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DEPROTECTION OF THE CARBAZOLE PMB GROUP USING HYPERVALENT IODINE REAGENT COMBINED WITH *N*-HYDROXYPHTHALIMIDE

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Manuscript dedicated to Prof. Dr. Yasuyuki Kita on the celebration of his 77th birthday

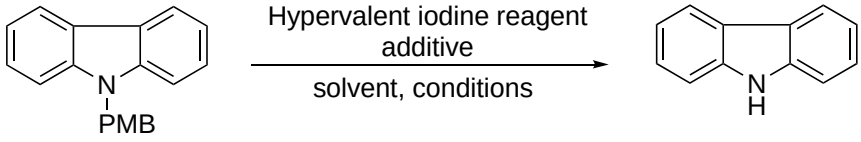
Abstract – We developed a novel method for deprotecting the *N*-PMB group of carbazoles. The combination of $PhI(OAc)_2$ and *N*-hydroxyphthalimide cleaved the *N*-PMB group with moderate to good yields depending on the substituents on the carbazole ring.

Carbazole is an important structure in natural products and pharmaceuticals with a variety of biological activities.[1] Carbazoles are also used in functional materials with interesting optical and electronic properties.[2] Therefore, various synthetic methods have been reported.[1a,1b,3] In some cases, a nitrogen atom must be protected since the nitrogen atom of carbazole may participate in the reaction. The *p*-methoxybenzyl (PMB) group is a useful protective group and is deprotected under acidic, oxidative, and hydrogenation conditions.[4] However, strongly acidic or basic conditions are sometimes adopted.[5] We have reported the oxidative deprotection of the carbazole PMB group using dichlorodicyanobenzoquinone (DDQ), which required a prolonged reaction time even with heating.[6] Therefore, we investigated another approach to oxidative deprotection of the PMB group using a hypervalent iodine reagent. Katoh and co-workers reported the hypervalent iodine-mediated deprotection of 3,4-dimethoxybenzyl group of a hydroxy group[7] and on a γ-lactam nitrogen[8] using $PhI(OCOCF_3)_2$, and their method can selectively cleave 3,4-dimethoxybenzyl ether keeping benzyl and *p*-methoxybenzyl ethers remained.

We have investigated hypervalent iodine-mediated reactions, such as the construction of heterocycles using oxidative rearrangement,[9] the oxidation of aldoxime to carboxylic acid,[10] Beckmann rearrangement,[11] and decarboxylative halogenation.[12] We first attempted deprotection using $PhI(OAc)_2$ as a hypervalent iodine reagent in $(CH_2Cl)_2$ at room temperature, but the reaction did not proceed (Table 1,

Entry 1). The deprotection proceeded at 70 °C for 48 h, but the yield was 12% (Entry 2). We used other hypervalent iodine reagents, which resulted in complex mixtures (Entries 3 and 4). We then chose 1,4-dioxane as a solvent, which resulted in slightly lower reactivity since the 9*H*-carbazole (**2a**) generated seemed to react with the remaining $PhI(OAc)_2$. No reaction occurred when using 3.0 equivalents of $PhI(OAc)_2$ and heating from room temperature to 50 °C (Entry 5). We next examined additives such as Lewis acids and bases; only $NaHCO_3$ yielded a trace amount of product (3%) (Entry 9), while the others were ineffective (Entries 6-8). Finally, we evaluated the addition of TEMPO and *N*-hydroxyphthalimide (NHPI) (Entries 10 and 11). The combination of $PhI(OAc)_2$ and NHPI was effective, and the deprotected product was obtained at a 35% yield (Entry 11), whereas the reaction of **1a** with NHPI did not afford the desired product (Entry 12).

Table 1. Deprotection of *N*-PMB group on carbazole with hypervalent iodine reagent



