Cent. Eur. J. Chem. • 11(6) • 2013 • 1019-1022
DOI: 10.2478/s11532-013-0233-4

VERSITA

Central European Journal of **Chemistry**

Reaction of barbituric acid with organic azides and phosphonium ylides

Research Article

Iryna O. Lebedyeva[1], Sean M. Sileno[1], Kunal Patel[1], Ion Ghiviriga[2], Peter J. Steel[3], Alan R. Katritzky[1,4*]

[1]*Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, USA*

[2]*Department of Chemistry, University of Florida, PO box 117200, Gainesville, FL 32611, USA*

[3]*Chemistry Department, University of Canterbury, Christchurch 8140, New Zealand*

[4]*Chemistry Department, King Abdulaziz University, Jeddah 21589, Saudi Arabia*

Received 25 January 2013; Accepted 17 February 2013

Abstract: Amination by organic azides has been carried out to provide aminobarbiturates by fusion of a triazole ring to the 5,6-positions of barbituric acid followed by cleavage and thermal elimination of nitrogen, whereas aza-Wittig reaction gave phosphoranylidene barbituric acid salts.

Keywords: *Azide • Aza-Wittig reaction • Pyrimidine • Barbiturate*

1. Introduction

Barbituric acid (BA) **1**, first synthesized in 1864, is used to provide barbiturate pigments [1], supramolecular units [2], and to perform colorimetric assays [3]. A great many barbiturates have been prepared many of which affect $GABA_A$ receptor functions in a concentration-dependent manner [4–6]. Barbiturates are used to treat insomnia, dementia, neonatal jaundice [7], and are known to inhibit tumor growth [8–9].

Barbituric acid remains an attractive target for modification due to the extensive medicinal properties of its derivatives as sedatives and anticonvulsants. Numerous C5 mono- and bis functionalizations include Knoevenagel condensation of **1** with substituted aromatic aldehydes producing merocyanine-type dyes [10], pigments [1], and protein tyrosine phosphatase inhibitors [11].

2. Experimental procedure

Melting points were determined on a capillary point apparatus equipped with a digital thermometer and are uncorrected. ^{1}H NMR spectra were recorded at 300 and 500 MHz and ^{13}C NMR spectra were recorded at 75 and 125 MHz on Gemini or Mercury spectrometers at room temperature. The chemical shifts were reported in ppm relative to TMS as internal standard (^{1}H NMR) or to the residual solvent peak (^{13}C NMR). Elemental analysis was performed on a Carlo Erba-1108 instrument. High Resolution Mass Spectra were recorded using Thermo Scientific LCQ Ion Trap. Crystallographic data of **6f** including atomic coordinates, bond lengths and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from CCDC, 12 Union Road, Camridge

* *E-mail: katritzky@chem.ufl.edu*

CB2 1EZ, UK, fax: +44 1223 336 033, or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 909437.

General procedure for synthesis of 4a-b:

To a solution of organic azide **2a-b** (0.150 mmol) in dry THF (20 mL), barbituric acid **1** (116 mg, 0.1 mmol) was added and the mixture was heated in a sealed tube at 110°C for 12 h. The solvent was evaporated and the solid residue was recrystallized from ethyl acetate/hexanes (1:2).

5-(Benzylamino)-6-hydroxypyrimidine-2,4(1H,3H)-dione 4a:

Pink solid (63%, 0.147 g, 0.063 mmol). Mp 287.8–290.9°C (lit. Mp 290 [13]); ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.60 (s, 3H), 7.33–7.31 (m, 5H), 4.22 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 160.5, 151.5, 132.2, 130.4, 128.7, 128.2, 86.9, 50.7. Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.77; H, 4.43; N, 18.38.

5-((4-Chlorobenzyl)amino)-6-hydroxypyrimidine-2,4(1H,3H)-dione 4b:

Pink solid (67%, 0.169 g, 0.067 mmol). Mp ≥ 300°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.14 (br s, 2H), 7.47–7.37 (m, 4H), 4.45 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.2, 151.3, 132.1, 130.2, 128.4, 128.0, 86.5, 50.5. Anal. Calcd for $C_{11}H_{10}ClN_3O_3$: C, 49.36; H, 3.77; N, 15.70. Found: C, 49.60; H, 3.81; N, 15.88.

