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DEPROTECTION OF 3,4-DIMETHOXYBENZYL (^{3,4}DMB) GROUP ON γ-LACTAM NITROGEN USING PHENYLIODINE(III) *BIS*(TRIFLUOROACETATE) (PIFA): APPLICATION TO ISOINDOLINONE COMPOUNDS

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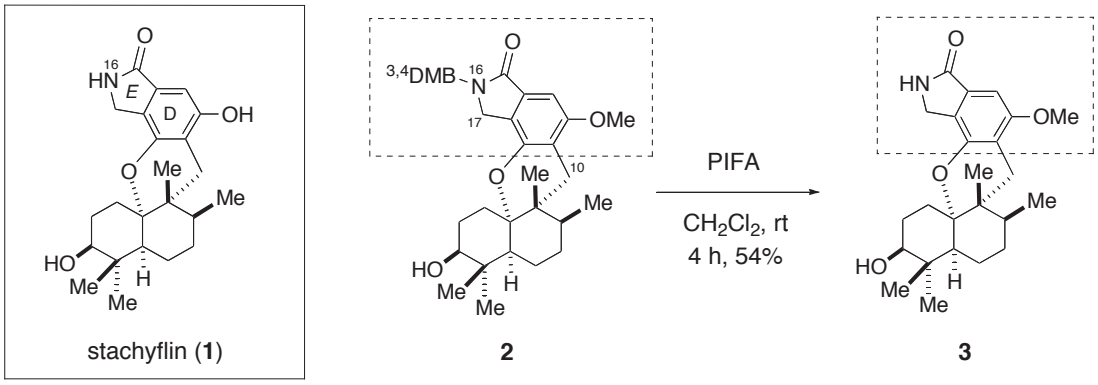
#Dedicated to Professor Albert Padwa on the occasion of his 75th birthday

Abstract – The secondary amide (γ-lactam) moiety of an isoindolinone ring exhibits high polarity in an unprotected condition. Problems with solubility make handling difficult; therefore, introduction of a protective group is necessary. We discovered that the 3,4-dimethoxybenzyl (^{3,4}DMB) group is an optimal protective group, and that the ^{3,4}DMB group alone could be deprotected under mild conditions with the use of a hypervalent iodine(III) reagent, phenyliodine(III) bis(trifluoroacetate) (PIFA).

Protection and deprotection reactions represent an extremely important process in basic research for organic synthesis chemistry, and numerous examples of these reactions have been reported.[1] In particular, in the field of total synthesis research, these protection and deprotection reactions can be sufficiently critical to influence subsequent synthetic plans.

Previously, in our total synthesis research for (+)-stachyflin (**1**) with anti-influenza A virus activity, we reported on the synthesis of the isoindolinone ring (D and E in **Scheme 1**).[2] In syntheses where the amide moiety (γ-lactam) at position 16 on the isoindolinone ring was unprotected, we learned that solubility in the reaction solvent presented a problem, because the compound itself had high polarity. Consequently, we synthesized isoindolinone compound **2**, protecting the amide moiety (γ-lactam) with a 3,4-dimethoxybenzyl (^{3,4}DMB or veratryl)[1,3] group, and performed a deprotection reaction at room

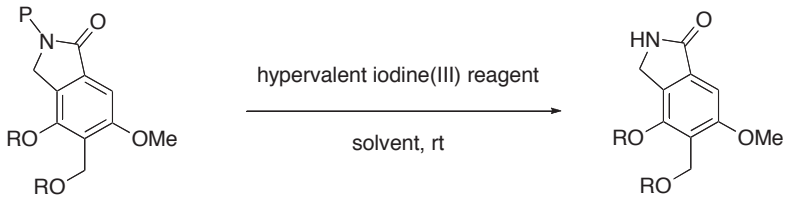
temperature with the hypervalent iodine(III) reagent phenyliodine(III) bis(trifluoroacetate) (PIFA)[4] in CH_2Cl_2 solvent. Although the yield was moderate, the deprotected product **3** was successfully obtained with the [3,4]DMB group selectively removed. In the deprotection reaction for **2**, the [3,4]DMB group is a protective benzyl group located at position 16, but benzyl positions also exist at C10 and C17. Thus, ordinary debenzylation conditions such as general catalytic reduction conditions (Pd-C, H_2, etc.) or oxidizing agents (such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[3b,5] and ceric ammonium nitrate (CAN)[6]) do not allow the reaction to proceed, or else generate complex mixtures. We discovered that this deprotection reaction worked only when PIFA was used. No previous reports have discussed a deprotection reaction for the [3,4]DMB group using PIFA.[2] This deprotection reaction is thus expected to be very useful in the field of organic synthesis chemistry.



