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CHEMISTRY OF HETEROARYLTRIPHENYLPHOSPHONIUM IODIDES: PREPARATION FROM IODOHETEROAROMATICS AND ELIMINATION OF THE PHOSPHONIUM IODIDE GROUP USING BASIC SOLVENTS

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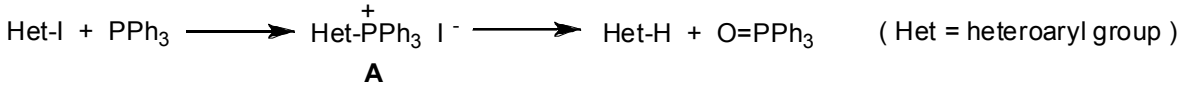
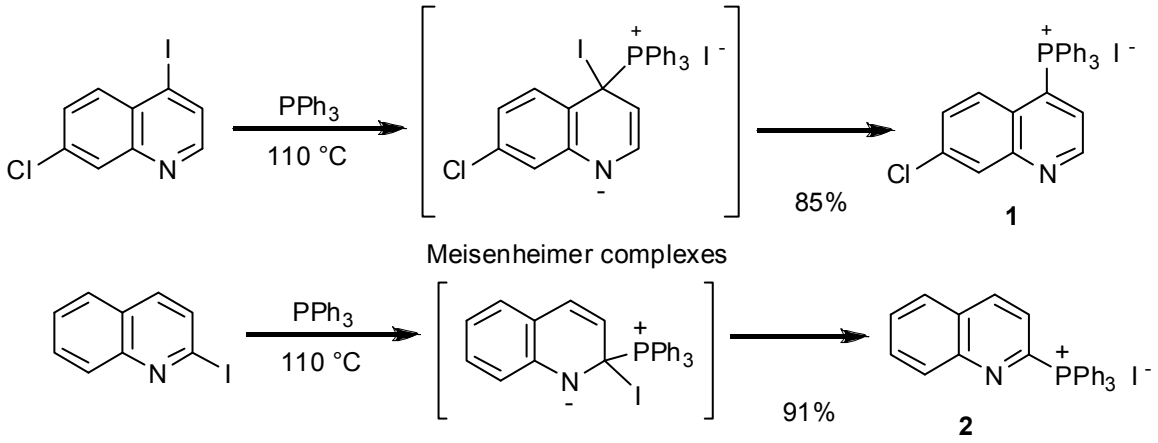
Abstract – α- and γ-Iodoheteroaromatics were found to react with triphenylphosphine to give heteroaromatictriphenylphosphonium iodides in excellent yields. β-Iodoheteroaromatics, which are less reactive with triphenylphosphine compared to α- or γ-compounds, were converted into the corresponding phosphonium iodides using palladium catalysts. Treatment of heteroaryltriphenylphosphonium iodides resulted in the elimination of the phosphonium iodide group using basic solvents such as aqueous sodium hydroxide or ethanol - triethylamine.

Since phosphorus has a strong affinity for oxygen, phosphorus compounds are widely used for the activation of oxygen-containing groups. For example, phosphorus ylides react with carbonyl compounds to give alkenes (the Wittig reaction)[1] and alcohols are converted into alkyl halides by phosphorus pentahalides,[2] phosphorus oxyhalides,[3] or triphenylphosphonium halides.[4,5] In this paper we report a novel preparation of heteroaryltriphenylphosphonium iodides (**A**), followed by elimination of the phosphonium iodide group, resulting in deiodination of the starting heteroaromatic iodides (Scheme 1).



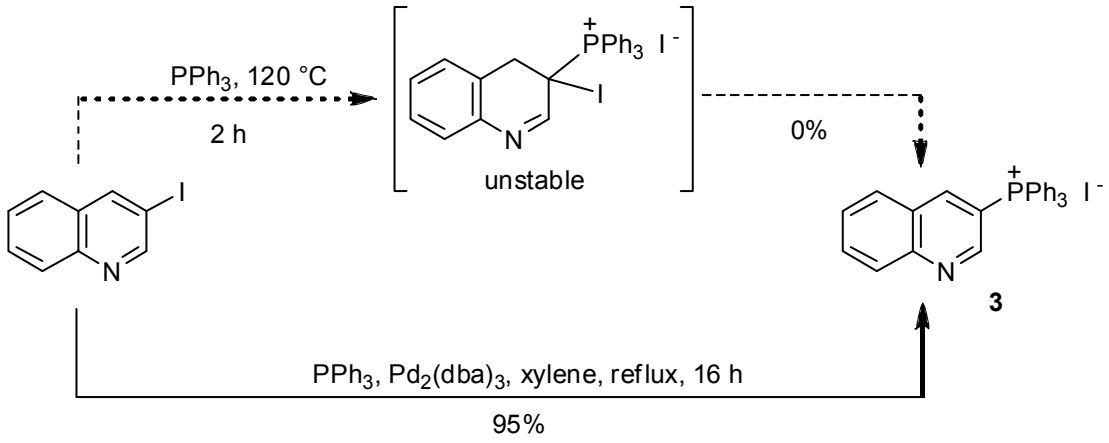
Scheme 1 Abstract of this study: Novel preparation and reaction of heteroaryltriphenylphosphonium iodides (**A**)

