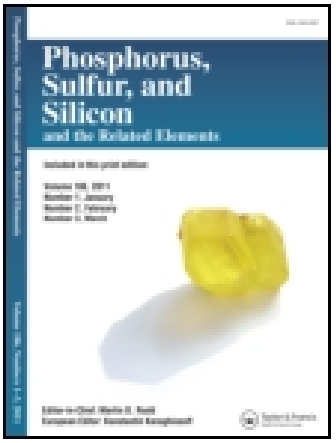

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

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Published online: 02 Aug 2010.

To cite this article: Abdolreza Iraj Mansouri , Zahra Hassani & Mohammad Reza Islami (2010) Synthesis of oxo-Phosphoranylidene Aminobenzoic Acid Derivatives by a Multicomponent Reaction, Phosphorus, Sulfur, and Silicon and the Related Elements, 185:8, 1753-1758, DOI: 10.1080/10426500903258790

To link to this article: http://dx.doi.org/10.1080/10426500903258790

Phosphorus, Sulfur, and Silicon, 185:1753–1758, 2010

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500903258790

SYNTHESIS OF OXO-PHOSPHORANYLIDENE AMINOBENZOIC ACID DERIVATIVES BY A MULTICOMPONENT REACTION

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2-Aminobenzoic acids or 4-aminobenzoic acid react with dimethyl acetylenedicarboxylate/triphenylphosphine in less than 20 min at 15–25°C to produce new organic phosphorus compounds in good to excellent yields. The conversion occurs with selective N- over O-alkylation of the amino group and isolation of the products is accomplished simply by filtration.

Keywords Aminobenzoic acids; dimethyl acetylenedicarboxylate; phosphonium ylide

INTRODUCTION

We have recently described the use of Meldrum's acid **1** and *N*,*N*'-dimethyl barbituric acid **2** as CH-acids for the synthesis of 1,4-diionic compounds (Figure 1).[1] H. J. Bestmann and co-workers reported such compounds as an intermediate in the reaction of vinyl ketone and an ylide.[2–4] We have shown that 1,4-diionic compounds **3** possess two vicinal stereogenic centers and are formed as a mixture of two diastereoisomers.[1] Interconversion between the two isomers via C-H proton exchange reactions of the Ph_3P^+-CH moieties precludes their separation. We were interested to examine aminobenzoic acids as precursors for the synthesis of these betaines, although, as far as we are aware, no example of this family has been reported. We report in this article the behavior of aminobenzoic acids on applying this methodology. However, in this case 1,4-diionic compounds were not formed, and the final isolated products were identified as phosphonium ylides.

RESULTS AND DISCUSSION

It is known that the reaction of acetylenic esters and Ph_3P produced the intermediate **4**, which is sufficiently stabilized by resonance.[5,6] Thus, compounds **5a**,**b** were apparently

Received 13 April 2009; accepted 12 August 2009.
The authors thank the International Center for Science, High Technology and Environmental Sciences for the support of this investigation.
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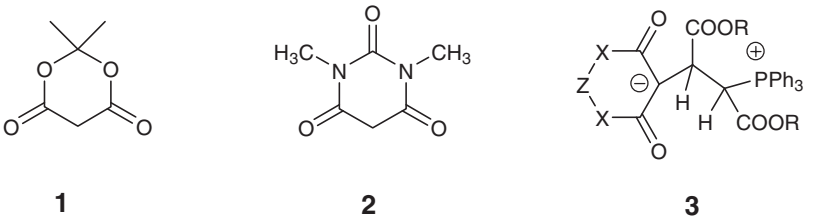
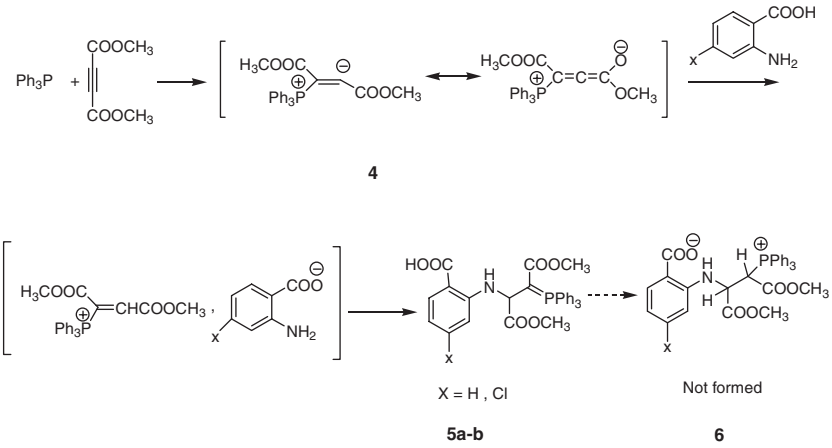