1a **2a**

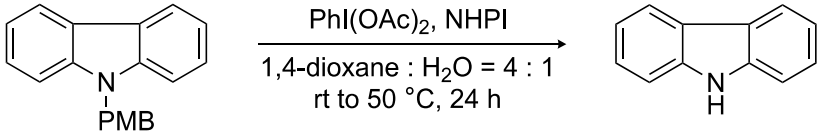
Entry	Hypervalent iodine reagent	Solvent	Additive	Conditions	Yield (%)
1	$PhI(OAc)_2$ (1.2 eq)	$(CH_2Cl)_2$	-	rt, 24 h	-
2	$PhI(OAc)_2$ (1.2 eq)	$(CH_2Cl)_2$	-	70 °C, 48 h	12
3	$PhI(OCOCF_3)_2$ (1.2 eq)	$(CH_2Cl)_2$	-	70 °C, 24 h	complex mixture
4	PhI(OH)OTs (1.2 eq)	$(CH_2Cl)_2$	-	70 °C, 24 h	complex miture
5	$PhI(OAc)_2$ (3.0 eq)	1,4-dioxane	-	rt to 50 °C, 24 h	-
6	$PhI(OAc)_2$ (3.0 eq)	1,4-dioxane	$BF_3{\cdot}Et_2O$ (3.0 eq)	rt to 50 °C, 24 h	complex mixture
7	$PhI(OAc)_2$ (3.0 eq)	1,4-dioxane	$ZnCl_2$ (3.0 eq)	rt to 50 °C, 24 h	-
8	$PhI(OAc)_2$ (3.0 eq)	1,4-dioxane	ZnO (3.0 eq)	rt to 50 °C, 24 h	trace
9	$PhI(OAc)_2$ (3.0 eq)	1,4-dioxane	$NaHCO_3$ (3.0 eq)	rt to 50 °C, 24 h	3
10	$PhI(OAc)_2$ (3.0 eq)	1,4-dioxane	TEMPO (3.0 eq)	rt to 50 °C, 24 h	-
11	$PhI(OAc)_2$ (3.0 eq)	1,4-dioxane	NHPI (3.0 eq)	rt to 50 °C, 24 h	35 (38)[a]
12	-	1,4-dioxane	NHPI (3.0 eq)	rt to 50 °C, 24 h	-

[a] The parenthesis indicated the yield of starting material.

We re-investigated the solvent used (Table 2). The best result was obtained using 1,4-dioxane (Entry 1), although the reaction also proceeded using CH_2Cl_2 and MeCN (Entries 4 and 5). Thin layer

chromatography was performed to examine the reaction conditions and indicated that the reaction proceeded via an intermediate, which might be converted to the product by hydrolysis. When H_2O was used as a co-solvent (Entries 6–8), the reaction was significantly enhanced in the mixed solvent (1,4-dioxane:H_2O = 4:1), yielding 72% **1a** (Entry 7). Finally, we optimized the amounts of the reagents (Entries 9–12). Decreasing the $PhI(OAc)_2$ or NHPI amount reduced the yield of **1a** (Entries 9 and 10). Increasing the amounts of both reagents gave no significant improvement (Entries 11 and 12). The optimal conditions were 3.0 equivalents of $PhI(OAc)_2$ and NHPI in 1,4-dioxane–H_2O.

Table 2. Optimization of reaction conditions



1a **2a**

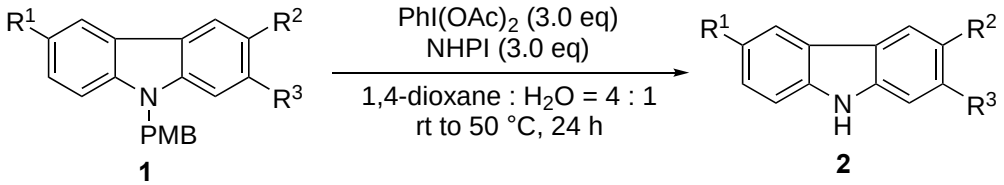
Entry	$PhI(OAc)_2$ (eq)	NHPI (eq)	Solvent	Yield (%)[a]
1	3.0	3.0	1,4-dioxane	35 (38)
2	3.0	3.0	THF	- (93)
3	3.0	3.0	toluene	3 (20)
4	3.0	3.0	CH_2Cl_2	12
5	3.0	3.0	MeCN	18
6	3.0	3.0	1,4-dioxane : H_2O (2 : 1)	60 (17)
7	3.0	3.0	1,4-dioxane : H_2O (4 : 1)	72 (24)
8	3.0	3.0	1,4-dioxane : H_2O (10 : 1)	57 (20)
9	2.0	3.0	1,4-dioxane : H_2O (4 : 1)	65 (20)
10	3.0	2.0	1,4-dioxane : H_2O (4 : 1)	61 (10)
11	3.5	3.5	1,4-dioxane : H_2O (4 : 1)	75 (4)
12	4.0	4.0	1,4-dioxane : H_2O (4 : 1)	75[b]

[a] The parenthesis indicated the yield of starting material. [b] The reaction was conducted for 5 h.

