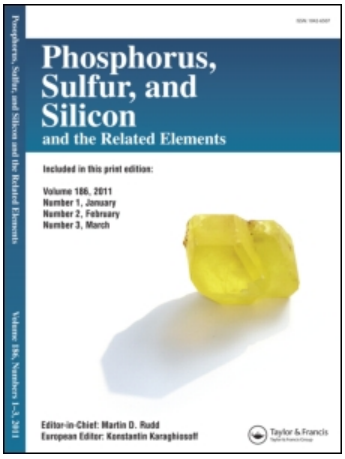


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS OF DIALKYL α-(*p*-TOLUENESULFONUREADO) PHOSPHONATES AND THEIR QUANTITATIVE STRUCTURE-ANTI-TMV ACTIVITY RELATIONSHIP

Qing Dai[a]; Ruyu Chen[a]
[a] Institute and State's key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin, P. R. China

To cite this Article Dai, Qing and Chen, Ruyu(1997) 'SYNTHESIS OF DIALKYL α-(*p*-TOLUENESULFONUREADO) PHOSPHONATES AND THEIR QUANTITATIVE STRUCTURE-ANTI-TMV ACTIVITY RELATIONSHIP', Phosphorus, Sulfur, and Silicon and the Related Elements, 122: 1, 261 — 267
To link to this Article: DOI: 10.1080/10426509708043515
URL: http://dx.doi.org/10.1080/10426509708043515

Phosphorus, Sulfur, and Silicon, 1997, Vol. 122, pp. 261-267
Reprints available directly from the publisher
Photocopying permitted by license only

SYNTHESIS OF DIALKYL α-(P-TOLUENESULFONUREADO) PHOSPHONATES AND THEIR QUANTITATIVE STRUCTURE-ANTI-TMV ACTIVITY RELATIONSHIP

QING DAI* and RUYU CHEN

Institute and State's key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin, 300071, P. R. China

(Received 21 October 1996; In final form 14 January 1997)

A series of 0,0-diethyl-α-(*p*-toluenesulphonureado) phosphonates have been synthesized by the Mannich-type reaction of *p*-toluenesulphonurea, (substituted) benzaldehydes and dialkyl phosphites with acetyl chloride as the solvent. The bioassay results showed that some of them possess good anti-TMV (Tobacco Mosaic Virus) activities and the quantitative structure-anti-TMV activity relationship (QSAR) has also been studied.

Keywords: Mannich-type reaction; nonequivalence; QSAR; anti-TMV activity

INTRODUCTION

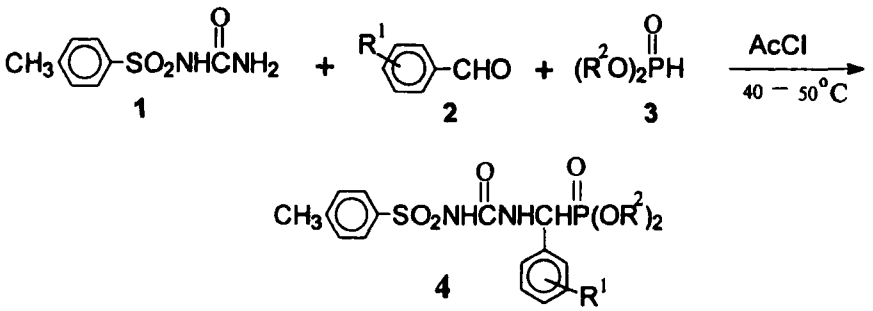
It is well-known that some derivatives of α-amino phosphonic acid possess good herbicidal activities[1]. Of them, Glyphosate and Glyphosine are two herbicides which have been commercialized. Therefore, we hope to prepare some new herbicides by modifying the structure of α-amino phosphonic acid. Another type of herbicide with high activities is the sulfonylurea herbicides. For this reason, we have designed a synthesis to introduce the sulfonureado group to the structure of α-amino phosphonic acid. We have also investigated the biological activity of these new compounds.

*Corresponding author.

