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SOLVENT-FREE REACTION USING PHOSPHONIUM SALTS : CHLORINATION OF HYDROXYHETEROAROMATICS AND DEHYDRATION OF PRIMARY AMIDES

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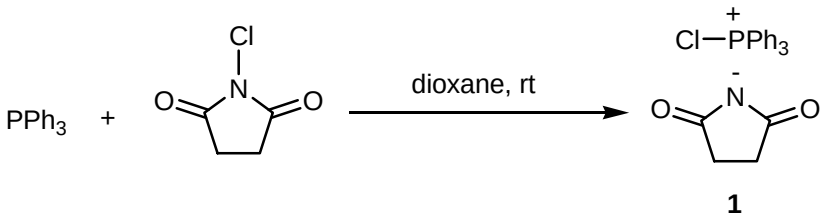
Abstract - Solvent-free chlorination of heteroaromatics using the phosphonium salt, prepared by reaction of triphenylphosphine with *N*-chlorosuccinimide, was accomplished by microwave-irradiation or heating to give the corresponding chloroheteroaromatics. Similarly, primary amides was converted into nitriles by this method.

π-Deficient chloroheteroaromatics play a versatile role in organic synthesis. For example, they react with nucleophiles to introduce nucleophilic substituents into the heteroaromatic ring.[1] Introduction of electrophilic substituents into the heteroaromatic ring can be accomplished by lithiation[2] or magnesiation[3] of chloroheteroaromatics followed by reaction with electrophiles.

Figure 1. Structure of phosphonium salt (**1**)



1

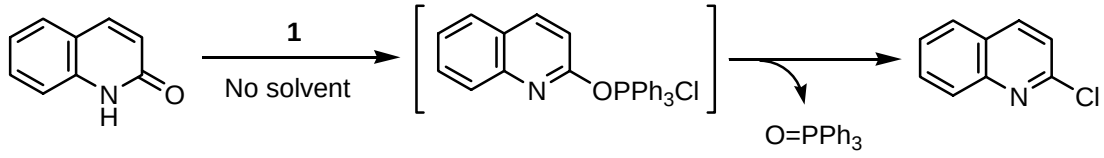
It is found that the chlorophosphonium salt (**1**, Figure 1), prepared by reaction of triphenylphosphine with *N*-chlorosuccinimide, is useful for chlorination of nitrogen - containing heteroaromatics or dehydration of primary amides.[4] The phosphonium salts (**1**) show mild reactivity with water compared to the

conventional chlorinating reagent such as phosphoryl chloride (phosphorus oxychloride, $POCl_3$) and thionyl chloride, and addition of water to the reaction mixture at the work-up is not needed.

In organic reactions, use of an organic solvent is a general method to mix a substrate with reagents. However, from the viewpoint of protection of the environment and reduction of chemical resources, development of solvent-free organic reactions would be helpful for us. Recently, microwave-irradiated reaction[5] of hydroxyheteroaromatics and primary amides using **1** without a solvent was preliminarily reported by us.[6] Here, we would like to report our further study using **1** under a solvent-free condition, heating and microwave-irradiation.

At first, chlorination of 2(1*H*)-quinolinone using **1** was carried out under a variety of conditions in order to optimize the condition as shown in Table 1. Microwave-irradiation was discontinued when the reaction mixture melted and turned black. Both heating and microwave-irradiation gave the product, 2-chloroquinoline, in good yields when excess amount of **1** (2 - 4 eq) was used. Under the heating condition, the use of **1** (2 eq) was found to be the best condition (Table 1, Entry 5). Under microwave-irradiating condition, on the contrary, at least 4 eq of **1** was required to afford the product in good yield (Table 1, Entry 16). However, it is useful that the reaction of microwave-irradiated chlorination requires shorter time than that of the heating condition.

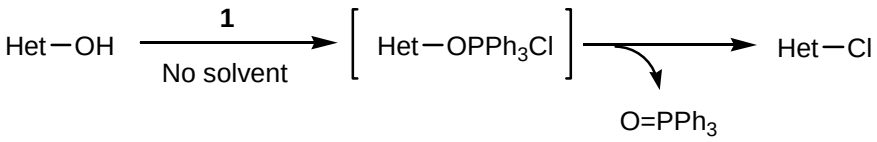
Table 1. Optimization for solvent-free chlorination of 2(1*H*)-quinolinone using **1**