General procedure for the *in situ* synthesis of 1,1,1-tributyl-*N*-substituted-λ^5-phosphanimines 5a-g:

To a solution of azide **2a-g** (0.01 mmol) in dry THF (20 mL), tributyl phosphine (0.025 mmol, 0.615 mL) was added and the solution was stirred vigorously for 20 mins at room temperature.

General procedure for synthesis of 6a-g:

To a solution of 1,1,1-tributyl-*N*-substituted-λ^5-phosphanimine **5a-g** (0.1 mmol) in dry THF (20 mL) barbituric acid **1** was added (116 mg, 0.1 mmol). The reaction was stirred at room temperature for 2 h and consumption of the starting materials was monitored by TLC. The precipitate formed was filtered off and recrystallized from ethyl acetate/hexanes (1:2).

N-(Tributyl-λ^5-phosphanylidene)pentan-1-aminium 2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate 6a:

Pink solid (89%, 0.369 g, 0.089 mmol). Mp 171.2–173.7°C; ^{1}H NMR (300 MHz, CD_3OD): δ 2.94 (q, *J* = 7.2 Hz, 2H), 2.63–2.54 (m, 2H), 2.25–2.09 (m, 6H), 1.69 (s, 2H), 1.61–1.45 (m, 12H), 1.43–1.32 (m, 4H), 1.32–1.23 (m, 2H), 1.09–0.92 (m, 9H); ^{13}C NMR (75 MHz, CD_3OD): δ 169.4, 78.2, 42.2, 32.6, 30.1, 25.1, 24.8, 24.2, 23.6, 22.5, 21.7, 14.5, 13.9. Anal. Calcd for $C_{21}H_{42}N_3O_3P$: C, 60.70; H, 10.19; N, 10.11. Found: C, 60.92; H, 10.38; N, 10.29.

N-(Tributyl-λ^5-phosphanylidene) cyclohexanaminium 2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate 6b:

Light yellow solid (81%, 0.346 g, 0.081 mmol). Mp 266.3–268.5°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.87 (br s, 3H), 5.25 (t, *J* = 9.5 Hz, 1H), 2.94 (br s, 1H), 2.14 (br s, 6H), 1.80–1.60 (m, 4H), 1.60-1.10 (m, 18H), 0.91 (br s, 9H); ^{13}C NMR (75 MHz, CD_3OD): δ 176.1, 161.9, 114.0, 59.6, 45.3, 34.4, 32.9, 32.7, 32.1, 30.7, 30.0, 23.0. Anal. Calcd for $C_{22}H_{42}N_3O_3P$: C, 61.80; H, 9.90; N, 9.83. Found: C, 62.01; H, 9.97; N, 10.03.

1-Phenyl-N-(tributyl-λ^5-phosphanylidene) methanaminium 2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate 6c:

Light yellow solid (90%, 0.392 g, 0.09 mmol). Mp 131.0–133.8°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.04 (s, 2H), 7.42–7.22 (9m, 5H), 6.14–6.09 (m, 1H), 4.13 (dd, *J* = 11.3, 7.1 Hz, 2H), 3.74 (s, 1H), 2.23–2.13 (m, 6H), 1.43–1.22 (m, 12H), 0.86 (t, *J* = 6.9 Hz, 9H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.7, 153.0, 139.4, 128.4, 127.5, 127.3, 74.8, 43.5, 23.3, 23.1, 22.4, 20.8, 20.1, 13.3; HRMS (ESI) calcd for $C_{19}H_{35}NP$ $[M\text{-}C_4H_3N_2O_3+H]^+$ 308.2502, found 308.2491.