The preparation of quinolinyltriphenylphosphonium iodides (**1**, **2**) by reaction of iodoquinolines with triphenylphosphine (PPh_3) at 110 °C is shown in Scheme 2. It is well known that α- or γ-halogenated π-deficient nitrogen-containing heteroaromatics (abbreviated as heteroaromatics) react with nucleophiles such as amines,[6] alkoxides,[7] and mercaptans[8] to afford the corresponding nucleophile-substituted heteroaromatics by an S_NAE (Substitution Nucleophile, Addition Elimination) mechanism. The phosphonium salts, **1** and **2**, are generated by a similar reaction mechanism, *via* Meisenheimer complexes.



Scheme 2 Preparation of quinolinyltriphenylphosphonium iodides (**1**,**2**)

In contrast, β-halogenated heteroaromatics hardly react with nucleophiles because the β-position of the heteroaromatic ring is not influenced by the electron-withdrawing effect of the ring nitrogen. In fact, 3-iodoquinoline does not react at all with PPh_3 at 120 °C for 2 h. However, according to the method reported by Marcoux and Charette,[9] reaction of 3-iodoquinoline with PPh_3 in the presence of tris(dibenzylideneacetone)dipalladium gave 3-quinolinyltriphenylphosphonium iodide (**3**) in 95% yield (Scheme 3). Phosphonium salts (**1**-**3**) are stable at room temperature and are soluble in organic solvents such as dichloromethane.

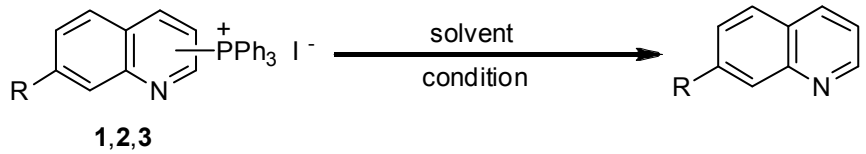


Scheme 3 Preparation of 3-quinolinyltriphenylphosphonium iodide (**3**) by palladium coupling reaction

The phosphonium salts (**1**-**3**) were next treated with several solvents (Table 1). Although a suspension of **1** in neutralized protic solvents (H_2O and EtOH) was heated to reflux, the product, 7-chloroquinoline, was not obtained (Entries 1 and 2). However, by using basic solvents such as 0.5 *N* NaOH, DMF-Et_3N, and EtOH-Et_3N, elimination of the phosphonium group proceeded to give the desired product in good yields (Entries 3-5). We have found that the use of EtOH-Et_3N as a solvent in this reaction is convenient and useful, since this solvent system requires no extraction and direct purification by silica gel column chromatography after removal of the solvent is possible. The use of **2** and **3** as substrates using EtOH-Et_3N under similar conditions gave the products in 87% and 73% yields, respectively (Entries 6

and 7). To the best of our knowledge, this type of aryl - phosphine cleavage does not exist except one report which shows tetrafluorophenyl - phosphine cleavage of (tetrafluorophenyl)triphenylphosphonium bromide by using aqueous NaOH at ambient temperature.[10]

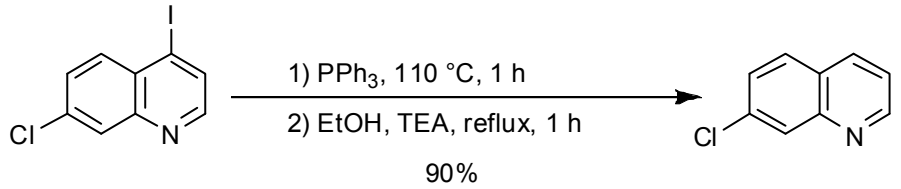
Table 1 Conversion of quinolinyltriphenylphosphonium iodides (**1**-**3**) into 7-chloroquinoline / quinoline



1,**2**,**3**

Entry	Substrate	Solvent	Condition	Yield (%)
1	**1**	H_2O	reflux, 5 h	trace
2	**1**	EtOH	reflux, 0.5 h	0
3	**1**	0.5 *N* NaOH	reflux, 1 h	82
4	**1**	DMF, Et_3N	120 °C, 1.5 h	67
5	**1**	EtOH, Et_3N	reflux, 1 h	87
6	**2**	EtOH, Et_3N	reflux, 1 h	87
7	**3**	EtOH, Et_3N	reflux, 1 h	73

