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Cl_3CCN/PPh_3 and CBr_4/PPh_3: two efficient reagent systems for the preparation of N-heteroaromatic halides

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ABSTRACT

Cl_3CCN/PPh_3 and CBr_4/PPh_3 are two highly reactive reagent systems for the conversion of N-heteroaromatic hydroxy compounds into N-heteroaromatic chlorides or bromides in moderate to excellent yields under mild and acid-free conditions.

The utility of N-heteroaromatic halides is well documented. They represent important intermediates in organic transformations and are of pharmaceutical interest. These halides often participate as valuable precursors for the formation of carbon–carbon bonds via cross-coupling reactions, such as Stille/Suzuki,[1] Heck[2] and Sonogashira.[3] They have been involved in nucleophilic substitutions with a wide range of nucleophiles including amines, alcohols, and thiols to generate the corresponding substituted products.[4] Some N-heteroaromatic chlorides are used as phase-transfer catalysts and are reported as starting materials for the production of various pharmaceutical products such as the antihistamine, pheniramine.[5]

N-Heteroaromatic halides can be prepared from various starting materials. The general protocols mostly stem from the conversion of N-heteroaromatic hydroxy compounds because of their commercial availability and easy transformations. $SOCl_2$, $POCl_3$, or PCl_5[6–8] are used as chlorinating agents in the synthesis of N-heteroaromatic chlorides. Similarly, N-heteroaromatic bromides can be synthesized by using $POBr_3$[9] or PBr_3.[10] However, such reagents are harmful, moisture sensitive, difficult to handle, or generate HCl, HBr, or SO_2 as by-product gases, hence they cannot be applied to acid-sensitive substrates. The utilization of combined reagents consisting of PPh_3 and various halogenating agents has received significant attention as convenient and efficient reagent systems for the preparation of various organic halides under acid-free conditions.

PPh_3 in combination with chlorinating agents: CCl_4,[11] Cl_3CCCl_3,[12] $Cl_3CCOCCl_3$,[13] Cl_3CCN,[14] or Cl_3CCONH_2[15] have been reported as efficient reagents for the conversion of alcohols into chlorides. The combination of PPh_3/Cl_3CCN has also been exploited to convert sulfonic acids into sulfonyl chlorides during the synthesis of sulfonamides.[16] PPh_3 in combination with CCl_4,[17] cyanuric chloride,[18] N-chlorosuccinimide (NCS),[19] $Cl_3CCOCCl_3$,[20] or Cl_3CCN[21] has been used for the conversion of carboxylic acids into acyl chlorides. Recently, the PPh_3/Cl_3CCONH_2 system was introduced as an alternative reagent for the transformation of carboxylic acids into their corresponding amides[22] and esters[23] via acid chlorides as reactive intermediates. Similarly, PPh_3/N-bromosuccinimide (NBS)[24] and PPh_3/Br_3CCO_2Et[25] have been documented for the conversion of carboxylic acids into acyl bromides. The latter system has also been used for the conversion of alcohols into alkyl bromides.[26] The $PPh_3/Br_3CCOCBr_3$ system has been described as a very efficient combined reagent system for the reaction of alcohols to give alkyl bromides,[26] and carboxylic acids to yield amides via acid bromides.[27]

There are only a few reports describing the preparation of N-heteroaromatic halides from N-heteroaromatic hydroxy compounds utilizing the combination of PPh_3/halogenating agents, such as an N-halosuccinimide[28] or trichloroisocyanuric acid.[29] These methods have disadvantages such as the requirement for a large amount of the reagent and low efficiencies. Alternatively,

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N-heteroaromatic bromides could be obtained with the use of P_2O_5/Bu_4NBr.[30] Due to the extensive number of PPh_3/halogenating agent systems available and there being no reports on the application of PPh_3/Cl_3CCN or PPh_3/CBr_4 to N-heteroaromatic hydroxy compounds, a new and convenient protocol for the preparation of N-heteroaromatic chlorides and bromides from N-heteroaromatic hydroxy compounds using the aforementioned systems is described herein.

To optimize the reaction conditions for the chlorination of N-heteroaromatic hydroxy compounds, several chlorinating agents (3 equiv) coupled with PPh_3 (3 equiv) were examined for the conversion of 2-hydroxypyridine into 2-chloropyridine in refluxing toluene over 4 h and the yield of product was quantified by HPLC (Table 1). In the absence of any chlorinating agent, the reaction did not proceed (entry 1). Cl_3CCN, a reagent bearing a strong electron-withdrawing group, was found to be the most reactive, affording the desired chloride in quantitative yield (entry 2).[28] Moderate yields were obtained using Cl_3CCO_2Et, Cl_3CCCl_3, and NCS (41–63%, entries 3, 4 and 7). The use of CCl_4 or Cl_3CCONH_2 gave the desired chloride in poor yields (7% and 22%, entries 5 and 6).

