p-METHOXYBENZYL GROUP AS A PROTECTING GROUP OF THE NITROGEN IN INDOLE DERIVATIVES: DEPROTECTION BY DDQ OR TRIFLUOROACETIC ACID

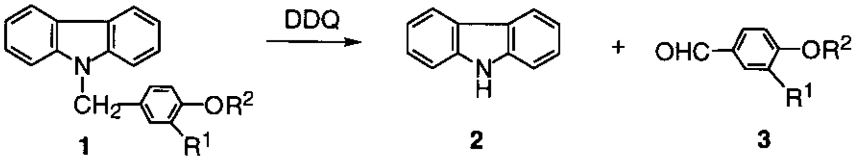
Yasuyoshi Miki,* Hiroko Hachiken, Yoshimi Kashima, Wakiko Sugimura, and Norihide Yanase
Faculty of Pharmaceutical Sciences, Kinki University, 3-4-1, Kowakae, Higashi-Osaka 577, Japan

Abstract - Deprotection of 9-*p*-methoxybenzylcarbazole with DDQ gave a carbazole. However, methyl 1-*p*-methoxybenzylindole-2-carboxylate and dimethyl 1-*p*-methoxybenzyl-2,3-indoledicarboxylate were treated with TFA to yield the corresponding methyl indole-2-carboxylate and dimethyl indole-2,3-dicarboxylate.

In a synthesis of indole natural products, protection of the nitrogen in an indole by alkyl groups,[1] e. g., benzyl and alkoxymethyl,[2] is usually necessary. Protection of the nitrogen in an indole by a benzyl group is frequently used, but the debenzylation sometimes resulted in low yields[3] or required severe conditions.[4] Deprotection of the *p*-methoxybenzyl[5] or 2,4-dimethoxybenzyl group[6] of the nitrogen in heterocycles was done by treatment with TFA. Yonemitsu and Oikawa[7] showed excellent results in the deprotection of *p*-methoxybenzyl or 2,4-dimethoxybenzyl group of alcohols by DDQ oxidation, but there are no reports regarding indole derivatives. Therefore, we were intrigued by the use of a *p*-methoxybenzyl group as a protecting group of the nitrogen in an indole.

We first investigated the effect of DDQ in the deprotection of 9-*p*-methoxybenzylcarbazole (**1a**) by using Yonemitsu and Oikawa's condition[7] (CH_2Cl_2, room temperature, 96 h), but **1a** was recovered (Scheme 1). As shown in Table 1, treatment of **1a** with DDQ (1.1 equivalent) at 50°C in the presence of water (30 equivalents) gave carbazole (**2**) in 27% yield, but **1a** was recovered in 42% yield (Entry 1). A mixture of **1a** and DDQ (2.2 equivalents) in toluene in the presence of water (30 equivalents) was heated at 80°C for 71 h to give **2** and *p*-methoxybenzaldehyde (**3a**) in 79 and 48% yields, respectively (Entry 2). Reaction of **1b** (R^2 = CH_2Ph) with DDQ gave **2** in 78% yield, but the corresponding hydroxy derivative (**1c**) was not isolated. This result shows that the benzyloxy group in **1b** is stable in this condition (Entry 3). **1c** (R^2 = H) and **1d** (R^2 = TBDMS) also afforded **2** in 64 and 84% yields, respectively (Entries 4 and 5). We next examined the reactivity of 9-(3,4-dimethoxybenzyl)carbazole (**1e**), which has an additional methoxy group on the benzene ring of **1a**. In a similar manner in the conversion of **1a** to **2**, debenzylation of **1e** was effected in 82% yield in shorter time compared with **1a** (Entry 6).

Scheme 1



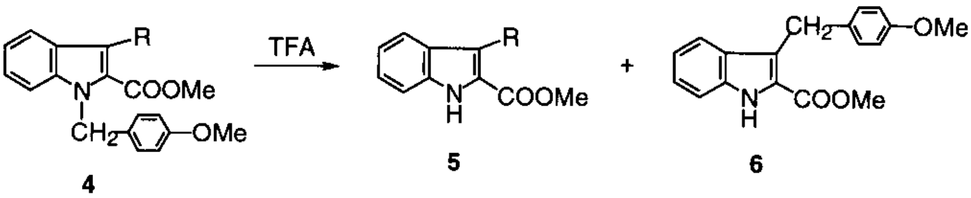
a; R^1 = H, R^2 = Me **b**; R^1 = H, R^2 = CH_2Ph **c**; R^1 = R^2 = H
d; R^1 = H, R^2 = TBDMS **e**; R^1 = OMe, R^2 = Me

Table 1

Entry	1	R^1	R^2	Solvent	Condition		Yield(%) 2	3	1
1	a	H	Me	benzene	50°C	104 h	27	22	42
2	a	H	Me	toluene	80°C	71 h	79	48	5
3	b	H	CH_2Ph	toluene	80°C	101 h	78	52	-
4	c	H	H	toluene	80°C	40 h	64	28	9
5	d	H	TBDMS	toluene	80°C	79 h	84	33	10
6	e	OMe	Me	toluene	80°C	48 h	82	80	6

When methyl 1-*p*-methoxybenzylindole-2-carboxylate (**4a**), which has a methoxycarbonyl group at the 2-position on an indole ring, was treated with DDQ (2.2 equivalents) in benzene at 50°C for 55 h, **4a** was recovered (Scheme 2). However, reaction of **4a** with TFA (5 equivalents) in CH_2Cl_2 at room temperature gave a mixture of the NH derivative (**5a**) and 3-*p*-methoxybenzylindole (**6**) in 6 and 50% yields, respectively, but in the presence of *m*-dimethoxybenzene (DMB)(3 equivalents), **4a** gave **5a** in 77% yield as shown in Table 2 (Entries 1 and 2). Next, we investigated the reactivity of dimethyl 1-*p*-methoxybenzylindole-2,3-dicarboxylate (**4b**), which has an additional methoxycarbonyl group at the 3-position on the indole ring. **4b** was also recovered by treatment with DDQ (2.2 equivalents) in benzene at 50°C for 55 h, but the reaction of **4b** in hot TFA provided **5b** in 52% yield (Entry 4).