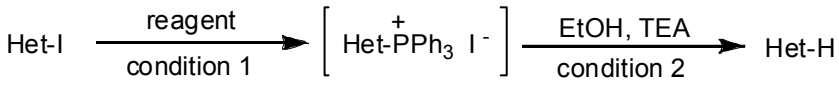
The one-pot conversion of iodoheteroaromatics into the corresponding deiodinated compounds was examined next (Scheme 4). The experiment was performed as follows: A solution of 7-chloro-4-iodoquinoline (434 mg, 1.50 mmol) and PPh_3 (393 mg, 1.50 mmol) in dichloromethane (10 mL) was heated to remove dichloromethane, and the residue was heated at 110 °C for 1 h followed by treatment with EtOH (10 mL) and Et_3N (3 mL) at reflux for 1 h. The reaction mixture was purified by silica gel column chromatography [eluted with hexane-ethyl acetate (3:1)] to give the product, 7-chloroquinoline (221 mg, 90%).

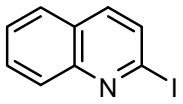
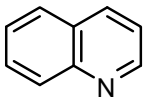
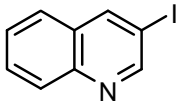
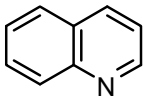
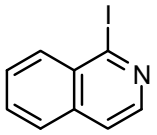
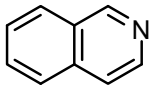
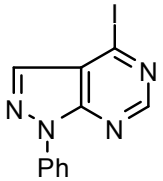
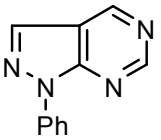
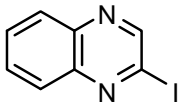
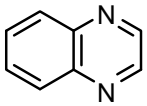
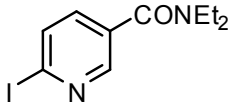
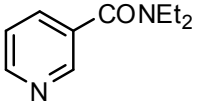
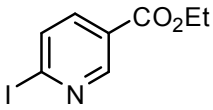
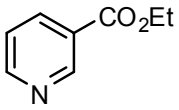
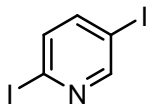
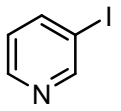
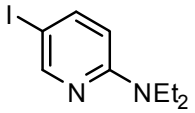
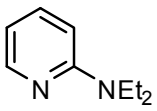


Scheme 4 The one-pot conversion of 7-chloro-4-iodoquinoline into 7-chloroquinoline

In order to clarify the generality of this deiodination, several iodoheteroaromatics were used as substrates in the one-pot reaction (Table 2). When iodoquinolines (Entries 1-3) or iododiazines (Entries 4 and 5), were used as substrates, the deiodination proceeded smoothly to afford the corresponding deiodinated heteroaromatics in excellent to good yields.

Table 2 Deiodination of iodoheteroaromatics via heteroaryltriphenylphosphonium iodides



Entry	Substrate (Het-X)	Reagent Condition 1	Condition 2	Product (Het-H)	Yield (%)
1		PPh_3, no solvent 130 °C, 1 h	reflux, 1 h		85
2		PPh_3, $Pd(PPh_3)_4$ xylene, reflux, 24 h	reflux, 1 h		76
3		PPh_3, no solvent 110 °C, 1 h	reflux, 1 h		84
4		PPh_3, no solvent 90 °C, 0.5 h	reflux, 1 h		71
5		PPh_3, no solvent 100 °C, 1 h	reflux, 1.5 h		94
6		PPh_3, no solvent 120 °C, 1 h	reflux, 1 h		88
7		PPh_3, no solvent 120 °C, 1 h	reflux, 1 h		71
8		PPh_3, no solvent 150 °C, 1 h	reflux, 1 h		32
9		PPh_3, $Pd(PPh_3)_4$ xylene, reflux, 15 h	reflux, 1 h		39

Reaction of iodopyridines gave various results: both 2,5-diiodopyridine (Entry 8) and 2-diethylamino-5-iodopyridine (Entry 9) were converted to the deiodinated product in fair yields whereas

N,*N*-diethyl 6-iodopyridine-3-caroxamide (Entry 6) and ethyl 6-iodopyridine-3-carboxylate (Entry 7) reacted to give the products in 88% and 71% yields, respectively.

Some conventional methods for the dehalogenation of haloheterocycles, e. g. using H_2 with Pd-C,[11] using In in H_2O,[12] using $PhSiH_3$ and $In(OAc)_3$,[13] or using alkyl(aryl)metals followed by addition of H_2O,[14] are already known. However, the method reported in this paper, the aryl - phosphine cleavage reaction, proceeds under mild condition such as ethanol - triethylamine, so that the reaction hardly affect functional groups of the substrate and would be one of the useful methods for the deiodination of iodoheterocycles.

In conclusion, a novel preparation of some heteroaryltriphenylphosphonium iodides and elimination of the phosphonium group using basic solvent was accomplished, resulting in deiodination of the starting heteroaromatic iodides.

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