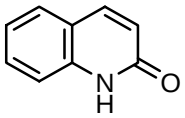
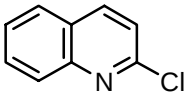
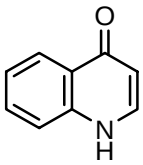
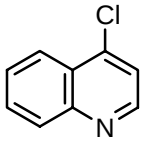
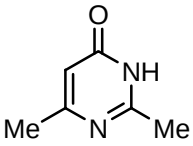
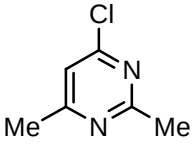
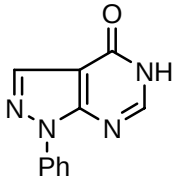
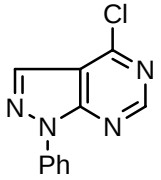
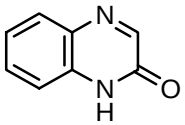
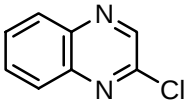
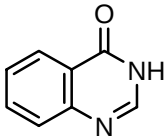
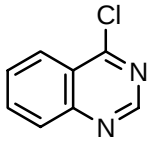
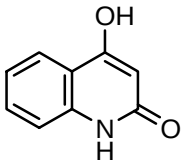
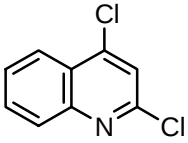
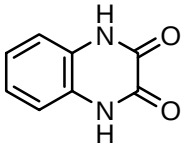
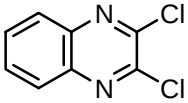


Heating				Microwave-irradiation			
Entry	**1** (eq)	Condition	Yield (%)	Entry	**1** (eq)	Condition	Yield (%)
1	1	80 ˚C, 2 h	38	9	1	150 W, 30 min	15
2	1	105 ˚C, 2 h	41	10	1	300 W, 11.5 min	21
3	1	130 ˚C, 2 h	54	11	1	600 W, 8 min	3
4	1	150 ˚C, 2 h	21	12	1	700 W, 3.5 min	13
5	2	130 ˚C, 2 h	72	13	1	1000 W, 5.5 min	11
6	2	130 ˚C, 4 h	62	14	2	300 W, 8 min	22
7	3	130 ˚C, 2 h	66	15	3	300 W, 7.5 min	38
8	4	130 ˚C, 2 h	67	16	4	300 W, 7 min	64

Table 2 shows the results of solvent-free chlorination of hydroxyheteroaromatics. The optimized condition obtained in Table 1 was used (heating : 130 ˚C, 2 h with 2 eq of **1**; microwave-irradiation : 300 W with 4 eq of **1**). It was found that a variety of nitrogen-containing heteroaromatics can be applied to the chlorination.

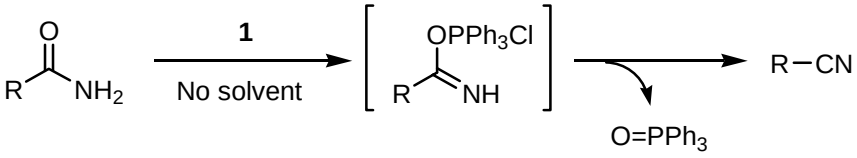
Table 2. Solvent-free chlorination of hydroxyheteroaromatics

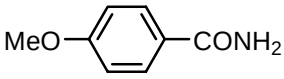
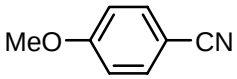
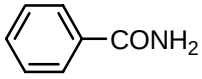
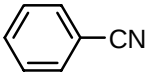
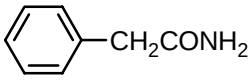
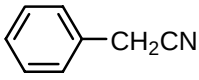


Entry	Het-OH	Amount of **1** (eq)	Condition	Het-Cl	Yield (%)
1		2	130 °C, 2 h		72
2		4	300 W, 7 min		64
3		2	130 °C, 2 h		83
4		4	300 W, 8.5 min		61
5		2	130 °C, 2 h		81
6		4	300 W, 10.5 min		18
7		2	130 °C, 2 h		12
8		4	300 W, 6 min		19
9		2	130 °C, 2 h		51
10		4	300 W, 5 min		64
11		2	130 °C, 2 h		30
12		4	300 W, 3 min		27
13		2	130 °C, 2 h		28
14		4	300 W, 5 min		42
15		2	130 °C, 2 h		20
16		4	300 W, 2.5 min		10

As an application, dehydration of primary amides using **1** was carried out under solvent-free condition as shown in Table 3. In order to find the optimized condition, the reaction temperature was varied. It was found that heating at 60-100 °C for 2 h was the best condition to give the product.

Table 3. Solvent - free dehydration of primary amides



Entry	R-$CONH_2$	Amount of **1** (eq)	Condition	R-CN	Yield (%)
1		2	50 °C, 2 h		75
2		2	60 °C, 2 h		90
3		2	80 °C, 2 h		90
4		2	105 °C, 2 h		75
5		2	130 °C, 2 h		56
6		1	300 W, 6.5 min		23
7		2	300 W, 6.5 min		46
8		4	300 W, 5 min		95
9		2	60 °C, 2 h		19
10		2	105 °C, 2 h		53
11		2	130 °C, 2 h		24
12		4	300 W, 4.5 min		56
13		2	60 °C, 2 h		77
14		2	105 °C, 2 h		81
15		4	300 W, 6 min		66

In conclusion, solvent-free chlorination of hydroxyheteroaromatics and dehydration of primary amides was accomplished. Although it is useful that microwave-irradiated reaction using **1** is complete in a few minutes, the reaction sometimes results in a lowering of yields of the products. On the contrary, heatintg reaction using **1** generally afforded the products in higher yields than microwave-irradiated reaction.

