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An Efficient Synthesis of 2-Propyl-5-phenyl-1,4-dioxo-1,2,3,4,5,6,7,8-octahydro-[1,4,2]diazaphosphorino[1,2-a][1,3,2] benzodiazaphosphorine 3-oxide

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Abstract: The novel 2-propyl-5-phenyl-1, 4-dioxo-1,2,3,4,5,6,7,8-octahydro-[1,4,2]diaza phosphorino[1,2-a][1,3,2]benzodiazaphosphorine 3-oxide has been synthesized by incorporating the proximate carbonyl and phosphoryl groups into the benzoannulated phosphdiamide heterocycle in good yield.

Keywords: Synthesis, [1,4,2]diazaphosphorino[1,2-a][1,3,2]benzodiazaphosphorine.

During the past two decades, α-ketophosphonates and their derivatives have attracted considerable attention because of their special physical, chemical and pharmacological properties due to the proximity of the carbonyl and the phosphoryl groups[1-12]. In the study on new pharmaceuticals and agrochemicals, the application of heterocycles is suggested to improve the biological activity. A sizeable number of endogenous fused heterocyclic compounds play a key role in regulation of various life processes. Moreover, benzoannulated and related analogs of cyclophosphamide possess antitumor activity, and have also been received an increasingly interest in chemistry, medicine, and agricultural science[13-16]. As a part of our ongoing program aimed at searching for novel antitumor and antiviral agents with high activity and low toxicity, we have designed to synthesize the 2-propyl-5-phenyl-1,4-dioxo-1,2,3,4,5,6,7,8-octahydro-[1,4,2]diaza phosphorino[1,2-a][1,3,2]benzodiazaphosphorine 3-oxide **2** by incorporating the proximate carbonyl and phosphoryl groups into the benzoannulated phosphadiamide heterocycle, as shown in **Scheme 1**.

There has been a considerably growing interest in heterocyclic compounds due to their pharmaceutical importance and extensive application in organic synthesis[17]. Methods of formation of the bond connecting the carbonyl and the phosphoryl groups have been reported[1,18]. However, to the best of our knowledge, that the successful approach of formation such a bond in fused heterocyclic compounds is very few in the literatures. Coppola reported that (**Scheme 2**) when **3** was treated with lithium diisopropylamide in tetrahydrofuran at −10°C, no reaction occurred while at room temperature, extensive decomposition resulted. Furthermore, under more forcing

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conditions (sodium hydride in dioxane), no reaction was observed even at 60°C for 24 hours[19].

According to the capability of possible cyclization between the amido functionality and the bromoethyl group forming the proximate carbonyl and phosphoryl groups in the fused heterocyclic structure, herein we report a one-pot procedure as shown in **Scheme 1**. 1-(2-Bromoethyl)-3-propyl-2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1*H*)-one 2-oxide **1** was refluxed with phenyl isocyanate in toluene in the presence of triethylamine, two reaction, *i. e.* the addition reaction to form the amido functionality and the intramolecular cyclization between the bromoethyl and amido functionality occurred in one step. In the result **2** was formed.

Scheme 1

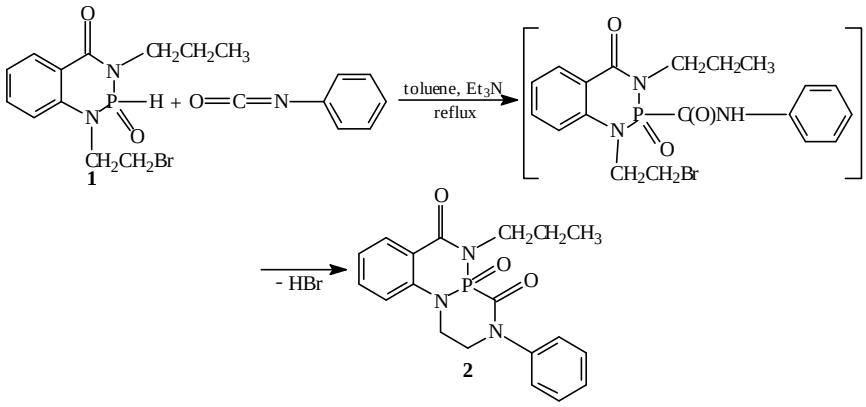
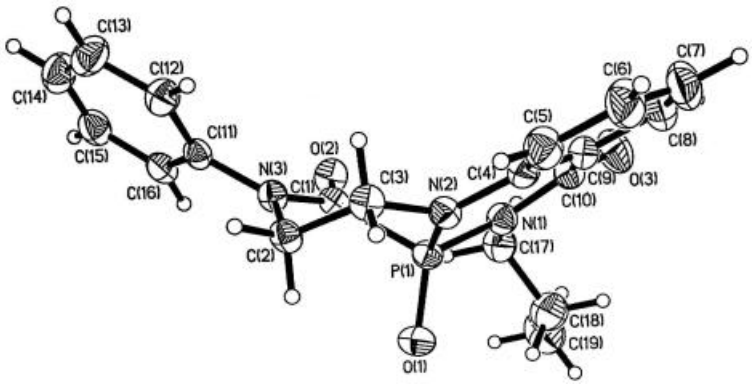
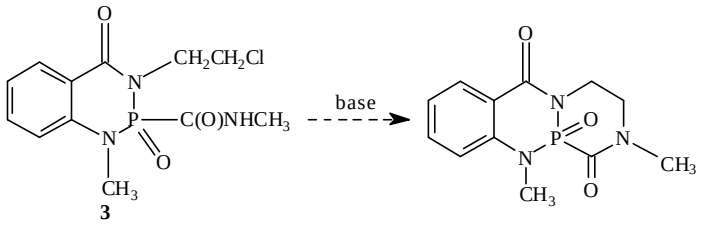


