JOC *Note*

Indium-Mediated Reductive Elimination of Halohydrins

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Abstract: Olefin formation has been successfully carried out by reductive elimination reactions of halohydrins with $Pd(PPh_3)_4/In/InCl_3$ in aqueous media.

The carbon−carbon double bond is a basic structural unit in organic chemistry, particularly in complex natural products with interesting biological activities, and numerous reports have been published on the syntheses and chemical reactivities of alkenes.[1] Among many reported methods, the 1,2-elimination reaction is one of the most effective for forming alkenes.[2] Halohydrins are good alkene precursors for the reductive 1,2-elimination because they can be prepared by diverse methods.[3] A number of reductive elimination reactions of halohydrin compounds proceed under various metal-mediated conditions.[4] However, these reactions are limited by their poor stereoselectivities, acidic conditions, or application of heat. Therefore, an investigation of the mild and stereoselective methodology for carbon−carbon double bond formation should be valuable.

Indium-mediated organic reactions in aqueous media have become one of the most challenging areas in organic synthesis due to the environmental benefits and favorable effects of indium metal on chemical transformations.[5] Among many indium-mediated organic reactions, the allylation reaction of carbonyl compounds with allylic halides to afford the homoallylic alcohols is probably the most widely used one in organic synthesis.[6]

SCHEME 1. Indium-Mediated Reductive Elimination of Halohydrin Compounds

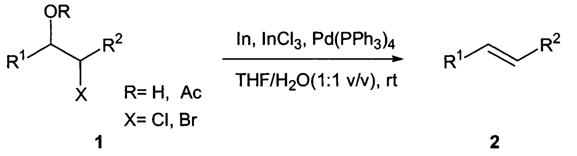
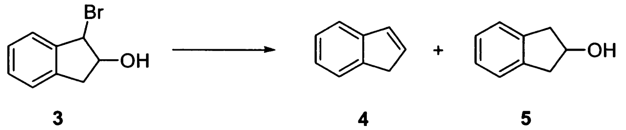


TABLE 1. Reaction of 1-Bromo-2-indanol under Various Conditions[a]



entry	solvent	reagent	yield of product **4**[b] (%)	yield of debrominated compd **5**[b] (%)
1	THF/H_2O	$Pd(PPh_3)_4/In/InCl_3$	65	0
2	THF/H_2O	$Pd(PPh_3)_4/In$		28
3	THF/H_2O	$Pd(PPh_3)_4/InCl_3$	NR[d]	
4	THF/H_2O	$Pd(PPh_3)_4/InI$		43
5	$MeOH/H_2O$	$Pd(PPh_3)_4/In/InCl_3$		25
6	DMF/H_2O	$Pd(PPh_3)_4/In/InCl_3$		23
7[c]	THF/H_2O	$Pd(PPh_3)_4/Zn/InCl_3$		18
8[c]	THF/H_2O	$Pd(PPh_3)_4/Sn/InCl_3$	NR[d]	

[a] Reactions were carried out on a 0.5 mmol scale at rt; halohydrin:$Pd(PPh_3)_4$:metal:$InCl_3$ = 1:0.02:2:0.5. [b] GC yield. [c] 50 °C. [d] No reaction.

In the course of our extensive studies on utilizing indium metal, we reported carbon−carbon bond formation reactions[7] and reductive dehalogenation reactions.[8] To further explore the potentials of indium metal, we studied the roles of indium metal on the reductive 1,2-elimination. The use of indium metal in reductive elimination reactions has not been studied as widely as other transformations. Herein we report that halohydrin compounds undergo reductive elimination to produce the corresponding olefins when treated with indium metal in the presence of $Pd(PPh_3)_4$ catalyst and $InCl_3$ in aqueous media (Scheme 1).

Thus, halohydrins were reacted with indium powder (200 mol %) and $InCl_3$ (50 mol %) in the presence of tetrakis(triphenylphospine)palladium(0) (2 mol %) in a mixture of THF and H_2O (1:1, v/v) at ambient tempera-