Scheme 2



a; R = H, **b**; R = COOMe

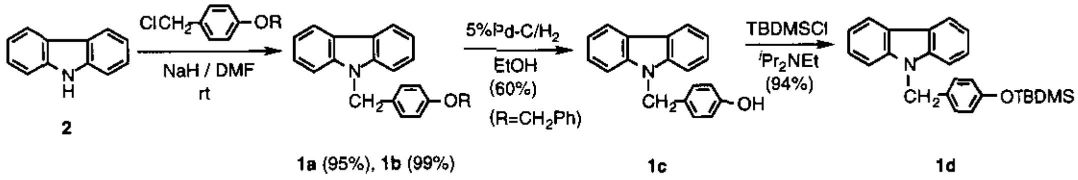
Table 2

Entry	**4**	R	Additive	Solvent	Condition		Yield(%)	
							5	**6**
1	a	H	—	CH_2Cl_2	rt	8 h	6	50
2	a	H	DMB	$(CH_2Cl)_2$	reflux	8 h	77	23
3	b	COOMe	—	$(CH_2Cl)_2$	reflux	20 h	recovered	
4	b	COOMe	—	TFA	reflux	0.5 h	52	—

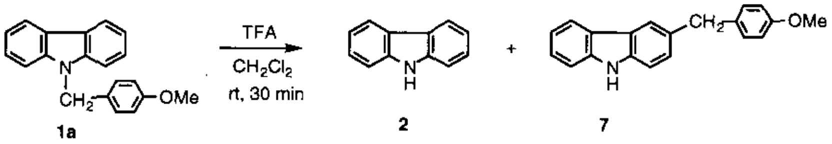
DMB = *m*-dimethoxybenzene

REFERENCES AND NOTES

1. T. W. Green and P. G. M. Wuts, 'Protective Groups in Organic Synthesis,' 2nd ed., John Wiley and Sons, Inc. New York, 1991.
2. R. J. Sundberg and H. F. Russell, *J. Org. Chem.*, 1973, **38**, 3324; M. P. Edwards, A. M. Doherty, S. V. Ley, and H. M. Organ, *Tetrahedron*, 1986, **42**, 3723; J. E. Macor, K. Ryan, and M. E. Newman, *J. Org. Chem.*, 1989, **54**, 4785; J. E. Macor, J. T. Forman, R. J. Post, and K. Ryan, *Tetrahedron Lett.*, 1997, **38**, 1673.
3. Y. Miki, Y. Tada, N. Yanase, H. Hachiken, and K. Matsushita, *Tetrahedron Lett.*, 1996, **37**, 7753.
4. Y. Murakami, T. Watanabe, A. Kobayashi, and Y. Yokoyama, *Synthesis*, 1984, 738; T. Watanabe, A. Kobayashi, M. Nishiura, H. Takahashi, T. Usui, I. Kamiyama, N. Mochizuki, K. Noritake, Y. Yokoyama, and Y. Murakami, *Chem. Pharm. Bull.*, 1991, **39**, 1152; Y. Miki and H. Hachiken, *Synlett*, 1993, 333; H. Suzuki, A. Tsukuda, M. Kondo, M. Aizawa, Y. Senoo, M. Nakajima, T. Watanabe, Y. Yokoyama, and Y. Murakami, *Tetrahedron Lett.*, 1995, **36**, 1671.
5. D. R. Buckle and C. J. M. Rockell, *J. Chem. Soc., Perkin Trans. I*, 1982, 627.
6. E. D. Edstrom and Y. Wei, *J. Org. Chem.*, 1993, **58**, 403.
7. K. Hirota, T. Yoshioka, T. Tanaka, Y. Oikawa, and O. Yonemitsu, *Tetrahedron*, 1986, **42**, 3032.
8. Fremy's salt, CAN,[9] and RuO_4 / $NaIO_4$[10] were not effective for the oxidative debenzylation of **1a**.
9. H. Yoda, T. Nakajima, and K. Tanabe, *Tetrahedron Lett.*, 1996, **37**, 5531.
10. P. H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, *J. Org. Chem.*, 1981, **46**, 3938.
11. 9-*p*-Alkoxybenzylcarbazoles (**1a-d**) were synthesized as follows:



12. Treatment of **1a** with TFA (5 equivalents) in CH_2Cl_2 gave **2** and 3-*p*-methoxybenzylcarbazole (**7**) in 14 and 66% yields, respectively. However, when 9-benzylcarbazole was treated with hot TFA for 3 h, the starting material was recovered.



13. Typical Experimental Procedure

A mixture of **1a** (57 mg, 0.2 mmol) and DDQ (100 mg, 0.44 mmol) in toluene (2 mL) and H_2O (0.1 mL) was stirred at 80 ℃ for 71 h. Saturated aqueous $NaHCO_3$ solution was added to the reaction mixture and the mixture was extracted with $CHCl_3$. The extracts were washed with water, dried over Na_2SO_4, and evaporated off. The residue was purified by TLC on silica gel (*n*-hexane : CH_2Cl_2 = 4 : 1) to give **2** (26 mg, 79%), **3a** (13 mg, 48%), and **1a** (3 mg, 5%).

Received, 5th September, 1997