Scheme 1

For this detailed report, we studied the optimal conditions for the deprotection reaction believed to be useful in the synthesis of isoindolinone compounds containing a secondary amide (γ-lactam). Hence, isoindolinone compounds **4a-d**[2] containing benzyl-type protective groups were synthesized and reacted with the hypervalent iodine(III) reagent PIFA, and detailed reaction conditions were studied in order to efficiently remove the benzyl-type protective groups (**Scheme 2**).

From previous research, we know that catalytic reduction conditions (such as H_2-Pd/C and H_2-Raney Ni) or usage of DDQ as an oxidizing agent applied to isoindolinone compounds **4a-d** do not allow the expected debenzylation reaction to proceed at all, and instead, starting materials are recovered. Nonetheless, we learned that **4b** containing the PMB group and **4c** containing the [3,4]DMB group afforded isoindolinone **5a** in moderate yield when CAN was used as an oxidizing agent. Subsequently, we studied in detail the deprotection reaction of PIFA, the hypervalent iodine(III) reagent found to be effective in the total synthesis of (+)-stachyflin (**1**) (**Scheme 2**, **Table 1**).



4a: P = Bn, R = Ac
4b: P = PMB, R = Ac
4c: P = ^{3,4}DMB, R = Ac
4d: P = ^{3,4}DMB, R = $C(CH_3)_2$

5a: R = Ac
5b: R = H
5c: R = $C(CH_3)_2$

Scheme 2

Table 1. Deprotection of isoindolinones **4a**-**d** using hypervalent iodine(III) reagents

entry	substrate	hypervalent iodine(III) reagents (equiv.)	solvent	time (h)	yield (%)[a] of **5**
1	**4a**	PIFA[b] (10)	CH_2Cl_2	24 <	NR[c]
2	**4a**	PIFA (10)	benzene	24 <	NR
3	**4b**	PIFA (10)	CH_2Cl_2	24 <	trace (**5a**)
4	**4b**	PIFA (10)	benzene	24 <	trace (**5a**)
5	**4c**	PIDA[d] (10)	CH_2Cl_2	24 <	NR
6	**4c**	PIFA (10)	CH_2Cl_2	8	83 (**5a**)
7	**4c**	PIFA (5)	CH_2Cl_2	8 <	66 (**5a**)
8	**4c**	PIFA (2)	CH_2Cl_2	10 <	22 (**5a**)
9	**4c**	PIFA (10)	CH_2ClCH_2Cl	18	54 (**5a**)
10	**4c**	PIFA (10)	benzene	7	93 (**5a**)
11	**4c**	PIFA (10)	EtOH	24 <	NR
12	**4c**	PIFA (10)	MeCN	5	decomp.[e]
13	**4c**	PIFA (10)	TFEA[f]	1	decomp.
14	**4c**	PIFA (10)	HFIP[g]	1	decomp.
15	**4d**	PIFA (10)	benzene	8	68 (**5b**)
16[h]	**4d**	PIFA (10)	benzene	12	77 (**5c**)

[a] Isolated yields. [b] Phenyliodine(III) *bis*(trifluoroacetate) [c] No reaction. [d] Phenyliodine(III) diacetate.
[e] Decomposition. [f] 2,2,2-Trifluoroethanol. [g] 1,1,1,3,3,3-Hexafluoro-2-propanol.
[h] This reaction was carried out in the presence of K_2CO_3 (20 equiv.) as a base.

