The novel and efficient direct synthesis of *N*,*O*-acetal compounds using a hypervalent iodine(III) reagent: an improved synthetic method for a key intermediate of discorhabdins

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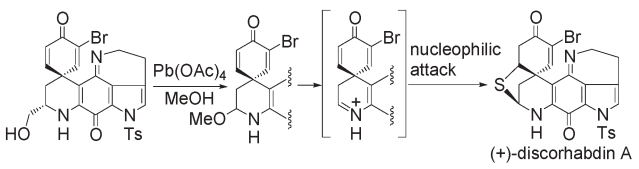
The use of hypervalent iodine(III) reagents allowed us to develop the novel and efficient direct synthesis of *N*,*O*-acetal compounds *via* the oxidative fragmentation reaction of α-amino acids or α-amino alcohols; furthermore, we succeeded in developing an improved synthesis of the key intermediate of discorhabdins.

N,*O*-acetal compounds are important intermediates since they are relatively stable, but readily generate unstable *N*-imines, which are attacked by nucleophiles to produce functionalized and unnatural amine or amino acid derivatives.

α-Amino acids and α-amino alcohols have recently attracted much attention because they are easily available and versatile building blocks and chiral auxiliaries. Therefore, the synthesis of *N*,*O*-acetal compounds from α-amino acids or α-amino alcohols facilitates the asymmetric synthesis of functionalized and unnatural amine or amino acid derivatives and natural products containing a nitrogen atom. In fact, by using this methodology, we recently diastereoselectively accomplished the first total synthesis of the marine anti-cancer alkaloid, (+)-discorhabdin A, but there has remained the problem of using highly toxic lead tetraacetate (Scheme 1).[1]

Several methods have appeared for the synthesis of *N*,*O*-acetal compounds from α-amino acids and α-amino alcohols, *e.g.*, the electrochemical oxidation of α-amino acids,[2] the oxidation by lead tetraacetate[3] or the radical reaction[4] of α-amino acids and α-amino alcohols. However, these methods have some problems in terms of using highly toxic reagents and complex handling. Furthermore, most of them produced *N*,*O*-Ac-acetals because of the ligand insertion, but this type of acetal is often quite unstable.[5] Therefore, it is advantageous to accomplish the direct synthesis of the more stable *N*,*O*-acetals.

Over the past several years, hypervalent iodine(III) reagents have received much attention due to their low toxicity, ready availability, easy handling, and reactivities similar to those of heavy metal reagents. As a continuation of our studies of hypervalent iodine chemistry, we have already reported various oxidation reactions of carbonyl, alkynyl, phenol and phenyl ether derivatives[6] using phenyliodine(III) bis(trifluoroacetate) (PIFA) and phenyliodine(III) diacetate (PIDA). We now report the novel and efficient direct synthesis of *N*,*O*-acetal compounds *via* the oxidative fragmentation reaction of α-amino acids or α-amino alcohols using bis(trifluoroacetoxy)iodo(III) pentafluorobenzene ($C_6F_5I(OCOCF_3)_2$). This reagent is very easily prepared from pentafluoroiodobenzene and nitric acid.[7] Furthermore, we succeeded in the improved synthesis of the key intermediate of discorhabdins by using this method.



Scheme 1 First total synthesis of (+)-discorhabdin A

First, we examined the oxidation of the *N*-Fmoc serine methyl ester using hypervalent iodine(III) reagents to optimize the reaction conditions. These results are shown in Table 1. Surprisingly, the reaction was found to smoothly proceed only by using $C_6F_5I(OCOCF_3)_2$ to give *N*,*O*-acetal compounds under slightly diluted condition, while almost no reaction occurred using other hypervalent iodine(III) reagents (entries 6, 7) and lead tetraacetate (entries 8–10). Molecular sieves 3 Å are necessary to keep the reaction conditions anhydrous in order to prevent water insertion.

Similarly, the reactions of other *N*-protected-α-amino alcohols (**1**) with $C_6F_5I(OCOCF_3)_2$ were investigated. These results are shown in Table 2. The *N*,*O*-acetal compounds (**2**) were produced in high yields (entries 1–7), and the relatively low yield of alaninol was caused by the instability of the product (entry 4). When the protective groups of nitrogen were changed from carbamates to benzoyl, the yield of **2h** was moderate (entry 8). The products **2a, b, f–h** are important compounds because they can be transformed into unnatural amino acids followed by Ben-Ishai's or Boto's method.[8] Furthermore, we found that this reaction could be applied to the discorhabdin intermediate having functionalized and unstable pyrroloiminoquinone moieties (entry 9), which leads to the improved synthetic method for the key intermediate of discorhabdins.

Next, we applied this method to α-amino acid derivatives (**3**). These results are shown in Table 3. The *N*,*O*-acetal compounds (**4**) were produced in moderate yields (entries 1–5).

A plausible reaction mechanism for the preparation of **2** or **4** *via* the oxidative fragmentation reaction of **1** or **3** is shown in Scheme 2. It is possible that the reaction proceeds *via* the radical path way, but no signal was found in the ESR spectroscopic studies. We rather propose that the reaction proceeds *via* the five-membered ring intermediate as shown in Scheme 2. A similar mechanism was proposed using lead tetraacetate.[3]

A typical experimental procedure is as follows. To a stirred solution of the amino alcohol (**1**) or amino acid (**2**) in

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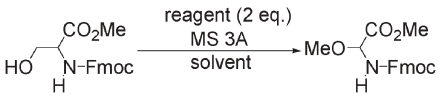
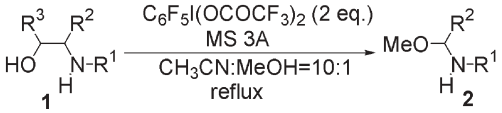
Table 1 Optimization of the reaction conditions with *N*-Fmoc serine methyl ester