Figure 1 The single crystals X-ray-analysis of **2**



Scheme 2



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Experimental

Melting points were determined with a model YANACO MP-500 apparatus and the thermometer was uncorrected. IR spectra were recorded on a SHIMADZU-435 spectrometer. The ^{1}H and ^{31}P NMR spectra were recorded on a BRUKER AC-P200 instrument. TMS was used as an internal standard for ^{1}H NMR, and 85% phosphoric acid was used as an external standard for ^{31}P NMR spectroscopy. Mass spectra were recorded on a Hewlett-Packard 5988 instrument. Elemental analysis was carried out on a Yana MT-3 instrument. Column chromatography was performed using silica gel H (10-40 μm, Haiyang Chemical Factory of Qingdao).

Compound **1** was prepared according to literature methods[9,16].

Preparation of **2**: A mixture of **1** (0.99 g, 3 mmol), phenyl isocyanate (3 mmol), triethylamine (0.61 g, 6 mmol) and 30 mL dry toluene was refluxed for 8-10 hours, then the produced triethylamine hydrobromide was filtered off. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using a mixture of 40% ethyl acetate/light petroleum as eluate. 0.78 g of **2** was obtained. 70.4% yield, mp 152-154°C. Anal. calcd. for $C_{19}H_{20}N_3O_3P$: C, 61.79; H, 5.46; N, 11.38. Found: C, 61.52; H, 5.35; N, 11.16. IR (KBr, cm^{-1}): 2950.5, 1669.1, 1643.4 (s, C=O); 1602.7 (s, C=O); 1486.6, 1398.0, 1346.2 (s, P=O), 1236.7, 1213.9, 1034.0 (m, P=N); 939.4, 904.7, 758.5, 701.8. EI-MS (*m/z*, %): 369 (7.5); 341 (41.6); 326, 312, 299 (93.2); 284, 258, 235, 207, 194, 180, 152, 132 (47.5); 104 (69.8); 77 (100). ^{1}H NMR ($CDCl_3$/TMS, δ_{ppm}; *J* Hz): 0.96 (t, 3H, $^{3}J_{HH}$=7.4, $NCH_2CH_2CH_3$), 1.88 (m, 2H, $NCH_2C\mathbf{H}_2CH_3$), 3.60-4.15 (m, 5 H, $NCH_2CH_2CH_3$ +$PNCH_2CH_2N$ + 1/2 × $PNCH_2C\mathbf{H}_2N$), 4.96 (m, 1H, 1/2 × $PNCH_2C\mathbf{H}_2N$), 6.92-8.35 (m, 9H, C_6H_5 + C_6H_4). ^{31}P NMR ($CDCl_3$, δ_{ppm}): −7.74. The single crystals of **2** suitable for X-ray analysis were obtained by recrystallization from the mixture solvent of ethyl acetate and petroleum ether (bp 90-120°C).

Results and Discussion

The crystal structure of **2** is shown in **Figure 1**: mono-clinic, space group P2 (1)/c, with *a*=9.7585 (9), *b*=21.4319 (19), *c*=17.7900 (16) Å. *b*=100.823 (2)°. *Z*=8, *V*=3654.5 (6) $Å^3$. The compound shows that the proximate carbonyl and phosphoryl groups are not coplanar due to their being jointly located in the fused heterocycle with the ring tension, and the [1,4,2]diazaphosphorino moiety prefers the boat conformation. In the ^{1}H NMR

spectra, the two methylene protons in the $PNCH_2CH_2N$ group of the [1,4,2] diazaphosphorino moiety resonated as two multiplets at δ 3.60-4.15 and δ 4.96 respectively, which could be explained by the anisotropic effect of the adjacent P=O group. This assumption was verified by X-ray crystallographic analysis of the title compound as shown in **Figure 1**.

Acknowledgments

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