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A NEW DEPROTECTION PROCEDURE FOR THE *N*-METHOXYMETHYL GROUP OF *N*-METHOXYMETHYL-HETEROCYCLIC COMPOUNDS†

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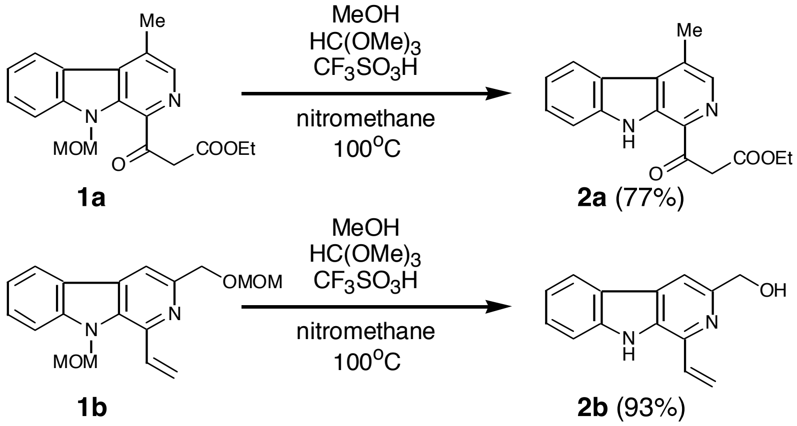
Abstract- A new deprotection procedure regarding the *N*-methoxymethyl (MOM) group was revealed during the total synthesis of oxopropalines D and G. We describe the deprotection method of *N*-MOM-heterocyclic compounds and its utilization.

Chloromethyl methyl ether (MOMCl) has been often used as a reagent for the protection of certain functional groups, such as hydroxy-, carboxy- and amino-groups.[1] Regarding them, there have been relatively few reports describing the protection of *N*-heterocyclic compounds. In 1960, the first example of the *N*-methoxymethylation and its deprotection for the Birch reduction of carbazole was reported by O'Brien and Smith.[2] Subsequently, the utilization of the *N*-MOM group for the imidazole[3] or indole[4] nitrogen atom was attempted and deprotected by hydrochloric acid[3] or a combination of lithium bromide-boron trifluoride in acetic anhydride,[4] respectively. In addition, the *N*-MOM group has been applied to the asymmetric synthesis of yohimban alkaloids by the Meyers group;[5] however, they reported that the removal of the *N*-MOM group was quite difficult and troublesome.

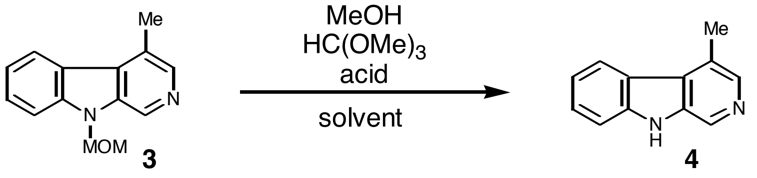
Recently, we have performed the total synthesis of novel β-carboline alkaloids, oxopropalines G and D, through the construction of a 4-methyl-β-carboline framework based on the thermal electrocyclic reaction of the 1-azahexatriene system involving the indole 2,3-bond.[6] During the development of this work, we examined the ketalization of □-keto ester (**1a**) using the ketalization procedure described by Rice and co-workers,[7] [the combination of methanol (10 eq.), methyl orthoformate (10 eq.), and trifluoromethanesulfonic (triflic) acid (0.2 eq.) in nitromethane as solvent at 100°C] for a selective reduction of the ester group to an alcohol. However, the ketalization of **1a** did not occur. When the amount of triflic acid was increased in 2.0 mole equivalents, it was found that the *N*-MOM-group in □-carboline (**1a**) was removed to provide the □-carboline (**2a**) in a 77% yield without influencing the □-keto ester part.[6] Based on this finding, this modified procedure for the deprotection of the *N*-MOM group of *N*,*O*-bismethoxymethyl-□-carboline (**1b**) has been successfully applied to yield □-carboline (**2b**) along with cleavage of the *O*-MOM group in an excellent yield (93%) in the total synthesis of □-carboline alkaloids, pyridindolols (Scheme 1).[8]



