An Unexpected Synthesis of 7,8-Polymethyleneimidazo-1,3,2-diazaphosphorines – Heteroanalogues of Mercaptopurine Derivatives

Dmitry B. Nilov,* Alexander V. Kadushkin, Natalia P. Solov'eva and Vladimir G. Granik

Centre for Medicinal Chemistry, All-Russian Research Chemical-Pharmaceutical Institute, 119815 Moscow, Russian Federation. Fax: +7 095 246 7805

A new synthesis of 7,8-polymethyleneimidazodiazaphosphorines, involving the interaction of cyclic 1-carbamoylmethyl-2-cyanamidines with phosphorus pentasulfide in the presence of pyridine, is described.

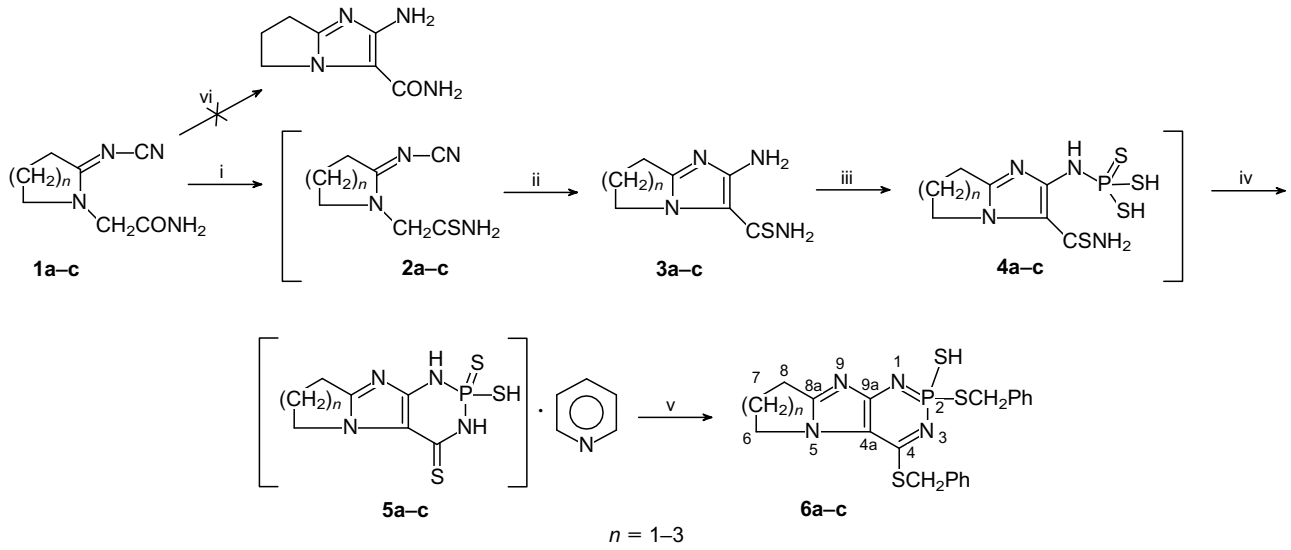
This article is devoted to an approach to new compounds with nootropic activity which involves thionation of the carbamoyl group of the previously obtained 1-carbamoylmethyl-2-cyaniminopyrrolidine **1a**, which exhibits high nootropic and anticonvulsant activity.[1] We tried to use for this goal one of the best reagents for C=O to C=S transformation, namely phosphorus pentasulfide.[2]

However, when **1** and P_2S_5 react in pyridine the process does not stop at the stage of thioamide **2a** formation. The end product of this reaction is compound **5a**, yield 87%, m.p. > 300 °C (DMF–water). This result shows that the methylene group activation in **2a** is sufficient for Thorpe–Ziegler[3] cyclisation to 1,2-trimethylene-4-amino-5-thiocarbamoyl- imidazole **3a** to take place. The latter transforms smoothly under the action of P_2S_5 into 7,8-trimethyleneimidazophosphorinthione **5a**, isolated as a solvate with a pyridine molecule. The structure of tricycle **5a** was established by ^1H and ^{13}C NMR spectroscopy and mass spectrometry. Since the different reaction conditions lead to a variable quantity of pyridine in the solvate (for a synthesis of similar solvates from anthranylamides see ref. 4) the latter is alkylated by benzyl chloride to obtain the stable and pure compound 7,8-trimethylene-2,4-dibenzylmercapto-1*H*-imidazo[4,5-*d*]-1,3,2-diazaphosphorine-2-thione **6a**, yield 80%, m.p. 187–189 °C (DMF–water), identified also by ^1H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis.†

By analogy, the amidines of the piperidine and hexahydroazepine series **1b,c** were transformed into **6b**, yield 67%, m.p. 214–218 °C (DMF–water) and **6c**, yield 41%, m.p. 182–186 °C (DMF–water), respectively, by the successive action of P_2S_5 and $PhCH_2Cl$. Spectral data for **6b,c** are similar to **6a**.

Thus, the interaction of P_2S_5 and *N*-carbamoylmethylcyanamidines **1a–c** in pyridine leads to an unexpected series of transformations connected with the thionation of amide function, *i.e.* Thorpe–Ziegler cyclisation, *N*-acetylation of the 4-amino-group of the bicyclic 4-amino-5-thiocarbamoylimidazoles **3a–c** obtained and cyclisation of phosphorus compounds **4a–c** into imidazophosphorines **5a–c**.

We have demonstrated that the starting carbamide **1a** does not cyclise under Thorpe–Ziegler conditions (prolonged reflux in pyridine). So, the cyclisation to **5** proceeds during or after the thionation of the amide CO group of **1a**.



Scheme 1 *Reagents and conditions*: i–iv, pyridine, P_2S_5, b.p., 5 min; v, EtOH/EtONa, $PhCH_2Cl$, b.p., 5 min; vi, pyridine, b.p., 4 h.

† *Spectroscopic data for* **6a**: ^1H NMR ($[^2H_6]Me_2SO_4$) δ 2.49 (m, 7-CH_2), 2.77 (t, 8-CH_2), 4.06 (t, 6-CH_2), 3.81 (m, P–SCH_2Ph), 4.32 (m, 4-SCH_2–Ph), 10.26 (d, 1-NH); ^{13}C NMR ($[^2H_6]Me_2SO_4$) δ 23.8 (7-C), 25.0 (8-C), 32.2 (4-C–SC_2), 37.7 (P–S–CH_2), 46.9 (6-C), 108.9 (4a-C), 155.4 (9a-C), 159.4 (8a-C), [2Ph: 127.4 (1C), 127.6 (1C), 128.7 (2C), 128.8 (4C), 129.5 (2C), 137.4 (1C), 137.7 (1C)], 160.9 (4-C); MS *m/z* 456(3)[M^+], 334(3) [M^+–S=CH–Ph]$^+$, 333(3) [M^+–SCH_2Ph]$^+$, 301(17) [M^+–SCH_2Ph-S]$^+$, 211(2) [M^+–SCH_2PhS=CHPh]$^+$, 124(33) [$HSCH_2Ph$]$^+$, 91(100) [$PhCH_2$]$^+$.

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