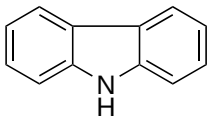
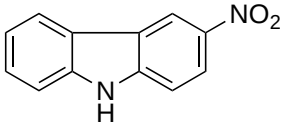
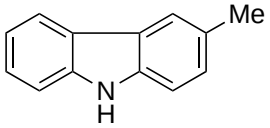
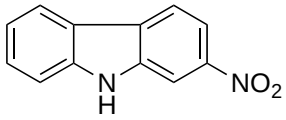
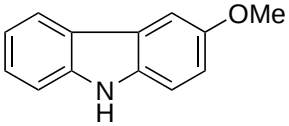
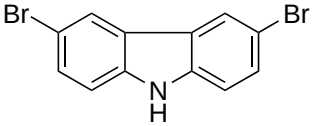
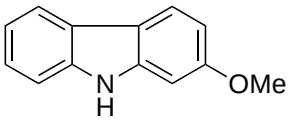
Under the optimal conditions, we investigated the substrate scope (Table 3). Unexpectedly, the reaction was significantly affected by substituents on carbazole. The deprotection of *N*-PMB-3-methylcarbazole (**1b**) resulted in a lower yield (22%), whereas the reaction of non-substituted **1a** afforded a 72% yield (Table 3, Entries 1 and 2). In the case of **1b**, the starting material was consumed completely, and the product seemed to overreact with the reagents. *N*-PMB-3-methoxycarbazole (**1c**) also provided the product, but at only a 5% yield (entry 3). However, the reaction of *N*-PMB-2-methoxycarbazole (**1d**)

resulted in a 51% yield under the same conditions (Entry 4), indicating that the electron density of the carbazole ring is important for this reaction. *N*-PMB-3-nitrocarbazole (**1e**) underwent deprotection at a 19% yield, and 60% of the starting material was recovered (Entry 5). In comparison, the deprotection of *N*-PMB-2-nitrocarbazole (**1f**) led to 2-nitrocarbazole (**2f**) at a 45% yield and 54% recovery of the starting material (entry 7). *N*-PMB-3,6-dibromocarbazole (**1g**) was also deprotected at a low yield (22%), with recovery of 69% of the starting material (Entry 9). From these results, electron-rich *N*-PMB carbazoles were reactive toward the deprotection conditions. However, the products were also reactive and decomposed under the reaction leading to low yields. The reactivity was strongly affected by the *p*-substituents of nitrogen. On the other hand, electron-poor *N*-PMB carbazoles were low reactive, resulting in the starting material remained. We tried to improve the deprotection of **1e**, **1f**, and **1g**, keeping the starting materials after the reaction. When MeCN was used as a more reactive solvent, the yield of **2e** was improved to 40% (Entry 6). For **1f** and **1g**, increasing the reaction temperature to 80 °C accelerated the reaction, leading to improved yields (Entries 8 and 10).

Table 3. Scope of substrates



1 **2**

Entry	Substrate	Yield (%)[a]	Entry	Substrate	Yield (%)[a]
1	 **2a**	72	5 6	 **2e**	19 (60) 40 (5)[b]
2	 **2b**	22	7 8	 **2f**	45 (54) 50 (45)[c]
3	 **2c**	5	9 10	 **2g**	22 (69) 52 (38)[c]
4	 **2d**	51 (2)			

[a] The parenthesis indicated the yield of starting material. [b] The reaction was conducted in MeCN. [c] The reaction was conducted at rt to 80 °C.

In summary, we developed a new oxidative deprotection method for the *N*-PMB group on carbazoles. The combination of $PhI(OAc)_2$ and NHPI was effective for the deprotection reaction from room temperature to 50 °C for 24 h. The substituents on carbazole affected the reaction, but a slight change in reaction conditions improved yields. Further applications to other heterocycles, such as indoles and imidazoles, are underway.

EXPERIMENTAL

General: Column chromatography and TLC were performed on Merck Silica gel 60 (230–400 mesh) and Merck Silica gel F254 plates (0.25 mm), respectively. The melting point was measured using the Stuart® melting point apparatus SMP3 with an AC input of 100 V. ^{1}H-NMR spectra were recorded on the JEOL JMN-400 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Data are reported as follows: chemical shift in ppm (δ), integration, multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, m = multiplet), and coupling constant (Hz).