Scheme 1

In the present paper, we describe a novel deprotection procedure regarding the *N*-MOM group including its applications. Namely, we have investigated the influences of acids, additives (methanol and methyl orthoformate), and solvents using *N*-MOM-4-methyl-□-carboline (**3**)[6b] as a standard substrate (Table 1). Initially, when the amount of triflic acid was examined, at least three equivalents of triflic acid were required for the completion of the reaction (Runs 1-3). The use of other acids such as methanesulfonic acid or trifluoroacetic acid instead of triflic acid did not provide good results (Runs 6, 7). Although the presence of additive methyl orthoformate might be not essential, as shown in Run 4, the absence of methyl orthoformate was found to decrease the yield of deprotected □-carboline (**4**) (Run 5). We considered that the combination of methyl orthoformate and methanol might be required. Next, the alternative solvents of nitromethane were studied, but the uses of dioxane (Run 10), CH_2Cl_2 (Run 12), toluene (Run 14), and EtOAc (Run 15) were not effective in this deprotection method, respectively. In addition, the uses of MeCN (Run 8), THF (Run 9), DMF (Run 11), and DMSO (Run 13) as solvents could not give the corresponding product. Consequently, Run 3 seemed to be the best condition in the case of this substrate. A reaction time of within three hours was the best condition. If the reaction time was longer than three hours, the yield of the deprotected products tended to decrease.

Table 1. Deprotection of the *N*-MOM-□-Carboline 3



Run	MeOH (eq)	HC(OMe)$_3$ (eq)	Acid (eq)	Solvent	Temp. (^{o}C)	Time (h)	Yield (%)[a]
1	10	10	CF_3SO_3H (0.2)	$MeNO_2$	100	overnight	n.r.[b]
2	10	10	CF_3SO_3H (2.0)	$MeNO_2$	100	2	65
3	10	10	CF_3SO_3H (3.0)	$MeNO_2$	100	3	92
4	-	10	CF_3SO_3H (3.0)	$MeNO_2$	100	1	76
5	10	-	CF_3SO_3H (3.0)	$MeNO_2$	100	overnight	65
6	10	10	$MeSO_3H$ (3.0)	$MeNO_2$	100	overnight	—
7	10	10	CF_3CO_2H (3.0)	$MeNO_2$	100	overnight	n.r.
8	10	10	CF_3SO_3H (3.0)	MeCN	80	overnight	n.r.
9	10	10	CF_3SO_3H (3.0)	THF	70	1	n.r.
10	10	10	CF_3SO_3H (3.0)	dioxane	100	overnight	21
11	10	10	CF_3SO_3H (3.0)	DMF	100	overnight	—
12	10	10	CF_3SO_3H (3.0)	CH_2Cl_2	50	1	25
13	10	10	CF_3SO_3H (3.0)	DMSO	100	3	n.r.
14	10	10	CF_3SO_3H (3.0)	toluene	100	overnight	37
15	10	10	CF_3SO_3H (3.0)	EtOAc	70	overnight	8

a) Isolated yield of **4**. b) n.r.: not reacted.

Furthermore, we examined whether this deprotection procedure of the *N*-MOM group could be used for the □-carbolines (**5a-e**) possessing the other functional groups. As shown in Table 2, each of the □-carbolines (**6a-e**) was isolated in moderate to excellent yields (45-94%). It was presumed that the procedure could be used without influencing the other functional groups.

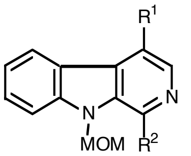
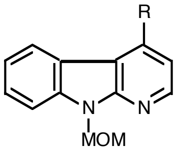
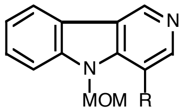
This deprotection procedure regarding the *N*-MOM group was applied to the other *N*-MOM heterocyclic compounds, including □-carbolines (**5f-g**), □-carbolines (**5h-I**), carbazole (**5j**), 2-formylindole (**5k**), 3-methylindole (**5l**), benzimidazole (**5m**), and 2-methylthioimidazole (**5n**). Although the closely related *N*-MOM □-carbolines and □-carbolines were smoothly converted into the corresponding □- and □-

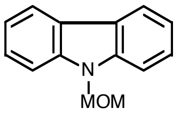
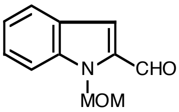
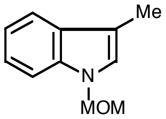
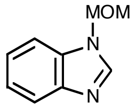
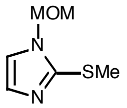
carbolines (**6f-i**) in good to excellent yields (70-97%), applications to carbazole (**5j**), indoles (**5k-l**), benzimidazole (**5m**), and imidazole (**5n**) were unsuccessful. In the case of 2-formylindole (**5k**), even an acetalization failed to occur.