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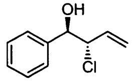
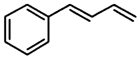
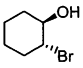
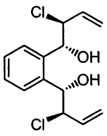
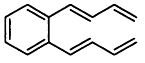
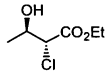
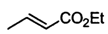
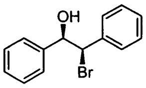
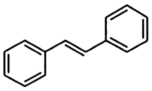
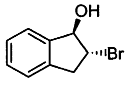
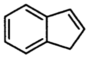
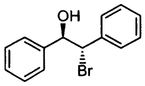
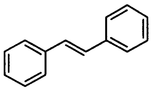
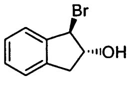
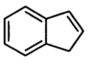
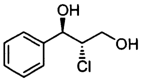
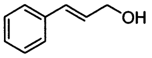
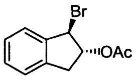
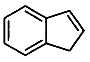
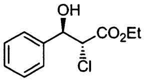
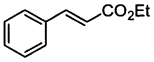
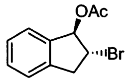
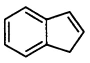
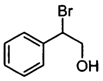
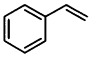
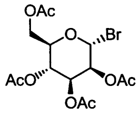
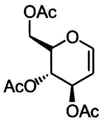
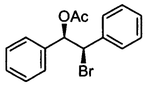
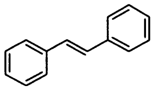
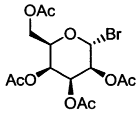
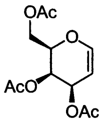
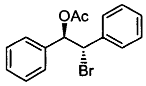
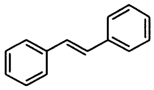
TABLE 2. Reductive Elimination of Various Halohydrins[a]

Entry	Halohydrin **1**	Time (hr)	Product **2**	Yield (%)	Entry	Halohydrin **1**	Time (hr)	Product **2**	Yield (%)
1		8		76	10		6		47[b]
2		8		80	11		8		55[b]
3		9		73	12		19		10
4		8		75	13		9		65
5		13		34	14		8		78
6		8		75	15		8		53
7		4		55[b]	16		8		98
8		10		82	17		8		60
9		10		86					

[a] All reactions were carried out on a 0.5 mmol scale at rt; halohydrin:Pd$(PPh_3)_4$:In:$InCl_3$ = 1:0.02:2:0.5. [b] GC yield.

ture for 8−12 h. After the addition of 1 N HCl to the reaction mixture, the desired olefins were obtained in good to moderate yields. To elucidate the optimized reaction conditions, we first used a model substrate, 1-bromo-2-indanol (**3**),[9] under various systems. As shown in Table 1, only the reaction conditions of entry 1 afforded desired indene product **4**. With the absence of either In or $InCl_3$ from the system of Pd$(PPh_3)_4$/In/$InCl_3$, the reaction did not occur (entry 3) or gave a debrominated compound, **5** (entries 2 and 4). Employing other solvent systems besides THF/H_2O also led to poor results (entries 5 and 6). When other metals, such as Zn and Sn instead of In, were used, the reaction did not proceed (entry 8) or gave a debrominated compound, **5** (entry 7), even at 50 °C for 10 h.

The results of indium-mediated reductive elimination of various halohydrins are summarized in Table 2. The requisite halohydrin derivative starting materials were easily prepared from the commercially available alkenes following known procedures.[3] Some halohydrins were then acylated to give good yields of the corresponding O-acetylated starting materials. As shown in Table 2, the Pd$(PPh_3)_4$/In/$InCl_3$ system was effective for the reductive elimination of various halohydrin compounds in aqueous media. The reactions proceeded smoothly under mild conditions, and simple workup of the reaction mixture

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[9] Kotsuki, H.; Shimanouchi, T. *Tetrahedron Lett.* **1996**, *37*, 11, 1845.

allowed generation of the corresponding product olefins in good yields. Generally, with a few exceptions, the yields of the desired products **2** were not much affected by the nature of the halohydrins such as chlorohydrin, bromohydrin, and *O*-acetyl halohydrin. Under the same conditions of the $Pd(PPh_3)_4/In/InCl_3$ system, the reductive elimination reaction of cyclic halohydrins of entries 12−15 gave the (*Z*)-olefins and the reaction of the acyclic *syn*- and *anti*-halohydrins afforded the corresponding (*E*)-olefins exclusively. The stereochemistry of the product olefins was determined by comparison of the ^{1}H NMR spectrum and GC−MS spectrum of the authentic olefins, and only a single stereoisomer was shown. The reductive elimination also proceeded for unactivated halides (entries 5, 10, 12, and 15).

