HETEROCYCLES, Vol. 65, No. 1, 2005, pp. 181 - 185
Received, 8th October, 2004, Accepted, 17th November, 2004, Published online, 19th November, 2004

AN IMPROVED METHOD FOR CHLORINATION OF NITROGEN-CONTAINING π-DEFICIENT HETEROAROMATICS USING TRIPHENYLPHOSPHINE AND TRICHLOROISOCYANURIC ACID

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Abstract – Phosphorus compound prepared by reaction of triphenylphosphine with trichloroisocyanuric acid was found to be applied to chlorination of nitrogen-containing π-deficient heteroaromatics. As self-decomposition of the chlorinating reagent hardly proceeds, the reagent is more useful than phosphorus compound prepared by triphenylphosphine and *N*-chlorosuccinimide.

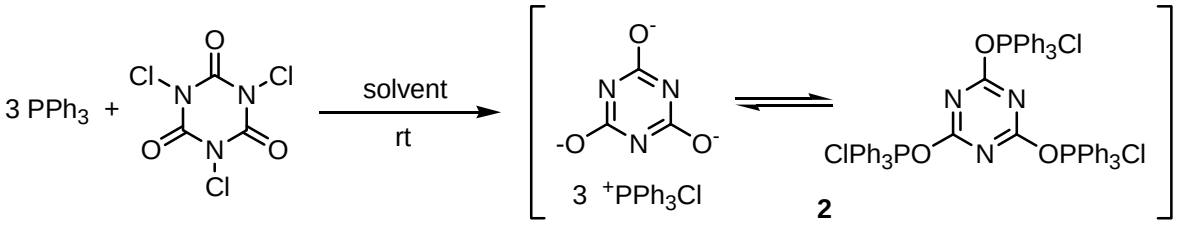
Since many nitrogen-containing π-deficient heteroaromatics (abbreviated as heteroaromatics) have biological activities, derivatives of these compounds have been prepared in order to find more available lead-compounds. Chloroheteroaromatics are a versatile synthetic precursor to synthesize derivatives of the heteroaromatics: Chloroheteroaromatics react with nucleophiles such as carbanions,[1] amines, [2] alkoxides,[3] or thiols[4] to introduce nucleophilic substituents into the heteroaromatic moiety. Metalation of chloroheteroaromatics *via* tellurium-lithium exchange[5-8] or oxidative addition of magnesium[9,10] provides electrophilic substituents into the heteroaromatic moiety.

Chloroheteroaromatics are synthesized by the reaction of hydroxyheteroaromatics with phosphoryl chloride,[11] phosphorus pentachloride, [12] or *N*-chlorosuccinimide / triphenylphosphine (**1**).[13,14] Although phosphoryl chloride or phosphorus pentachloride has been used for the chlorination of hydroxyheteroaromatics for more than 100 years, addition of water to the reaction mixture at the work-up process results in evolution of hydrochloric acid and heat from the exothermic reaction. The use of **1** as a chlorinating reagent is of greater advantage than the use of phosphoryl chloride or phosphorus pentachloride from the reaction due to its inertness to water. However, the black byproduct derived from

decomposition of **1** interferes with the purification of chloroheteroaromatics. In this paper we wish to report an improved chlorination of hydroxyheteroaromatics.

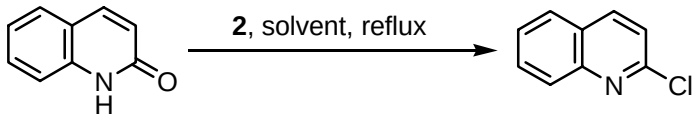
It is reported that chlorinating reagent (**2**), prepared by the reaction of triphenylphosphine with trichloroisocyanuric acid (Scheme 1), reacts with alcohol to afford alkyl chloride.[15]

Scheme 1 Chlorinating reagent (**2**) generated from triphenylphosphine and trichloroisocyanuric acid



So we applied **2** to the chlorination of 2(1*H*)-quinolinone as shown in Table 1. When an equimolecular amount of **2** was used and heated to reflux in toluene for 2 h, 2-chloroquinoline was obtained in 50% yield (entry 1). Elongation of the reaction time gave an analogous result (entry 2), and xylene (bp 137-140 °C) was used as a solvent instead of toluene (bp 109 °C). However, the yield of 2-chloroquinoline was slightly lowered (entry 3). On the other hand, when two equivalents of **2** was used, the yield of 2-chloroquinoline was improved (entry 4).