Table 2. Deprotection of the *N*-MOM-heterocyclic compounds 5a-n

$$\underset{\mathbf{5}}{\text{Ar—MOM}} \xrightarrow[\text{MeNO}_2,\ 100^{\circ}\text{C}]{\text{CF}_3\text{SO}_3\text{H},\ \text{MeOH},\ \text{HC(OMe)}_3} \underset{\mathbf{6}}{\text{Ar—H}}$$

Ar: heteroaromatic

Substrates		Yields (%) of **6a-i**	
	**5a** : R^1=Me, R^2=OH[6b]	**6a**	81
	5b : R^1=Me, R^2=CHO[6b]	**6b**[6b]	68
	5c : R^1=Me, R^2=OSO_2CF_3[6b]	**6c**	45
	5d : R^1=Me, R^2=COOMe[6b]	**6d**[6b]	94
	5e : R^1=H, R^2=COOMe	**6e**	88
	**5f** : R=H a)	**6f**	74
	5g : R=Me a)	**6g**	70
	**5h** : R=H	**6h**	97
	5i : R=Me	**6i**	87

Substrates		Yields (%) of **6j-n**
	**5j**[4]	unknown products
	**5k**[10]	**6k** b)
	**5l**[9]	**6l** b)
	**5m**[11]	**6m** b)
	**5n**	**6n** b)

a) 5 eq. of CF_3SO_3H was used. b) **6k-n** were not isolated.

In summary, it was found that the ketalization method regarding diaryl ketones developed by the Rice group[7] can be applicable as a *N*-MOM deprotection method by employing a slightly modification. The *N*-MOM deprotection procedure for □-, □-, □-carbolines has been successfully established, but a mechanism of the deprotection process and a reason that the deprotection is not observed in other substrates are not clear. As a result, the extreme restriction of the substrate for the deprotection of the *N*-MOM group was demonstrated.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were measured with a Horiba FT-720 spectrophotometer, and ^{1}H-NMR spectra were taken with a JEOL JNM AL-300 spectrometer using tetramethylsilane as an internal standard. MS spectra were recorded on a Shimadzu QP-5050 spectrometer. Column chromatography was performed on silica gel (60-100 mesh, Merk Art 7734) throughout the present study. All reactions were carried out under nitrogen atmosphere. The substrates (**3**, **5a**, **5b**, **5c**, **5d**, **5j**, **5k**, **5l**, and **5m**) were arranged by means of the known procedures. [4,6b, 9-11] The substrates (**5e**, **5f**, **5g**, **5h**, **5i**, and **5n**) were prepared from □, □, □-carbolines and imidazole, respectively. **5e**: mp 79-80°C (Et$_2$O-hexane); IR(KBr) *v* : 1650 cm^{-1}; ^{1}H-NMR(CDCl$_3$) □: 3.03 (3H, s), 4.07 (3H, s), 5.86 (2H, s), 7.17-7.66 (3H, m), 8.07 (1H, d, *J*=6.0 Hz), 8.09 (1H, dd, *J*=2.0, 8.0 Hz), 8.50 (1H, d, *J*=6.0 Hz); MS *m*/*z*: 270 (M$^+$). **5f**: pale yellow liquid; ^{1}H-NMR(CDCl$_3$) □: 3.35 (3H, s), 5.90 (2H, s), 7.22 (1H, dd, *J*=5.5, 7.7 Hz), 7.33 (1H, t, *J*=8.0 Hz), 7.54 (1H, t, *J*=8.0 Hz), 7.64 (1H, d, *J*=8.0 Hz), 8.07 (1H, d, *J*=8.0 Hz), 8.32 (1H, d, *J*=1.5, 7.7 Hz), 8.50 (1H, dd, *J*=1.5, 5.5 Hz); MS *m*/*z*: 212 (M$^+$). **5g**: pale yellow liquid; ^{1}H-NMR(CDCl$_3$) □: 2.86 (3H, s), 3.34 (3H, s), 5.90 (2H, s), 7.01 (1H, d, *J*=5.2 Hz), 7.34 (1H, t, *J*=8.0 Hz), 7.53 (1H, t, *J*=8.0 Hz), 7.65 (1H, d, *J*=8.0 Hz), 8.13 (1H, d, *J*=8.0 Hz), 8.36 (1H, d, *J*=5.2 Hz); MS *m*/*z*: 226 (M$^+$). **5h**: pale yellow liquid; ^{1}H-NMR(CDCl$_3$) □: 3.30 (3H, s), 5.68 (2H, s), 7.34-7.62 (4H, m), 8.15 (1H, d, *J*=8 Hz), 8.58 (1H, d, *J*=6 Hz), 9.32 (1H, s); MS *m*/*z*: 212 (M$^+$). **5i**: mp 124-126 °C (MeOH); ^{1}H-NMR(CDCl$_3$) □: 2.61 (3H, s), 3.17 (3H, s), 5.57 (2H, s), 7.17-7.24 (1H, m), 7.39-7.41 (2H, m), 7.98 (1H, d, *J*=8.5 Hz), 8.20 (1H, s), 7.99 (1H, s), 9.05 (1H, s); MS *m*/*z*: 226 (M$^+$). **5n**: pale yellow liquid; ^{1}H-NMR(CDCl$_3$) □: 2.62 (3H, s), 3.30 (3H, s), 5.23 (2H, s), 7.06 (1H, d, *J*=1.5 Hz), 7.09 (1H, d, *J*=1.5 Hz); MS *m*/*z*: 158 (M$^+$).

