# Short step syntheses of a natural product, 6-cyano-5-methoxy-12-methylindolo[2,3-a]carbazole and novel 6-aminoindolo[2,3-a]-thiazolo[5,4- c]carbazoles


| メタデータ | 言語: English<br>出版者:<br>公開日: 2017-10-04<br>キーワード (Ja):<br>キーワード (En):<br>作成者: Hayashi, Hiroyuki, Suzuki, Yoshiaki, Somei, Masanori<br>メールアドレス:<br>所属: |
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| URL | http://hdl.handle.net/2297/4352 |

# SHORT STEP SYNTHESES OF A NATURAL PRODUCT, 6-CYANO-5-METHOXY-12-METHYLINDOLO[2,3-*a*]CARBAZOLE AND NOVEL 6-AMINOINDOLO[2,3-*a*]-THIAZOLO[5,4-*c*]CARBAZOLES[1]

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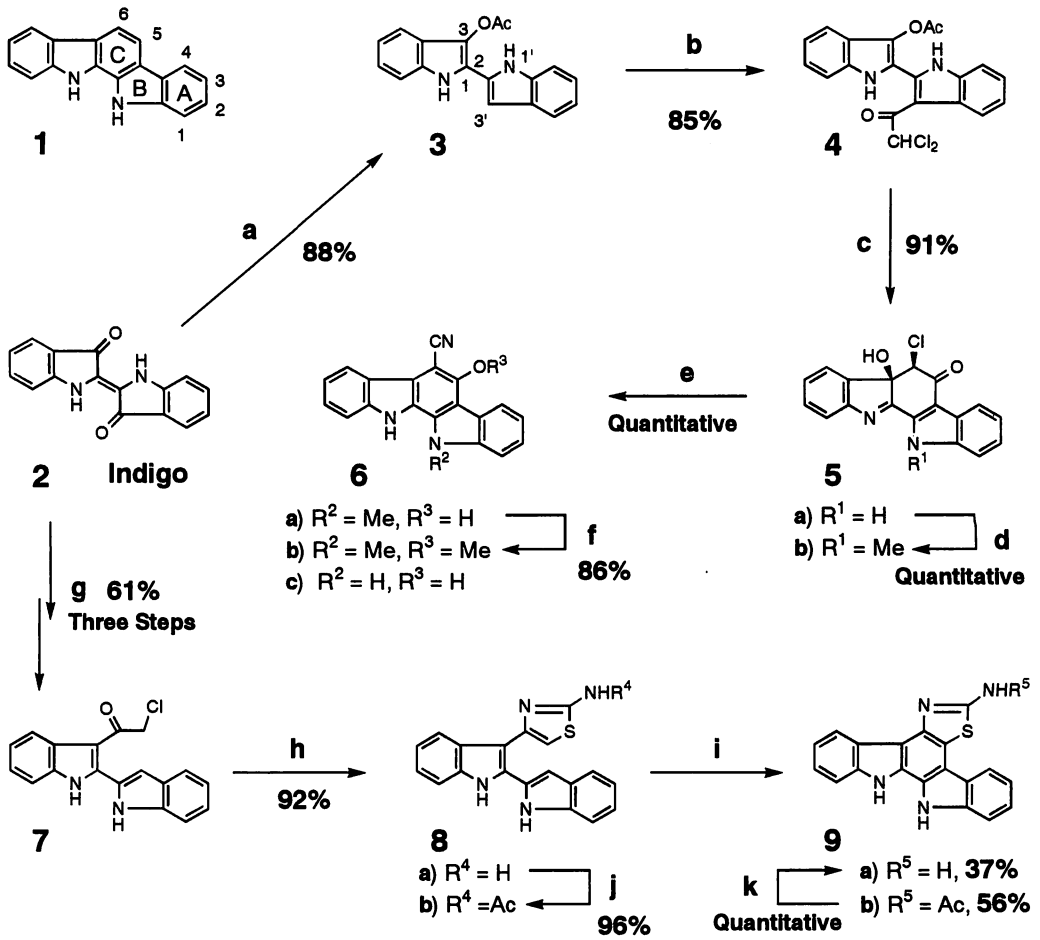
*Abstract* ——— Starting from indigo, simple synthetic methods for 6-cyano-5-methoxy-12-methylindolo[2,3-*a*]carbazole and novel 6-aminoindolo[2,3-*a*]thiazolo-[5,4-*c*]carbazoles are achieved using only conventional reagents.