EXPERIMENTAL

Microwave-irradiation was carried out using a microwave oven (Matsushita NE-J720, Japan). ^{1}H-NMR spectra was measured with HITACHI R-90H spectrometer using tetramethylsilane as an internal standard.

Preparation of **1** : To a solution of triphenylphosphine (2623 mg, 10.0 mmol) in dioxane (100 ml), *N*-chlorosuccinimide (1335 mg, 10.0 mmol) was added little by little and stirred for 30 min. The white solid was filtered and dried under reduced pressure to give **1** in quantitative yield.

2-Chloroquinoline : A mixture of 2(1*H*)-quinolinone (290 mg, 2.00 mmol) and **1** (1583 mg, 4.00 mmol) was heated at 130 °C for 2 h. After the reaction mixture was dissolved in dichloromethane and basified

with triethylamine, dichloromethane and triethylamine was removed under reduced pressure. The residue was treated with silica gel column chromatography (eluted with hexane-ethyl acetate (5:1)) to give 2-chloroquinoline (236 mg, 72%). ^{1}H-NMR ($CDCl_3$) ppm : 7.37 (1H, *d*, J=8.7 Hz, C^3-H), 7.43-7.68 (1H, *m*, C^6-H), 7.68-7.89 (2H, *m*, C^5 and C^7-H), 8.03 (1H, *d*, J=8.1 Hz, C^8-H), 8.08 (1H, *d*, J=8.7 Hz, C^4-H).

4-Chloroquinoline : A mixture of 4(1*H*)-quinolinone (290 mg, 2.00 mmol) and **1** (1583 mg, 4.00 mmol) was heated at 130 °C for 2 h. After the reaction mixture was dissolved in dichloromethane and basified with triethylamine, dichloromethane and triethylamine was removed under reduced pressure. The residue was treated with silica gel column chromatography (eluted with hexane-ethyl acetate (5:1)) to give 4-chloroquinoline (272 mg, 83%). ^{1}H-NMR ($CDCl_3$) ppm : 7.49 (1H, *d*, J=4.7 Hz, C^3-H), 7.57-7.90 (2H, *m*, C^6 and C^7-H), 8.00-8.33 (2H, *m*, C^5 and C^8-H), 8.78 (1H, *d*, J=4.7 Hz, C^2-H).

4-Chloro-2,6-dimethylpyrimidine : A mixture of 2,6-dimethyl-4(3*H*)-pyrimidinone (248 mg, 2.00 mmol) and **1** (1583 mg, 4.00 mmol) was heated at 130 °C for 2 h. After the reaction mixture was dissolved in dichloromethane and basified with triethylamine, dichloromethane and triethylamine was removed under reduced pressure. The residue was treated with silica gel column chromatography (eluted with hexane-ethyl acetate (3:2)) to give 4-chloro-2,6-dimethylpyrimidine (228 mg, 81%). ^{1}H-NMR ($CDCl_3$) ppm : 2.48 (3H, *s*, CH_3), 2.67 (3H, *s*, CH_3), 7.03 (1H, *s*, C^5-H).

4-Chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine : A mixture of 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (424 mg, 2.00 mmol) and **1** (3167 mg, 8.00 mmol) was treated with microwave-irradiation at 300 W for 6 min. After the reaction mixture was dissolved in dichloromethane and basified with triethylamine, dichloromethane and triethylamine was removed under reduced pressure. The residue was treated with silica gel column chromatography (eluted with hexane-ethyl acetate (5:1)) to give 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (44 mg, 19%). ^{1}H-NMR ($CDCl_3$) ppm : 7.30-7.70 (3H, *m*, phenyl-H), 8.06-8.28 (2H, *m*, phenyl-H), 8.34 (1H, *s*, C^3-H), 8.87 (1H, *s*, C^6-H).

2-Chloroquinoxaline : A mixture of 2(1*H*)-quinoxalinone (292 mg, 2.00 mmol) and **1** (3167 mg, 8.00 mmol) was treated with microwave-irradiation at 300 W for 5 min. After the reaction mixture was dissolved in dichloromethane and basified with triethylamine, dichloromethane and triethylamine was removed under reduced pressure. The residue was treated with silica gel column chromatography (eluted with hexane-ethyl acetate (4:1)) to give 2-chloroquinoxaline (211 mg, 64%). ^{1}H-NMR ($CDCl_3$) ppm : 7.65-7.91 (2H, *m*, C^6 and C^7-H), 7.91-8.24 (2H, *m*, C^5 and C^8-H), 8.78 (1H, *s*, C^3-H).

