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Indium tribromide-catalyzed deacetoxylation of propargylic acetate with triethylsilane

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Abstract—Indium(III) bromide catalyzed the deacetoxylation of propargylic acetates with Et_3SiH to produce the corresponding internal alkynes containing a variety of functional groups in good yields.

Indium(III) halide has attracted considerable attention in synthetic organic chemistry due to its low toxicity in the laboratory, high stability under aqueous conditions, and strong tolerance to oxygen- and nitrogen containing functional groups.[1] As a result, many groups have utilized indium halide and indium metal to develop synthetic methodologies including high regio- and chemo selectivity and to synthesize key compounds and material sources in material and medicinal chemistry.[2] On the other hand, during our continuing research on the indium halide-promoted substitution of functional groups on propargylic alcohols and acetates,[3] one of us found that the use of triethylsilane as a nucleophile in a reaction involving propargylic acetate in the presence of quite a small amount of $InBr_3$ leads to the smooth production of an internal alkyne. Thus, we became interested in developing a method for a highly efficient reduction of propargylic acetate, prepared from propargylic alcohol and acetic anhydride in the presence of a catalytic amount of $InBr_3$, by an indium halide–hydrosilane catalytic system leading to an internal alkyne. In this context, Baba and co-workers reported that a combination of $InCl_3$ and diphenylchlorosilane effectively reduced secondary and tertiary alcohol derivatives to form alkane derivatives,[4] and Gevorgyan and Yamamoto et al. found that $B(C_6F_5)_3$–Et_3SiH catalyzed the reduction of alcohols including a primary alcohol.[5] In addition, Hatakeyama and co-workers reported that TFA–Et_3SiH promoted the removal of benzylic acetoxy groups under cryophilic conditions.[6] We report herein on a highly simple method for the deacetoxylation of secondary propargylic acetates by Et_3SiH in the presence of a catalytic amount of $InBr_3$ under mild conditions, to give internal alkynes containing a variety of functional groups.

Initially, we investigated the reduction of propargylic acetate **1a**, which was prepared from 1,3-diphenyl-1-hydroxy-2-propyne and acetic anhydride in the presence of $InBr_3$ (0.1 equiv),[7] with $InBr_3$ and triethylsilane as a model reaction.[8] Table 1 shows the results of a search for optimized conditions. Consequently, we found that dichloromethane was the best solvent for this reaction. When the reaction was conducted in ether and tetrahydrofuran, the reaction did not proceed (entries 3 and 4), and the use of toluene and acetonitrile also resulted in decreased yields (entries 5 and 6). On the other hand, increasing the amount of triethylsilane shortened the reaction time to 10 min, and dramatically improved the yield of **2a** up to 67% (entries 7 and 8). Moreover, when 0.05 equiv of indium salt per mole of propargylic acetate was used, the yield of the internal alkyne further increased up to 80% (entry 9). Needless to say, in the absence of indium salt, no reduction occurred (entry 10), and running this reaction with $InCl_3$ gave the product in slightly lower yield than a reaction with $InBr_3$ (entry 11). A combination of $InBr_3$ and reducing reagents, such as DIBAL, $LiAlH_4$, and $NaBH_4$ were not effective for this reaction. Consequently, it was found that the combination of 0.05 equiv of indium

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Keywords: Indium bromide; Propargylic acetate; Silane; Internal alkyne; Deacetoxylation.

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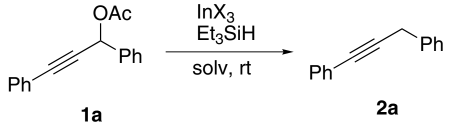
Table 1. Examination of the reduction of propargylic acetate