Next, the ratio of PPh_3 and Cl_3CCN and the reaction time were investigated in order to obtain the maximum yield of 2-chloropyridine (Table 2). Decreasing the ratio of PPh_3/Cl_3CCN from 3:3 to 3:1.5 (based on 2-hydroxypyridine) did not reveal a significant effect on the yield of the target product. The desired chlorides were obtained quantitatively in 4 and 8 h (entries 2, 3, 5, and 6), whereas a moderate yield of the chloride was obtained over 1 h (44–48%, entries 1 and 4). A moderate yield was also furnished when reacting 2-hydroxypyridine with a 2:1.5 ratio of PPh_3 and Cl_3CCN for 4 h (64%, entry 5). However, when the ratio was reduced to 3:1, the yield of the chloride was reduced significantly to 40, 60, and 92% (1, 4, and 8 h), respectively (entries 7–9).

The effect of the solvent was also investigated in order to improve the yield of the chloride. 2-Hydroxypyridine was treated with PPh_3 and Cl_3CCN in organic solvents such as CH_2Cl_2, CH_3CN, toluene, and *p*-xylene at reflux for 1 h. The chlorination of 2-hydroxypyridine in CH_2Cl_2 and CH_3CN led to the recovery of only the starting material. In refluxing toluene, a 44% yield of the chloride was achieved. 2-Hydroxypyridine could be transformed into 2-chloropyridine in quantitative yield when *p*-xylene was used. However, *p*-xylene is difficult to remove from the reaction mixture, making the reaction inconvenient to perform. After screening a number of solvents, toluene was found to meet the requirements for the chlorination of N-heteroaromatic hydroxy compounds.

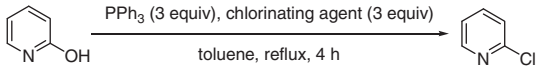
Various factors including the type of brominating agent, the ratio of PPh_3 and brominating agent, and the reaction time were next scrutinized to evaluate the conditions for the conversion of N-heteroaromatic hydroxy compounds into N-heteroaromatic bromides. 2-Hydroxypyridine was used as a model substrate and the yield of the product, 2-bromopyridine was quantified by HPLC (see Table 3).

On refluxing in toluene for 4 h, the reaction of 2-hydroxypyridine with Br_3CCO_2Et and NBS provided the desired bromides in 3% and 25% yields, respectively (entries 1 and 4).[28] CBr_4 and $Br_3CCOCBr_3$ were promising candidates in terms of new brominating agents for N-heteroaromatic hydroxy compounds, affording 2-bromopyridine in 15% and 45% yield, respectively (entries 2 and 3). Although, the use of $Br_3CCOCBr_3$ gave rise to the bromide in higher yield than CBr_4, several by-products were also obtained, whereas CBr_4 gave only the desired bromide. Thus, CBr_4 was considered the best brominating agent for further investigation.

The ratio of PPh_3 and CBr_4 and the reaction time were investigated to obtain the most appropriate conditions and the results are presented in Table 4.

When the ratio of PPh_3 and CBr_4 was increased from 1:1 to 2:1 and 2:1.5 (based on 2-hydroxypyridine), the yield of the desired bromide increased (entries 1–3). In contrast, the yield of the target bromide decreased when increasing the ratio to 3:1 and 3:1.5 (entries 4 and 5). Despite the fact that a 2:1 ratio of PPh_3 and CBr_4 provided a higher yield than a 3:1 ratio (entries 2 vs 4), from the HPLC chromatogram, it is worth noting that the amount of aryloxyphosphonium salt, generated from the combination of PPh_3 with CBr_4, significantly increased using the ratio of 3:1. Thus, a 3:1 ratio of PPh_3/CBr_4 was selected to examine the effect of reaction time on the yield of the desired bromide. Fortunately, the substrate could be converted into the desired bromide quantitatively when the refluxing time was extended from 4 to 8 h (entry 4).

Table 1
The effect of chlorinating agent on the conversion of 2-hydroxypyridine into 2-chloropyridine

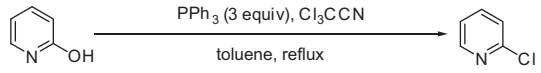


0.25 mmol, 1 equiv

Entry	Chlorinating agent	% Yield[a] 2-chloropyridine	% Recovery[a] 2-hydroxypyridine
1	None	—	100
2	Cl_3CCN	Quant.	0
3	Cl_3CCO_2Et	63	37
4	Cl_3CCCl_3	46	54
5	CCl_4	22	78
6	Cl_3CCONH_2	7	93
7	NCS	41	59

[a] The yield was determined based on HPLC analysis.