Indolo[2,3-*a*]carbazole (**1**, Scheme 1) is a common skeleton of a class of compounds such as staurosporine,[2a] tjipanazoles,[2b] BE-13793C,[2c] and so on. We have expected that manipulation of **1** is a promising method for finding a new biologically active compound. As a simple derivative of **1**, we have focused our attention to cytotoxic and antiviral 6-cyano-5-methoxy-12-methylindolo[2,3-*a*]carbazole (**6b**), isolated from blue-green alga *Nostoc sphaericum* (strain EX-5-1) by Moore and co-workers.[3] Although we have established two synthetic routes to **6b** in the previous communications,[4] their overall yields (13% and 5%, respectively) are still not satisfactory to carry out structure-activity relationship project. Now, we wish to report a satisfactory six step synthetic method for **6b** from indigo (**2**). In addition, simple preparation of novel 6-aminoindolo[2,3-*a*]thiazolo[5,4-*c*]carbazoles (**9a** and **9b**) is also developed.

First, 3-acetoxy-2,2'-biindolyl (**3**), prepared in one step from **2** in 88% yield,[4] reacted with dichloroacetyl chloride in refluxing ethyl acetate to give 3-acetoxy-3'-dichloroacetyl-2,2'-biindolyl (**4**) in 85% yield. Treatment of **4** with aqueous 1.3% ammonia in MeOH-DMF at room temperature afforded *cis*-6-chloro-6a-hydroxy-5-oxo-5,6,6a,12-tetrahydroindolo[2,3-*a*]carbazole[5] (**5a**) in 91% yield. Methylation of **5a** with dimethyl sulfate in the presence of $K_2CO_3$ produced 12-methyl compound (**5b**) in a quantitative yield. A novel reductive cyanation of **5b** was found to produce **6a** in a quantitative yield by the reaction with NaCN in DMF-$H_2O$. Finally methylation of **6a** with diazomethane afforded **6b** in 86% yield. Thus the natural product (**6b**) is available in six steps with an overall yield of 59% using only conventional reagents. The originality rate[6] for **6b** from **2** is 57% based on our three reaction steps, **a**, **c**, and **e**.

## Scheme 1




a) Sn, AcOH, $Ac_2O$, 64—66°C; b) $Cl_2CHCOCl$, EtOAc, reflux; c) aq. 1.3% $NH_3$, MeOH, DMF, rt; d) $Me_2SO_4$, $K_2CO_3$, rt; e) NaCN, DMF, $H_2O$, 70°C; f) $CH_2N_2$, rt; g) i) Zn, AcOH, $Ac_2O$; ii) NaOMe, MeOH, then Salcomine, $O_2$ ; iii) $ClCH_2COCl$, benzene, reflux; h) $(NH_2)_2CS$, MeOH, reflux; i) nitrobenzene, 190—225°C; j) $Ac_2O$, pyridine, rt; k) NaOH, MeOH, reflux.

On the other hand, 3-chloroacetyl-2,2'-biindolyl (**7**) was prepared in three steps with an overall yield of 61% from **2** as described before.[4] Treatment of **7** with thiourea in refluxing MeOH afforded 3-(2-aminothiazol-4-yl)-2,2'-biindolyl (**8a**) in 92% yield. Subsequent oxidative cyclization of **8a** proceeded in refluxing nitrobenzene to give 6-aminoindolo[2,3-*a*]thiazolo[5,4-*c*]carbazole (**9a**) in 37% yield. Similar cyclization of **8b**, prepared in 96% yield by reacting **8a** with $Ac_2O$-pyridine, produced **9b** in 56% yield. Alkaline hydrolysis of **9b** with NaOH-MeOH afforded a quantitative yield of **9a**. According to the present synthetic methodology, it would be possible to obtain compounds fused with various heterocycles[7] on the

C ring of **1**, since a chloroacetyl group of **7** is suitable for forming heterocycles.

With useful building blocks at hand such as **6a**, **9a**, and **6c** which is available from **5a** as reported previously,[4] the structure-activity relationship project is in progress.

ACKNOWLEDGMENT

This work is supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan, which is gratefully acknowledged.

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7. Related indolo[2,3-*a*]oxazolo[4,5-*c*]carbazol-6-one and indolo[2,3-*a*]imidazolo[4,5-*c*]carbazol-6-one derivatives were reported: E. R. Pereira, M. Prudhomme, M. Sancelme, M. Ollier, D. Severe, J. F. Riou, H. Crevel, J. P. Savineau, D. Fabbro, and T. Meyer, *Chem. Pharm. Bull.*, 1997, **45**, 733 and references cited therein.

Received, 24th February, 1999