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A facile bromination of hydroxyheteroarenes

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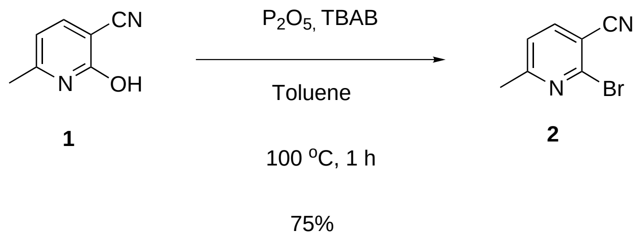
Abstract—Bromination of hydroxyheteroarenes using P_2O_5/Bu_4NBr proceeds under mild conditions to afford high yields of various bromoheteroarenes. This procedure is successfully applied to large-scale syntheses of bromoheteroarenes. © 2001 Elsevier Science Ltd. All rights reserved.

Halogenoheteroarenes are useful intermediates for the syntheses of bioactive natural products and pharmaceutical drugs. Thus, these halides undergo carbon–carbon bond formation via cross-coupling reactions, such as the Stille/Suzuki,[1] Heck,[2] Sonogashira[3] or carbon–heteroatom bond formation, via recent aromatic functionalization protocols.[4] Although a variety of syntheses starting from chloroheteroarenes has been reported in recent years,[5] bromo- and iodoheteroarenes are still widely used as common substrates. In particular, the former heteroarenes are preferably utilized due to their availability compared to the iodo compounds. In general, the bromoheteroarenes have been prepared by treatment of hydroxyheteroarenes with PBr_3[6] or $POBr_3$,[7] but those bromination procedures suffer from some drawbacks such as the handling of hazardous reagents, exact reaction-temperature control and evolution of toxic hydrogen bromide by quenching with water. Therefore, a convenient method is highly desirable for laboratory-scale as well as large-scale preparations. Herein, we wish to report a facile bromination of hydroxyheteroarenes using P_2O_5 and a quaternary ammonium bromide as a bromide-ion source.

The halogenation of hydroxyheteroarenes with POX_3 involves initial formation of dihalogenophosphate ester followed by nucleophilic displacement by halide ion along with removal of the phosphate ion. We found that P_2O_5 and Bu_4NBr play roles in the bromination for formation of the leaving moiety and the supply of bromide ion, respectively. For example, compound **1** was converted by treatment with P_2O_5 and Bu_4NBr in toluene at 100°C for 1 h into the corresponding bromide **2** in 75% yield (Scheme 1).

Several variations of this reaction are summarized in Table 1. Heteroarenes carrying an electron-withdrawing substituent such as a cyano or a carboxylic group were smoothly brominated, in which the reaction was completed within 1.5 h. In contrast, the bromination of 2-pyridone, which has no activating substituent, needed more severe conditions (entry 6). The use of Bu_4NCl instead of the bromo analogue similarly led to chlorination of pyridone (entry 7). This procedure was successfully applied to the bromination of pyrone and coumarin (entries 11 and 12) as well as various types of heteroarenes such as pyrimidine, quinoxaline and benzothiazole (entries 8–10).

2-Bromo-6-butyl-3-cyanopyridine is the key intermediate for the synthesis of an endothelin receptor antagonist;[8] therefore, this bromination method was applied to large-scale preparation (entry 2). The procedure is as follows: A mixture of 6-butyl-3-cyanopyrid-2-one (15.6 kg, 88.5 mol), P_2O_5 (30.0 kg, 211 mol) and Bu_4NBr



Scheme 1.

Keywords: bromination; hydroxyheteroarene; bromoheteroarene; phosphorus pentoxide; tetrabutylammonium bromide.

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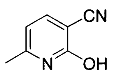
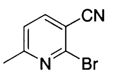
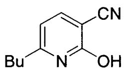
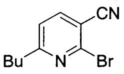
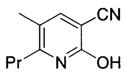
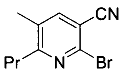
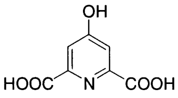
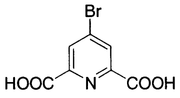
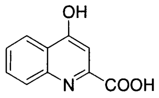
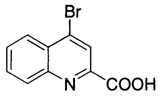
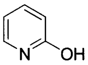
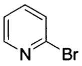
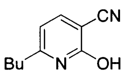
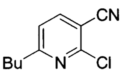
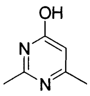
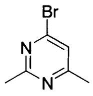
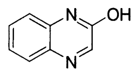
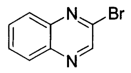
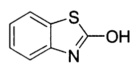
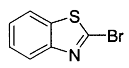
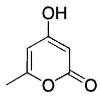
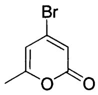
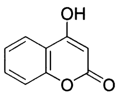
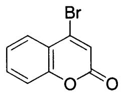
Table 1. Bromination of various hydroxyheteroarenes using P_2O_5/Bu_4NX (X = Br or Cl)

Entry	Substrate	Solvent	Temp. (°C)	Time (hr)	product	Yield (%)
1		Toluene	100	1		75
2		Toluene	100	1		82
3		Toluene	100	1		91
4		Toluene	100	1		80
5		Toluene	100	1.5		58
6		1,2-Cl_2Ph	180	10		75
7		ClPh	125	3		90
8		Toluene	100	3		68
9		Toluene	100	2.5		79
10		Toluene	100	10		95
11		Toluene	100	1		95
12		Toluene	100	1		79

(33.2 kg, 103 mol) in toluene (230 L) was heated at 94°C for 1.5 h with stirring. After cooling to room temperature, the resulting upper toluene layer was separated. The lower layer was extracted with toluene (50 L). The combined organic layers were washed with aqueous $NaHCO_3$ (110 L) and brine (50 L), dried over anhydrous $MgSO_4$ and then concentrated in vacuo to give the desired product (21.9 kg, 19.1 kg potency) in 90% yield.

This bromination method is more convenient than the existing procedures in terms of safety for large-scale application, ease in controlling the reaction and no evolution of hazardous gas.

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