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



entry	amount of **2** (eq.)	solvent	condition	yield (%)
1	1	toluene	reflux, 2 h	50
2	1	toluene	reflux, 8 h	53
3	1	xylene	reflux, 8 h	38
4	2	toluene	reflux, 4 h	73

Next, chlorination of fused diazinones (1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one, 2(1*H*)-quinoxalinone, 4(3*H*)-quinazolinone) and fused diazinedione (2,4(1*H*,3*H*)-quinazolinedione) using two equivalents of **2** was carried out (Table 2).

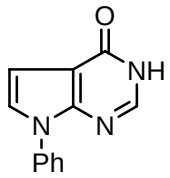
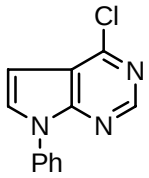
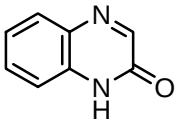
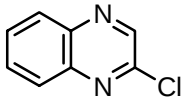
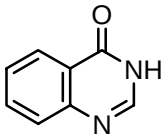
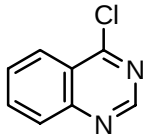
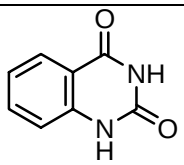
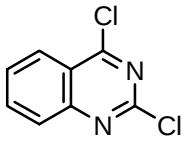
A mixture of 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one and **2** in toluene was heated to reflux for 4 h and 8 h, and 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine was obtained in 61% and 65% yields,

respectively (entries 1,2). Differences in the yield of 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine were not observed between the reaction times, 4 h and 8 h.

Both 2(1*H*)-quinoxalinone and 4(3*H*)-quinazolinone were chlorinated using two equivalents of **2** to afford 2-chloroquinoxaline and 4-chloroquinazoline in good yields (entries 3,4). However, chlorination of 2,4(1*H*,3*H*)-quinazolinedione gave 2,4-dichloroquinazoline only in 11% yield (entry 5). From these results, it was clarified that chlorination of azinones or diazinones proceeded smoothly than dichlorination of diazinediones.

Table 2 Chlorination of fused diazinones or fused diazinedione using **2**

substrate —**2** (2 eq.), solvent, reflux→ product

entry	substrate	solvent	condition	product	yield (%)
1		toluene	reflux, 4 h		61
2		toluene	reflux, 8 h		65
3		toluene	reflux, 4 h		77
4		toluene	reflux, 3.5 h		89
5		xylene	reflux, 3 h		11

Chlorination of azinone using two equivalents of **2** proceeded smoothly to give a chloro compound, whereas chlorination using **1** required up to five equivalents of **1** and the resulting mixture turned black resulting from a side reaction of **1**.

In summary, chlorination of nitrogen-containing π-deficient heteroaromatics was accomplished by the reaction of the corresponding hydroxyheteroaromatics with **2**. Compared with the usual chlorinating reagents such as phosphoryl chloride, phosphorus pentachloride, or **1**, **2** provided more facile chlorination.

EXPERIMENTAL

Melting points were not corrected. ^{1}H-NMR spectra were measured with HITACHI R-90H spectrometer using TMS as an internal standard.

Preparation of 2-chloroquinoline: Trichloroisocyanuric acid (1549 mg, 6.66 mmol) was added to a solution of triphenylphosphine (5246 mg, 20.0 mmol) in toluene (250 mL) and the reaction mixture was stirred at rt for 23 h. To the reaction mixture, 2(1*H*)-quinolinone (1452 mg, 10.0 mmol) was added and the mixture was heated to reflux for 4 h. After toluene was removed from the resulting mixture under reduced pressure, the residue was treated with silica gel column chromatography (eluted with hexane-ethyl acetate (6:1)) to afford 2-chloroquinoline (1197 mg, 73%). White solids. mp 31-32 °C (lit.,[16] 37-38 °C). ^{1}H-NMR ($CDCl_3$) ppm: 7.37 (1H, *d*, J=8.6 Hz, C^3-H), 7.47-7.66 (1H, *m*, C^6-H), 7.66-7.87 (2H, *m*, C^5 and C^7-H), 8.03 (1H, *d*, J=8.6 Hz, C^8-H), 8.09 (1H, *d*, J=8.6 Hz, C^4-H).