Table 2
The effect of the amount of Cl_3CCN and reaction time on the conversion of 2-hydroxypyridine into 2-chloropyridine

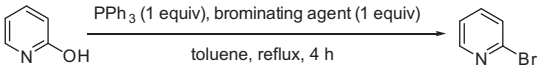


0.25 mmol, 1 equiv

Entry	Equivalents Cl_3CCN	Time (h)	% Yield[a] 2-chloropyridine	% Recovery[a] 2-hydroxypyridine
1	3	1	48	52
2	3	4	Quant.	0
3	3	8	Quant.	0
4	1.5	1	44	56
5	1.5	4	Quant. (64)[b]	0 (36)[b]
6	1.5	8	Quant.	0
7	1	1	40	60
8	1	4	60	40
9	1	8	92	8

[a] The yield was determined based on HPLC analysis.
[b] 2 equiv of PPh_3 and 1.5 equiv of Cl_3CCN were used.

Table 3
The effect of brominating agent on the conversion of 2-hydroxypyridine into 2-bromopyridine

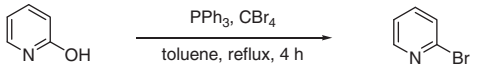


0.25 mmol, 1 equiv

Entry	Brominating agent	% Yield[a] 2-bromopyridine	% Recovery[a] 2-hydroxypyridine
1	Br_3CCO_2Et	3	97
2	CBr_4	15	85
3	$Br_3CCOCBr_3$	45	14 (41)[b]
4	NBS	25	75

[a] The yield was determined based on HPLC analysis.
[b] Unwanted by-product was obtained.

Table 4
The effect of the amount of PPh_3 and CBr_4 on the conversion of 2-hydroxypyridine into 2-bromopyridine



0.25 mmol, 1 equiv

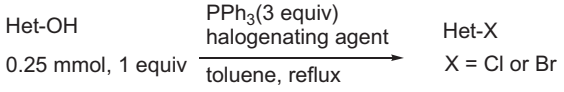
Entry	Equivalents		% Yield[a] 2-bromopyridine	% Recovery[a] 2-hydroxypyridine
	PPh_3	CBr_4		
1	1	1	15	85
2	2	1	69	31
3	2	1.5	61	39
4	3	1	30 (70)[b] (quant.)[c]	70 (30)[b] (0)[c]
5	3	1.5	30	70

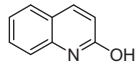
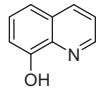
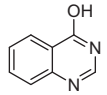
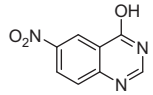
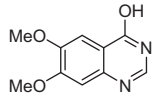
[a] The yield was determined based on HPLC analysis.
[b] Reflux for 6 h.
[c] Reflux for 8 h.

To investigate the generality and scope of this method, several N-heteroaromatic hydroxy compounds were converted into the corresponding halide using PPh_3 (3 equiv)/Cl_3CCN (1.5 equiv) and PPh_3 (3 equiv)/CBr_4 (1 equiv) (Table 5).

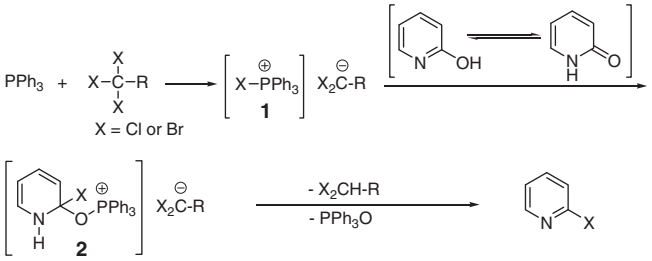
2-Hydroxypyridine and 2-hydroxyquinoline gave excellent yields of 2-halo products (90–100%, entries 1, 2, 7, and 8).[28] In the case of 4-hydroxypyridine, the desired chloride was obtained in a 94% yield, whereas none of the expected bromide was obtained (entries 5[31] and 6[32]). 3-Hydroxypyridine and 8-hydroxyquinoline gave no halo-product (entries 3[33], 4[34], 9[35] and 10[36]). The reaction also proceeded with hydroxyquinazolines, however, the conditions needed to be modified slightly. Since they contain two nitrogen atoms, quinazolines exhibit higher reactivity than hydroxypyridines and quinolines. In the case of 4-hydroxyquinazoline, the refluxing time was decreased from 1 h and then to 20 min to provide the desired chloride in a 75% and an 87% yield, respectively (entry 11).[37] The bromide was isolated in a 37% yield after 20 min (entry 12).[37] In the case of 6-nitroquinazolin-4-ol, the highest yield of the desired chloride was 61% after reaction for 2 h. In contrast to 6-nitroquinazolin-4-ol, decreasing the refluxing time to 1 h and then 20 min did not improve the yield of the desired chloride, entry 11 versus 13.[38] A low yield of the bromide was obtained when reaction times of 2 h and 30 min were employed (11–31%, entry 14).[39] In addition, 6,7-dimethoxyquinazolin-4-ol could be transformed into the desired chloride and bromide in an 84% and a 61% yield, respectively, within 1 h (entries 15[40] and 16[41]).

