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THE SELECTIVE DEIODINATION OF IODOHETEROCYCLES USING THE $PhSiH_3$ – $In(OAc)_3$ SYSTEM

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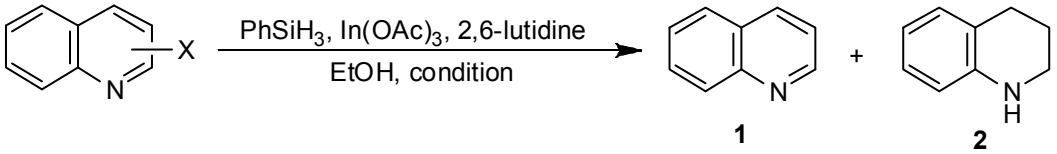
Abstract – Nitrogen-containing π-deficient heterocyclic iodides such as iodoquinolines or iodopyridines were deiodinated by treatment with phenylsilane catalyzed by indium acetate to give the corresponding deiodinated heterocycles at ambient temperature.

Halogen groups on heterocyclic rings are among the most useful and versatile functional groups in organic synthesis. Heterocyclic halides react with organometallics, such as alkyllithiums,[1] alkylmagnesium halides,[2] lithium naphthalenide,[3] and active magnesium[4] to give the corresponding metalated heterocycles. Subsequent addition of electrophiles introduces an electrophilic substituent into the heterocyclic ring. π-Deficient nitrogen-containing heterocyclic iodides, in which the iodo group is at the α- or γ- position relative to the ring nitrogen, react with nucleophiles to give addition-elimination substitution (S_NAE) products.[5] On the other hand, removal of the halogen group is often required. Commonly, the dehalogenation of aromatic halides is carried out by palladium-catalyzed hydrogenations[6] or halogen-metal exchange reactions.[7] However, the reagents used in these reactions, e.g., H_2 gas, Pd-C, or alkyllithiums, require careful handling. Recently we have developed a facile deiodination of nitrogen-containing π-deficient heterocyclic iododes using indium metal in aqueous media.[8] In this paper we report the facile deiodination of nitrogen-containing π-deficient heterocyclic iodides in organic

solvents using phenylsilane ($PhSiH_3$) in the presence of indium acetate [$In(OAc)_3$] according to the method reported by Hosomi, *et al*.[9]

First, the dehalogenation of haloquinolines using $PhSiH_3$ in the presence of $In(OAc)_3$ and 2,6-lutidine was carried out according to the method reported by Hosomi, *et al.* (Table 1). 3-Iodoquinoline was used as the substrate in order to determine the optimized reaction conditions (Entries 1-3). When the reaction time was extended to 120 h, the desired deiodinated product **1** and 1,2,3,4-tetrahydroquinoline (**2**) were obtained in 88% and 8% yields, respectively. The yield of **2** was improved when the amount of $PhSiH_3$ was increased to 3.0 eq (Entry 4). The results of entries 5-7 shows that $In(OAc)_3$ and 2,6-lutidine are indispensable for this deiodinating system. The debromination of 3-bromoquinoline failed even when the reaction was carried out under reflux for 22 h (Entry 8). Both 4-iodoquinoline and 2-iodoquinoline were deiodinated to give **1** in high yield with some of **2** (Entries 9 and 10).

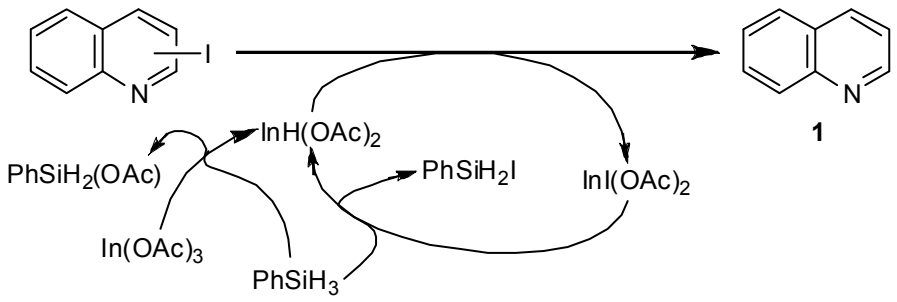
Table 1 Indium-catalyzed dehalogenation of haloquinolines



1 **2**

Entry	X	Reagents (eq)	Condition	Yields (%)		
		$PhSiH_3$ / $In(OAc)_3$ / 2,6-lutidine		**1**	**2**	Recovery
1	3-I	1.3 / 0.2 / 0.5	rt, 8 h	53	0	31
2	3-I	1.2 / 0.2 / 0.6	rt, 25 h	79	0	13
3	3-I	1.2 / 0.2 / 0.5	rt, 120 h	88	8	0
4	3-I	3.0 / 0.2 / 0.6	rt, 48 h	29	48	0
5	3-I	1.3 / 0.2 / 0	rt, 62 h	23	44	11
6	3-I	3.0 / 0 / 0.5	rt, 162 h	0	0	98
7	3-I	3.0 / 0 / 0	rt, 47 h	0	0	88
8	3-Br	1.2 / 0.2 / 0.5	reflux, 22 h	0	0	96
9	4-I	1.3 / 0.2 / 0.5	rt, 23 h	85	9	0
10	2-I	1.2 / 0.2 / 0.6	rt, 19 h	84	16	0