1 **2** **3**

Figure 1 Structures of CH-acids and 1,4-diionic compound.

obtained from initial addition of triphenylphosphine to the acetylenic ester as a Michael acceptor[7] and concomitant protonation of the intermediate **4** by the COOH group. Then the positively charged ion is attacked by the nitrogen of amino group to form compounds **5a–b** (Scheme 1).



4

X = H , Cl

5a-b

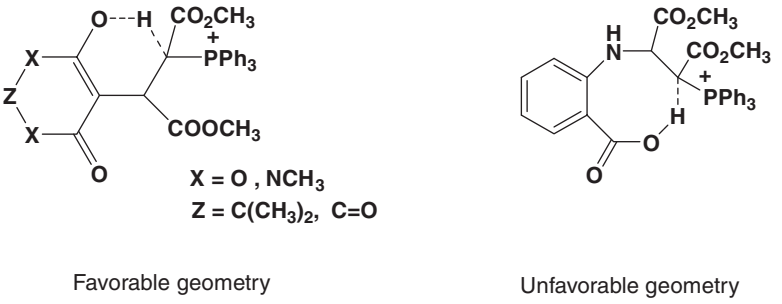
Not formed

6

Scheme 1

We have in fact found that under the present reaction conditions, the compounds **5a–b** cannot be converted to compound **6**. Instead the very mild reaction conditions proved to be ideal for the formation of *N*-substituted aminobenzoic acid derivatives containing ylide moiety in good to excellent yields with high chemoselectivity of *N*-over *O*-alkylation. The reason for such difference between products from Meldrum's acid or *N*,*N*'-dimethyl barbituric acid and products from the aminobenzoic acids is not clear to us, but the stability of such betaines as dipolar systems depends on the balance between the energy required to separate unlike charges and the energy of ylide formation, which could play an important role. Also the transition state for proton exchange between ylide moiety and CH-acid or COOH group might play a role in these reactions. As shown in Scheme 2, in Meldrum's acid or *N*,*N*'-dimethyl barbituric acid, the proton is transferred via a six-membered ring, and this represents a favorable transition state geometry, whereas in amino acids the eight-membered cyclic transition state is not favorable for transfer of the proton.

Compounds **5a–c** were characterized on the basis of their spectroscopic data (^{1}H NMR, ^{13}C NMR, IR) and elemental analysis data. These data are consistent with the



Scheme 2

presence of two rotational isomers.[8–12] The ylide moiety in these compounds is strongly conjugated with the adjacent carbonyl group, and rotation about the partial C.C double bond in **5-(*E*)** and **5-(*Z*)** geometrical isomers is slow at room temperature (Figure 2).

Thus the ^{1}H NMR spectrum of compound **5a** showed four sharp lines due to the methoxy protons at $\delta = 2.99$, 3.44, 3.53, and 3.55 ppm along with signals for the methine protons at $\delta = 4.05$ and 4.34 ppm, which appear as two doublets ($^3J_{PH} = 18.2$ Hz) for the *Z* and *E* geometrical isomers. The aromatic protons appear at $\delta = 6.42$–8.51 ppm. Protons of COOH and two NH groups are observed as three broad signals at $\delta = 12.41$, 5.65, and 5.98 ppm, respectively. These signals disappear when D_2O is added. The ^{13}C NMR spectrum of **5a** displayed 30 distinct resonances in agreement with the mixture of two rotational isomers. Although the presence of the ^{31}P nucleus complicates both the ^{1}H and ^{13}C NMR spectra of **5a**, it helps in assignment of signals by long-range spin–spin couplings with ^{1}H and ^{13}C nuclei. The ^{1}H and ^{13}C NMR spectra of compound **5b** are similar to those of **5a**, except for the signals resulting from the aromatic ring. With these results in hand, we next tried to study the behavior of 4-aminobenzoic acid in the preparation of 1,4-diionic compounds. It was assumed that the transfer of the proton would be intermolecular and betain **8** could be formed. However, the expected compound **8** was not formed when 4-aminobenzoic acid was used and the phosphorus compound **7** was obtained instead, although the COOH group in the para position can act as an acid and the ylide moiety is very active for attracting such protons (Scheme 3).

