Pergamon

Tetrahedron Letters, Vol. 36, No. 18, pp. 3103-3106, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00478-5

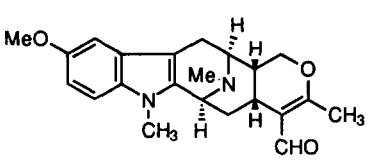
Regiospecific Bromination of 3-Methylindoles With *N*-Bromosuccinimide

Puwen Zhang, Ruiyan Liu, and James M. Cook*

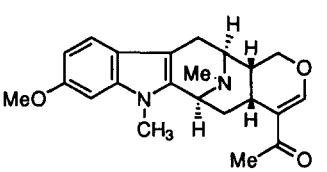
Department of Chemistry, University of Wisconsin-Milwaukee, Milwaukee, WI 53211

Abstract: The regiospecific bromination of various substituted 3-methylindoles at either C(2) or the C(3) alkyl moiety was accomplished *via* an electrophilic or free radical bromination process to provide intermediates for indole alkaloid total synthesis. The regiospecificity of the bromination could be controlled by variation of both the substituent and the N(1) protecting group on the indole ring.

In the course of studies directed toward the total synthesis of C-10 and C-11 ring-A oxygenated indole alkaloids[1,2] such as 19, 20-dehydro-10-methoxytalcarpine and alstophylline *via trans* 1,3-transfer of asymmetry during the Pictet-Spengler reaction,[3-5] 5- and 6-methoxy-D(+)-tryptophans or their derivatives were required. To this end, we have recently developed enantiospecific approaches[6,7] to these amino acids *via* the Schöllkopf protocol using 3-bromomethylindoles as key intermediates. However, when N(1) protected 5- or 6-methoxy-3-methylindoles were stirred with NBS under free radical conditions (benzoyl peroxide) electrophilic attack at the C(2) position and free radical bromination of the 3-methyl group were found to be competing processes which afforded the 3-bromomethylindoles accompanied by some of the 2-bromo-3-methylindole regioisomer. The competition between electrophilic and free radical bromination is well recognized[8,9] in methyl-substituted anisoles when they are treated with NBS. To the best of our knowledge, the related competing bromination of N(1) protected 3-methylindoles has not been studied. In the present paper, we report the results of regiospecific bromination of 3-methylindoles at either the C(3) alkyl group or C(2) *via* a free radical *vs* electrophilic process.



19,20-dehydro-10-methoxytalcarpine



alstophylline

When 5-methoxy-3-methylindoles **1a** or **1b** were heated in refluxing CCl_4 and then treated with NBS and AIBN,[10] 3-bromomethylindoles **2a** or **2b** were formed, respectively. In the absence of the radical initiator (AIBN), treatment of **1a** or **1b** with NBS at reflux in CCl_4 afforded the corresponding regioisomers **3a** or **3b** in excellent yield. The free radical reaction at the 3-methyl moiety of indoles **1a** and **1b** was not surprising since a similar bromination has been observed in the formation of 1-benzenesulfonyl-5-bromo-3-bromomethylindole.[11] Although the presence of an electron withdrawing

group at the N(1) position of **1a** or **1b** should deactivate the C(2) position, the electrophilic bromination of indoles **1a** and **1b** occurred readily at C(2) when they were stirred with NBS in the absence of a radical