2-Chloro-N-(tributyl-λ^5-phosphanylidene) benzenaminium 2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate 6d:

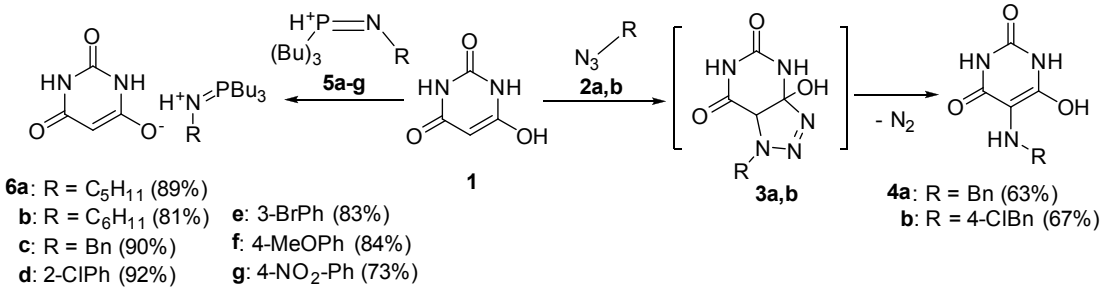
Light yellow solid (92%, 0.419 g, 0.092 mmol). Mp 183.3–185.6°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.18 (br s, 3H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.27 (s, 2H), 7.12 (br s, 1H), 2.44–2.12 (m, 6H), 1.78–1.22 (m, 12H), 0.86 (t, *J* = 6.9 Hz, 9H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.6, 152.2, 137.0, 130.2, 128.2, 125.1, 124.8, 23.3, 23.1, 22.6, 22.2, 21.4, 13.3. Anal. Calcd for $C_{22}H_{35}ClN_3O_3P$: C, 57.95; H, 7.74; N, 9.22. Found: C, 58.11; H, 7.93; N, 9.45.

3-Bromo-N-(tributyl-λ^5-phosphanylidene) benzenaminium 2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate 6e:

Light yellow solid (83%, 0.410 g, 0.083 mmol). Mp 139.4–141.0°C; ^{1}H NMR (300 MHz, CD_3OD): δ 7.38–7.24 (m, 4H), 7.12 (dd, *J* = 3.2, 2.3 Hz, 1H), 2.54–2.38 (m, 6H), 1.64–1.28 (m, 12H), 0.86 (t, *J* = 6.8 Hz, 9H); ^{13}C NMR (75 MHz, CD_3OD): δ 169.4, 141.4, 132.7, 128.3, 124.6, 124.5, 119.6, 119.5, 24.9, 24.7, 24.2, 24.1, 22.8, 22.1, 13.8. Anal. Calcd for $C_{22}H_{35}BrN_3O_3P$: C, 52.80; H, 7.05; N, 8.40. Found: C, 53.08; H, 7.24; N, 8.85.

4-Methoxy-N-(tributyl-λ^5-phosphanylidene) benzenaminium 2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate 6f:

Light yellow solid (84%, 0.379 g, 0.084 mmol). Mp 178.9–180.1°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.12



Scheme 1. Synthesis of C5-amino barbiturates **4a-b** and tributylphosphoranylidene salts of BA **6a-g**.

(br s, 1H), 7.07 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 3.72 (s, 3H), 2.42–2.22 (m, 6H), 1.62–1.24 (m, 12H), 0.87 (t, *J* = 7.1 Hz, 9H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.8, 155.7, 152.9, 131.2, 122.6, 114.9, 55.3, 23.2, 23.0, 22.4, 21.2, 20.5, 13.3. Anal. Calcd for $C_{23}H_{38}N_3O_4P$: C, 61.18; H, 8.48; N, 9.31. Found: C, 61.27; H, 8.71; N, 9.22.

Crystal data for 6f: $C_{23}H_{38}N_3O_4P$, MW 451.53, orthorhombic, space group Pbca, *a* = 12.0018(3), *b* = 14.1177(2), *c* = 28.6949(6) Å, V = 4858.6(2) Å^3, F(000) = 1952, Z = 8, T = -153°C, μ (CuKα) = 1.269 mm^{-1}, D_{calcd} = 1.235 g.cm^{-3}, $2\theta_{max}$ 135 ° (Supernova Dual CCD area detector, CuKα radiation), GOF = 1.03, wR(F^2) = 0.101 (all 4380 data), R = 0.037 (3595 data with I > 2σI).

