Indium-Mediated Debromination of *gem*-Bromonitroalkanes under Mild Conditions in Aqueous Medium

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Abstract: *gem*-Bromonitroalkanes are efficiently reduced into the corresponding dehalogenated products in excellent yields with indium metal in the presence of a palladium(0) catalyst and indium(III) chloride in aqueous medium. The addition of bromonitromethane to carbohydrate-derived aldehydes or imines, followed by debromination of the intermediate bromonitro compounds represents an extremely efficient method for the stereoselective preparation of nitrosugars.

Key words: reductive dehalogenation, indium, bromonitroalkanes, nitroalkanes, nitrosugars

Nitroalkanes are important synthons for the preparation of more complex molecules. Under basic conditions, they readily form a nitronate anion that can undergo aldol reactions with aldehydes and ketones (Henry reaction),[1] or imines (aza-Henry reaction),[2] and additions to α,β-unsaturated carbonyl compounds (Michael reaction).[3] Moreover, a wide variety of other organic compounds can be accessed by transformations of the nitro group into other chemical functionalities, such as amines,[4] carbonyl groups,[5] hydroxylamines[6] and oximes or nitriles.[7]

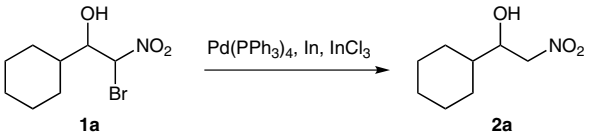
gem-Bromonitroalkanes are useful analogues of nitroalkanes and have been employed in organic synthesis as precursors of aliphatic nitro derivatives, with the aim of improving diastereoselection and avoiding dimerization.[8] For example, the enantioselective conjugate addition of *gem*-bromonitroalkanes to α,β-unsaturated ketones followed by debromination of the resulting products, afforded the corresponding nitroalkanes with excellent enantioselectivity.[9] Similarly, debromination of the enantiopure products arising from the addition of bromonitromethane to aldehydes or imines gave the corresponding nitroalkanols[10] or nitroamines,[11] whilst preserving the absolute configuration at the β-position. Radical dehalogenation promoted by tri-*n*-butyltin hydride has been widely used to transform *gem*-halonitroalkanes into nitroalkanes.[12]

During our recent investigations on the use of bromonitromethane in organic synthesis,[13] we became interested in the use of *gem*-bromonitrosugars as precursors of the corresponding enantiopure nitrosugars. This, combined with our long-term interest in the use of indium in organic chemistry,[14] prompted us to initiate a search for an indium-promoted procedure for the reduction of *gem*-bromonitroalkanes that would avoid using highly toxic tri-*n*-butyltin hydride.

The very low first ionization energy of indium(0) makes it an ideal candidate to be used in single-electron transfer (SET) reactions.[15] This property, together with its stability toward oxygen and water, has prompted exhaustive studies focused on indium-mediated carbon–carbon bond-forming reactions[16] and reductions of functional groups.[17] Various reactions in which a carbon–halogen bond is reduced by indium have been reported.[18] However, to the best of our knowledge, the indium-promoted transformation of *gem*-halonitroalkanes into nitroalkanes has not been described to date.

Herein, we describe a novel dehalogenation reaction of 2-bromo-2-nitroalkan-1-ols and 2-bromo-2-nitroamines promoted by indium metal in the presence of tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] as the catalyst and indium(III) chloride ($InCl_3$) in aqueous medium.[19]

To determine the optimum reaction conditions, we first used a model substrate, 2-bromo-1-cyclohexyl-2-nitroethanol (**1a**), and various reagent systems (Scheme 1, Table 1).