Preparation of 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine: Trichloroisocyanuric acid (232 mg, 1.00 mmol) was added to a solution of triphenylphosphine (787 mg, 3.00 mmol) in toluene (25 mL) and the reaction mixture was stirred at rt for 17 h. To the reaction mixture, 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (318 mg, 1.50 mmol) was added and the mixture was heated to reflux for 8 h. After toluene was removed from the resulting mixture under reduced pressure, the residue was treated with silica gel column chromatography (eluted with hexane-ethyl acetate (9:1)) to afford 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (226 mg, 65%). White solids. mp 131-132 °C (lit.,[17] 126-127 °C). ^{1}H-NMR ($CDCl_3$) ppm: 7.32-7.70 (3H, *m*, phenyl-H), 8.07-8.29 (2H, *m*, phenyl-H), 8.34 (1H, *s*, C^3-H), 8.87 (1H, *s*, C^6-H).

Preparation of 2-chloroquinoxaline: Trichloroisocyanuric acid (2324 mg, 10.0 mmol) was added to a solution of triphenylphosphine (7869 mg, 30.0 mmol) in toluene (300 mL) and the reaction mixture was stirred at rt for 23.5 h. To the reaction mixture, 2(1*H*)-quinoxalinone (2192 mg, 15.0 mmol) was added and the mixture was heated to reflux for 4 h. After toluene was removed from the resulting mixture under reduced pressure, the residue was treated with silica gel column chromatography (eluted with hexane-ethyl acetate (10:1)) to afford 2-chloroquinoxaline (1890 mg, 77%). Pale yellow solids. mp 47-47.5 °C (lit.,[18] 46-47 °C). ^{1}H-NMR ($CDCl_3$) ppm: 7.67-7.93 (2H, *m*, C^5 and C^8-H), 7.93-8.23 (2H, *m*, C^6 and C^7-H), 8.78 (1H, *s*, C^3-H).

Preparation of 4-chloroquinazoline: Trichloroisocyanuric acid (1549 mg, 6.66 mmol) was added to a solution of triphenylphosphine (5246 mg, 20.0 mmol) in toluene (300 mL) and the reaction mixture was stirred at rt for 19 h. To the reaction mixture, 4(3*H*)-quinazolinone (1462 mg, 10.0 mmol) was added and the mixture was heated to reflux for 3.5 h. After toluene was removed from the resulting mixture under

reduced pressure, the residue was treated with silica gel column chromatography (eluted with hexane-ethyl acetate (4:1)) to afford 4-chloroquinazoline (1473 mg, 89%). White solids. mp 97-98 °C (lit.,[12] 96.5-97.5 °C). ^{1}H-NMR ($CDCl_3$) ppm: 7.73 (1H, *ddd*, J=8.1, 6.4, 1.7Hz, C^6-H), 7.91-8.17 (2H, *m*, C^7 and C^8-H), 8.28 (1H, *dd*, J=8.1, 0.8 Hz, C^5-H), 9.05 (1H, *s*, C^2-H).

Preparation of 2,4-dichloroquinazoline: Trichloroisocyanuric acid (620 mg, 2.67 mmol) was added to a solution of triphenylphosphine (2098 mg, 8.00 mmol) in xylene (120 mL) and the reaction mixture was stirred at rt for 46 h. To the reaction mixture, 2,4(1*H*,3*H*)-quinazolinedione (324 mg, 2.00 mmol) was added and the mixture was heated to reflux for 3 h. After xylene was removed from the resulting mixture under reduced pressure, the residue was treated with silica gel column chromatography (eluted with hexane-ethyl acetate (5:1)) to afford 2,4-dichloroquinazoline (42 mg, 11%). White solids. mp 121 °C (lit.,[19] 120 °C). ^{1}H-NMR ($CDCl_3$) ppm: 7.57-7.90 (1H, *m*, C^6-H), 7.90-8.09 (2H, *m*, C^7 and C^8-H), 8.25 (1H, *dd*, J=8.1, 0.9 Hz, C^5-H).

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