4-Chloroquinazoline : A mixture of 4(3*H*)-quinazolinone (292 mg, 2.00 mmol) and **1** (1583 mg, 4.00 mmol) was heated at 130 °C for 2 h. After the reaction mixture was dissolved in dichloromethane and basified with triethylamine, dichloromethane and triethylamine was removed under reduced pressure. The residue was treated with silica gel column chromatography (eluted with hexane-ethyl acetate (2:1)) to give 4-chloroquinazoline (99 mg, 30%). ^{1}H-NMR ($CDCl_3$) ppm : 7.72 (1H, *ddd*, J=8.7 Hz, 6.4 Hz, 1.7 Hz,

C^6-H), 7.82-8.17 (2H, *m*, C^7 and C^8-H), 8.27 (1H, *dd*, J=8.1 Hz, 0.8 Hz, C^5-H), 9.05 (1H, *s*, C^2-H).

2,4-Dichloroquinoline : A mixture of 4-hydroxy-2(1*H*)-quinolinone (322 mg, 2.00 mmol) and **1** (3167 mg, 8.00 mmol) was treated with microwave-irradiation at 300 W for 5 min. After the reaction mixture was dissolved in dichloromethane and basified with triethylamine, dichloromethane and triethylamine was removed under reduced pressure. The residue was treated with silica gel column chromatography (eluted with hexane-ethyl acetate (10:1)) to give 2,4-dichloroquinoline (165 mg, 42%). ^{1}H-NMR ($CDCl_3$) ppm : 7.51 (1H, *s*, C^3-H), 7.51-7.91 (2H, *m*, C^6 and C^7-H), 8.04 (1H, *d*, J=7.7 Hz, C^8-H), 8.21 (1H, *d*, J=7.5 Hz, C^5-H).

2,3-Dichloroquinoxaline : A mixture of 2,3(1*H*,4*H*)-quinoxalinedione (324 mg, 2.00 mmol) and **1** (1583 mg, 4.00 mmol) was heated at 130 °C for 2 h. After the reaction mixture was dissolved in dichloromethane and basified with triethylamine, dichloromethane and triethylamine was removed under reduced pressure. The residue was treated with silica gel column chromatography (eluted with hexane-ethyl acetate (10:1)) to give 2,3-dichloroquinoxaline (80 mg, 20%). ^{1}H-NMR ($CDCl_3$) ppm : 7.65-7.90 (2H, *m*, C^6 and C^7-H), 7.90-8.16 (2H, *m*, C^5 and C^8-H).

4-Methoxybenzonitrile : A mixture of 4-methoxybenzamide (302 mg, 2.00 mmol) and **1** (3167 mg, 8.00 mmol) was treated with microwave-irradiation at 300 W for 5 min. After the reaction mixture was dissolved in dichloromethane and basified with triethylamine, dichloromethane and triethylamine was removed under reduced pressure. The residue was treated with silica gel column chromatography (eluted with hexane-ethyl acetate (2:1)) to give 4-methoxybenzonitrile (253 mg, 95%). ^{1}H-NMR ($CDCl_3$) ppm : 3.85 (3H, *s*, OCH_3), 6.94 (2H, *d*, J=9.0 Hz, C^3 and C^5-H), 7.59 (2H, *d*, J=9.0 Hz, C^2 and C^6-H).

Benzonitrile : A mixture of benzamide (242 mg, 2.00 mmol) and **1** (3167 mg, 8.00 mmol) was treated with microwave-irradiation at 300 W for 4.5 min. After the reaction mixture was dissolved in dichloromethane and basified with triethylamine, dichloromethane and triethylamine was removed under reduced pressure. The residue was treated with silica gel column chromatography (eluted with hexane-ethyl acetate (10:1)) to give benzonitrile (115 mg, 56%). ^{1}H-NMR ($CDCl_3$) ppm : 7.40-7.75 (5H, *m*, phenyl-H).

Phenylacetonitrile : A mixture of phenylacetamide (270 mg, 2.00 mmol) and **1** (1583 mg, 4.00 mmol) was heated at 105 °C for 2 h. After the reaction mixture was dissolved in dichloromethane and basified with triethylamine, dichloromethane and triethylamine was removed under reduced pressure. The residue was treated with silica gel column chromatography (eluted with hexane-ethyl acetate (5:1)) to give phenylacetonitrile (190 mg, 81%). ^{1}H-NMR ($CDCl_3$) ppm : 3.73 (2H, *s*, CH_2), 7.34 (5H, *s*, phenyl-H).

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