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Synthesis of phosphorus-containing barbiturates by the N-arylation of P-zwitterions with 2,4,6-trinitrofluorobenzene

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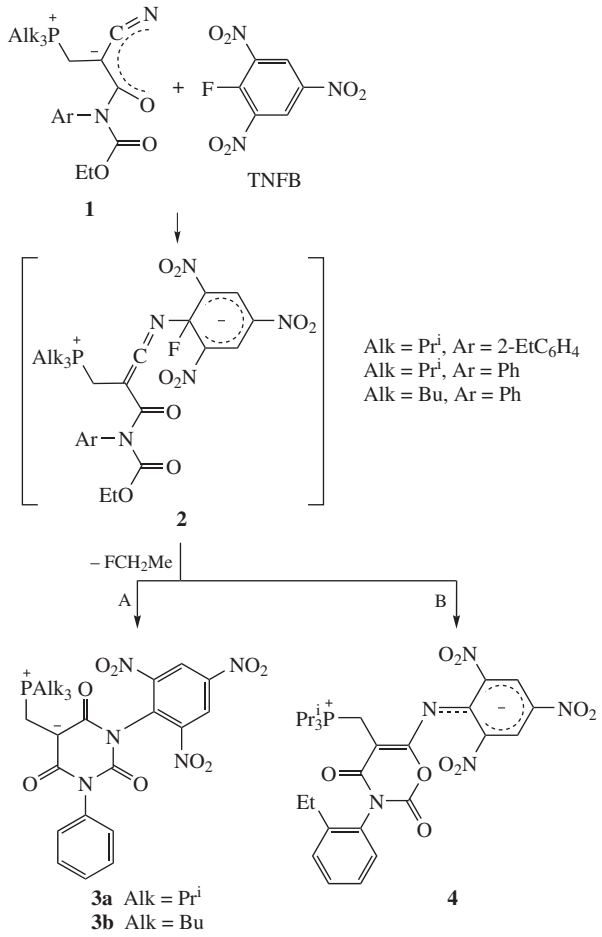
Barbiturates containing a phosphonium and an *N*-2,4,6-trinitrophenyl groups were synthesized by the reactions of P-zwitterions with 2,4,6-trinitro-1-fluorobenzene.

Barbiturates are important medical preparations; however, compounds of such a series comprising phosphorus-containing functional groups have been described only by solitary examples,[1–3] and barbiturates having nitro groups in N-aromatic rings remained unknown.

In continuation of studying the reactivity of phosphorus-containing zwitterions with respect to polynitrohalobenzenes,[4–8] we reacted cyano carbanions **1** with 2,4,6-trinitro-1-fluorobenzene (TNFB). Judging from changes in the composition of the reaction mixture with time (monitoring by ^{19}F and ^{31}P NMR spectroscopy), the process A (Scheme 1) was multi-step through apparently the formation of σ^F complex **2**. As the result, substituted barbiturates **3** and ethyl fluoride were obtained.



3a Alk = Pr^i
3b Alk = Bu

4

Scheme 1

The reaction proceeded in a methylene chloride solution at room temperature for two weeks (according to ^{31}P NMR spectroscopy). The formation of a fluorinated compound having a chemical shift at –211 ppm was recorded in the ^{19}F NMR spectrum; this chemical shift was consistent with that published for ethyl fluoride. After completion of the reaction, mixture was kept in an open vessel, the above signal was not found in the spectrum of the solution, obviously, because of the evaporation of low-boiling ethyl fluoride. The removal of the solvent and crystallization of the residue from ethyl acetate gave orange crystalline compounds **3a**,**b** in 50–60% yields. The composition and structures of the compounds were determined using elemental analysis, IR and NMR (^{1}H, ^{13}C, ^{19}F, ^{31}P) spectroscopy[†] and X-ray diffraction analysis (for **3b**) (Figure 1).[‡]

Most likely, the better steric availability of the nitrogen atom than the carbon atom in the cyano group of zwitterion **1** toward the attack of TNFB is the main reason behind such an unusual behaviour. Two *ortho*-nitro groups in TNFB also create addi-

[†] A solution of 2,4,6-trinitrofluorobenzene (0.5 mmol) in CH_2Cl_2 (15 ml) was added dropwise to zwitterion **1** (0.5 mmol) in CH_2Cl_2 (15 ml). The solution was kept in a closed vessel at room temperature for two weeks. Then, the solvent was removed and the residue was crystallized from ethyl acetate to give compounds **3a** and **3b** in 52 and 62% yields, respectively.