Gerneral Deprotection Procedure of *N*-Methoxymethyl Heterocyclic compounds

4-Methyl-9*H*-pyrido[3,4-*b*]indole (4)

Trifluoromethanesulfonic acid (60 □L, 0.68 mmol) was added to an ice-cooled mixture of the *N*-MOM-□-carboline (**3**) (50 mg, 0.23 mmol), MeOH (97 □L, 2.25 mmol), and trimethyl orthoformate (246 □l, 2.25 mmol) in nitromethane (5 mL). The resulting mixture was heated at 100°C for 1 h. After cooling to rt, the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na$_2$SO$_4$, and evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc−hexane (7:3) as eluent to give the *N*-deprotected □-carboline (**4**) (37 mg, 92%), mp 132-134 °C (EtOAc-hexane). ^{1}H-NMR(CDCl$_3$) □: 2.78 (3H, s), 7.18-7.26 (1H, m), 7.48 (2H, d, *J*=3.3 Hz), 8.15 (2H, t, *J*=8.0 Hz), 8.73 (1H, s), 8.95 (1H, s); MS *m*/*z*: 182 (M$^+$). *Anal.* Calcd for C$_{12}$H$_{10}$N$_2$: C, 79.10; H, 5.53; N, 15.37. Found: C, 79.12; H, 5.70; N, 15.29.

4-Methyl-9*H*-pyrido[3,4-*b*]indol-1(2*H*)-one (6a)

The same procedure as above was carried out using **5a** (154 mg, 0.64 mmol) to give the □-carboline (**6a**) (102 mg, 81%), mp 250-253 °C (EtOH). IR(KBr) *v* : 1650 cm^{-1}; ^{1}H-NMR($CDCl_3$) □ : 2.64 (3H, s), 6.85 (1H, m), 7.27 (1H, t, *J*=8.1 Hz), 7.50 (1H, t, *J*=8.1 Hz), 7.61 (1H, d, *J*=8.1 Hz), 7.99 (1H, s), 8.13 (1H, d, *J*=8.1 Hz); MS *m*/*z*: 198 (M^+). *Anal.* Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.84; H, 5.13; N, 14.06.

4-Methyl-9*H*-pyrido[3,4-*b*]indole-1-carbaldehyde (6b)

The same procedure as above was carried out using **5b** (50 mg, 0.20 mmol) to give the □-carboline (**6b**) (28 mg, 68%), mp 209-211 °C (Et_2O)(lit.,[6b] mp 209-211°C). IR(KBr) *v* : 1656 cm^{-1}; ^{1}H-NMR($CDCl_3$) □ : 2.95 (3H, s), 7.26-7.41 (2H, m), 7.61-7.63 (2H, m), 8.23 (1H, d, *J*=8.0 Hz), 8.43 (1H, s), 10.31 (1H, s); MS *m*/*z*: 210 (M^+).