First, for substrate **4a** containing the benzyl group and substrate **4b** containing the PMB group, 10 equivalents of PIFA were employed to perform deprotection reactions at room temperature in CH_2Cl_2 or benzene solvent. Trace amounts of the deprotection target isoindolinone **5a** were obtained (entries 3, 4) from substrate **4b**, but the reaction scarcely progressed for **4a** and starting materials were recovered (entries 1, 2). For isoindolinone **4c** containing the ^{3,4}DMB group, a protective group more rich in electrons than the PMB group and believed to be more easily removed in deprotection, phenyliodine(III) diacetate

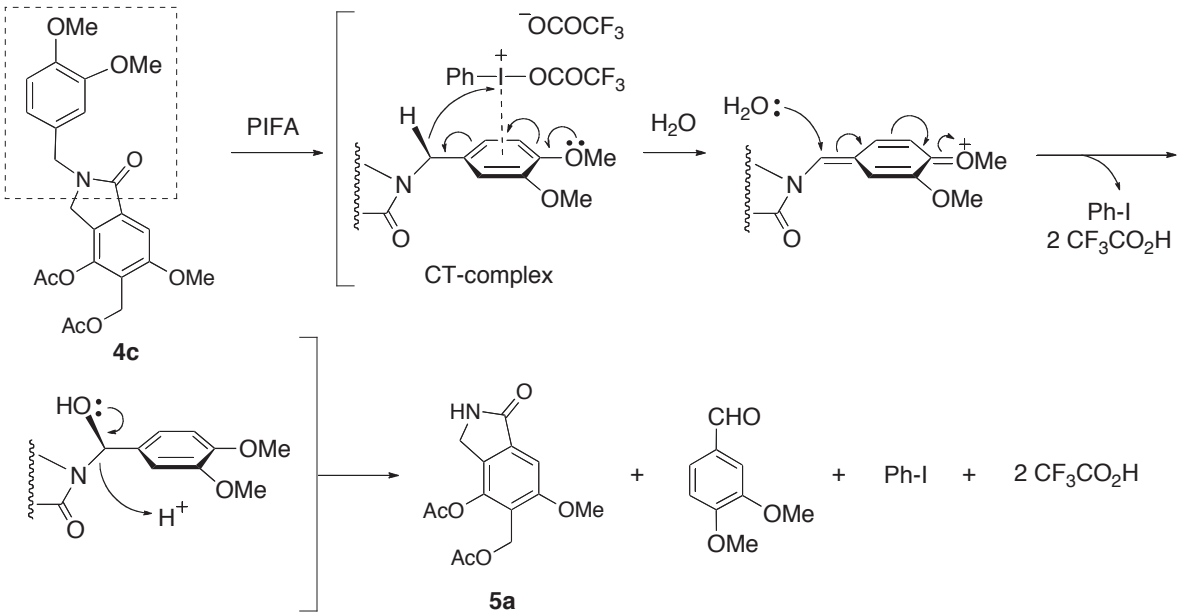
(PIDA), a hypervalent iodine(III) reagent, was allowed to react in CH_2Cl_2 solvent for 24 hours or more, but **5a** was not obtained (entry 5). A deprotection reaction for **4c** performed in CH_2Cl_2 solvent employing 10 equivalents of PIFA was completed in 8 hours, and successfully provided the desired deprotection target isoindolinone **5a** at 83% yield (entry 6). Based on these reaction conditions, the optimization of PIFA equivalents and reaction solvent was studied (entries 6 to 14). First, the study of PIFA equivalents revealed that a decrease from 5 to 2 equivalents led to extended reaction time and decreased yield, while the use of 10 equivalents of PIFA gave satisfactory results (entries 6 to 8).

