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A New Technique of Synthesizing 10-Hydroxy-5-methyl- 5,10-dihydrophenophosphazine 10-Oxide

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Abstract: 10-Hydroxy-5-methyl-5, 10- dihydrophenophosphazine 10-oxide (**1)** was prepared by a new technique of treating 10-methoxy-5,10-dihydrophenophosphazine 10-oxide (**2**) with an equivalent of NaH in anhydrous DMF, and then at 120°C for 3~4 h, which not only avoided poisonous and expensive methyl iodide used in literature, but made the consumption of NaH greatly decrease as well. The possible reaction mechanism was also described. The chemical structure of **1** was confirmed by IR, NMR, and mass spectroscopy.

Keywords: 10-Dihydrophenophosphazine, synthesis, structure identification.

The amino derivatives of title compound **1** are nonmutagenic intermediates[1] which are potential substitute for strong carcinogenic intermediates of β-naphthylamine and benzidine residue in some well-known carcinogenic β-naphthylamine- and benzidine-based azo dyes which are now banned[2-4]. The compound **1** was usually prepared by interaction of methyl iodide (MeI) and a bis-anion obtained from 10-hydroxy-5,10-dihydrophenophosphazine 10-oxide (by deprotonation with a base with stronger basicity, *e.g.*, NaH). In stoichiometry, two moles of NaH and one mole of MeI were usually needed when one mole of **1** was prepared. However, it was found on attempting to repeat the reported method[1] to prepare **1** that over three moles of NaH and more than one mole of MeI were needed when only one mole of **1** obtained because of the volatility of MeI and low yield of **1**. Now, the present paper reports a new technique of synthesizing **1** in which MeI was completely avoided and the consumption of NaH will greatly decrease for the same equivalent **1** obtained.

In principle, the NH group of 10-methoxy-5, 10-dihydrophenophosphazine 10-oxide (**2**) can be alkylated to form 10-methoxy-5-methyl-5,10-dihydrophenophosphazine 10-oxide (**3**) by deprotonation with a base and then treatment of the resulting anion (**4**) with an alkyl halide (*e.g.* MeI) in nonproton polar solvent (*e.g.* DMF, see **Scheme 1**). However, when preparing **3** *via* interaction of **4** and MeI in DMF, the expected product **3** was not obtained, but **1** was obtained, no matter how the amount of MeI was altered. It was therefore supposed that the anion **4** shifted the methyl group from oxygen to nitrogen atom intermolecularly during the reaction.

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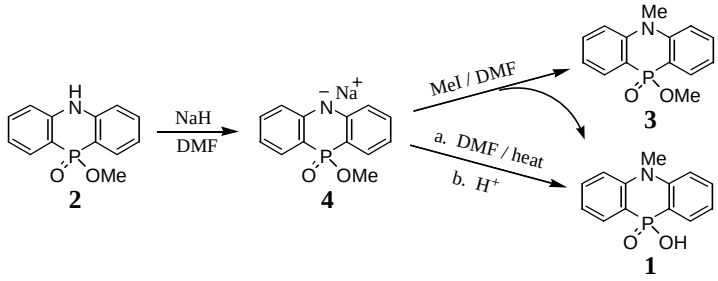
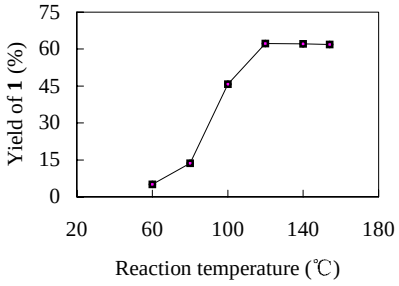
Scheme 1



And when directly heated to over 120°C for 3.5 h without MeI, the anion **4** was indeed coverted to **1** in a moderate yield (*ca*. 60%, see **Figure 1**). It was therefore supposed that the reaction may be carried out in an intermolecular nucleophilic substitution. It was also found in the experiment (see also **Figure 1**) that **1** was hardly obtained at lower temperature than 60°C. The reason may be that the energy barrier of the intermolecular nucleophilic substitution above mentioned was higher.