4-Methyl-1-trifluoromethanesulfonyl-9*H*-pyrido[3,4-*b*]indole (6c)

The same procedure as above was carried out using **5c** (30 mg, 0.08 mmol) to give the □-carboline (**6c**) (12 mg, 45%), mp 109-110 °C (pet. Et_2O). IR(KBr) *v* : 1415 cm^{-1}; ^{1}H-NMR($CDCl_3$) □ : 2.86 (3H, s), 7.26-7.41 (1H, m), 7.59-7.66 (2H, m), 7.92 (1H, s), 8.19-8.22 (1H, m), 8.49 (1H, s); MS *m*/*z*: 330 (M^+). *Anal.* Calcd for $C_{13}H_9N_2O_3F_3S$: C, 47.27; H, 2.75; N, 8.48. Found: C, 47.31; H, 2.85; N, 8.37.

Methyl 4-Methyl-9*H*-pyrido[3,4-*b*]indole-1-carboxylate (6d)

The same procedure as above was carried out using **5d** (84 mg, 0.30 mmol) to give the □-carboline (**6d**) (67 mg, 94%), mp 184-185°C (EtOAc-hexane)(lit.,[6b] mp 184-185°C).

Methyl 9*H*-pyrido[3,4-*b*]indole-1-carboxylate (6e)

The same procedure as above was carried out using **5e** (42 mg, 0.16 mmol) to give the □-carboline (**6e**) (31 mg, 88%), mp 154-156 °C ($CHCl_3$-hexane). IR(KBr) *v* :1650 cm^{-1}; ^{1}H-NMR($CDCl_3$) □ : 4.15 (3H, s), 7.26-7.40 (1H, m), 7.60-7.68 (2H, m), 8.17-8.22 (2H, m), 8.64 (1H, d, *J*=6.0 Hz), 9.96 (1H, s); MS *m*/*z*: 226 (M^+). *Anal.* Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.21; H, 4.64; N, 12.30.

9*H*-Pyrido[2,3-*b*]indole (6f)

The same procedure as above was carried out using **5f** (48 mg, 0.23 mmol) with 5 equivalents of triflic acid to give the □-carboline (**6f**) (28 mg, 74%), which was identical with commercially available **6f** in all respect.

4-Methyl-9*H*-pyrido[2,3-*b*]indole (6g)

The same procedure as above was carried out using **5g** (50 mg, 0.22 mmol) with 5 equivalents of triflic acid to give the □-carboline (**6g**) (28 mg, 70%), mp 190-192 °C (EtOAc-hexane). ^{1}H-NMR($CDCl_3$) □ : 2.88 (3H, s), 7.01 (1H, d, *J*=5.2 Hz), 7.30 (1H, t, *J*=8.0 Hz), 7.49 (1H, t, *J*=8.0 Hz), 7.55 (1H, d, *J*=8.0 Hz), 8.12 (1H, d, *J*=8.0 Hz), 8.35 (1H, d, *J*=5.2 Hz), 9.94 (1H, br s); MS *m/z*: 182 (M^+). *Anal.* Calcd for $C_{12}H_{10}N_2$: C, 79.10; H, 5.53; N, 15.37. Found: C, 79.06; H, 5.66; N, 15.28.

9*H*-Pyrido[4,3-*b*]indole (6h)

The same procedure as above was carried out using **5h** (78 mg, 0.37 mmol) to give the □-carboline (**6h**) (60 mg, 97%), mp 232-235 °C (MeOH). ^{1}H-NMR($CDCl_3$) □ : 7.24-7.31 (2H, m), 7.40-7.47 (2H, m), 8.09 (1H, d, *J*=7.4 Hz), 8.46 (1H, d, *J*=7.4 Hz), 8.60 (1H, s), 9.27 (1H, s), MS *m/z*: 168 (M^+). *Anal.* Calcd for $C_{11}H_8N_2$: C, 78.55; H, 4.79; N, 16.66. Found: C, 78.74; H, 4.97; N, 16.50.

1-Methyl-9*H*-pyrido[4,3-*b*]indole (6i)

The same procedure as above was carried out using **5i** (73 mg, 0.32 mmol) to give the □-carboline (**6i**) (51 mg, 87%), mp 238-240 °C (EtOH). ^{1}H-NMR($CDCl_3$) □ : 2.44 (3H, s), 7.18-7.24 (2H, m), 7.36-7.47 (2H, m), 8.01 (1H, d, *J*=8.0 Hz), 8.11 (1H, s), 8.97 (1H, s), MS *m/z*: 182 (M^+). *Anal.* Calcd for $C_{12}H_{10}N_2$: C, 79.10; H, 5.53; N, 15.37. Found: C, 79.22; H, 5.59; N, 15.25.

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