Next, the study of reaction solvents showed that 1,2-dichloroethane (CH_2ClCH_2Cl), a halogenated hydrocarbon solvent similar to CH_2Cl_2 extended the reaction time (18 h) with a moderate yield of **5a** (entry 9), but the nonpolar solvent benzene caused the reaction to conclude in 7 hours and the deprotected target isoindolinone **5a** was successfully obtained at 93% yield (entry 10). As compared with the reaction performed in CH_2Cl_2 solvent, the yield improved and reaction time was slightly shorter. In contrast, the reaction made no progress in protic solvent EtOH (entry 11), and yielded a complex mixture in aprotic solvent MeCN (entry 12). Furthermore, in solvents 2,2,2-trifluoroethanol (TFEA) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) used extensively for PIFA reactions, disappearance of starting materials was observed in a short period of time, but similarly to MeCN solvent, decomposition products were obtained (entries 13,14). These results made it clear that the use of the nonpolar solvent benzene was optimal for this deprotection reaction.

Under the optimized reaction condition, a wide range of deprotective reaction of isoindolinone **4d** containing acetonide was investigated using PIFA (10 equiv.) and the results are shown in Table 1 (entries 15, 16). Not surprisingly, due to the instability of acetonide moiety under acidic conditions, the TFA formed from reduction of the PIFA reagent cleaved the acetonide, and provided diol **5b** as the major product from **4d**. In the case of entry 16, the reaction of **4d** was carried out under usual condition (PIFA, benzene, rt) in the presence of K_2CO_3 (20 equiv.) as a base, to increase the selectivity of deprotected product **5c** (77% yield).

The present deprotection reaction mechanism was elucidated based on the following: i) Yonemitsu *et al*.[3a] reacted DDQ with a compound containing an alcohol protected by a PMB group and a ^{3,4}DMB group within the same molecule, and reported that the ^{3,4}DMB group with a higher electron density than the PMB group was deprotected earlier; and ii) the deprotection reaction for isoindolinone **4c** employing PIFA was confirmed to generate 3,4-dimethoxybenzaldehyde together with **5a** (**Scheme 3**). PIFA was probably involved in the same sort of deprotection mechanism of the ^{3,4}DMB group as DDQ. In other words, PIFA formed a charge transfer (CT) complex under a single-electron-transfer (SET) mechanism for the ^{3,4}DMB group that had a higher electron density within its aromatic ring and that subsequently cleaved as 3,4-dimethoxybenzaldehyde from trace amounts of water in post-processing or in the reaction

system after the hydrogen at the benzyl position was removed. The desired isoindolinone **5a** with secondary amide was thus obtained, in accordance with the above supposition.



Scheme 3

As described above, the [3,4]DMB group represents the optimal protective group for the secondary amide (γ-lactam) moiety of an isoindolinone ring with an extraordinarily high polarity and difficult handling characteristics. This protective element also has good solubility towards solvents and can be handled relatively stably against general acidic or alkaline conditions. In addition, experimental results showed that the [3,4]DMB group of isoindolinone **4c** had sufficient capacity to endure hydrogenation and oxidizing agents such as DDQ. Moreover, the use of PIFA for deprotection of the [3,4]DMB group of **4c** enables simple removal under mild reaction conditions (in benzene solvent at room temperature), and deprotected isoindolinone **5a** can be obtained in high yield.

EXPERIMENTAL

Routine monitorings of reaction were carried out using glass- supported Merck silica gel 60 F_{254} TLC plates. Flash column chromatography was performed on Kanto Chemical Silica Gel 60N (spherical, neutral 40–50 nm) with the solvents indicated. Measurements of optical rotations were performed with a JASCO DIP-370 automatic digital polarimeter. ^{1}H and ^{13}C NMR spectra were measured with a JEOL AL-400 (400 MHz) spectrometer. Chemical shifts were expressed in ppm using Me_4Si ($\delta = 0$) as an internal standard. The following abbreviations is used: singlet (s) and broad singlet (brs). Infrared (IR) spectral measurements were carried out with a JASCO FT/IR-4100 spectrometer. Low- and High-resolution mass (HRMS) spectra were measured on a JEOL JMS-DX 303/JMA-DA 5000 SYSTEM

high resolution mass spectrometer.

