

Indium-mediated dehalogenation of haloheteroaromatics in water

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Abstract

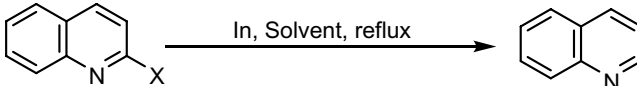
It turned out that indium metal was applicable to the dehalogenation of aromatic halides in water. This method is facile and safe compared with the conventional methods such as Pd–C, Raney Ni, or halogen–metal exchange.
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In recent years, indium derivatives have been increasingly recognized as an important reagent in organic synthesis. It is known that the reaction of aromatic halides with indium derivatives afford functionalized aromatic compounds by several methods such as a cross-coupling reaction with triorganoindium compounds,^{1–3} introduction of alkenyl^{4,5} or alkyl⁶ group by hydroindation, indium-mediated radical cyclization,⁷ palladium/indium/indium (III) chloride-mediated cross-coupling reaction,⁸ and reductive homocoupling reaction.^{9,10} This time we directed our attention to the reductive ability of indium. In this Letter, we report the novel indium-mediated dehalogenation of aromatic halides using water as a cheap and safe solvent.

At first, the reaction of 2-haloquinolines with indium using various kinds of solvents was carried out as shown in Table 1. Interestingly, deiodination proceeded to afford the deiodinated product, quinoline, in 91% yield using water as a solvent (entry 4) whereas 2-iodoquinoline was recovered quantitatively when organic solvents such as ethanol, dioxane, or toluene were used (entries 1–3). Both 2-bromoquinoline and 2-chloroquinoline reacted with indium to give quinoline in 68% and 51% yields, respectively (entries 5 and 6). It was found that the reactivity of

Table 1
Reaction of 2-haloquinolines with indium under several conditions



Entry	Solvent	X	In (equiv)	Time (h)	Yields (%)	
					Product	Recovery
1	Ethanol	I	1	2	0	95
2	Dioxane	I	1	2	0	98
3	Toluene	I	1	2	0	95
4	H ₂ O	I	1	2	91	7
5	H ₂ O	Br	1	2	68	15
6	H ₂ O	Cl	1	2	51	39
7	H ₂ O	I	1	1	57	33
8	H ₂ O	I	1	3	83	6
9	H ₂ O	I	1	5	91	3
10	H ₂ O	I	1	10	92	0
11	H ₂ O	I	2	5	92	4
12	H ₂ O	I	2	10	83	3
13	H ₂ O	I	3	10	81	6
14	H ₂ O	I	10	2	70	Trace
15	H ₂ O	I	10	48	84	0
16	aq NH ₄ Cl	I	1	2.5	64	0
17	aq NH ₄ Cl	I	1	24	84	0
18	aq NH ₄ Cl	I	10	48	8 ^a	0

^a 1,2,3,4-Tetrahydroquinoline (73%) was obtained.

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bromo and chloro compounds was inferior to that of iodo compounds.

Next, deiodination of 2-iodoquinoline under a variety of amount of indium and reaction time was carried out to optimize the condition (entries 7–18). It was clarified that the use of equimolecular amounts of indium for 2 h or above suffice for deiodination of 2-iodoquinoline. It is reported by Pitts et al.¹¹ that the reaction of quinoline with 9 equiv of indium in aq NH₄Cl and ethanol under reflux gave 1,2,3,4-tetrahydroquinoline in 52% yield. It should be noted that the reaction of 2-iodoquinoline with 10 equiv of indium in water under reflux for 48 h afforded quinoline in 84% yield (entry 15), whereas similar reaction using water as a solvent instead of aq NH₄Cl gave 1,2,3,4-tetrahydroquinoline in 73% yield (entry 18). From these results, it was found that the use of water as a solvent in the reaction is effective against the deiodination of 2-iodoquinoline.

The typical procedure is shown as follows: a mixture of indium powder (–100 mesh, 99.99%, Aldrich), 2-iodoquinoline, and water was heated under reflux for 2 h. After the reaction mixture was neutralized with 1 N NaOH, the mixture was extracted with ethyl acetate and the organic layer was dried over sodium sulfate. After ethyl acetate was removed under reduced pressure, the residue was treated with silica gel column chromatography (eluted with hexane–ethyl acetate (2:1)) to give quinoline in 91% yield. Slight yellow liquids. ¹H NMR (90 MHz, in CDCl₃): δ 7.38 (1H, dd, *J* = 8.3 Hz, 4.2 Hz, C³–H), 7.45–7.90 (3H, m, C⁵, C⁶, and C⁷–H), 8.13 (1H, d, *J* = 8.3 Hz, C⁴ and C⁸–H), 8.90 (1H, dd, *J* = 4.2 Hz, 1.4 Hz, C²–H).

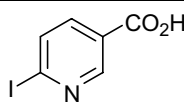
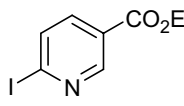
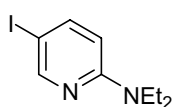
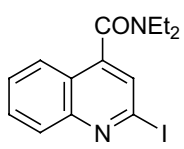
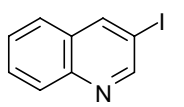
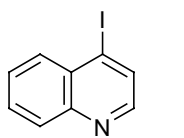
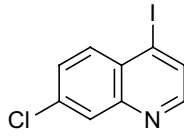
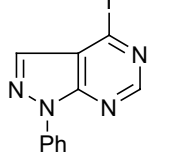
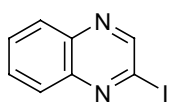
Reaction of some iodoheteroaromatics with indium in water was carried out to clarify the generality of the deiodination (Table 2). All substrates were deiodinated to afford the corresponding products in high to moderate yields. It is noteworthy that the chloro group substituted at the 7-position of quinoline ring was inert to indium (entry 7), whereas the reaction of 2-chloroquinoline with indium gave the corresponding dechlorinated product, quinoline as shown in Table 1. Some of the substrates were recovered when β-iodoheteroaromatics, 2-diethylamino-5-iodopyridine (entry 3), or 3-iodoquinoline (entry 5) was used as a substrate.

