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Selective C–N bond oxidation: demethylation of *N*-methyl group in *N*-arylmethyl-*N*-methyl-α-amino esters utilizing *N*-iodosuccinimide (NIS)

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Abstract

Demethylation of *N*-methyl group in *N*-methyl-*N*-arylmethyl-α-amino esters was accomplished by the oxidation of the amino group using the *N*-iodosuccinimide (NIS)/acetonitrile system followed by treatment with *O*-methylhydroxylamine hydrochloride. This combination of reagents could provide a complementary method to catalytic hydrogenolysis, which certainly cleaves *N*-arylmethyl groups, in organic synthesis.

Recently, a number of asymmetric Michael additions, where chiral amines having a benzyl group attack α,β-unsaturated esters as a nucleophile, have been reported, mainly to establish general procedures for the synthesis of β-amino acids,[1] since structure moieties are crucial to express biological and pharmaceutical activities in many naturally occurring compounds and medicines. Therefore, the development of a method to remove the benzyl group or chiral auxiliaries from Michael adducts is an important issue in organic synthesis. In general, the benzyl group is easily removed by hydrogenolysis performed on palladium carbon[2a–d] or palladium hydroxide (Pearlman's catalyst)[2e] or by hydrolysis of imines generated by the oxidation of the benzylic C–N bond with various reagents.[1a,3–15] On the other hand, the *N*-methyl group is not easily cleaved compared with the *N*-benzyl group. In spite of much effort by several research groups to develop unique reagents for demethylation of the *N*-methyl group, for example, several chloroformates,[16] iodine/calcium oxide (I_2/CaO),[17] ruthenium chloride hydrate/hydrogen peroxide ($RuCl_3 \cdot nH_2O$/H_2O_2),[18] *N*,*N*-dimethyl-2,7-diazapyrenium (DAP^{2+})/visible light,[19] and benzeneselenol,[20] practical methods to cleave the C–N bond of alkyl groups in the presence of the *N*-benzyl group have not been reported to date. Thus, we embarked on a study to develop a novel method to cleave the *N*-methyl bond selectively, even in the presence of *N*-benzyl or *N*-arylmethyl groups.

At the beginning of the study, we focused on the fact that *N*-iodosuccinimide (NIS), which is employed as an iodonium source in organic synthesis, that is, the activation of thioglycosides in glycosylation,[21] iodination of hydroxyl groups[22] and direct iodination of aromatic rings,[23] has been utilized for the oxidation of tertiary amines to afford aldehyde and secondary amine. Actually, Abbott's group availed the reaction for the demethylation of *N*,*N*-dimethyl-amino group on the glycosyl moiety of a macrolide antibiotic.[24] Later, Davis and his co-workers reported a debenzylation of *N*,*N*-dibenzyl- and *N*-benzyl-amino alcohols by the oxidation of the C–N bond with iodonium ion from NIS;[25] however, the method utilized excess amounts of NIS, requiring a tedious work-up procedure.

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Recently, we have further found that oxidation with NIS could cleave *N*-alkyl groups quickly even in the presence of the benzylic C–N bond during a study on the development of a novel asymmetric Michael addition of a chiral alkyl amine.[26] Thus, making a small modification, we applied the method to the selective N-demethylation of *N*-arylmethyl-*N*-methylated amino acid derivatives to test its general applicability.

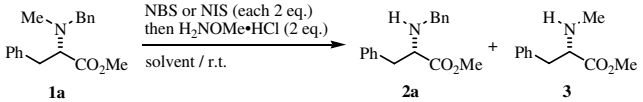
In the present Letter, we would like to report an excellent result obtained in reactions where *N*-arylmethyl-*N*-methyl-α-amino esters were treated with just two equimolars of NIS.