1-Phenyl-3-(2,4,6-trinitro)phenyl-5-triisopropylphosphoniomethyl barbiturate **3a**: mp 249–250 °C. IR (KBr, ν/cm^{-1}): 1345, 1542 (NO_2), 1643, 1696 (C=O). ^{31}P NMR, δ: 41.5. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.35 (dd, 18H, *Me*CH, J_{HH} 7.2 Hz, J_{HP} 8.0 Hz), 2.74 (m, 3H, MeC*H*), 3.20 (d, 2H, PCH_2, J_{HP} 10.3 Hz), 7.07 (d, 2H, *o*-H, J_{HH} 7.2 Hz), 7.36 (t, 1H, *p*-H, J_{HH} 7.0 Hz), 7.44 (t, 2H, *m*-H, J_{HH} 7.0 Hz), 9.07 (s, 2H, *m*-H). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ: 14.34 (d, CH_2P, J_{CP} 46 Hz), 16.85 (*Me*CH), 21.24 (*C*HMe, J_{CP} 39 Hz), 74.84 (C$^–$), 124.23 (*C*HCNO$_2$), 128.05 (*o*-CH), 128.06 (*p*-CH), 129.57 (*m*-CH), 130.32 (*C*NC=O), 136.86 (N*C*CNO$_2$), 146.38 (*p*-CNO$_2$), 148.15 (*o*-CNO$_2$), 150.44 [NC(O)N], 159.66 [C*C*(O)N], 162.97 [*C*(O)CCH$_2$]. Found (%): C, 53.42; H, 5.27; N, 12.01; P, 5.30. Calc. for $C_{26}H_{30}O_9N_5P$ (%): C, 53.15; H, 5.11; N, 11.92; P, 5.28.

1-Phenyl-3-(2,4,6-trinitro)phenyl-5-tributylphosphoniomethyl barbiturate **3b**: mp 244 °C. IR (KBr, ν/cm^{-1}): 1342, 1538 (NO_2), 1642, 1690 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.91 (t, 9H, Me, J_{HH} 7.0 Hz), 1.39 (m, 6H, MeCH_2), 1.51 (m, 6H, MeCH_2CH_2), 2.09 (m, 6H, CH_2CH_2P), 3.15 (d, 2H, CH_2P, J_{HP} 11.0 Hz), 7.05 (d, 2H, *o*-H, J_{HH} 7.1 Hz), 7.36 (t, 1H, *p*-H, J_{HH} 7.0 Hz), 7.44 (t, 2H, *m*-H, J_{HH} 7.0 Hz), 9.08 (s, 2H, *m*-H). ^{13}C NMR (100.68 MHz, DMSO-d_6) δ: 13.75 (C^{21}), 17.30 (d, C^{17}, $^1J_{CP}$ 33 Hz), 18.50 (d, C^{18}, $^1J_{CP}$ 30 Hz), 23.28 (d, C^{19}, $^2J_{CP}$ 3 Hz), 23.97 (d, C^{20}, $^3J_{CP}$ 10 Hz), 74.33 (C^2), 124.30 (C^{15}), 128.08 (C^8), 129.11 (C^6), 129.50 (C^7), 130.19 (C^5), 150.46 (C^4), 159.64 (C^1), 162.84 (C^3). Found (%): C, 55.02; H, 5.93; N, 10.90; P, 4.85. Calc. for $C_{29}H_{36}O_9N_5P$ (%): C, 55.30; H, 5.72; N, 11.13; P, 4.93.