1a **2a**

Scheme 1 Indium-mediated reductive debromination of 2-bromo-1-cyclohexyl-2-nitroethanol (**1a**)

Thus, treatment of bromoalkanol **1a** with indium powder (200 mol%) and indium(III) chloride (50 mol%) in the presence of tetrakis(triphenylphosphine)palladium(0) (2 mol%) in a 2:1 (v/v) mixture of tetrahydrofuran–water afforded the desired nitroalkane product **2a** in 93% yield (Table 1, entry 1).[20,21]

The reaction did not occur in the absence of either indium(III) chloride or indium (Table 1, entries 2 and 3). The indium/indium(III) chloride reagent system in the absence of $Pd(PPh_3)_4$ reduced the C–Br bond at a very low rate, resulting in a poor yield of **2a** (Table 1, entry 4). Employing other solvent systems also led to poor results (Table 1, entries 5–7). When zinc metal was used instead of indium, the reaction did not proceed (Table 1, entry 8).

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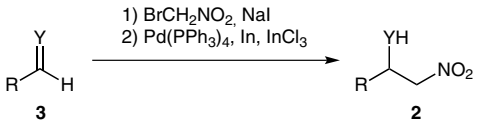
Table 1 Optimization of the Conditions for the Synthesis of 1-Cyclohexyl-2-nitroethanol (**2a**)

Entry	Reagents[a]	Solvent	Yield
1	$Pd(PPh_3)_4$, In, $InCl_3$	THF–H_2O	93%
2	$Pd(PPh_3)_4$, In	THF–H_2O	NR
3	$Pd(PPh_3)_4$, $InCl_3$	THF–H_2O	NR
4	In, $InCl_3$	THF–H_2O	13%
5	$Pd(PPh_3)_4$, In, $InCl_3$	DMF–H_2O	32%
6	$Pd(PPh_3)_4$, In, $InCl_3$	MeOH–H_2O	28%
7	$Pd(PPh_3)_4$, In, $InCl_3$	H_2O	21%
8	$Pd(PPh_3)_4$, Zn, $InCl_3$	THF–H_2O	NR

[a] Ratio of bromonitroalkanol/$Pd(PPh_3)_4$/metal/$InCl_3$ = 1:0.02:2:0.5. NR = no reaction.

Given this satisfactory result (Table 1, entry 1), the indium-mediated reductive elimination was applied to various *gem*-halonitro compounds (Scheme 2, Table 2), the requisite starting materials being readily prepared by reactions of aldehydes or imines with bromonitromethane.[10,11a,22] After aqueous work-up, the intermediate bromonitro derivatives were submitted, without any further purification, to the debromination reaction.

As shown by the results compiled in Table 2, the $Pd(PPh_3)_4$/In/$InCl_3$ system was effective for the reductive dehalogenation of various 2-bromo-2-nitro intermediates in aqueous medium, affording the corresponding nitroalkanes **2a–f** in good to excellent yields.[23] Accordingly, the combination of a sodium iodide catalyzed addition followed by dehalogenation was an effective procedure for the preparation of nitroalkanes from either aldehydes or imines.



Scheme 2 Addition of bromonitromethane to aldehydes and imines **3** followed by an indium-mediated reductive debromination

Table 2 Synthesis of Nitroalkanes **2a–f**

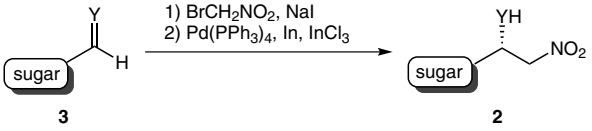
Entry	Substrate	R	Y	Product	Yield
1	**3a**	*c*-C_6H_{11}	O	**2a**	93%
2	**3b**	*n*-C_7H_{15}	O	**2b**	90%
3	**3c**	Ph	O	**2c**	51%
4	**3d**	*i*-Bu	O	**2d**	83%
5	**3e**	*c*-C_6H_{11}	NPMP[a]	**2e**	72%
6	**3f**	*n*-C_7H_{15}	NPMP[a]	**2f**	78%