4-Acetoxy-5-acetoxymethyl-6-methoxyisoindolin-1-one (5a)

General procedure (Table 1, entry 10): Phenyliodine(III) bis(trifluoroacetate) (PIFA) (194 mg, 0.45 mmol) was added in small portions to a stirred solution of **4c** (20 mg, 45 μmol) in dry benzene (5 mL) at room temperature. After 7 h, the reaction was quenched with 10% aqueous $Na_2S_2O_3$ (10 mL) at room temperature, and the mixture was extracted with $CHCl_3$ (3 x 10 mL). The combined extracts were washed with brine (10 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/AcOEt 3:1) to give **5a** (12.3 mg, 93%) as a colorless amorphous powder; IR (KBr) 1767, 1738, 1699, 1474, 1433, 1368, 1336, 1110, 1024, 769, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 3H), 2.36 (s, 3H), 3.94 (s, 3H), 4.28 (s, 2H), 5.23 (s, 2H), 6.74 (brs, 1H), 7.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5, 20.8, 43.9, 55.3, 56.5, 103.5, 120.9, 128.3, 134.6, 145.6, 159.9, 168.2, 170.7, 170.8; HRMS (EI): *m/z*: calcd for $C_{14}H_{15}NO_6$, 293.2720, found 293.2718 $[M]^+$.

4-Hydroxy-5-(hydroxymethyl)-6-methoxyisoindolin-1-one (5b)

Table 1, entry 15: Phenyliodine(III) bis(trifluoroacetate) (PIFA) (215 mg, 0.5 mmol) was added in small portions to a stirred solution of **4d** (20 mg, 50 μmol) in dry benzene (5 mL) at room temperature. After 8 h, the reaction was quenched with 10% aqueous $Na_2S_2O_3$ (10 mL) at room temperature, and the mixture was extracted with $CHCl_3$ (3 x 10 mL). The combined extracts were washed with brine (10 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/AcOEt 1:5 to 0:1) to give **5b** (7.1 mg, 68%) as a colorless solid; Recrystallization from EtOAc afforded colorless prisms, mp 197–199 °C; IR (KBr) 1738, 1699, 1474, 1433, 1336, 1110, 1024, 769, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.53 (s, 1H), 3.84 (s, 3H), 4.34 (s, 2H), 4.88 (s, 2H), 6.13 (brs, 1H), 6.92 (s, 1H), 8.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.9, 54.4, 56.1, 98.3, 123.0, 127.6, 134.6, 151.4, 156.1, 173.7; HRMS (EI): *m/z*: calcd for $C_{10}H_{11}NO_4$, 209.0688, found 209.0684 $[M]^+$.

5-Methoxy-2,2-dimethyl-8,9-dihydro-[1,3]dioxino[4,5-*e*]isoindol-7(4*H*)-one (5c)

Table 1, entry 16: Phenyliodine(III) bis(trifluoroacetate) (PIFA) (215 mg, 0.5 mmol) was added in small portions to a stirred solution of **4d** (20 mg, 50 μmol) and K_2CO_3 (138 mg, 1.0 mmol) in dry benzene (5 mL) at room temperature. After 12 h, the reaction was quenched with 10% aqueous $Na_2S_2O_3$ (10 mL) at room temperature, and the mixture was extracted with $CHCl_3$ (3 x 10 mL). The combined extracts were washed with brine (10 mL), then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/AcOEt 1:1 to 0:1) to give **5c** (9.6 mg, 77%) as a pale yellow solid; Recrystallization from EtOAc afforded colorless prisms, mp 205–207 °C; IR (KBr) 3200, 2227, 1696, 1628, 1607, 1477, 1374, 1354, 1108, 839, 733 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$): δ 1.56 (s, 6H), 3.87 (s, 3H), 4.31 (s, 2H), 4.84 (s, 2H), 6.93 (s, 1H), 7.27 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.6 (2C), 42.8, 55.5, 58.5, 66.9, 96.3, 111.9, 123.9, 132.3, 146.9, 156.5, 171.9; HRMS (FAB): *m/z*: calcd for $C_{13}H_{15}NO_4$, 249.1001, found 249.0989 $[M]^+$.

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