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Synthesis of Aminobenzonitrile by Dehydration of Aminobenzamide Using Phenylphosphonic Dichloride in Pyridine

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2-Aminobenzamide was dehydrated to 2-aminobenzonitrile without protection of the amino group in the presence of phenylphosphonyl dichloride and pyridine. Other structural isomers (3-aminobenzamide and 4-aminobenzamide) did not give corresponding aminobenzonitriles.

Key Words: 2-Aminobenzonitrile, Phenylphosphonic dichloride, Dehydration.

INTRODUCTION

Dehydration reactions of primary amides by phosphoryl chloride are known as conventional methods for making nitriles[1-10]. However, phosphoryl chloride and phenylphosphonic dichloride readily react with amino group to give formamidine[11] in N,N-dimethylformamide and phosphamides in benzene, respectively. Therefore, this type of dehydration reactions have not been applied to amide compounds containing non-protected amino groups in the same molecule.

In this paper, the dehydration reactions of 2-aminobenzamide (**1a**) to 2-aminobenzonitrile (**3a**) using phosphoryl chloride (**2a**), phenyl phosphoryl dichloride (**2b**), 4-chlorophenyl phosphoryl dichloride (**2c**) or phenylphosphonic dichloride (**2d**) in pyridine are reported.

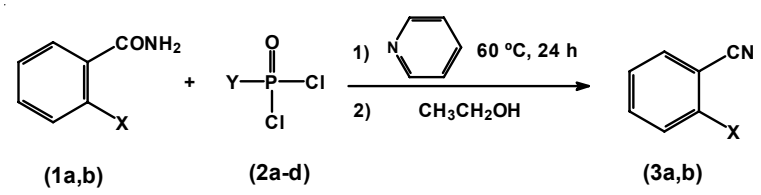


Fig. 1. Formation of aminobenzonitriles by dehydrating reagents in the presence of pyridine; **1a**, X: -NH_2, **1b**, X: -H; **2a**, Y: -Cl, **2b**, Y: -OPh, **2c**, Y: -OPh(4-Cl), **2d**, Y: -Ph; **3a**, X: -NH_2, **3b**, X: H

EXPERIMENTAL

Aminobenzamides (**1**), phosphoryl chloride (**2a**), phenyl phosphoryl dichloride (**2b**), 4-chlorophenyl phosphoryl dichloride (**2c**) and phenylphosphonic dichloride (**2d**) and pyridine were purchased from Wako pure chemical company or Tokyo Kasei Inc.

^{1}H NMR Spectra were measured with a Jeol NMR spectrophotometer EX-270. IR spectra were measured with a Hitachi infrared spectrophotometer 260-30. Melting Points were measured with a Buchi Melting Point B-530.

Typical synthetic procedure: Phenylphosphonic dichloride (2.04 g, 15 mmol) was dissolved in 10 mL pyridine. The solution was heated at 60 °C for 2 h. To this solution was added a pyridine solution composed of 10 mL pyridine and 2-aminonenzamide (**1a**) (15 mmol). After the reaction was carried out for 24 h at 60 °C, the reaction mixture was evaporated *in vacuo* to give an oily product. The product was redissolved in ethanol and was evaporated again. The evaporation of ethanol solution was repeated three more times. The resulted residue was purified with silica gel column chromatography (eluting solvent: chloroform-hexane (1:3) in volume ratio) to afford 1.70 g (96 %). ^{1}H NMR (CD_3OD) δ = 3.32 (1H, br); 6.55-6.65 (1H, m); 6.75-6.85 (1H, m); 7.20-7.35 ppm (2H, m). IR (ν_{max}, nujol): 3470; 3380 (-NH_2); 2210 (-CN); 1630, 740 (Ph) cm^{-1}. Elemental analysis (%): Calcd. for $C_7H_6N_2$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.09; H, 5.19; N, 23.58.

Molecular modeling: Molecular calculation software MOPAC in CAChe Work system Version 4.5 (Fujitsu) on Macintosh was used for calculating heat of formation of benzamides and benzonitriles. The heat of formation was calculated at MM2/PM3 geometry.

RESULTS AND DISCUSSION

The chemical yield and melting point of 2-aminobenzonitrile (**3a**) obtained by four dehydrating reagents (**2a-d**) are listed in Table-1. 2-Aminobenzamide was dehydrated by reagents **2a-c** to give 2-aminobenzonitrile in the yield lower than 60 %, while the reaction by reagent (**2d**) gave the highest yield, 96 %. On the other hand, benzamide (**1b**) without amino groups afforded benzonitrile (**3a**) in the yield of 43 %.