Figure 1 Influence of reaction temperature on the yield of **1**



Some spectral data of **1** and **2** were listed in **Table 1**. It was especially noted that the ^{1}H NMR of *O*-methyl of **2** was split to doublet peak because of coupling with ^{31}P atom. In contrast, the ^{1}H NMR of *N*-methyl in **1** (singlet peak) was not split because it was far from the ^{31}P atom.

Experimental

The starting material **2** was prepared according to literature[5]. The other reagents were commercial products of analytical grade, and the anhydrous DMF was obtained *via* treatment of commercial DMF following reported method[6]. Melting points were determined with a Mel-Temp capillary melting point apparatus (made in Shanghai, China) and uncorrected. IR spectra were obtained by a FT/IR-430 infrared spectrophotometer (made in JASCO Ltd. Co., Japan). Mass spectra were taken at CID=50~200 V with a HP1100 System of HPLC/MS (HEWLETT PACKARD Ltd. Co., USA). ^{1}H NMR (d^{6}-DMSO as solvent, TMS as inner standards), ^{31}P NMR (85%H_3PO_4 as inner standards) and ^{13}C NMR spectra were obtained on a Varian INOVA 400 NMR spectrograph (Varian

Table 1 Spectral data of **1** and the starting material **2**[8]

Compds.	m.p. /°C	IR /cm^{-1}	MS /*m/z*	NMR / 10^{-6}		
				^{13}C	^{1}H	^{31}P
1	251~253 (253~254[7])	2229.31(B); 1169.62(S); 1132.97(S); 965.20(S)	246.1 ([M+H]$^+$) 228.1 ([M-OH]$^+$)	146.0(2C); 131.9(2C); 128.4(2C); 120.3(2C); 119.4(2C); 115.4(2C); 36.5(1C)	3.60(s, 3H); ~4.8(B); 7.20(t, *J*=7.2, 6.5, 2H); 7.36(t, *J*=8.4, 2H); 7.58(t, J=6.5, 8.4, 2H); 7.80(q, *J*=7.2, 2H);	12.1
2	226.6 (221~223[5])	3265.86(W); 3166.54(W); 1183.11(VS); 943.98(VS)	246.1 ([M+H]$^+$) 214.1 ([M-OMe]$^+$)	143.3(2C); 132.2(2C); 128.6(2C); 119.5(2C); 116.2(2C); 110.5(1C); 109.2(1C); 50.7(1C)	3.34(d, *J*=11.9, 3H); 7.08(t, *J*=7.1, 6.5, 2H); 7.23(t, J=8.1, 2H); 7.51(t, *J*=6.5, 8.1, 2H); 7.73(q, *J*=7.1, 2H); 10.18(s, 1H)	19.3

INOVA Ltd. Co., USA).

10-Methoxy-5, 10-dihydrophenophosphazine 10-oxide (**2**), 2 g (*ca*. 0.0085 mol), was dissolved in 40 mL of anhydrous DMF at room temperature, then an equimolar amount of NaH (60% in mineral oil) was added, which would turn the reaction solution green. When hydrogen evolution ceased, the reaction mixture was heated to above 120°C and maintained at that temperature for 3~4 h. After most of solvent was distilled out under reducing pressure, the reaction mixture was cooled, an earth-white precipitate that was collected by filtration was re-dissolved in 100 mL of water. When a little of mineral oil was removed, the filtrate was acidified by dilute HCl to precipitate the milk-white solid, *viz*., 10-hydroxy-5-methyl-5, 10-dihydrophenophosphazine 10-oxide (**1**). This milk-white solid was filtrated and washed with water, and then the crude product was recrystallized from 95% ethanol to give the pure product.

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8. In IR spectra, M=moderate, S=strong, W=weak, B=band, VS=very strong. In mass spectra, CID=100 V, the number of fragment peaks will become more as the volt of CID increases. In ^{1}H NMR, the dimension of coupling constants *J* is Hz.

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