[a] NPMP = *N*-*p*-methoxyphenyl

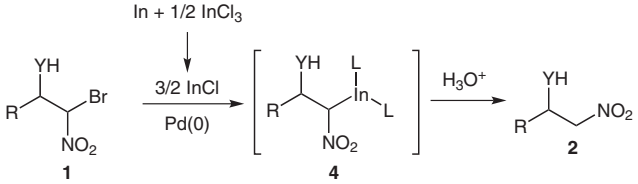
The interest in this procedure lies in the better diastereoselection achieved on the addition of bromonitromethane to aldehydes and imines, rather than on the addition of simpler nitromethane. Thus, the addition of nitromethane to sugar aldehydes[13a–c,e] or imines[11a,13d,f] gave moderate to good diastereoselectivity, while the addition of bromonitromethane resulted in excellent *anti*-selectivity.[13d,g] Accordingly, the sequence of bromonitromethane addition/debromination would be predicted to afford the *anti*-isomers with superior diastereoselection than the addition of nitromethane alone. In order to prove our hypothesis, we explored the sequence of bromonitromethane addition/debromination on several sugar-derived aldehydes and imines **3g–l**. The corresponding nitrosugars **2g–l** were obtained in good yields and with excellent diastereoselectivities (Scheme 3, Table 3).[24] The absolute configurations were established by comparison with the literature data on nitrosugars **2g–l**.

The observed stereochemistry of products **2** can be explained by assuming Felkin–Ahn-type addition of the bromonitronate anion. The stereochemistry at the β-nitro position is preserved during the dehalogenation reaction.

A mechanistic proposal for the debromination process is depicted in Scheme 4. Thus, treatment of *gem*-bromonitroalkanes **1** with indium(I), generated in situ by the reaction of indium metal and indium(III) chloride, in the presence of a catalytic amount of palladium(0) would generate indium nitronate intermediates **4**, hydrolysis of which would afford the corresponding nitroalkanes **2**. Even though the role of palladium(0) is not clear, it is probably involved in some kind of palladium insertion into the C–Br bond, which would facilitate the metallation.



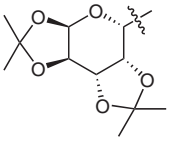
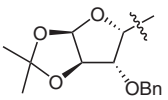
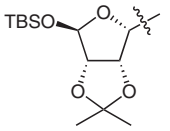
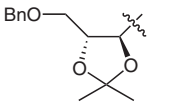
Scheme 3 Addition of bromonitromethane to sugar-derived aldehydes and imines **3g–l** followed by an indium-mediated reductive debromination



Scheme 4 Mechanistic proposal for the conversion of **1** into **2**

In summary, we have developed an easy, efficient and general reductive debromination procedure for converting *gem*-bromonitroalkanes into the corresponding nitroalkanes using a palladium(0) catalyst, indium metal and indium(III) chloride. The reactions proceeded smoothly

Table 3 Synthesis of Nitrosugars **2g–l**

Entry	Substrate	Sugar	Y	Product	dr	Yield[a]
1	**3g**		O	**2g**	95:5	83%
2	**3h**		O	**2h**	>98:2	88%
3	**3i**		NPMP[b]	**2i**	>98:2	69%
4	**3j**		O	**2j**	>98:2	81%
5	**3k**		NPMP[b]	**2k**	>98:2	65%
6	**3l**		O	**2l**	95:5	81%

[a] Yield of isolated product after column chromatography based on the starting aldehyde or imine **3**.
[b] NPMP = *N*-*p*-methoxyphenyl

under mild conditions in neutral aqueous medium, preserving the stereochemistry of any existing stereogenic centers. In combination with the sodium iodide catalyzed addition of bromonitromethane to aldehydes or imines, the present method offers an efficient alternative for the stereoselective preparation of nitrosugars.