Table 5
The conversion of N-heteroaromatic hydroxy compounds into N-heteroaromatic halides



Entry	Het-OH	Halogenating agent[a]	% Isolated yield of Het-X
1		Cl_3CCN	99[b]
2		CBr_4	Quant.[b]
3		Cl_3CCN	—
4		CBr_4	—
5		Cl_3CCN	94
6		CBr_4	—
7		Cl_3CCN	95
8		CBr_4	90
9		Cl_3CCN	—
10		CBr_4	—
11		Cl_3CCN	42 (75)[c] (87)[d]
12		CBr_4	37[d]
13		Cl_3CCN	61[e] (52)[c] (31)[d]
14		CBr_4	11[e] (31)[f]
15		Cl_3CCN	84[c]
16		CBr_4	61[c]

[a] 1.5 equiv of Cl_3CCN, 4 h; 1 equiv of CBr_4, 8 h.
[b] The yield was determined based on HPLC analysis.
[c] Reflux for 1 h.
[d] Reflux for 20 min.
[e] Reflux for 2 h.
[f] Reflux for 30 min.



Scheme 1. Proposed mechanism.

The mechanism for the reaction of alcohols and carboxylic acids using PPh_3/chlorinating agents has been addressed.[42] The reactions of N-heteroaromatic hydroxy compounds using PPh_3/chlorinating or brominating agents are considered to operate via a similar mechanism (Scheme 1). PPh_3 reacts with the halogenating agent $X_3C–R$ to generate intermediate **1**, which then reacts with the N-heteroaromatic hydroxy compound to yield aryloxyphosphonium salt **2**. This salt decomposes to give the desired N-heteroaromatic halide and triphenylphosphine oxide. Therefore, the more reactive halogenating agent should contain the stronger electron-withdrawing group (*R*) connecting to $–CX_3$ to stabilize the negative charge presented in the intermediate **1**.

In summary, a new, simple, and convenient method for the synthesis of N-heteroaromatic chlorides using PPh_3/Cl_3CCN and N-heteroaromatic bromides using PPh_3/CBr_4 has been established.

A typical experimental procedure is as follows: to a stirred solution of a selected N-heteroaromatic hydroxy compound (0.25 mmol, 1 equiv) and PPh_3 (196.7 mg, 0.75 mmol, 3 equiv) in toluene (2.5 mL) was added Cl_3CCN (38 μL, 0.375 mmol, 1.5 equiv) or CBr_4 (82.9 mg, 0.25 mmol, 1 equiv) at reflux under an N_2 atmosphere. The mixture was stirred for the indicated time and the progress was monitored using TLC. The amounts of products in the crude mixtures were determined by HPLC on an Alltech C18 reverse-phase column (4.6 × 250 mm, 5 μm, Alltech Associates, Inc., USA) with isocratic water/MeOH (90:10) as the mobile phase, flow rate 1.0 mL/min over 20 min, injection volume 10 μL. Alternatively, they were separated by chromatography on a chromatotron eluting with hexane/EtOAc (10:1).

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39. *4-Bromo-6-nitroquinazoline* (Table 5, *entry 14*): Yellow solid; R_f = 0.30 (10% EtOAc-hexane); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.85 (1H, d, J = 8.8 Hz), 8.38 (1H, s), 8.53 (1H, dd, J = 8.8, 2.4 Hz), 8.77 (1H, d, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 122.4, 123.0, 128.9, 129.0, 145.5, 149.5, 152.5, 160.4; HRMS calcd for $C_8H_5BrN_3O_2$ $(M+H)^+$ 253.9565, found 253.9666.
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41. *4-Bromo-6,7-dimethoxyquinazoline* (Table 5, *entry 16*): White solid; R_f = 0.33 (30% EtOAc–hexane); ^{1}H NMR ($CDCl_3$) δ (ppm): 4.08 (6H, d, J = 3.6 Hz), 7.32 (1H, s), 7.36 (1H, s), 8.80 (1H, s); ^{13}C NMR ($CDCl_3$) δ (ppm): 56.5, 56.7, 105.0, 106.9, 122.1, 148.3, 151.6, 152.3, 153.4, 156.8; HRMS calcd for $C_{10}H_{10}BrN_2O_2$ $(M+H)^+$ 268.9926, found 268.9965.
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