

Synthesis of Phosphorus, Arsenic and Antimony Ylides Containing the 1,3-Dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione Fragments

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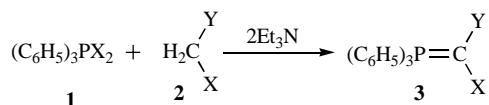
Abstract: The ylides $\text{Ph}_3\text{E}-\text{C}_6\text{H}_6\text{N}_2\text{O}_3$ (**7**, E = P (**a**), As (**b**), Sb (**c**)) have been prepared through the reaction of Ph_3E and 5-bromo-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (5-bromo-1,3-dimethylbarbituric acid) **6** in the presence of triethylamine. Their characterisation was performed by nuclear magnetic resonance (NMR), mass spectrometry (MS) and elemental analysis.

Keywords: 1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (1,3-dimethylbarbituric acid), nuclear magnetic resonance, synthesis, zwitterionic state.

INTRODUCTION

Barbituric acid derivatives have found increasing attention due to their interaction with the central nervous system. Recently, new biomedical applications have been developed for cancer and AIDS therapy [1]. 5-Diaminomethyl-enebarbiturate derivatives were synthesized starting from barbituric acid and carbodiimide. Those compounds exhibit marked charge separation as demonstrated by X-ray structural analysis [2].

Phosphorus ylides (**3**) [3] are stabilized by methylene fragments C(X)Y in which X and Y have π -acceptor properties the negative charge being delocalized efficiently [4], as shown in Scheme 1. This has been demonstrated by *Horner*, *Oediger* and *Pappas* [5-7] reacting triphenylphosphine dihalides (**1**) with heterocycles containing a CH-acidic methylene group (**2**) in the presence of bases.



Scheme 1.

Other procedures for the synthesis of Wittig type barbituric acid ylides using a multistep sequence of reactions [8] have been reported. The cyclopentadienyl ylides of the heavier group 15 elements (**4**) [9-10] and the corresponding Meldrum's acid derivatives (**5**) (E = As, Sb, Bi) [4] have been published previously, Fig. (1).

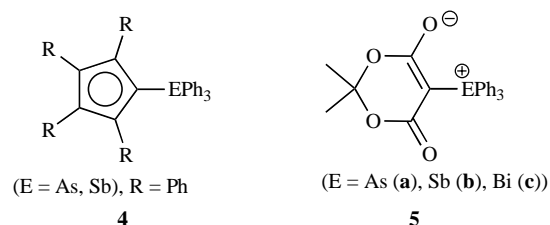


Fig. (1). Chemical structures of cyclopentadienyl (**4**) and Meldrum's acid derivatives (**5**) ylides.

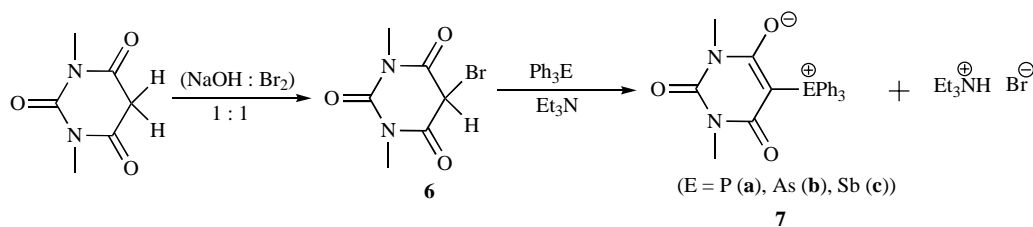
We now report the synthesis of the barbituric acid ylides $\text{Ph}_3\text{E}-\text{C}_6\text{H}_6\text{N}_2\text{O}_3$ (**7**, E = P (**a**), As (**b**), Sb (**c**)) by the direct reaction of Ph_3E and 5-bromo-1,3-dimethylbarbituric acid (**6**) and their characterization with NMR, MS and elemental analyses.