Typical procedure for deprotection of *N*-PMB group on carbazole: To a solution of **1** in 1,4-dioxane-H_2O (2 : 1) (0.1 M) was added *N*-hydroxyphthalimide (3.0 eq) and $PhI(OAc)_2$ (3.0 eq) at room temperature and stirred for 1 h. The reaction mixture was heated at 50 °C for 24 h. To the reaction mixture was added 10% aqueous sodium sulfite, and the mixture was extracted with AcOEt. The organic layer was washed with 10% aqueous sodium sulfite and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to give **2**.

9*H*-Carbazole (2a)[13]

Silica gel column chromatography (hexane/AcOEt = 15/1) gave 24 mg of **2a** (72%) as white solid, mp 234-245 °C. ^{1}H-NMR($CDCl_3$) δ: 7.22-7.26 (2H, m), 7.41-7.43 (4H, m), 8.04-8.09 (3H, m).

3-Methyl-9*H*-carbazole (2b)[13]

Silica gel column chromatography (hexane/AcOEt = 10/1) gave 7.9 mg of **2b** (22%) as white solid, mp 207-208 °C. ^{1}H-NMR($CDCl_3$) δ: 2.53 (3H, s), 7.19-7.41 (5H, m), 7.88 (1H, s), 7.96 (1H, brs), 8.04 (1H, d, *J* = 8.0 Hz).

3-Methoxy-9*H*-carbazole (2c)[13]

Silica gel column chromatography (hexane/AcOEt = 5/1) gave 1.0 mg of **2c** (5%) as light pink solid, mp 146-148 °C. ^{1}H-NMR($CDCl_3$) δ: 3.93 (3H, s), 7.07 (1H, dd, *J* = 2.8, 8.8 Hz), 7.19-7.23 (1H, m), 7.34 (1H, d, *J* = 8.8 Hz), 7.40-7.41 (2H, m), 7.56 (1H, d, *J* = 2.4 Hz), 7.92 (1H, brs), 8.03 (1H, d, *J* = 7.6 Hz).

2-Methoxy-9*H*-carbazole (2d)[13]

Silica gel column chromatography (hexane/AcOEt = 5/1) gave 20 mg of **2d** (51%) as light pink solid, mp 233-234 °C. ^{1}H-NMR($CDCl_3$) δ: 3.91 (3H, s), 6.85-6.87 (1H, m), 6.92 (1H, s), 7.19-7.22 (1H, m), 7.32-7.40 (2H, m), 7.93-7.99 (3H, m).

3-Nitro-9*H*-carbazole (2e)[14]

Silica gel column chromatography (hexane/AcOEt = 10/1), then preparative TLC (hexane/AcOEt = 5/1) gave 8.0 mg of **2e** (19%) as deep yellow solid, mp 212-213 °C. ^{1}H-NMR($CDCl_3$) δ: 7.34-7.38 (1H, m), 7.48 (1H, d, *J* = 8.8 Hz), 7.51-7.54 (2H, m), 8.15 (1H, d, *J* = 8.4 Hz), 8.36 (1H, dd, *J* = 2.8, 8.8 Hz), 8.50 (1H, brs), 9.02 (1H, d, *J* = 2.0 Hz)

2-Nitro-9*H*-carbazole (2f)[13]

Silica gel column chromatography (hexane/AcOEt = 8/1), then preparative TLC (hexane/AcOEt = 20/1) gave 19 mg of **2f** (45%) as deep yellow solid, mp 172-173 °C. ^{1}H-NMR($CDCl_3$) δ: 7.31-7.35 (1H, m), 7.51-7.55 (2H, m), 8.13-8.15 (3H, m), 8.37 (1H, s), 8.49 (1H, brs)

3,6-Dibromo-9*H*-carbazole (2g)[15]

Silica gel column chromatography (hexane/AcOEt = 15/1) gave 14 mg of **2g** (22%) as white solid, mp 210-211 °C. ^{1}H-NMR($CDCl_3$) δ: 7.31 (2H, d, *J* = 8.8 Hz), 7.52 (2H, d, *J* = 2.0, 8.2 Hz), 8.13-8.14 (3H, m).

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