4-Nitro-N-(tributyl-λ^5-phosphanylidene) benzenaminium 2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate 6g:

Light yellow solid (73%, 0.341 g, 0.073 mmol). Mp 171.1–174.4°C; ^{1}H NMR (300 MHz, CD_3OD): δ 16.0 (br s, 1H), 7.06 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 2.60–2.50 (m, 6H), 1.62–1.47 (m, 12H), 0.97 (t, *J* = 7.1 Hz, 9H); ^{13}C NMR (75 MHz, CD_3OD): δ 169.4, 147.0, 144.7, 127.1, 119.8, 119.7, 24.9, 24.7, 24.2, 22.7, 21.9, 13.8. Anal. Calcd for $C_{22}H_{35}BrN_4O_5P$: C, 56.64; H, 7.56; N, 12.01. Found: C, 56.92; H, 7.81; N, 12.33.

3. Results and discussion

In this work we investigated the reaction of barbituric acid C5 enol with various organic azides and phosphoro aza-ylides.

To provide amination of **1** at C5 it was reacted it with benzyl and 4-chlorobenzyl azides **2a,b** following the previously described method [12-14] (Scheme 1). 2D NMR spectroscopy showed that the isolated products **4a,b** were formed by amination reaction at C5 (Fig. 1). Enol **1** undergoes a regioselective two-step amination to form triazolines **3a,b** which were observed in the ^{1}H spectrum crude reaction mixture**.** The C5 proton was detected as doublet of doublets at 6.63 ppm (*J* =

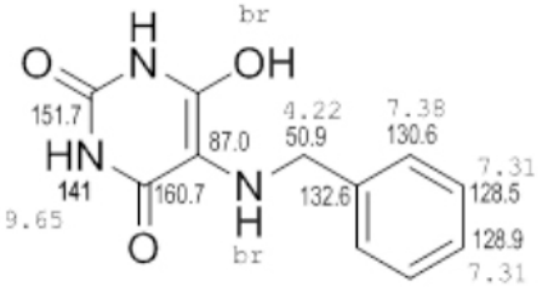


Figure 1. Structure determination for C5-amino barbiturate **4a** with gHMBC experiment.

10.5, 0.3 Hz). Thermal elimination of nitrogen led to the formation of **4a,b**.

The structure of **4a** was determined based on the one-bond and long-range couplings seen in the gHMBC spectra. The benzyl protons at 4.22 ppm, excluding the expected cross-peaks with the phenyl carbons, display a coupling with the carbon at 87.0 ppm, which in turn couples with the protons at 9.65 ppm. As seen in the ^{1}H-^{15}N gHMBC spectrum, these protons are on the nitrogen at 141 ppm and they couple with two carbonyl carbons. The apparent symmetry of the barbiturate moiety is due to the rapid exchange of the OH proton between positions 4 and 6. The NH protons are also involved in this exchange, and the two of them appear as a broad peak in the 7.5–10.0 ppm region.

A potential route towards C2 (4 or/and 6) iminobarbiturates **6a-g** was studied using aza-Wittig reaction [15] of phosphoro aza-ylides **5a-g** with **1**. This reaction was expected to give either one or a mixture of mono-, di- or tri-iminosubstituted barbiturates. In fact, reaction of **5a-g** with **1** gave stable tributylphosphorano aza-ylidenes **6a-g** (Scheme 1).

The structure of the reaction products **6a-g** was determined by an X-Ray study of **6f** which confirmed that the NH of the cation was H-bonded to the anion of the salt. Interestingly, the positive charge transfer of **5** from phosphorus to nitrogen stabilized the salt **6** thus preventing the usual aza-Witting imine formation. Salts **6a-g** occurred on addition of **1** to the *in situ* formed tributylphosphoran aza-ylidenes **5a-g**.