Scheme 1

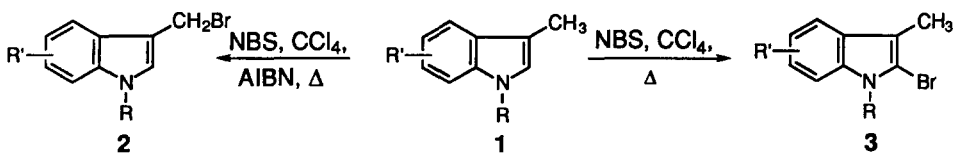


Table 1 The Bromination of Indoles by NBS

compd.	R	R'	reaction conditions (initiator, time)	product[1] (yield%)	melting point (°C)
1a	$SO_2C_6H_5$	5-OMe	AIBN, 2 hour	**2a** (83)	116-118
1a	$SO_2C_6H_5$	5-OMe	none, 3 hour	**3a** (86)	148-150
1b	BOC	5-OMe	AIBN, 1 hour	**2b** (92)[2]	
1b	BOC	5-OMe	none, 2 hour	**3b** (95)	82-84
1c	$SO_2C_6H_5$	H	AIBN, 3 hour	**2c** (94)	132-134
1c	$SO_2C_6H_5$	H	none, 10 hour	**2c** (92)	132-134
1d	BOC	H	AIBN, 2 hour	**2d** (95)	106-107
1d	BOC	H	none, 10 hour	**2d** (92)	106-107
1e	$SO_2C_6H_5$	5-Cl	AIBN, 2 hour	**2e** (93)	139-142
1e	$SO_2C_6H_5$	5-Cl	none, 10 hour	**2e** (90)	139-142
1f	BOC	5-Cl	AIBN, 2 hour	**2f** (91)	100-102
1f	BOC	5-Cl	none, 9 hour	**2f** (89)	100-102
1g	H	5-Cl	AIBN, 1 hour	**3g** (87)	96-98
1g	H	5-Cl	none, 1 hour	**3g** (98)	96-98
1h	H	H	AIBN, 1 hour	**3h** (92)	91-93
1h	H	H	none, 3 hour	**3h** (97)	91-93[3]

[1] All products have been characterized (^{1}H-NMR, IR, MS, CHN). [2] **2b** was converted into 3-hydroxymethylindole (mp 144-146 °C) and was thus characterized. [3] Lit.[12] 88-89 °C.

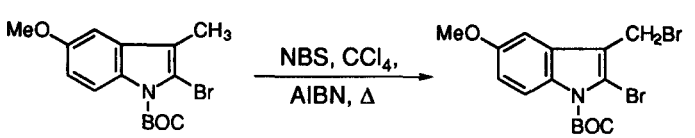
initiator. Two factors which contribute to the electrophilic process are presented here. Indoles are highly reactive aromatic systems[13] and would be expected to react with electrophiles despite the presence of an electron withdrawing group at the N(1) position.[13] Secondly, since the methoxyl group has been suggested to promote the electrophilic bromination of methyl-substituted anisoles,[8] presumably it plays

the same role in the bromination of indoles **1a** and **1b** at the C(2) position. To determine the effect of the methoxyl and N(1) protecting groups on the electrophilic *vs* free radical bromination, the reaction of various indoles with NBS in the presence or absence of AIBN has been examined (Scheme 1).[10]

As shown in Table I, when the methoxyl group was removed and the aromatic ring substituted with a hydrogen atom, the reaction of N(1) protected 3-methylindoles **1c-f** (in the presence or absence of AIBN) afforded only the 3-bromomethylindoles **2**. Although the N(1) protecting group (BOC or $SO_2C_6H_5$) deactivated the indole nucleus to electrophilic attack, the presence of the methoxyl group overrides this effect. Consequently, in order to brominate N(1) protected 3-methylindoles which bear a deactivating group at N(1) at the C(2) position, the activation of the indole nucleus by a group such as a methoxyl was required. When simple 3-methylindoles (e.g. **1g** and **1h**) were treated with NBS in the presence or absence of a radical initiator, indoles **1g** and **1h** were smoothly brominated at the C(2) position and furnished 2-bromoindoles **3g** and **3h**, respectively, in excellent yield.

Clearly, the results indicate that the regiospecific bromination of 3-methylindoles can be controlled by judicious choice of the N(1) substituent *vs* a hydrogen atom. Thus, in the presence of an activating group such as a methoxyl moiety, the protection of indoles at the N(1) position can proceed before the bromination. The 3-methylindoles protected in this fashion (e.g. **1a** and **1b**) should lead to either 3-bromomethylindoles or 2-bromo-3-methylindoles subject to the reaction conditions (electrophilic *vs* free radical). In the absence of activating groups, the free radical bromination at the 3-methyl group should be facilitated by protection of the 3-methylindoles with an electron withdrawing substituent. On the other hand, in order to obtain the 2-bromoindoles **3** which lack the activating group, the bromination should proceed before the protection sequence is executed. Using this regiospecific bromination process, the bisbromination of **1b** (as shown in Scheme 2) can also be readily carried out and extends the scope of this process for the synthesis of other potential intermediates for indole alkaloid synthesis.

Scheme 2



3b **4**

In conclusion, the regiospecificity of the electrophilic *vs* free radical bromination of 3-methylindoles is directed by the presence of the substituent on the indole ring. Under these conditions, deactivation of the indole ring by an electron withdrawing group such as a BOC moiety at N(1) excludes the electrophilic bromination at the C(2) position if ring A is devoid of an activating group. The 3-methylindole itself is electron rich and the activation *via* an electron donating group on ring A is not required for attack at C(2). These mild bromination reactions permit entry into several versatile indole building blocks. The 3-bromomethylindoles can be employed to construct the tryptophan-related amino acids.[6,7,11,14] The 2-bromoindoles and their N(1) protected derivatives have been synthesized previously

via N(1) protected 2-lithioindole species as well as others.[15-17] The procedure described herein should permit easy entry into various 3-substituted 2-bromoindoles which should be useful in vinylation, acetylation, and arylation reactions *via* transition-metal catalysts.[18-21] In addition, access to bisbromoindoles such as **4** will permit entry into important bifunctional indole building blocks for total synthesis.