RESULTS AND DISCUSSION

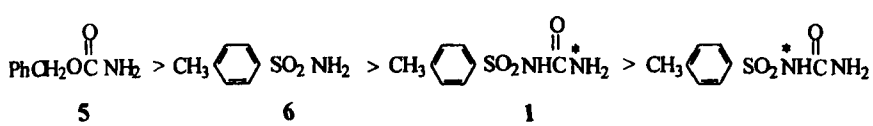
A. Synthesis of the Title Compounds

With acetyl chloride as the solvent, *p*-toluenesulfonurea **1** reacted readily with aromatic aldehydes **2** and dialkyl phosphites **3** to give the title compounds **4**. The reaction took placed selectively at the N atom of the NH_2 group.



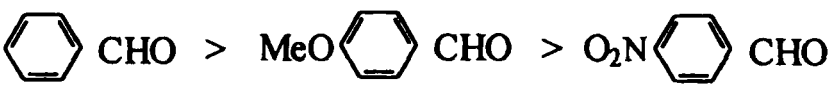
$R^1 = H, p-Me, o-Cl, m-Cl, p-Cl, p-MeO, m-NO_2, p-NO_2$; $R^2 = Me, Et, Pr, {}^{i}Pr$

Among numerous synthetic methods for the preparation of α-amino phosphonic derivatives, the three-component condensation involving substituted amide, aldehydes and a phosphorus reagents is of significant interest.[2–7] With acetyl chloride as the solvent, benzyl carbamate[2] **5** (or *p*-toluenesulfonamide **6**)[7] have been reported to react with **2** and **3** to give the corresponding products. In order to compare the relative reaction activities of **1**, **5** and **6**, equal molar quantities of **1**, **2b** (R^1 = *p*-Cl), **3b** (R^2 = Et), **5** and **6** were reacted in one system. The reaction was traced by TLC. After all the **3b** was used up, the ratio of the three possible products was checked by ^{31}P NMR spectrum. It was found that 90.3% of **5** was converted to diethyl 1-(benzyloxycarbonylamido)-*p*-chloro-phenylmethylphosphonate (**7b**), and 9.3% of **6** was converted to diethyl 1-(*p*-toluenesulfonamido)-*p*-chloro-phenylmethylphosphonate (**8b**) while there was no corresponding **4b**. Obviously, the reactive activity order is:



It could be seen that the higher the nucleophilicity of the N atom was, the easier the reaction was. However, if the nucleophilicity of the N atom was too high, the N atom will be acetylized by the solvent. for example, when N-methyl *p*-toluenesulfonamide was used instead of **4**, acetylated by-product N-methyl, N-acetyl *p*-toluenesulfonamide was formed immediately even below 0°C. Obviously, with acetyl chloride as the solvent, general amines could not be used as nucleophilic reagents.

In order to compare the effects of the substitutent group in benzene ring of the compound **2** on the reaction activity, equal molar quantities of **1**, **3**, and **2** (the mixture of the equal molar quantities of the *p*-methoxy-benzaldehyde, benzaldehyde and *p*-nitro-benzaldehyde) were reacted in one system. The reaction was traced by TLC. After all the **1** was used up, the ^{31}P NMR spectrum of the mixture indicated that the ratio of the three possible products was **4b**:**4e**:**4f** ≅ 2.5:1.7:1.0. So the reactive activity order of the aromatic aldehydes was as follows:



This order, however, was quite different from that of the similar reaction of **6**, in which the reactive activity of *p*-nitro-benzaldehyde was the highest, while that of the other two was almost equal[7]. This phenomenon implied that the mechanism of the Mannich-type is very complicated.

B. Spectral Properties of the Title Compounds

All the compounds prepared were characterized by ^{1}H NMR and elemental analysis, some of them were also characterized by ^{31}P NMR spectroscopy and MS (see Table I and II).

The ^{1}H NMR spectra of compound **4** clearly show that the two alkoxy groups are magnetic nonequivalent. By taking **4a** as an example, its ^{1}H NMR spectrum shows that one methoxy group exhibits double peaks at 3.79 ppm while the other exhibits double peaks at 3.57 ppm. The possible reason was that there exists a benzene ring at the α-C atom so that the free rotation of P-C bond is hindered, and the two methoxy groups exist in the different position of α-benzene ring, which causes the magnetic nonequivalence.[7].

