_2$N$\underline{H}$); 6.37(dd, 1H, C$\underline{H}$P); 6.74–7.63(<br>13H, H$_{arom}$) |
| -[a] | 6.14(q, 1H, CH), 6.86–8.52(m, 18H, H$_{arom}$) |

| P (ppm) | $^1H$ NMR (δ, ppm) |
|---|---|
| – | 2.19(s, 3H, $H_3CC$=); 3.03(s, 3H, $NCH_3$); 6.26(q. 1H, CH); 6.97–7.33(m, 18H, $H_{arom}$); 7.93(br. 1H, NH); 8.39(br. 1H, NH) |
| – | 2.38(s, 6H, 2×($CH_3$); 5.87(q, 1H, CH); 6.62(s, 1H,-CH=); 6.93–7.54(m, 15H, $H_{arom}$) |
| – | 6.57(q, 1H, CH); 6.75–8.16(m, 18H, $H_{arom}$); 9.57(s, 1H, NH); 11.00(br, 1H, NH) |
| – | 5.92(d, 1H, CH), 6.48(br, 1H, NH), 6.88–8.08(m, 18H, $H_{arom}$) |
| – | 2.32(s, 3H, $CH_3$), 5.91(d, 1H, CH), 6.13(br, 1H, NH), 6.88–8.06(m, 18H, $H_{arom}$) |

re not recorded.

TABLE III Specific rotations of compounds **3a–3g**

| *concentration, solvent* | *specific rotation* $[\alpha]_D$ | *compound* | *concentration, solvent* | *specific rotation* |
|---|---|---|---|---|
| 1, $CHCl_3$ | −5.5 | **3e** | 1, $CHCl_3$ | +32.0 |
| 1, $CHCl_3$ | −2.5 | **3f** | 1, $CHCl_3$ | +31.0 |
| 1, $CHCl_3$ | +30.2 | **3g** | 1, $CHCl_3$ | +2.5 |
| 1, $CHCl_3$ | +41.2 | | | |

The nucleophilic attack of **1** on triphosgene forms α-trichloromethoxy-carbonylamino-alkylphosphonates **4**, which decompose automatically to give α-chlorocarbonylamino-phosphonates **5**. Then **2** are obtained from **5** by eliminating a molecular of hydrochloride.

In some cases, small amount of **7** was isolated as by product They can be formed by the reaction of α-ammoalkylphosphonates **1** with **2**. The formation of **7** can be retarded bv lowering the reaction temperature.

When optically active aminocarboxylate was used, a mixture of two diastereoisomers was obtained. The $^{1}H$ NMR and $^{31}P$ NMR of them are different. The hydrogens on the aminocarboxylate moiety exhibited two groups of peaks in the $^{1}H$ NMR spectra, while the $^{31}P$ NMR spectrum showed two signals, one for each isomer.

In the synthesis of **5**, the intermediates **4** were not separated, but undergo cyclization reaction in one pot in the presence of DCC.



## BIOACTIVITY

The preliminary bioassay indicated that compounds **3** showed no significant herbicidal and anti-TMV (tobacco mosaic virus) activities.

## EXPERIMENTAL

Melting points were determined on a Yanaco MP-500 apparatus and are uncorrected. $^{1}H$ NMR and $^{31}P$ NMR spectra were taken on a Bruker AC-P200 spectrometer operating at 200 MHz with TMS and 85% $H_3PO_4$ as internal and external standard respectively. The elemental analyses were measured with a Yanaco CHN Cored MT-3 apparatus.

α-Aminoalkylphosphonates (**1**) were prepared according to the reported procedure[9]. Triphosgene was synthesized by chlorination of dimethyl carbonate[10]. α-Aminocarboxylate hydrochlorides were obtained following M. Brenner's report[11].

### Typical procedure for the preparation of 3a~3h

A solution of α-aminoalkylphosphonate **1** (3.68mmol) and triethylamine (18mmol) in 10mL dichloromethane was added dropwise to a solution of

triphosgene (1.78mmol) in 5mL dichloro-methane during 30 minutes under magnetic stirring at −10°C. The mixture was stirred at room temperature for 30 minutes. Then a solution of α-aminocarboxylate hydrochloride (3.13mmol) in 15mL dichloromethane was added while stirring at the same temperature. The reaction mixture was stirred at room temperature for 3 hours. After the solvent was removed under vacuum, the residue was dissolved in 20ml ethyl acetate and filtered, then the filtration was evaporated and the residue was purified by chromatography on silica gel.

### Typical procedure for the preparation of 3i~3l

The procedure is the same as the preparation of **3a~3h** except that 15mmol triethylamine was used.



### Typical procedure for the preparation of 5a-b

A solution of α-aminoalkylphosphonates **1** (3.68mmol) and triethylamine (15mmol) in 10mL dichloromethane was added dropwise to a solution of triphosgene (1.78mmol) in 10mL dichloromethane at -10°C. The solution was stirred at room temperature for 30 minutes. After a solution of o-aminobenzoic acid (3.13mmol) in 10mL dichloromethane was added, the mixture was stirred at room temperature for 30 minutes, then DCC (3.76mmol) was added and the reaction mixture was refluxed for 2 hours. The solvent was removed by vacuum and the residue was purified by chromatography on silica gel to give **5** as white solids.

### *Acknowledgements*

We thank the National Natural Science Foundation of China and the Natural Science Foundation of Tianjin for financial support.

### *References*

1. M.C. Allen, W. Fuhrer, B. Tuck, R. Wade, J.M. Wood, J. Med. Chem., 1989, 32, 1652.
2. (a) F.R. Atherton, C.H. Hassel, R.W. Lambert, J. Med. Chem., 1986, 29, 29
   (b) J.G. Allen, F.R. Atherton, C.H. Hassel, et al., Nature, 1978, 272, 56.
3. F.A. Hartman US Patent 3894861 (1975).
4. Stauffer Co. US Patent 4170463 (1979).
5. Y.X. Long, K.S. Zhang, D.W. Qiu, Chem. J. Chinese Universities, 1996, 17(8), 1247.
6. G.H. Birum, US 4031170 (1977).
7. G.H. Biram, J. Org. Chem., 1974, 39(2), 209.
8. D. Qing. R.Y. Chen, Chem. J Chinese Universities, 1997, 18(1), 64.

9. Jozef Oleksyszyn, et al., Synthesis, 1979, 985.
10. H. Eckert. et al., Angew Chem., Int. Ed. Engl., 1987, 26(9), 894.
11. M. Brenner. W.Huber, Helv. Chim. Acta., 1953, 36, 1109.