RESULTS AND DISCUSSION

In general, phosphorus ylides (**3**) and their heavier analogues are prepared by the reaction of R_3E with *in situ* generated carbenes [9-11] or from the reaction of CH-acidic methylene derivatives with R_3EX_2 ($\text{X}_2 = \text{O}, \text{CO}_3, 2 \text{Cl}$) compounds [4,12-14]. Starting from 5-bromo-1,3-dimethylbarbituric acid (**6**) [15], which is more reactive compared to the corresponding chlorine derivative [16], and Ph_3E (E = P, As, Sb) in the presence of triethylamine we obtained the title compounds $\text{Ph}_3\text{E}-\text{C}_6\text{H}_6\text{N}_2\text{O}_3$ (**7**, E = P (**a**), As (**b**), Sb (**c**)), as shown in Scheme 2; for compound **6**, an improved synthesis is given which bases on a bromination reaction that takes place in an alkaline aqueous medium under mild conditions with cheap reagents and high yield.

Supposedly, the reaction starts with the nucleophile attack of Ph_3E at C(5) of compound **6** followed by deprotonation of the onium salt formed as an intermediate. The rate of

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Scheme 2.

ylide formation monitored by TLC, decreases in the order $E = P \gg As \approx Sb$.

Compounds **7** are obtained after recrystallisation in good yields as stable solids, their composition and structures are confirmed by NMR and MS data and by elemental analysis (see Experimental). The properties of **7a** correspond to those reported in the literature [8]. Comparison of **7a** with the data of the methylene compound **8** [17] reveals a slight downfield shift of the ^{31}P NMR signal the hybridization of the carbon atom attached at the phosphonium centre being subject of change. On comparison with similar 1,3-dimethylbarbituric acid derivatives [18], we found the 1H and ^{13}C NMR data of the compounds **7** to be in the expected range. It should be noted that the pyridinium ylide **9**, prepared from 5,5-dibromo-1,3-dimethylbarbituric acid and pyridine [19], could not be obtained by the method reported here, Fig. (2).

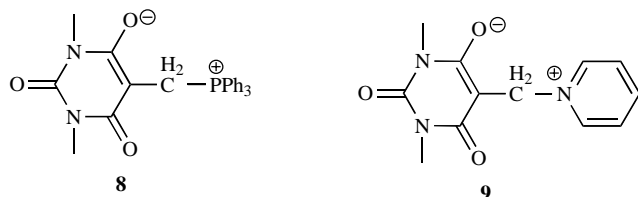


Fig. (2). Chemical structures of phosphonium (**8**) and pyridinium (**9**) ylides of 1,3-dimethyl-5-methylene barbituric acid.

In addition, all attempts to prepare the phosphorus ylide **5** ($E = P$) by the analogous reaction described for the synthesis of the corresponding arsenic, antimony and bismuth derivatives (**5**), failed. The barbituric acid ylides presented here may serve as useful precursors for the synthesis of 5-methylenobarbituric acid derivatives in the direction of a Wittig type reaction. We are currently investigating reactions of compounds **7a** with carbonyl compounds and will report on our results as well as on the evaluation of their therapeutic and pharmacological efficiency in near future.

EXPERIMENTAL

Materials and Instruments

All experiments have been performed in purified solvents under argon. All the following chemicals and reagents were purchased from Aldrich: 1,3-dimethylbarbituric acid, bromine, sodium hydroxide, triethylamine, triphenylphosphine, triphenylarsenic and triphenylantimony. Nuclear magnetic resonance (NMR) spectra were acquired by a Bruker DRX 250 NMR spectrometer with tetramethylsilane (TMS) and 85% H_3PO_4 as external standards of (1H & ^{13}C) and ^{31}P NMR, respectively. The FAB-mass spectra were obtained on

a Finnigan TQS 70 by 70 eV in nitrobenzylalcohol-matrix at 30 °C. Elemental analysis was determined by elemental analyzer from Carlo Erba Company, model 1106. Melting points were obtained by device from Buechi, model 510.

5-Bromo-1,3-dimethyl-2,4,6-(1H,3H,5H)-pyrimidinetrione (**6**)

5 mmol of 1,3-dimethylbarbituric acid was dissolved in 10.0 mL of 0.5 M of NaOH solution, the resulting solution was kept at 0-3 °C while 0.26 mL of Br_2 was added slowly. The mixture was stirred at 25 °C for further 2 h. The resulting precipitate was filtered and washed with water. The product was dried under vacuum.