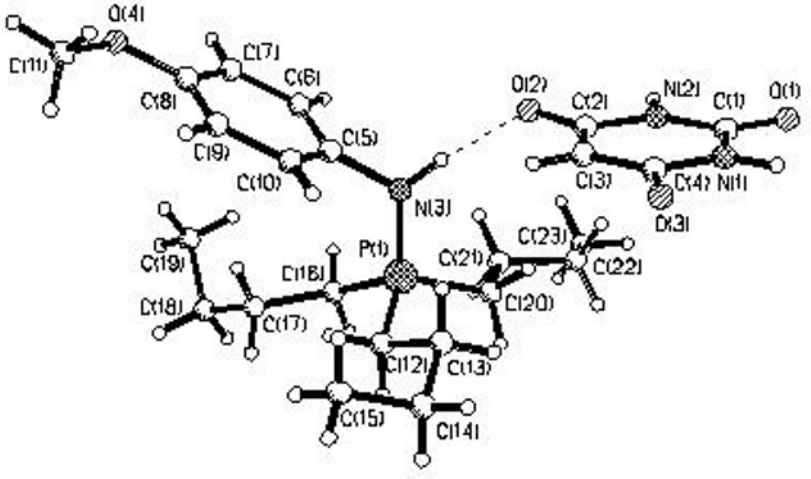


Figure 2. Molecular structure of **6f** according to an X-ray diffraction study.

4. Conclusions

We report amination of barbituric acid at C5 with organic azides (benzyl and 4-chlorobenzyl azides) through the *in situ* formation of triazolines followed by thermal elimination of nitrogen. The aza-Wittig reaction of barbituric acid with phosphoro aza-ylides led to the unexpected formation of barbituric acid tributylphosphoranylidene salts. The structure of the final product representatives was determined using X-ray and 2D NMR techniques.

Acknowledgements

This work was supported by the Kenan Foundation (University of Florida) and the King Abdulaziz University (Saudi Arabia). The authors are grateful to Dr. C. D. Hall, Mrs. Galyna Vakulenko, Dr. Eric Scriven and Mr. Khanh Ha for reading the manuscript, and to Dr. M. C. A. Dancel (University of Florida) for HRMS analyses.

References

[1] D. Thetford, A.P. Chorlton, J. Hardman, Dyes Pigm. 59(2), 185 (2003)
[2] N.D. McClenaghan, C. Absalon, D.M. Bassani, J. Am. Chem. Soc. 125(43), 13004 (2003)
[3] R. Bartzatt, J. Pharm. Biomed. Anal. 29(5), 909 (2002)
[4] I. Bolz, M. Bauer, A. Rollberg, S. Spange, Macromol. Symp. 287, 8 (2010)
[5] J.A. Vida, C.M. Samour, M.H. O'Dea, J.F. Reinhard, J. Med. Chem. 18(7), 694 (1975)
[6] P.Y. Savechenkov, X. Zhang, D.C. Chiara, D.S. Stewart, R. Ge, X. Zhou, D.E. Raines, J.B. Cohen, S.A. Forman, K.W. Miller, K.S. Bruzik, J. Med. Chem. 55(14), 6554 (2012)
[7] S.R. Guillen, C.M. Guzman, Pharmazie 43(12), 827 (1988)
[8] K.M. Khan, M. Ali, A. Ajaz, S. Perveen, M.I. Choudhary, Atta-ur-Rahman, Lett. Drug Des. Discovery 5(4), 286 (2008)
[9] P. Singh, M. Kaur, P. Verma, Bioorg. Med. Chem. Lett. 19(11), 3054 (2009)
[10] M.C. Rezende, P. Campodonico, E. Abuin, J. Kossanyi, Spectrochim. Acta, Part A 57(6), 1183 (2001)
[11] B. Kafle, R.B. Bhattarai, H. Cho, Bull. Korean Chem. Soc. 32(1), 31 (2011)
[12] Th. Curtius, Ber. Dtsch. Chem. Ges. 56B, 1577 (1923)
[13] Th. Curtius and K. Kaschig, J. Prakt. Chem. 125, 466 (1930)
[14] M. Regitz, Justus Liebigs Ann. Chem. 676, 101 (1964)
[15] F. Palacios, C. Alonso, D. Aparicio, G. Rubiales, J. M. de los Santos, Tetrahedron 63 (3), 523 (2007)