Run	InX_3 (equiv)	Et_3SiH (equiv)	Solvent	Time (h)	Yield (%)[a]
1	$InBr_3$ (0.1)	1.1	CH_2Cl_2	<0.2	47
2	$InBr_3$ (0.1)	1.1	CH_3Cl	1	46
3	$InBr_3$ (0.1)	1.1	Et_2O	10	NR
4	$InBr_3$ (0.1)	1.1	THF	10	NR
5	$InBr_3$ (0.1)	1.1	PhMe	10	28
6	$InBr_3$ (0.1)	1.1	MeCN	10	22
7	$InBr_3$ (0.1)	1.5	CH_2Cl_2	<0.2	48
8	$InBr_3$ (0.1)	2	CH_2Cl_2	<0.2	67
9	$InBr_3$ (0.05)	2	CH_2Cl_2	<0.3	80
10	None	1.1	CH_2Cl_2	10	NR
11	$InCl_3$ (0.05)	2	CH_2Cl_2	3	58

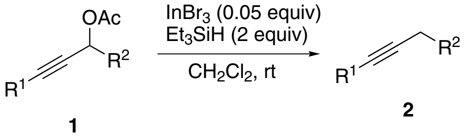
[a] Isolated yields.

bromide and 2 equiv of triethylsilane showed the best result for the reaction.

To extend generality of this reaction, the reduction of various propargylic acetates was then carried out under optimized conditions, in which the reactions were typically run at room temperature in a CH_2Cl_2 solution, the results of which are displayed in Table 2. Reduction of an acetate having two benzene rings was complete in a short time, producing the corresponding internal alkynes in good yields (runs 1–5). A longer reaction time was required for the reaction of an acetate having an electron-withdrawing group on the R^2 group to reach completion (runs 4, 5, and 8). A propargylic acetate having an alkyl group, such as a hexyl group and a *tert*-butyl group next to the triple bond also underwent the desired reaction to produce the corresponding products in good to excellent yields (runs 6–10). In addition, when the reaction of a compound containing a silyl group was carried out, the corresponding products were produced in moderate to good yields along with the starting materials (runs 11–13). Moreover, we found that this system selectively reduces only the acetoxy moiety without dehalogenation and reduction of the nitro group.[9,10] On the other hand, in case of 3-acetoxy-1-(4-methoxyphenyl)-1-butyne ($R^1 = 4\text{-MeO–}C_6H_4$, $R_2 = Me$), the yield of the desired reductive product was rather low (<2%).

Although, there is no clear explanation for the reaction path at present, we assume that an indium radical species, such as $Br_2In^{\bullet}$ mediates this reaction process. Actually, when 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO), a radical trapping agent, was added to the

Table 2. Reduction of various propargylic acetates by $InBr_3$–Et_3SiH leading to internal alkynes[a]



Run	Propargylic acetate **1**			Time (h)	Yield (%)[b]	
	R^1	R^2				
1	Ph	Ph	**1a**	0.2	**2a**	80
2	Ph	4-MeO–C_6H_4	**1b**	0.2	**2b**	84
3	Ph	4-Me–C_6H_4	**1c**	0.2	**2c**	58
4	Ph	4-NO_2–C_6H_4	**1d**	3	**2d**	50
5	Ph	4-Cl–C_6H_4	**1e**	0.5	**2e**	74
6	C_6H_{13}	Ph	**1f**	0.2	**2f**	99
7	C_6H_{13}	4-MeO–C_6H_4	**1g**	0.2	**2g**	97
8	C_6H_{13}	4-Cl–C_6H_4	**1h**	3	**2h**	87
9	*t*-Bu	Ph	**1i**	0.2	**2i**	77
10	*t*-Bu	4-MeO–C_6H_4	**1j**	0.1	**2j**	70
11	Me_3Si	Ph	**1k**	0.2	**2k**	61
12	Me_3Si	4-Cl–C_6H_4	**1l**	0.5	**2l**	45
13	Me_3Si	4-MeO–C_6H_4	**1m**	0.2	**2m**	44

[a] Propargylic acetate **1** (0.5 mmol), $InBr_3$ (0.05 equiv), and Et_3SiH (2 equiv) were used in CH_2Cl_2 solution (2 mL).
[b] Isolated yields.

reaction mixture including acetate **1a**, $InBr_3$, and triethylsilane, the desired reduction did not proceed, and the starting acetate was recovered in 94% yield. In this context of these radical species, quite recently, Baba and co-workers reported that the $InCl_3$–Et_3SiH or –Bu_3SnH system acts as a radical reagent.[11]

In conclusion, we demonstrated that the $InBr_3$ and Et_3SiH reagent system promotes the deacetoxylation of propargylic acetates to produce internal alkynes. This simple catalytic system is remarkably tolerant of a variety of functional groups on the acetate, and a radical intermediate is generated in situ. Further investigations of the mechanism of this reaction are currently in progress.