Yield: 90%; m.p. 95-97 °C; 1H NMR (250.13 MHz, $CDCl_3$): 3.26 (s, 6H, 1,3_B-Me); 5.81 (s, 1H, C⁵_BH) ppm. ^{13}C NMR (62.90 MHz, $CDCl_3$): 28.7 (1,3_B-Me); 49.4 (C⁵_B); 151.4 (C²_B); 162.3 (C^{4,6}_B) ppm. Anal. Calcd. for $C_6H_7N_2O_3Br$: C, 30.7; H, 3.0; N, 11.9. Found: C, 30.3; H, 3.2; N, 11.6%.

General Procedure for the Synthesis of Ylides $Ph_3E-C_6H_6N_2O_3$ (**7**)

5 mmol of corresponding Ph_3E [$E = P$ (**a**), As (**b**), Sb (**c**)] was added to a stirred solution of 5 mmol of **6** in 30 mL of dichloromethane. After addition of 0.90 mL (6.5 mmol) of triethylamine, stirring was continued at 25 °C for a specified time (5 h for (**7a**), 24 h for (**7b** & **7c**)). The resulting solution was extracted with 10 mL of water. The organic layer was dried over anhydrous sodium sulfate and evaporated in vacuum to dryness. The residue was recrystallised from dichloromethane/diethylether.

1,3-Dimethyl-5-(triphenylphosphoranylidene)-2,4,6-(1H,3H,5H) pyrimidinetrione (**7a**)

Yield: 82%; m.p. 264-266 °C; 1H NMR (250.13 MHz, $CDCl_3$): 3.15 (s, 6H, 1,3_B-Me); 7.55-7.85 (m, 15H, 3Ph) ppm. ^{13}C NMR (62.90 MHz, $CDCl_3$): 27.3 (1,3_B-Me); 123.7, 128.4, 132.3, 133.8 (Ph); 154.4 (C²_B); 163.4 (C^{4,6}_B) ppm. ^{31}P NMR (101.20 MHz, $CDCl_3$): 16.8 ppm. MS (FAB): m/z (%) = 417 (100) [M^+]; 403 (30); 390 (18); 375 (21); 209 (5). Anal. Calcd. for $C_{24}H_{21}N_2O_3P$: C, 69.2; H, 5.1; N, 6.7. Found: C, 68.8; H, 5.2; N, 7.1%.

1,3-Dimethyl-5-(triphenylarsoranylidene)-2,4,6-(1H,3H,5H) pyrimidinetrione (**7b**)

Yield: 74%; m.p. 270-272 °C; 1H NMR (250.13 MHz, $CDCl_3$): 3.11 (s, 6H, 1,3_B-Me); 7.44-7.63 (m, 15H, 3Ph) ppm. ^{13}C NMR (62.90 MHz, $CDCl_3$): 26.8 (1,3_B-Me); 125.4, 127.1, 133.0, 134.7 (Ph); 154.0 (C²_B); 164.4 (C^{4,6}_B) ppm. MS (FAB): m/z (%) = 460 (100) [M^+]; 421 (14); 407 (32); 314

(18). Anal. Calcd. for C₂₄H₂₁N₂O₃As: C, 62.6; H, 4.6; N, 6.1. Found: C, 62.9; H, 5.0; N, 6.5%.

1,3-Dimethyl-5-(triphenylstibanylidene)-2,4,6(1H,3H,5H)-pyrimidinetrione (7c)

Yield: 71%; m.p. 278-280 °C; ¹H NMR (250.13 MHz, CDCl₃): 3.21 (s, 6H, 1,3_B-Me); 7.52-7.75 (m, 15H, 3Ph) ppm. ¹³C NMR (62.90 MHz, CDCl₃): 27.9 (1,3_B-Me); 128.8, 129.8, 132.1, 135.9 (Ph); 153.1 (C²_B); 164.2 (C^{4,6}_B)ppm. MS (FAB): *m/z* (%) = 507 (100) [M⁺]; 481 (17); 452 (38); 466 (14); 403 (10). Anal. Calcd. for C₂₄H₂₁N₂O₃Sb: C, 56.8; H, 4.2; N, 5.5. Found: C, 56.3; H, 4.0; N, 5.1%.

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