Again, the spectroscopic data (^{1}H NMR, ^{13}C NMR, IR) and elemental analysis data were used for determination of the structure of the product. Thus the ^{1}H NMR spectrum of compound **7** showed four sharp lines due to the methoxy protons at $\delta = 2.97$, 3.43, 3.56, and 3.58 ppm along with signals for the methine protons at $\delta = 4.02$ and 4.31 ppm, which appear as two doublets ($^3J_{PH} = 18.2$ Hz) for the *Z* and *E* geometrical isomers. The aromatic protons appear as a multiplet at $\delta = 6.40$–7.77 ppm. Protons of COOH and NH

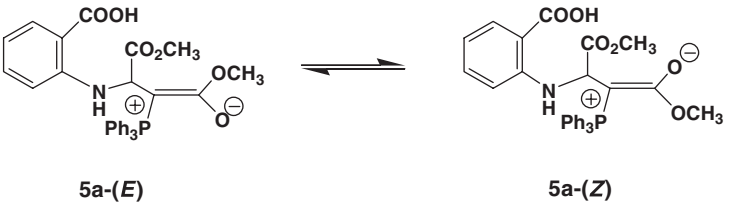
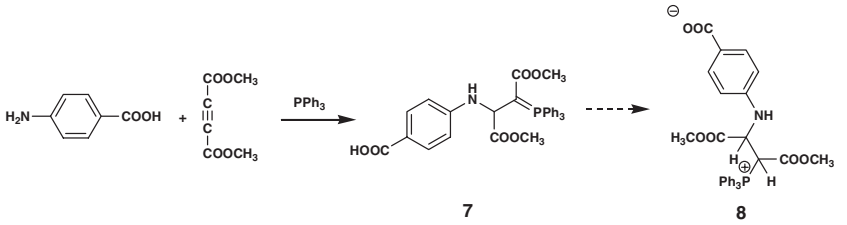


Figure 2 Structure of *Z* and *E* geometrical isomers.



7 8

Scheme 3

groups are observed as two broad signals at $\delta = 11.98$ and 6.12 ppm, respectively. The ^{13}C NMR spectrum of **7** displayed 28 distinct resonances in agreement with the mixture of two rotational isomers.

In conclusion, we have reported an efficient multiple component condensation reaction for the synthesis of phosphorus compounds using aromatic amino acids in good to excellent yields.

EXPERIMENTAL

Dimethyl acetylenedicarboxylates, 2-aminobenzoic acid, 5-chloro-2-aminobenzoic acid, 4-aminobenzoic acid, and triphenylphosphine were obtained from Merck Chemical Co. and were used without further purification. Melting points were obtained on a Gallenkamp melting point apparatus and were uncorrected. Elemental analyses for C, H, and N were performed by the Tarbiat Moallem University using a Heracus CHN-O-Rapid analyzer. IR spectra were measured on a Mattson 1000 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, respectively. Throughout this section, an asterisk (*) denotes two rotamers.

Synthesis of Ylides 5: General Procedure

At 15–25°C, dimethyl acetylenedicarboxylate (0.24 mL, 2 mmol) was added dropwise to a stirred solution of triphenylphosphine (0.53 g, 2 mmol) and 2-aminobenzoic acid (0.28 g, 2 mmol) in acetone (10 mL). After the addition was complete (approximately 5 min), the mixture was stirred for an additional 10 min and was subsequently filtered. The solid collected in the filter was washed thoroughly with cold acetone to give a pale yellow powder.