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8. General procedure for the reduction of propargylic acetate: propargyl acetate **1a** (0.50 mmol) and triethylsilane (1.0 mmol) were successively added to anhydrous CH_2Cl_2 (2 mL) at room temperature under a N_2 atmosphere. After 5 min, $InBr_3$ (5 mol %, 0.025 mmol) was added to the solution. The mixture was stirred at the same temperature until the reaction reached completion, as shown by TLC (hexane/AcOEt = 95:5). After an appropriate reaction time shown in Table 2, a saturated solution of $NaHCO_3$ was added to the reaction mixture to quench the reaction. The combined organic layer was washed with brine, dried over Na_2CO_3, and evaporated under reduced pressure. The crude product was purified by silica gel chromatography (hexane/AcOEt = 95:5) to give the corresponding internal alkynes **2a** (80%). Spectral data for new compounds: 1-(4-methoxyphenyl)-2-nonyne (**2g**): yellow oil; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.8 (t, 3H, $J = 7.0$ Hz), 1.2–1.4 (m, 8H), 2.1 (t, 2H, $J = 1.0$ Hz), 3.42 (s, 2H), 3.69 (s, 3H), 6.75 (d, 2H, $J = 8.5$ Hz), 7.16 (d, 2H, $J = 8.5$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 18.8, 22.5, 24.2, 28.6, 29.0, 31.4, 55.2, 77.9, 82.3, 113.7, 128.7, 129.7, 158.2; MS (EI) *m*/*z* 230; HRMS (FAB): calcd for $C_{16}H_{22}O$: 230.1671, found 230.1670; 1-(4-chlorophenyl)-2-nonyne (**2h**): yellow oil; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.8 (t, 3H, $J = 7.0$ Hz), 1.2–1.5 (m, 8H), 2.1 (m, 2H), 3.45 (s, 2H), 7.18 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 18.8, 22.6, 24.6, 28.6, 28.9, 31.3, 76.9, 83.1, 128.4, 129.1, 132.1, 136.1; MS (EI) *m*/*z* 234; HRMS (FAB): calcd for $C_{15}H_{20}Cl$ (M+H): 235.1253, found 235.1262; 4,4-dimethyl-1-(4-methoxyphenyl)-2-pentyne (**2j**): pale yellow oil, ^1H NMR ($CDCl_3$, 500 MHz) σ 1.25 (s, 9H), 3.50 (s, 2H), 3.81 (s, 3H), 6.81 (d, 2H, $J = 7.5$ Hz), 7.21 (d, 2H, $J = 7.5$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) σ 24.1, 27.4, 31.3, 55.2, 76.3, 91.1, 113.7, 128.6, 129.7, 158.1; MS (EI) *m*/*z* 222; HRMS (FAB): calcd for $C_{14}H_{18}O$: 222.1358, found 222.1361; 3-(4-chlorophenyl)-1-(trimethylsilyl)-1-propyne (**2l**): yellow oil; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.02 (s, 9H), 3.4 (s, 2H), 7.1 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 0.02, 25.6, 87.4, 103.6, 128.6, 129.2, 132.4, 134.8; MS (EI) *m*/*z* 222; HRMS (FAB): calcd for $C_{12}H_{15}ClSi$: 222.0632, found 222.0616.
9. When a reduction involving the secondary propargylic alcohol, 4-(1-hydroxy-3-phenyl-2-propynyl)-benzonitrile was conducted under optimized conditions, the desired internal alkyne was obtained in low yield (20%).
10. A referee pointed out that whether $B(C_6F_5)_3$–Et_3SiH catalytic system undertook the present reaction or not. Thus, when the reduction of alkyne **1a** with Et_3SiH was carried out in the presence of 0.10 equiv of $B(C_6F_5)_3$, the desired reaction proceeded smoothly (<0.2 h) to give the corresponding alkyne **2a** in 58% yield.
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