When R^2 = Et, the chemical shift of ^{31}P NMR signal of the title compound (δ_P) increases when the substituent groups in the α-benzene ring become more electron-withdrawing. However, δ_P does not have good linear relationship against the substituting group constant (σ).[7]

TABLE I Physical properties, elementary analysis data of the products **4**

NO	R^1	R^2	*inhibiting rate*	*m.p.*	*Yield*	*Elementary Analysis/Found (Calcd.)*		
$4_{a\text{-}r}$			(%)	(°C)	(%)	C(%)	H(%)	N(%)
a	*p*-Cl	Me	70	215–216	67.2	45.69(45.38)	4.48(4.60)	6.27(6.41)
b	H	Et	30	182–184	52.3	51.82(51.87)	5.68(5.77)	6.36(6.09)
c	*p*-Me	Et	60	167–168	58.41	52.86(52.94)	5.95(5.75)	6.17(5.99)
d	*p*-Cl	Et	70	203–204	50.6	48.05(48.21)	5.06(5.10)	5.90(5.72)
e	*p*-MeO	Et	45	179–180	50.0	51.06(51.27)	5.74(5.58)	5.96(5.92)
f	*p*-NO_2	Et	60	164–166	36.1	47.01(47.05)	4.95(4.93)	8.66(8.76)
g	*m*-Cl	Et	50	179–180	64.3	48.05(48.28)	5.06(5.17)	5.90(5.79)
h	*m*-NO_2	Et	30	142–144	59.8	47.01(46.94)	4.95(5.02)	8.66(8.54)
i	*o*-Cl	Et	35	181–182	60.6	48.05(48.33)	5.06(4.94)	5.90(5.79)
j	*p*-Cl	Pr	55	131–133	65.5	50.15(50.46)	5.57(5.38)	5.57(5.46)
k	*m*-NO_2	Pr	15	110–112	74.1	49.12(48.95)	5.46(5.55)	8.19(8.34)
l	*p*-Me	Pr	40	128–129	60.0	54.77(54.98)	6.43(6.30)	5.81(5.79)
m	*p*-MeO	Pr	45	115–117	40.3	53.01(53.42)	6.22(6.01)	5.62(5.50)
n	*p*-NO_2	Pr	50	170–172	40.5	49.12(49.30)	5.46(5.28)	8.19(8.34)
o	*p*-Cl	i-Pr	40	182–183	62.1	50.15(50.45)	5.57(5.42)	5.57(5.53)
p	*p*-MeO	i-Pr	20	154–156	60.2	53.01(52.86)	6.22(6.28)	5.62(5.78)
q	*p*-NO_2	i-Pr	40	208–209	40.5	49.12(49.46)	5.46(5.32)	8.19(8.21)
r	*m*-Cl	i-Pr	15	143–144	56.8	50.15(50.15)	5.57(5.44)	5.57(5.59)