2-{3-Methoxy-1-(methoxycarbonyl)-3-oxo-2-(1,1,1-triphenyl-λ^5-phosphanylidene)propyl]amino} benzoic acid (5a). Yellow powder (0.84 g, mp 149–152°C, yield 77.8%); IR (KBr) (υ_{max},cm^{-1}): 3365 (NH), 3055–2554 (OH), 1757, 1740 and 1670 (C=O), Anal. Calcd. for $C_{31}H_{28}NO_6P$ (541.53): C, 68.76; H, 5.21; N, 2.59%. Found: C, 68.68, H, 5.17; N, 2.43%. Major conformational isomer **5a**-(*Z*) (52.4%): ^1H NMR (DMSO): $\delta = 2.99$ (s 3H, OCH_3), 3.53 (s, 3H, OCH_3), 4.05 (d, $^3J_{PH} = 18.2$ Hz, 1H, P=C−CH), 5.69 (broad, 1H, NH), 6.42–8.51 (m, 38H, arom-H)*, 12.41 (broad, 1H, OH)*. ^{13}C NMR (DMSO): $\delta = 42.0$ (d, $^1J_{PC} = 128.6$ Hz, P=C), 48.5 (OCH_3), 51.7 (OCH_3), 55.1 (d, $^2J_{PC} = 13.2$ Hz, P=C−CH), 110.5 (C), 113.9 (CH), 116.2 (CH), 126.2 (d, $^1J_{PC} = 91.2$ Hz, C-*i*), 128.7 (d, $^3J_{PC} = 12.0$ Hz, C-*m*)*, 131.4 (CH), 132.2 (d, $^4J_{PC} = 2.0$ Hz, C-*p*), 133.2 (C-*o*)*, 133.5 (CH), 149.3 (C), 168.3 (C=O)*, 169.6 (d, $^2J_{PC} = 24.8$ Hz, C=O), 173.0 (C=O)*. Minor conformational isomer **5a**-(*E*) (47.6%): ^1H NMR (DMSO): $\delta = 3.44$ (s,

3H, OCH_3), 3.55 (s, 3H, OCH_3), 4.34 (d,$^3J_{PH}$ = 18.2 Hz, 1H, P=C−CH), 5.98 (broad, 1H, NH). ^{13}C NMR (DMSO): δ = 43.2 (d, $^1J_{PC}$ = 128.6 Hz, P=C), 49.4 (OCH_3), 51.7 (OCH_3), 54.2 (d, $^2J_{PC}$ = 10.3 Hz, P=C−CH), 110.9 (C), 114.7 (CH), 115.8 (CH), 126.2 (d, $^1J_{PC}$ = 93.2 Hz, C-*i*), 131.1 (CH), 131.9 (C-*p*), 132.9 (CH), 149.6 (C), 169.2 (d, $^2J_{PC}$ = 21.9 Hz, C=O).

5-Chloro-2-{3-methoxy-1-(methoxycarbonyl)-3-oxo-2-(1,1,1-triphenyl-λ^5-phosphanylidene)propyl]amino} benzoic acid (5b). Yellow powder (1.1 g, mp 148–151°C, yield 80.5%); IR (KBr) (υ_{max}, cm^{-1}): 3367 (NH), 3080–2519 (OH), 1753, 1741 and 1672 (C=O), Anal. Calcd. for $C_{31}H_{27}ClNO_6P$ (575.98): C, 64.64; H, 4.72; N, 2.43%. Found: C, 64.47; H, 4.60; N, 2.30%. Major conformational isomer **5b**-(*Z*) (54.7%): ^{1}H NMR (DMSO): δ = 2.97 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 4.33 (d, $^3J_{PH}$ = 17.1 Hz, 1H, P=C−CH), 5.73 (broad, 1H, NH), 6.21–8.51 (m, 36H, arom-H)*, 12.69 (broad, 1H, OH)*. ^{13}C NMR (DMSO): δ = 49.0 (d, $^1J_{PC}$ = 104.7 Hz, P=C)*, 51.8 (OCH_3), 51.7 (OCH_3), 55.4 (d, $^2J_{PC}$ = 17.0 Hz, P=C−CH), 111.7 (C), 113.3 (CH), 117.2 (CH), 125.9 (d, $^1J_{PC}$ = 96.6 Hz, C-*i*), 128.8 (d, $^3J_{PC}$ = 12.1 Hz, C-*m*)*, 132.1 (C-*p*), 131.4 (CH)*, 133.1 (d, $^2J_{PC}$ = 15.0 Hz, C-*o*), 133.8 (CH)*, 147.9 (C), 150.1 (C), 167.7 (C=O), 168.7 (d, $^2J_{PC}$ = 17.1 Hz, C=O)*, 172.7 (C=O). Minor conformational isomer **5b**-(*E*) (45.3%): ^{1}H NMR (DMSO): δ = 3.43 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 4.02 (d, $^3J_{PH}$ = 17.1 Hz, 1H, P=C−CH), 6.04 (broad, 1H, NH). ^{13}C NMR (DMSO): δ = 52.0 (OCH_3), 52.2 (OCH_3), 54.4 (d, $^2J_{PC}$ = 17.0 Hz, P=C−CH), 111.2 (C), 112.9 (CH), 118.1 (CH), 125.6 (d, $^2J_{PC}$ = 97.9 Hz, C-*i*), 130.3 (C-*p*), 133.0 (d, $^2J_{PC}$ = 15.6 Hz, C-*o*), 148.1 (C), 148.2 (C), 167.5 (C=O), 172.5 (C=O).