Speculated mechanisms of deiodination of iodoquinolines are shown in Scheme 1. When α- or γ-iodoquinoline is used as a substrate, the dihydroquinoline radical generates smoothly since the radical is stabilized by iodine atom. On the other hand, β-iodoquinoline reacts with indium in water more slowly than α- or γ-iodoquinoline because the dihydroquinoline radical is not stabilized by iodine atom.

Deiodination of iodobenzene using InCl₃ and Et₃SiH is the sole report⁶ for the indium-mediated dehalogenation of halobenzenes. So the In–H₂O system was applied to the deiodination of iodobenzene derivatives as shown in Table 3. When ethyl 4-iodobenzoate, 4-iodoaniline, and 3-iodoaniline were used as substrates, 24%, 19%, and 0% of the product were obtained, and 63%, 54%, and 38% of the substrates were recovered, respectively. From these results, it was found that iodobenzenes are less reactive to indium

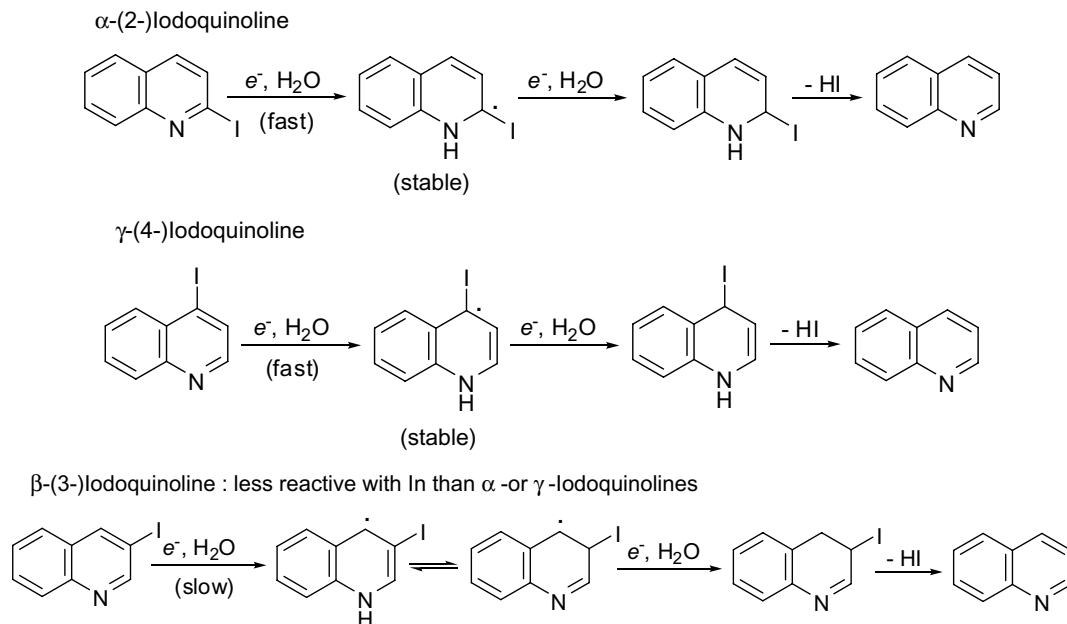
Table 2

Deiodination of haloheteroaromatics using indium metal in water

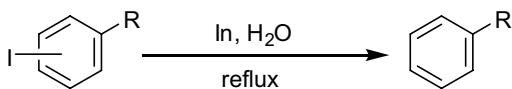
Entry	Substrate (Het-I)	Time (h)	Yields (%)	
			Product (Het-H)	Recovery
	$\text{Het-I} \xrightarrow[\text{reflux}]{\text{In (1 eq), H}_2\text{O}} \text{Het-H}$			
1		5	57	0
2		10	64	0
3		10	49	20
4		2	91	0
5		8	52	36
6		5	69	0
7		15	59	0
8		2	30	9
9		5.5	44	0

compared with iodoheteroaromatics such as 2-iodoquinoline.

In conclusion, deiodination of iodoheteroaromatics using indium in water was accomplished. Removal of halogen from an aromatic ring is an important technique in organic synthesis. Several methods are known and widely used, however, some of these methods are troublesome to execute. For example, a metal catalyst, Pd–C^{12,13} or Raney Ni¹⁴ ignites easily. Halogen–metal exchange reaction^{15,16} requires a dehydrated condition and low reaction tempera-



Scheme 1. Speculated mechanisms of dehalogenation of haloquinolines using indium in water.

Table 3
Deiodination of iodobenzene derivatives

Entry	R	In (equiv)	Time (h)	Yields (%)	
				Product	Recovery
1	4-CO ₂ Et	3	24	24	63
2	4-NH ₂	1	6	19	54
3	3-NH ₂	2	8	0	38

ture. Thus, the development of a facile method for the dehalogenation of heteroaromatic halide is of great value.

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