REFERENCES AND NOTES

1. Hamaker, L. K.; Cook, J. M. *The Synthesis of Macroline Related Sarpagine Alkaloids.* In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Elsevier Science: Amsterdam, 1995; Vol. 9; pp 23-84.
2. Bi, Y.; Hamaker, L. K.; Cook, J. M. *The Synthesis of Macroline Related Alkaloids.* In *Bioactive Natural Products, Part A*; Basha, F. Z. and Rahman, A., Eds.; Elsevier Science: Amsterdam, 1993; Vol. 13; pp 383-432.
3. Bi, Y.; Zhang, L. H.; Hamaker, L. K.; Cook, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 9027-9041.
4. Czerwinski, K. M.; Cook, J. M. *Stereochemical Control of the Pictet-Spengler Reaction in the Synthesis of Natural Products.* In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W., Ed.; JAI Press: Greenwich, in press.
5. Zhang, L. H.; Cook, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 4088-4094.
6. Zhang, P.; Cook, J. M. *Syn. Commun.* submitted.
7. Allen, M. S.; Hamaker, L. K.; La Loggia, A. J.; Cook, J. M. *Syn. Commun.* **1992**, *22*, 2077-2102.
8. Gruter, G. M.; Akkerman, O. S.; Bickelhaupt, F. *J. Org. Chem.* **1994**, *59*, 4473 and references cited therein.
9. Goldberg, Y.; Bensimon, C.; Alper, H. *J. Org. Chem.* **1992**, *57*, 6374.
10. A typical procedure for the bromination. (a) In the presence of AIBN: 3-methylindole (5 mmol) in wet CCl_4 (20 mL) was heated to reflux and NBS (5.5 mmol) and AIBN (20 mg) were then added in one portion to the refluxing solution under nitrogen. When all the NBS was converted into succinimide which floated on the surface of the CCl_4, the reaction solution was cooled to room temperature. The succinimide was removed by filtration and washed with CCl_4 (2x2 mL). The combined filtrates were concentrated under reduced pressure and the residue was crystallized from a mixture of CCl_4 and hexane to afford 3-bromomethylindole. (b) In the absence of AIBN: A mixture of 3-methylindole (5 mmol) and NBS (5.5 mmol) in anhydrous CCl_4 (10 mL) was heated to reflux under nitrogen. When all the NBS was converted into succinimide which floated on the surface of the CCl_4, the reaction solution was cooled to room temperature. The succinimide was removed by filtration and washed with CCl_4 (2x2 mL). The combined filtrates were concentrated under reduced pressure and the residue was crystallized from a mixture of CCl_4 and hexane to afford 2-bromomethylindole.
11. Nagarathnam, D.; Johnson, M. E. *Synth. Commun.* **1993**, *23*, 2011-2017.
12. Hinman, R. L.; Bouman, C. P. *J. Org. Chem.* **1964**, *29*, 1206.
13. Gilchrist, T. L. *Heterocyclic Chemistry;* John Wiley & Sons Inc.: New York, 1985, pp. 161-172.
14. Schöllkopf, U.; Lonsky, R.; Lehr, P. *Liebigs Ann. Chem.* **1985**, 413-417.
15. Mistry, A. G.; Smith, K.; Bye, M. R. *Tetrahedron Lett.* **1986**, *27*, 1051-1054.
16. Bergman, J.; Venemalm, L. *J. Org. Chem.* **1992**, *57*, 2495-2497.
17. Gribble, G. W.; Allison, B. D.; Conway, S. C.; Saulnier, M. G. *Org. Prep. Proced. Int.* **1992**, *24*, 649-654.
18. Hegedus, L. S.; Sestrick, M. R.; Michaelson, E. T.; Harrington, P. J. *J. Org. Chem.* **1989**, *54*, 4141.
19. Merlic, C. A.; Semmelhack, M. F. *J. Organomet. Chem.* **1990**, *391*, C23.
20. Somei, M.; Sayama, S.; Naka, K.; Yamada, F. *Heterocycles* **1988**, *27*, 1585.
21. Sakamoto, T.; Nagano, T.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 2238.

(*Received in USA* 14 *February* 1995; *revised* 7 *March* 1995; *accepted* 10 *March* 1995)