First, we tried the dealkylation of *N*-benzyl-*N*-methyl-L-phenylalanine methyl ester (**1a**) by oxidation with NIS or *N*-bromosuccinimide (NBS) followed by treatment with *O*-methylhydroxylamine hydrochloride, an effective reagent for the transoximation of iminium intermediates,[1a] in various solvents (Table 1). As expected from information in the literature,[24] the reaction performed with *N*,*N*-dimethylformamide (DMF) predominantly gave the debenzylated product **3** with either NIS or NBS [59% (NIS), 27% (NBS)] (Table 1, entry 1). Surprisingly, the reaction with NIS attained in acetonitrile, a solvent as polar as DMF, afforded the demethylated product **2a** (83%) accompanied with a small amount of debenzylated product **3** (14%) (Table 1, entry 2). On the other hand, the reaction with NBS in acetonitrile gave the debenzylated product **3** (52%) accompanied with a small amount of demethylated product **2a** (21%) (Table 1, entry 2). The reaction attained with NIS in dichloromethane, a less-polar solvent than DMF or acetonitrile, yielded both demethylated product **2a** (59%) and debenzylated product **3** (26%), while **3** (32%) was given as a sole product when NBS was employed instead of NIS (Table 1, entry 3).

In spite of the difficulty in explaining why the solvents changed the selectivities between demethylation and debenzylation, we could further generalize the selectivity in the demethylation of various tertiary amines **1a–i** by using the NIS/acetonitrile system to afford secondary amines **2a–i** (Table 2).[27] All reactions proceeded through selective C–N bond oxidation (1–2 h) followed by transoximation (1–2 h) and gave *N*-arylmethylated secondary amines **2a–i** as the major product (Table 2, entries 1–9). The reaction of **1d**,**e** having an electron-donating group such as the methoxybenzyl group (Table 2, entries 4 and 5) as well as those of **1f–i** having an electron-withdrawing group such as the chlorobenzyl or 4-nitrobenzyl group (Table 2, entries 6–9), gave the desired products **2d**,**e**, and **2f–i** in good yields, respectively. On the basis of the results obtained so far, it seems that the functional groups on the aromatic ring would not affect the reactivity.

Moreover, we applied the NIS/acetonitrile system to various types of derivatives, that is, *tert*-butyl ester **4a**, benzyl ester **4b**, allyl ester **4c**, leucine methyl ester **4d**, aspartic acid dimethyl ester **4e**, and serine derivatives **4f** to ascertain the generality. The reaction of L-phenylalanine derivatives with various ester groups **4a–c** proceeded in good yields without cleavage of the ester groups to give the demethylated products **5a–c** (Table 3, entries 1–3). In addition, methyl esters of the other *N*-benzyl-*N*-methyl-α-amino acids **4d–f** was also *N*-demethylated with high selectivity to give **5d–f** (Table 3, entries 4–7).

Table 1
Optimization of solvent

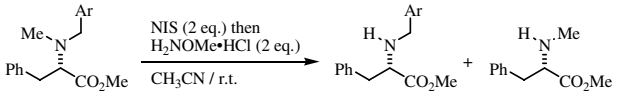


1a **2a** **3**

Entry	Solvent	NBS			NIS		
		Time (h)	Yield (%)		Time (h)	Yield (%)	
			2a	**3**		**2a**	**3**
1	DMF	2	15	27	2.5	5	59
2	CH_3CN	3	21	52	2.5	83	14
3	CH_2Cl_2	2.5	9	32	3.5[a]	59	26

[a] 2.5 equiv of NIS were used.