TABLE II ^{1}H NMR data of compound **4**

4a	9.42 (1H, br., N-H); 7.27 ~ 7.86 (9H, m, 2 × C_6H_4 + N-H); 5.26 (1H, dd, CH, $J^2_{P\text{-}H}$ = 20.87Hz, $J^3_{H\text{-}H}$ = 9.39Hz); 3.79 (3H, d, OCH_3, $J^3_{P\text{-}H}$ = 10.4Hz); 3.57 (3H, d, OCH_3, $J^3_{P\text{-}H}$ = 10.5Hz); 2.42 (3H, s, CH_3-Ph)
4b	9.76 (1H, br., N-H); 7.16 ~ 7.84 (10H, m, C_6H_5 + C_6H_4 + N-H); 5.20 (1H, dd, CH, $J^2_{P\text{-}H}$ = 22.0Hz, $J^3_{H\text{-}H}$ = 7.2Hz); 3.32 ~ 4.20 (4H, m, 2 × CH_2); 2.32 (3H, s, CH_3-Ph); 1.16 (3H, t, CH_3); 1.00 (3H, t, CH_3)
4c	9.60 (1H, br., N-H); 7.16 ~ 7.84 (9H, m, 2 × C_6H_4 + N-H); 5.20 (1H, dd, CH, $J^2_{P\text{-}H}$ = 21.6Hz, $J^3_{H\text{-}H}$ = 7.2Hz); 3.48 ~ 4.24 (4H, m, 2 × CH_2); 2.32 (3H, s, 2 × CH_3-Ph); 2.32 (3H, s, 2 × CH_3-Ph); 1.18 (3H, t, CH_3); 1.04 (3H, t, CH_3)
4d	9.52 (1H, br., N-H); 7.20 ~ 7.80 (9H, m, 2 × C_6H_4 + N-H); 5.21 (1H, dd, CH, $J^2_{P\text{-}H}$ = 23.4Hz, $J^3_{H\text{-}H}$ = 9.0Hz); 3.52 ~ 4.24 (4H, m, 2 × CH_2); 2.34 (3H, s, CH_3-Ph); 1.18 (3H, t, CH_3); 1.08 (3H, t, CH_3)
4e	9.60 (1H, br., N-H); 6.76 ~ 7.84 (9H, m, 2 × C_6H_4 + N-H); 5.16 (1H, dd, CH, $J^2_{P\text{-}H}$ = 19.4Hz, $J^3_{H\text{-}H}$ = 6.3Hz); 3.76 (3H, s, 2 × CH_3-Ph); 3.52 ~ 4.24 (4H, m, 2 × CH_2); 2.32 (3H, s, 2 × CH_3-Ph); 1.17 (3H, t, CH_3); 1.02 (3H, t, CH_3)
4f	9.46 (1H, br., N-H); 7.26 ~ 8.28 (9H, m, 2 × C_6H_4 + N-H); 5.42 (1H, dd, CH, $J^2_{P\text{-}H}$ = 22.3Hz, $J^3_{H\text{-}H}$ = 10.1Hz); 3.72 ~ 4.40 (4H, m, 2 × CH_2); 2.42 (3H, s, CH_3-Ph); 1.32 (3H, t, CH_3); 1.20 (3H, t, CH_3)
4g	9.62 (1H, br., N-H); 7.25 ~ 7.92 (9H, m, 2 × C_6H_4 + N-H); 5.28 (1H, dd, CH, $J^2_{P\text{-}H}$ = 25.2Hz, $J^3_{H\text{-}H}$ = 8.6Hz); 3.60 ~ 4.36 (4H, m, 2 × CH_2); 2.41 (3H, s, CH_3-Ph); 1.31 (3H, t, CH_3); 1.20 (3H, t, CH_3)
4h	10.24 (1H, br., N-H); 7.28 ~ 8.24 (9H, m, 2 × C_6H_4 + N-H); 5.30 (1H, dd, CH, $J^2_{P\text{-}H}$ = 23.8Hz, $J^3_{H\text{-}H}$ = 8.6Hz); 3.84 ~ 4.42 (4H, m, 2 × CH_2); 2.42 (3H, s, CH_3-Ph); 1.24 (3H, t, CH_3); 1.16 (3H, t, CH_3)
4i	9.56 (1H, br., N-H); 7.24 ~ 7.84 (9H, m, 2 × C_6H_4 + N-H); 5.90 (1H, dd, CH, $J^2_{P\text{-}H}$ = 20.9Hz, $J^3_{H\text{-}H}$ = 9.4Hz); 3.73 ~ 4.17 (4H, m, 2 × CH_2); 2.40 (3H, s, CH_3-Ph); 1.29 (3H, t, CH_3); 1.08 (3H, t, CH_3)