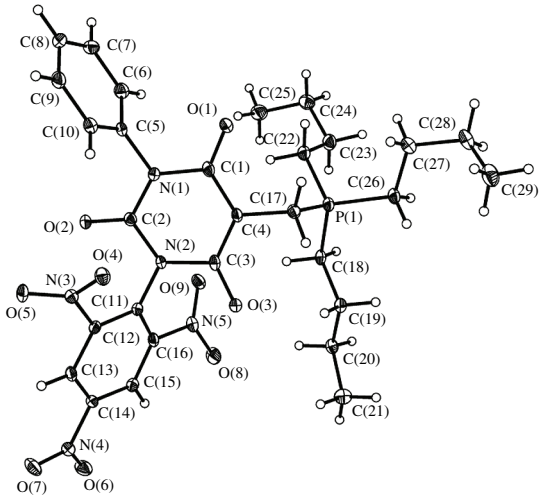


Figure 1 Molecular structure of **3b**. Selected bond lengths (Å): C(1)–O(1) 1.236(2), C(1)–N(1) 1.435(3), C(1)–C(4) 1.410(3), N(1)–C(5) 1.449(3), N(1)–C(2) 1.370(3), C(2)–O(2) 1.225(2), C(2)–N(2) 1.392(3), N(2)–C(11) 1.412(3), N(2)–C(3) 1.437(2), C(1)–O(1) 1.236(2), C(1)–N(1) 1.435(3), C(1)–C(4) 1.410(3), N(1)–C(5) 1.449(3), N(1)–C(2) 1.370(3), C(2)–O(2) 1.225(2), C(2)–N(2) 1.392(3), N(2)–C(11) 1.412(3), N(2)–C(3) 1.437(2), C(3)–O(3) 1.245(2), C(3)–C(4) 1.389(3), C(4)–C(17) 1.504(3), C(1)–C(4) 1.410(3), C(11)–C(12) 1.398(3), C(12)–C(13) 1.381(3), C(13)–C(14) 1.380(3), C(14)–C(15) 1.374(3), C(15)–C(16) 1.384(3), C(16)–C(11) 1.395(3), C(12)–N(3) 1.487(3), C(14)–N(4) 1.470(3), C(16)–N(5) 1.482(3); selected bond angles (°): C(3)–C(4)–C(1) 123.8(2), C(3)–C(4)–C(17) 119.3(2), C(1)–C(4)–C(17) 117.4(2).

‡ *Crystallographic data for* **3b**: $C_{29}H_{36}N_5O_9P$, $M = 629.60$), monoclinic, space group $P2_1/c$, at 120 K: $a = 14.548(1)$, $b = 9.0819(8)$ and $c = 22.855(2)$ Å, $\beta = 93.108(2)°$, $V = 3015.4(4)$ Å^3, $Z = 4$, $d_{calc} = 1.387$ g cm^{-3}, crystal dimensions 0.45×0.30×0.20 mm, μ(MoKα) = 1.53 cm^{-1}, $2\theta < 58°$. 32162 reflections were measured, 8018 unique reflections ($R_{int} = 0.0702$), 4053 reflections with $I > 2\sigma(I)$. The refinement converged to $R_1 = 0.0500$, $wR_2 = 0.1002$ with 400 refined parameters in a weighting scheme, GOOF = 0.995, $F(000) = 1328$, residual electron density ρ_{max}/ρ_{min}, 0.636/–0.494 eÅ^{-3}. Experiments were carried out with a Bruker SMART 1000 CCD area detector at 120 K and a Bruker APEX II CCD area detector at 100 K, using graphite monochromated MoKα radiation ($\lambda = 0.71073$ Å). The structures were solved by a direct method and refined by the full-matrix least-squares against F^2 in anisotropic (for non-hydrogen atoms) approximation. All hydrogen atoms were placed in geometrically calculated positions and were refined in an isotropic approximation in riding model with the $U_{iso}(H) = nU(C)$, where $n = 1.2$ or 1.5 for CH or Me groups, respectively. All calculations were performed using the SHELXTL software.[10]

CCDC 756574 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2010.

tional steric hindrances for an attack at the carbon atom of the cyano group in zwitterion **1**.

Note that a similar reaction[8] (pathway B in Scheme 1) using a zwitterion like **1** but possessing an *ortho*-ethylphenyl substituent at the carbamate nitrogen leads to formation of oxazindione **4**, probably, due to steric and electron effects provided by the *ortho*-ethyl group.

The molecular structure of **3b** was unambiguously established by single-crystal X-ray diffraction analysis (Figure 1).‡ Compound **3b** is a zwitterion with the positively charged phosphonium $CH_2P^+Bu_3$ fragment and a negative charge localized over the chain of conjugated bonds O(1)–C(1)–C(4)–C(3)–O(3).

The sum of angles at the carbanion centre C(4) is 360°; this fact in combination with the shortened bonds at the carbanion centre C(1)–C(4) [1.410(3) Å] and C(3)–C(4) [1.389(3) Å] and the elongated bonds C(1)–O(1) [1.236(2) Å] and C(3)–O(3) [1.245(2) Å] confirm that a delocalization of the anion charge takes place in O(1)–C(1)–C(4)–C(3)–O(3).

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