4-{3-Methoxy-1-(methoxycarbonyl)-3-oxo-2-(1,1,1-triphenyl-λ^5-phosphanylidene)propyl]amino} benzoic acid (7). Yellow powder (0.87 g, mp 118–120°C, yield 80.5%); IR (KBr) (υ_{max}, cm^{-1}): 3361 (NH), 3055–2544 (OH), 1753, 1741 and 1676 (C=O), Anal. Calcd. for $C_{31}H_{28}NO_6P$ (541.53): C, 68.76; H, 5.21; N, 2.59%. Found: C, 68.55; H, 5.21; N, 2.42%. Major conformational isomer **7**-(*Z*) (55.0%), ^{1}H NMR (DMSO): δ = 2.97 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 4.02 (d,$^3J_{PH}$ = 18.2 Hz, 1H, P=C−CH), 6.12 (broad, 1H, NH)*, 6.40–7.77 (m, 38H, arom-H)*, 11.97 (broad, 1H, OH)*. ^{13}C NMR (DMSO): δ = 41.5 (d, $^1J_{PC}$ = 122.8 Hz, P=C), 48.5 (OCH_3), 51.7 (OCH_3), 55.0 (d, $^2J_{PC}$ = 19.5 Hz, P=C−CH), 111.0 (C), 122.1 (CH)*, 126.2 (d, $^1J_{PC}$ = 90.6 Hz, C-*i*), 129.0 (d, $^3J_{PC}$ = 12.0 Hz, C-*m*), 130.4 (CH), 132.2 (C-*p*), 133.2 (d, $^2J_{PC}$ = 10.1 Hz, C-*o*)*, 151.2 (C), 167.5 (C=O), 168.3 (d, $^2J_{PC}$ = 14.6 Hz, C=O), 172.8 (d, $^3J_{PC}$ = 8.7 Hz, C=O). Minor conformational isomer **7**-(*E*) (45.0%): ^{1}H NMR (DMSO): δ = 3.43 (OCH_3), 3.58 (s, 3H, OCH_3), 4.31 (d, $^3J_{PH}$ = 18.2 Hz, 1H, P=C−CH). ^{13}C NMR (DMSO): δ = 42.8 (d, $^1J_{PC}$ = 140.4 Hz, P=C), 49.5 (OCH_3), 52.3 (OCH_3), 54.4 (d, $^2J_{PC}$ = 19.5 Hz, P=C−CH), 110.9 (C), 125.8 (d, $^1J_{PC}$ = 86.9 Hz, C-*i*), 128.8 (d, $^3J_{PC}$ = 12.2 Hz, C-*m*), 130.7 (CH), 132.7 (C-*p*), 156.5 (C); 167.4 (C=O), 169.2 (d, $^2J_{PC}$ = 19.0 Hz, C=O), 173.1 (d, $^3J_{PC}$ = 9.0 Hz, C=O).

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