4j	9.43 (1H, br., N-H); 7.27 ~ 7.84 (9H, m, 2 × C_6H_4 + N-H); 5.24 (1H, dd, CH, $J^2_{P\text{-}H}$ = 21.9Hz, $J^3_{H\text{-}H}$ = 10.4Hz); 3.62 ~ 4.24 (4H, m, 2 × CH_{20}); 2.43 (3H, s, CH_3-Ph); 1.42 ~ 1.80 (4H, m, 2 × CH_2); 0.77 ~ 0.93 (6H, m, 2 × CH_3)
4k	9.48 (1H, br., N-H); 7.23 ~ 8.18 (9H, m, 2 × C_6H_4 + N-H); 5.38 (1H, dd, CH, $J^2_{P\text{-}H}$ = 21.9Hz, $J^3_{H\text{-}H}$ = 9.4Hz); 3.78 ~ 4.30 (4H, m, 2 × CH_{20}); 2.40 (3H, s, CH_3-Ph); 1.48 ~ 1.82 (4H, m, 2 × CH_2); 0.76 ~ 0.96 (6H, m, 2 × CH_3)
4l	9.61 (1H, br., N-H); 7.15 ~ 7.86 (9H, m, 2 × C_6H_4 + N-H); 5.22 (1H, dd, CH, $J^2_{P\text{-}H}$ = 20.9Hz, $J^3_{H\text{-}H}$ = 9.4Hz); 3.52 ~ 4.18 (4H, m, 2 × CH_{20}); 2.41 (3H, s, CH_3-Ph); 2.37 (3H, s, CH_3-Ph); 1.36 ~ 1.94 (4H, m, 2 × CH_2); 0.74 ~ 0.93 (6H, m 2 × CH_3)
4m	9.55 (1H, br., N-H); 6.87 ~ 7.29 (9H, m, 2 × C_6H_4 + N-H); 5.26 (1H, dd, CH, $J^2_{P\text{-}H}$ = 22.6Hz, $J^3_{H\text{-}H}$ = 10.4Hz); 3.46 ~ 4.25 (4H, m, 2 × CH_{20}); 3.81 (3H, s, CH_3O-Ph); 2.41 (3H, s, CH_3-Ph); 1.40 ~ 1.94 (4H, m, 2 × CH_2); 0.77 ~ 1.00 (6H, m, 2 × CH_3)
4n	9.39 (1H, br., N-H); 7.25 ~ 7.82 (9H, m, 2 × C_6H_4 + N-H); 5.38 (1H, dd, CH, $J^2_{P\text{-}H}$ = 23.0Hz, $J^3_{H\text{-}H}$ = 9.4Hz); 3.85 ~ 4.18 (4H, m, 2 × CH_{20}); 2.42 (3H, s, CH_3-Ph); 1.42 ~ 1.86 (4H, m, 2 × CH_2); 0.77 ~ 0.95 (6H, m, 2 × CH_3)
4o	9.47 (1H, br., N-H); 7.40 ~ 7.92 (9H, m, 2 × C_6H_4 + N-H); 5.16 (1H, dd, CH, $J^2_{P\text{-}H}$ = 21.9Hz, $J^3_{H\text{-}H}$ = 10.4Hz); 4.59 (2H, m, 2 × CH); 2.42 (3H, s, CH_3-Ph); 0.93 ~ 1.32 (12H, m, 4 × CH_3)
4p	9.62 (1H, br., N-H); 6.86 ~ 7.83 (9H, m, 2 × C_6H_4 + N-H); 5.14 (1H, dd, CH, $J^2_{P\text{-}H}$ = 21.9Hz, $J^3_{H\text{-}H}$ = 10.4Hz); 4.70 (2H, m, 2 × CH); 2.42 (3H, s, CH_3-Ph); 0.84 ~ 1.30 (12H, m, 4 × CH_3)
4q	9.31 (1H, br., N-H); 7.27 ~ 8.06 (9H, m, 2 × C_6H_4 + N-H); 5.27 (1H, dd, CH, $J^2_{P\text{-}H}$ = 22.95Hz, $J^3_{H\text{-}H}$ = 9.4Hz); 4.64 (2H, m, 2 × CH); 2.42 (3H, s, CH_3-Ph); 0.95 ~ 1.34 (12H, m, 4 × CH_3)
4r	9.52 (1H, br., N-H); 6.93 ~ 7.48 (9H, m, 2 × C_6H_4 + N-H); 4.67 (1H, dd, CH, $J^2_{P\text{-}H}$ = 25.0Hz, $J^3_{H\text{-}H}$ = 9.4Hz); 4.68 (2H, m, 2 × CH); 2.27 (3H, s, CH_3-Ph); 0.85 ~ 1.47 (12H, m, 4 × CH_3)