During the course of this study to further explore the scope of this reaction, we have found that peracetylated glycosyl bromides undergo indium-mediated reductive elimination to form the corresponding glycals in neutral aqueous media (entries 16 and 17). Because of the importance of glycals as the key building blocks in carbohydrate chemistry and the synthesis of optically active natural products,[10] the development of new and improved methods for their preparation would be of great value. Along with some reported procedures,[11] the reaction system described here represents one of the most efficient and convenient procedures for the synthesis of peracetylated glycal derivatives.

In conclusion, we have developed a versatile, effective, and convenient reductive elimination procedure for converting various halohydrin compounds to the corresponding olefins using palladium catalyst, indium metal, and indium trichloride salts in neutral aqueous media in good yields. The present method also offers a simple and efficient alternative to other known procedures for the preparation of glycals.

Experimental Section

General Methods. All reagents were obtained from commercial sources and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts are given in δ units relative to the tetramethylsilane (TMS) signal as an internal reference in $CDCl_3$. Coupling constants (J) are reported in hertz. Electron-impact (EI) mass spectra were recorded in the form of m/z (intensity relative to base 100) on a GC−MSD system. High-resolution mass spectral analyses were carried out at the Korea Basic Science Institute, Taejon, or Korea Basic Science Institute, Seoul, Korea. For thin-layer chromatography (TLC), precoated plates (silica gel, 0.25 mm) were used. Silica gel (230−400 mesh) was used for column chromatography.

General Procedure for the Synthesis of Halohydrins. The halohydrin in entry 1 of Table 2 was prepared by indium-mediated allylation of benzaldehyde with 1,3-dichloropropene.[3f] That in entry 2 was prepared by indium-mediated allylation of phthalic dicarboxaldehyde with chloro-3-iodopropene. Those in entries 5 and 6 were prepared from the epoxidation of the corresponding alkenes with *m*-CPBA followed by halogenation with a 1.0 M HCl solution in Et_2O.[3g] Those in entries 3, 4, 7, and 12 were prepared from the reaction of the corresponding alkenes with *N*-bromosuccinimide in H_2O.[3h] That in entry 11 was prepared from the epoxidation of ethyl *trans*-crotonate with *tert*-butyl hydroperoxide followed by halogenation with a 1.0 M HCl solution in Et_2O.[3i] That in entry 13 was prepared from the epoxidation of indene with *m*-CPBA followed by treatment with 300 mol % lithium bromides.[9] Those in entries 8, 9, 14, and 15 were prepared from the acetylation of the corresponding halohydrins using Ac_2O, pyridine, and DMAP in CH_2Cl_2.

General Procedure for the Indium-Mediated Elimination of Halohydrins. The following procedure is representative. A mixture of chlorohydrin **1** (Table 2, entry 2) (580.0 mg, 2.87 mmol), indium (329.5 mg, 2.87 mmol), indium(III) chloride (159.7 mg, 0.72 mmol), and $Pd(PPh_3)_4$ (83.7 mg, 2 mol %) in THF/H_2O (1:1; 1 mL) was stirred at rt for 8 h. The reaction was quenched with 1 N HCl (1 mL) and EtOAc (1 mL), and the whole mixture was filtered through Celite. After general workup, purification by flash chromatography on silica gel using an *n*-hexane/EtOAc (6:1) mixture as an eluent afforded the product olefin **2** (18.6 mg, 0.14 mmol) in 80% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.42 (m, 2H), 7.23−7.16 (m, 2H), 6.86 (d, 2H, $J = 15.1$ Hz), 6.69−6.47 (m, 4H), 5.35−5.30 (d, 2H, $J = 15.3$), 5.20−5.16 (d, 2H, $J = 8.9$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 135.9, 132.4, 132.2, 131.5, 128.1, 126.9, 126.7, 126.0, 125.9, 118.3; MS (EI) m/z (rel intensity) 182 (M^+, 3), 167 (32), 140 (41), 111 (41), 71 (100), 57 (84); HRMS (EI) m/z 182.1069 (calcd for $C_{14}H_{14}$ 182.1096).

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Supporting Information Available: Text describing experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) Shull, B. K.; Wu, Z.; Koreeda, M. *J. Carbohydr. Chem.* **1996**, *15*, 955. (b) Kovacs, G.; Toth, K.; Dinya, Z.; Somsak, L.; Micskei, K. *Tetrahedron* **1999**, *55*, 5253. (c) Cavallaro, C. L.; Schwartz, J. *J. Org. Chem.* **1995**, *60*, 7055.