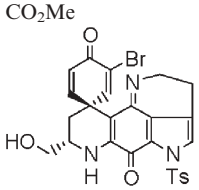
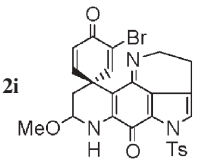


Entry	Reagent	Solvent	Temp./°C	Conc./M	Time/h	Yield (%)[a]
1	$C_6F_5I(OCOCF_3)_2$	CH_3CN : MeOH = 50 : 1	50	0.1	24	26
2	$C_6F_5I(OCOCF_3)_2$	CH_3CN : MeOH = 10 : 1	50	0.1	24	41
3	$C_6F_5I(OCOCF_3)_2$	CH_3CN : MeOH = 10 : 1	reflux	0.1	5	66
4	$C_6F_5I(OCOCF_3)_2$	CH_3CN : MeOH = 10 : 1	reflux	0.02	5	89
5	$C_6F_5I(OCOCF_3)_2$	AcOEt : MeOH = 10 : 1	reflux	0.02	5	76
6	PIFA	CH_3CN : MeOH = 10 : 1	reflux	0.02	24	trace
7	PIDA	CH_3CN : MeOH = 10 : 1	reflux	0.02	24	trace
8	$Pb(OAc)_4$	CH_3CN : MeOH = 10 : 1	reflux	0.02	24	trace
9	$Pb(OAc)_4$	AcOEt : MeOH = 10 : 1	reflux	0.02	24	trace
10	$Pb(OAc)_4$	CH_2Cl_2 : MeOH = 10 : 1	rt	0.02	24	trace

[a] Yield of isolated products.

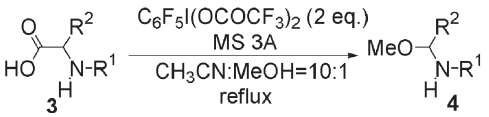
Table 2 Synthesis of *N*,*O*-acetals *via* oxidative fragmentation of α-amino alcohols with $C_6F_5I(OCOCF_3)_2$

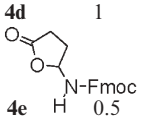


Entry	Substrate	R^1	R^2	R^3	Product	Time/h	Yield (%)[a]
1	**1a**	Fmoc	CO_2Me	H	**2a**	5	89
2	**1b**	Fmoc	CO_2Me	CH_3	**2b**	1	98
3	**1c**	Fmoc	H	H	**2c**	3	90[b]
4	**1d**	Fmoc	CH_3	H	**2d**	0.5	63
5	**1e**	Fmoc	$CH(CH_3)_2$	H	**2e**	0.5	76
6	**1f**	Cbz	CO_2Me	H	**2f**	7	80[b]
7	**1g**	Cbz	CO_2Bn	CH_3	**2g**	1	quant.
8	**1h**	Bz	CO_2Me	CH_3	**2h**	2	47 (92)[d]
9	**1i**				**2i** 	1.5	79[c]

[a] Yield of isolated products. [b] $C_6F_5I(OCOCF_3)_2$ (3 eq.) was used. [c] $NaHCO_3$ (7 eq.) was added at room temperature. [d] Yield in parentheses is based on the starting material consumed.

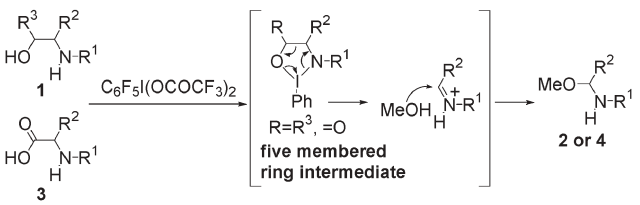
Table 3 Synthesis of *N*,*O*-acetals *via* oxidative fragmentation of α-amino acids with $C_6F_5I(OCOCF_3)_2$



Entry	Substrate	R^1	R^2	Product	Time/h	Yield (%)[a]
1	**3a**	Fmoc	H	**4a**	1	73
2	**3b**	Fmoc	CH_3	**4b**	0.25	54[b]
3	**3c**	Fmoc	$CH_2CH_2CO_2Me$	**4c**	0.25	55
4	**3d**	Cbz	CO_2Et	**4d**	1	46
5	**3e**	Fmoc	$CH_2CH_2CO_2H$	**4e** 	0.5	57[c]

[a] Yield of isolated products. [b] $C_6F_5I(OCOCF_3)_2$ (1.2 eq.) was used. [c] Without MeOH.

CH_3CN : CH_3OH = 10 : 1 were added molecular sieves 3 Å (850 mg $mmol^{-1}$) and $C_6F_5I(OCOCF_3)_2$ (2.0 equiv) at room temperature under a nitrogen atmosphere. The reaction mixture was refluxed at 95 °C with stirring for 0.25–7 h. The solution was then quenched with aqueous saturated $NaHCO_3$ and extracted with AcOEt. The combined organic layers were washed with brine, dried, and concentrated *in vacuo*. Purification of the residue by



Scheme 2 Plausible reaction mechanism to produce **2** or **4**.

column chromatography on silica gel gave the corresponding *N*,*O*-acetal compounds (**3**, **4**).

In summary, the use of $C_6F_5I(OCOCF_3)_2$ allowed us to develop the novel and efficient direct synthesis of *N*,*O*-acetal compounds *via* the oxidative fragmentation reaction of α-amino acids or α-amino alcohols. Furthermore, we succeeded in the improved synthesis of the key intermediate of discorhabdins using this method. Detailed studies along these lines are now in progress.

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