C. Biological Activity and QSAR

The results of bioassay showed that some products had good herbicidal activity. For example, the inhibiting rate of compound **4e** to alfalfa reached 93% at the dose of 1.5kg/ha. In addition, we found some of them possess good anti-TMV activity. At the dosage of 500ppm, the inhibiting rate of compound **4a** and **4d** even attained 70%. The activity of other products were listed in Table I. In order to know the correlation of the structure to anti-TMV activity, the quantitative structure-activity relationship (QSAR) of compounds **4** was studied.

The inhibiting rate (a) was converted to activity index (Y) according to the following formula:

$$Y = \log a/(1\text{-}a) + \log M$$

Four parameters $\Sigma\pi$ (lipophilicity parameter of R^1 and R^2), σ_{mp} (Electron parameter of the *para* and *meta* substituting groups of the α-benzene ring), Es_p(steric parameter of the *para* substituting groups of the α-benzene ring) and Es_{R2}(steric parameter of R^2) were chosen. After the stepwise analyses, the QSAR equation was obtained as follows:

$$Y = -6.3231 + 0.2666\,\Sigma\pi - 0.0787\sigma_{m+p} - 0.2997Es_p - 12.599Es_{R2} - 4.704ES^2R2$$

where $n = 18$, $r = 0.925$, $s = 0.151$, $F = 14.15$. The correlation was significant at a level of above 95%.[8]

From the equation, we could see that the activity was mainly affected by steric effect of R^2. The best result was given when R^2 is Et, Meanwhile, the activity also has some relation with $\Sigma\pi$ and steric effect of *para* substituting group of the α-benzene ring. More or less, these results are of some significance for predicting anti-TMV activity of new compounds and may help in designing some novel anti-TMV pesticides.

EXPERIMENTAL

The melting points are uncorrected. Elemental analyses were measured by Yanaco CHN Corder MT-3 apparatus. ^1H NMR and ^{31}P NMR spectra were recorded on a Bruker AC-P 200 spectrometer by using TMS and 85% H_3PO_3 as internal and external standards respectively.

The reagents and solvents were available commercially and were purified according to conventional methods.

O,O-Dialkyl α-(p-toluenesulfonureado) phosphonates **4** *(General procedure)*: A mixture of *p*-toluenesulfonamide **1** (5 mmol); dialkyl phosphite **3** (5 mmol), and 15 mL AcCl was stirred at r.t. The aldehyde **2** (6 mmol) was added dropwise. After stirring at 40 $\sim$ 50°C for 4 h, the solvent was removed under reduced pressure. The residue was recrystallized from EtOH/H_2O, and a colorless crystal was obtained. The compounds of **4a** $\sim$ **4j** were synthesized likewise. Their physical constants are listed in Table I, those of ^{1}H NMR in TABLE II.

Acknowledgements

The authors would like to thank the National Natural Science Foundation of China for financial support.

References

[1] P. Kafarski, B. Leiczak, P. Mastalerz, *Phosphonopeptides—Synthesis and Biological Activity*, Berlin: Beitrage zur wirkstropfforschung Heft-Nr. 25, (1985).
[2] C.Y. Yuan, G.H. Wang and S.J. Chen, *Synthesis*, 522, (1990).
[3] C.Y. Yuan and G.H. Wang, *Synthesis*, 256, (1990).
[4] R.Y. Chen and S.X. Den, *Phosphorus, Sulfur and Silicon*, **56**, 39, (1991).
[5] R. Y. Chen and K. S. Feng, *Science in China (Series B)*, **36**, 257, (1993).
[6] R.Y. Chen and Q. Dai, *Chinese Chemical Letters*, **3**, 181, (1995).
[7] R.Y. Chen, Q. Dai, D.Q. Zhang et al., *Science in China 1. (series B)*, **10**, 1153.
[8] H.L. Wang, J. Zhou, Y.G. Qiu et al., *Phosphorus, Sulfur, and Silicon*, **104**, 135, (1995).