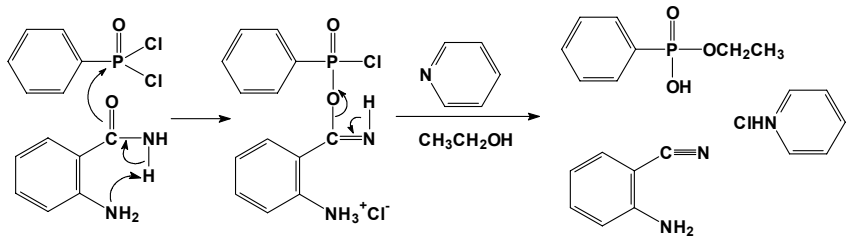
The amino group of 2-aminobenzamide could take a proton from neighbouring amide group to help P-O bond formation as illustrated in **Scheme-I**.

Chemo-selectivity of phenylphosphonic dichloride (**2d**) to amide group in benzamides bearing amino group was also examined as shown in Table-2. 3- and 4-Aminobenzamides, constitutional isomers of 2-aminobenzamide did not afford corresponding benzonitriles but phosphonylamides (21-33 %). The results suggest that an aminobenzamide possessing amino group at 2-position can be chemo-selectively dehydrated to aminobenzonitrile.

TABLE-1
FORMATION OF 2-AMINOBENZAMIDE IN PRESENCE OF DEHYDRATING REAGENT

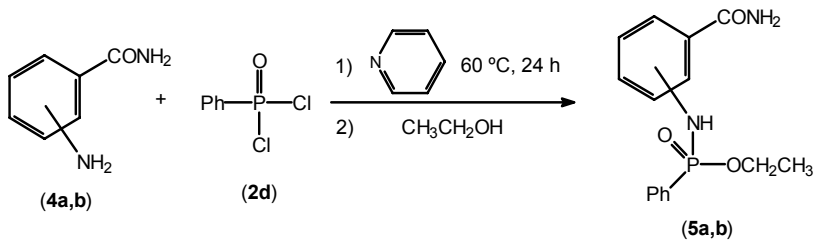
Benzamide	Dehydrating reagent	Reaction time (h)	Yield of benzonitrile (**3a**, **3b**) (%)	m.p.* (ºC)
1a	**2a**	24	43 (**3a**)	47-49
1a	**2b**	10	46 (**3a**)	48-49
1a	**2b**	24	58 (**3a**)	48-49
1a	**2c**	24	49 (**3a**)	47-49
1a	**2d**	24	96 (**3a**)	48-49
1b	**2d**	24	45 (**3b**)	Oil

1a, X: -NH_2, **1b**, X: -H; **2a**, Y: -Cl, **2b**, Y: -OPh, **2c**, Y: -OPh(4-Cl), **2d**, Y: -Ph; **3a**, X: -NH_2, **3b**, X: H; *lit.[12] 49-51 ºC



Scheme-I: Postulated mechanism of formation of 2-aminonitrile

TABLE-2
FORMATION OF PHENYLPHOSPHAMIDATE FROM 3- or 4-AMINOBENZAMIDE (**4a, 4b**)



Aminobenzamide	Reaction time (h)	Yield (%) of phosphoamidate	m.p. (ºC)
4a	24	33 (**5a**)	256-258
4b	24	51 (**5b**)	215-219
1a	24	0 (**5c**)	–

The non-formation of phosphoramidate from 2-aminobenzamide is explained by the relative stability of phosphoramidates from 3- and 4-aminobenzamides. Table-3 shows the semi-empirical calculation of heat of formation at 25 °C using MOPAC.

TABLE-3
HEAT OF FORMATION OF PHENYLPHOSPHORAMIDATES (**5a-c**)

Phenylphosphoamide	Heat of formation calculated by MOPAC (kacl/mol)
5a	-113.6
5b	-114.0
5c	-110.0

The results show that 4-substituted isomer (**5b**) is the most stable and 2-substituted isomer is unstable. The order in stability of structural isomers would be caused by the steric hindrance between amide group and the bulky phenyl phosphoramidate group.

The present work demonstrated chemo-selective dehydration of the amide group of 2-aminobenzamide without amino-protection. The unique reactivity of 2-aminobenzamide could be useful for synthetic choice of similar amino-nitriles.

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