Scheme 1 shows the speculated mechanism for the deiodination of iodoquinolines using $PhSiH_3$ / $In(OAc)_3$ system. In this mechanism, $In(OAc)_3$ plays as a deiodinating catalyst whereas indium metal which is used by deiodination of haloheterocycles, requires an stoichiometric amount.[8,10]

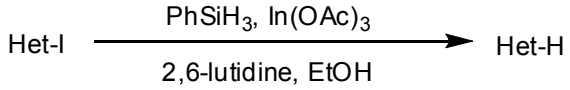


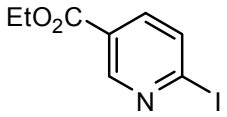
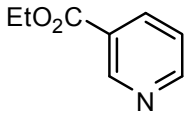
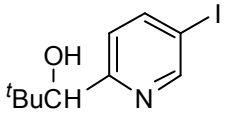
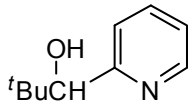
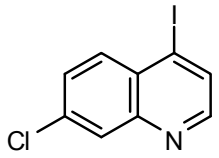
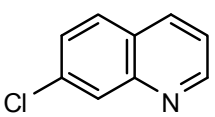
Scheme 1 Speculated mechanism for conversion of iodoquinolines into **1**

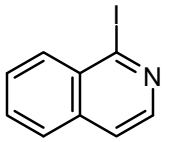
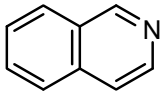
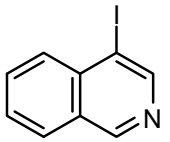
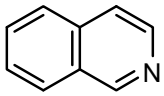
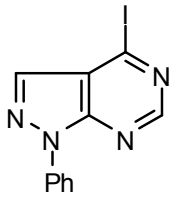
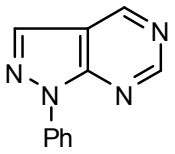
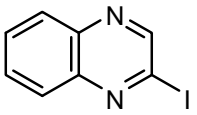
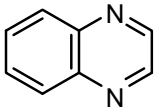
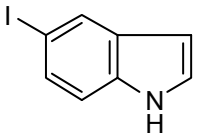
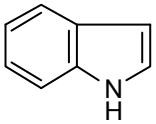
Next, the deiodination of several iodoheterocycles was carried out in order to clarify the generality of the deiodination as shown in Table 2. Iodopyridines (Entries 1,2), iodoquinolines (Entries 3,4), iodoisoquinolines (Entries 5,6), and 4-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidines (Entry 7) were deiodinated using $PhSiH_3$ (1.0 – 1.3 eq), $In(OAc)_3$ (0.2 eq), and 2,6-lutidine (0.5 – 0.7 eq) in EtOH to give the corresponding deiodinated heterocycles in good to moderate yields. On the other hand, deiodination of 2-iodoquinoxaline (Entry 8) and 5-iodoindole (Entry 9) did not proceed.

In conclusion, we have accomplished the selective deiodination of heterocycles. Since the reagents used in this method are safe to handle, this provides a useful synthetic method for many chemists.

Table 2 Deiodination of iodoheterocycles using $PhSiH_3$ in the presence of $In(OAc)_3$ and 2,6-lutidine



Entry	Substrate (Het-I)	$PhSiH_3$ / $In(OAc)_3$ / 2,6-lutidine (eq) Condition	Product (Het-H)	Yield (%)
1		1.2 / 0.2 / 0.5 rt, 18 h		75
2		1.3 / 0.2 / 0.5 rt, 22 h		51
3		1.0 / 0.2 / 0.5 rt, 16 h		64 (23)[1)]
4		1.2 / 0.2 / 0.5 rt, 48 h		69 (19)[2)]

5		1.2 / 0.2 / 0.5 rt, 16 h		40
6		1.2 / 0.2 / 0.5 rt, 89 h		41
7		1.2 / 0.2 / 0.7 rt, 23 h		48
8		1.2 / 0.2 / 0.5 rt, 64.5 h		0 (87)[1)]
9		1.2 / 0.2 / 0.5 rt, 66 h		0 (97)[1)]

1) Substrate was recovered.; 2) 7-Chloro-1,2,3,4-tetrahydroquinoline was obtained.

EXPERIMENTAL

Melting points were not corrected. ^{1}H-NMR spectra were measured with a Hitachi R-90H spectrometer (90 MHz) using tetramethylsilane as an internal standard.