Table 2
Selective demethylation of *N*-arylmethyl-*N*-methyl-L-phenylalanine methyl ester

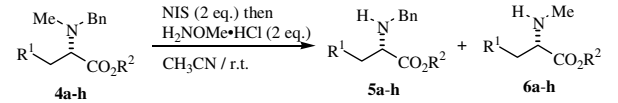


1a-i **2a-i** **3**

Entry	Ar	Time (h)	Yield (%)		
			2		**3**
1	**1a** Ph	2.5	**2a**	83	14
2	**1b** 1-Naphtyl	2	**2b**	77	4
3	**1c** 2-Naphtyl	3	**2c**	75	16
4	**1d** 4-MeO–Ph	2.5	**2d**	79	6
5	**1e** 3-MeO–Ph	2.5	**2e**	80	12
6	**1f** 4-Cl–Ph	2.5	**2f**	87	10
7	**1g** 3-Cl–Ph	2.5	**2g**	83	9
8	**1h** 2-Cl–Ph	2	**2h**	86	6
9[a]	**1i** 4-NO_2–Ph	3.5	**2i**	73	14

[a] 3.0 equiv of NIS were used.

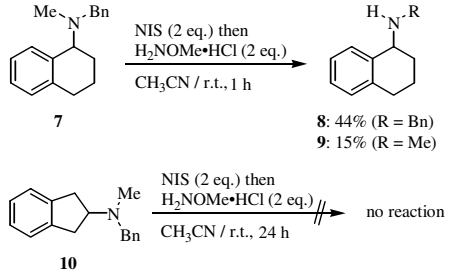
Table 3
Selective demethylation of *N*-arylmethyl-*N*-methyl-α-amino esters



4a-h **5a-h** **6a-h**

Entry		R^1	R^2	Time (h)	Yield (%)			
					5		**6**	
1	**4a**	Ph	^{t}Bu	2.5	**5a**	88	**6a**	—
2	**4b**	Ph	Bn	2	**5b**	80	**6b**	13
3[a]	**4c**	Ph	Allyl	2	**5c**	55	**6c**	10
4[a]	**4d**	^{i}Pr	Me	2.5	**5d**	85	**6d**	—
5	**4e**	CO_2Me	Me	3	**5e**	88	**6e**	—
6	**4f**	OTBS	Me	2	**5f**	64	**6f**	—

[a] NIS (3.0 equiv) was employed.



Scheme 1. Demethylation of *N*-methyl group of the other substrate.

Finally, we adopted our method to the N-demethylation of different types of compounds from **1**, in terms of having no ester groups such as *N*-benzyl-*N*-methyl-1-amino-1,2,3,4-tetrahydronaphthalene (**7**) and *N*-benzyl-*N*-methyl-2-aminoindane (**10**) (Scheme 1). The reaction of **7** showed the same selectivity [(**8**[28]: 44%, **9**[29]: 14%)] as in the case of α-amino ester derivatives, while the substrate **10** was not reacted but almost recovered (75%) under the same condition. It seems that the iminium cation intermediate is stabilized by the participation of the neighboring group, such as carbonyl and ether groups.[24]

In conclusion, we established the first practical method to attain the N-demethylation reaction of *N*-arylmethyl-*N*-methyl-α-amino esters **1** and **4**, affording *N*-arylmethylated secondary amines **2** and **5** in good yield. Since the *N*-methyl group tends to be cleaved more easily than *N*-benzyl groups under this condition, our method would be of use in organic synthesis and provides an attractive strategy in the synthesis of alkaloids. Further studies on the elucidation of the reaction mechanism and application to other substrates are in progress.

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27. General procedure of demethylation with NIS/acetonitrile system: To an acetonitrile (1 ml) solution of **3a** (40 mg, 0.14 mmol) was added NIS (64 mg, 0.28 mmol), and then the mixture was stirred at rt. After standing for 1 h, *O*-methylhydroxylamine hydrochloride (24 mg, 0.28 mmol) was added to the reaction mixture, which was stirred at rt for 1.5 h. The mixture was poured into a saturated aqueous solution of sodium hydrogen carbonate, which was extracted with chloroform. The combined organic layer was washed with a 5% aqueous solution of sodium thiosulfate and brine, dried over with potassium carbonate, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 8:1 to 1:1) to give **2a** (32 mg, 83%) and **4** (4 mg, 14%).
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