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(19) A similar system was used for the reductive elimination of halohydrins, see: Cho, S.; Kang, S.; Keum, G.; Kang, S. B.; Han, S.-Y.; Kim, Y. *J. Org. Chem.* **2003**, *68*, 180.
(20) **Nitroalkanes 2; General Procedure**
NaI (0.12 mmol, 0.15 equiv) was added to a stirred solution of bromonitromethane (0.8 mmol, 1 equiv) and the corresponding aldehyde **3** (0.8 mmol, 1 equiv) in THF

(10 mL), and the resulting mixture was stirred at r.t. for 5 h. After this period, the mixture was quenched with aq HCl (10 mL, 0.1 M) and extracted with Et_2O (1 × 20 mL). The combined extracts were washed with sat. aq $Na_2S_2O_3$ solution (1 × 20 mL), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford the crude 1-bromo-1-nitroalkan-2-ol. In metal (183 mg, 1.6 mmol), $InCl_3$ (88 mg, 0.4 mmol) and $Pd(PPh_3)_4$ (18 mg, 2 mol%) were added to a solution of the 1-bromo-1-nitroalkan-2-ol (0.8 mmol) in THF–H_2O (2:1, 6 mL). After stirring the mixture at r.t. for 12 h, it was quenched with HCl (3 mL, 1 M), diluted with H_2O (25 mL) and extracted with Et_2O (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford the nitroalkanes **2**.

(21) **1-Cyclohexyl-2-nitroethanol (2a)**
Yellow oil; R_f = 0.30 (hexane–EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.45–4.33 (2 m, 3 H), 1.73–0.90 (m, 11 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 79.3, 72.8, 41.4, 27.9, 26.1, 25.9, 25.7, 22.8.

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(23) ***N*-(1-Cyclohexyl-2-nitroethyl)-4-methoxybenzenamine (2e)**
Brown oil; R_f = 0.22 (hexane–EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.76 (d, *J* = 9.0 Hz, 2 H), 6.65 (d, *J* = 9.0 Hz, 2 H), 4.72 (dd, *J* = 12.3, 5.2 Hz, 1 H), 4.46 (dd, *J* = 12.3, 7.4 Hz, 1 H), 4.08–4.04 (m, 1 H), 3.73 (s, 3 H), 2.73 (s, 11 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.7 (C), 141.0 (C), 115.0 (2 × CH), 114.9 (2 × CH), 75.7 (CH_2), 60.9 (CH), 55.7 (CH_3), 43.0 (CH), 34.7 (2 × CH_2), 25.2 (CH_2), 21.6 (2 × CH_2). MS (ESI): *m*/*z* (%) = 279 (6) $[M + H]^+$, 234 (19), 216 (100), 214 (28). HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{23}N_2O_3$: 279.1709; found: 279.1703.

(24) **7-Deoxy-1,2:3,4-di-*O*-isopropylidene-7-nitro-D-*glycero*-β-D-*galacto*-heptopyranose (2g)**
Yellow oil; R_f = 0.20 (hexane–EtOAc, 3:1); $[\alpha]_D^{20}$ –49.4 (*c* 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.49 (d, *J* = 5.0 Hz, 1 H), 4.78 (apparent d, *J* = 11.2 Hz, 1 H), 4.65 (dd, *J* = 8.0, 2.5 Hz, 1 H), 4.51–4.47 (m, 2 H), 4.43 (dd, *J* = 8.0, 2.0 Hz, 1 H), 4.34 (dd, *J* = 4.9, 2.5 Hz, 1 H), 3.73 (dd, *J* = 8.2, 2.0 Hz, 1 H), 2.89 (d, *J* = 5.9 Hz, 1 H), 1.51 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 109.6, 108.9, 96.2, 78.1, 70.6, 70.5, 70.1, 67.7, 67.4, 25.9, 24.8, 24.3. MS (ESI): *m*/*z* (%) = 342 (24) $[M + Na]^+$, 337 (100) $[M + NH_4]^+$, 320 (19) $[M + H]^+$, 262 (48).