General procedure for dehalogenation of haloheterocycles using $PhSiH_3$ in the presence of $In(OAc)_3$ and 2,6-lutidine: A mixture of haloheterocycles (1.00 mmol), 2,6-lutidine (0.50 mmol), EtOH (3 mL), $PhSiH_3$ (1.20 mmol), and $In(OAc)_3$ (0.20 mmol) was stirred under the appropriate conditions. EtOH was removed under reduced pressure and the residue was purified by silica gel column chromatography to give the corresponding dehalogenated heterocycles.

Quinoline: Pale yellow liquids. Purified with silica gel column chromatography [eluted with hexane - EtOAc (2:1)]. ^{1}H-NMR ($CDCl_3$): δ 7.38 (1H, dd, J = 8.4 Hz, 4.1 Hz, C^3-H), 7.48-7.95 (3H, m,

C^5,C^6,C^7-H), 7.95-8.37 (2H, m, C^4,C^8-H), 8.91 (1H, dd, *J* = 4.1 Hz, 1.5 Hz, C^2-H).

1,2,3,4-Tetrahydroquinoline: Slightly yellow liquids. Purified with silica gel column chromatography [eluted with hexane - EtOAc (15:1)]. ^{1}H-NMR ($CDCl_3$): δ 1.72-2.11 (2H, m, C^3-H), 2.75 (2H, t, *J* = 6.4 Hz, C^4-H), 3.03 (1H, br s, N^1-H), 3.28 (2H, t, *J* = 5.5 Hz, C^2-H), 6.28-6.70 (2H, m, C^6,C^8-H), 6.76-7.07 (2H, m, C^5,C^7-H).

Ethyl nicotinate: Slightly yellow liquids. Purified with silica gel column chromatography [eluted with hexane - EtOAc (2:1)]. ^{1}H-NMR ($CDCl_3$): δ 1.41 (3H, t, *J* = 7.1 Hz, CH_3), 4.42 (2H, q, *J* = 7.1 Hz, CH_2), 7.37 (1H, dd, *J* = 8.0 Hz, 4.9 Hz, C^5-H), 8.29 (1H, dt, *J* = 8.0 Hz, 1.7 Hz, C^4-H), 8.76 (1H, dd, *J* = 4.9 Hz, 1.7 Hz, C^6-H), 9.22 (1H, d, *J* = 1.7 Hz, C^2-H).

2,2-Dimethyl-1-(2-pyridinyl)-1-propanol: White solids. Mp 53.7-58.2 °C (lit.,[8] 53-57 °C). ^{1}H-NMR ($CDCl_3$): δ 0.92 (9H, s, ^{t}Bu), 4.32 (2H, br s, CHOH), 6.98-7.37 (2H, m, C^3,C^5-H), 7.62 (1H, td, *J* = 7.6 Hz, 1.7 Hz, C^4-H), 8.53 (1H, d, *J* = 4.0 Hz, C^6-H).

7-Chloroquinoline: Slightly yellow liquids. Purified with silica gel column chromatography [eluted with hexane - EtOAc (7:1)]. ^{1}H-NMR ($CDCl_3$): δ 7.24-7.62 (2H, m, C^3,C^6-H), 7.76 (1H, d, *J* = 8.7 Hz, C^5-H), 7.97-8.28 (2H, m, C^4,C^8-H), 8.91 (1H, dd, *J* = 4.1 Hz, 1.5 Hz, C^2-H).

7-Chloro-1,2,3,4-tetrahydroquinoline: Yellow solids. Purified with silica gel column chromatography [eluted with hexane - EtOAc (7:1)]. Mp 58-60.5 °C (lit.,[11] 63-63.5 °C). ^{1}H-NMR ($CDCl_3$): δ 1.62-2.09 (2H, m, C^3-H), 2.70 (2H, t, *J* = 6.4 Hz, C^4-H), 3.28 (2H, t, *J* = 5.5 Hz, C^2 -H), 6.42 (1H, d, *J* = 1.9 Hz, C^8-H), 6.52 (1H, dd, *J* = 7.9 Hz, 1.9 Hz, C^6-H), 6.82 (1H, d, *J* = 7.9 Hz, C^5-H).

Isoquinoline: Slightly yellow liquids. Purified with silica gel column chromatography [eluted with hexane - EtOAc (4:1)]. ^{1}H-NMR ($CDCl_3$): δ 7.40-8.08 (5H, m, C^4,C^5,C^6,C^7,C^8-H), 8.51 (1H, d, *J* = 5.7 Hz, C^3-H), 9.24 (1H, s, C^1-H).

1-Phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine: White solids. Purified with silica gel column chromatography [eluted with hexane - EtOAc (2:1)]. Mp 82.2 °C (lit.,[12] 79-81 °C). ^{1}H-NMR ($CDCl_3$): δ 7.23-7.71 (3H, m, phenyl-H), 8.23 (2H, d, *J* = 8.2 Hz, phenyl-H), 8.31 (1H, *s*, C^3-H), 9.12 (1H, s, C^6-H), 9.26 (1H, s, C^4-H).

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