Simple synthesisi of 2-2'-bisindole from indigo and its application for the syntheses of indole[2,3-a]pyrrolo[3,4-c]carbazole-5,7-(6H9dione and -5-(6H9one derivatives

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SIMPLE SYNTHESIS OF 2,2'-BISINDOLE FROM INDIGO AND ITS APPLICATION FOR THE SYNTHESES OF INDOLO[2,3-*a*]PYRROLO[3,4-*c*]CARBAZOLE-5,7-(6*H*)DIONE AND -5-(6*H*)ONE DERIVATIVES[1]

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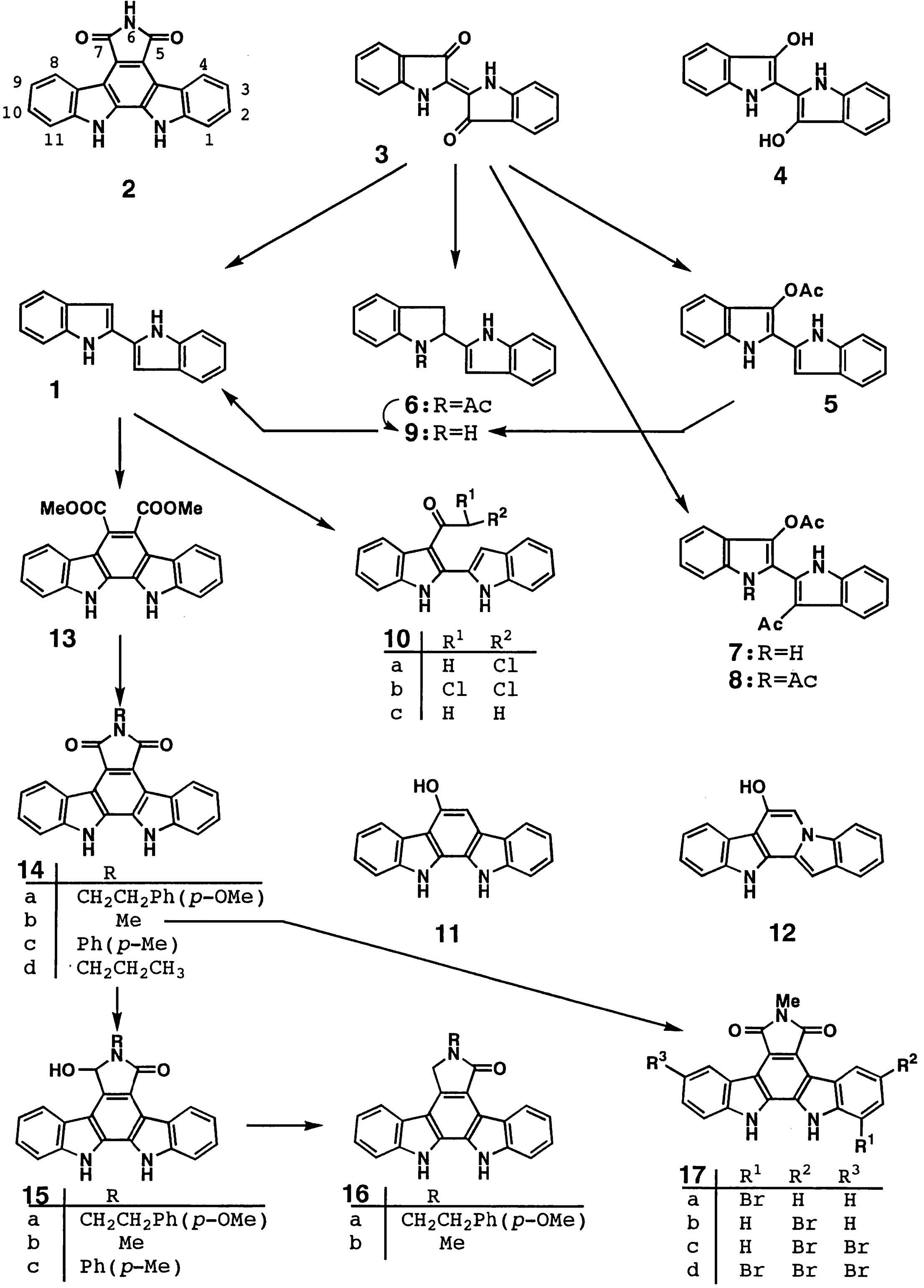
Abstract —— Indigo was converted to 2,2'-bisindole, from which 6-substituted indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-(6*H*)dione and -5-(6*H*)one derivatives were prepared in short steps. Bromination of 6-methylindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-(6*H*)dione is also reported.

In the previous communication,[2] we reported the synthesis of 2,2'-bisindole (**1**, Scheme 1), and its cycloaddition type reaction for preparations of indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-(6*H*)dione (**2**) derivatives. Since then, this method[2,3] has drawn much attention and some modifications have been examined by other groups.[4] However, we could not satisfy with the method,[2] because anhydrous reaction conditions were inevitable for the preparation of **1** due to employment of oxidative coupling of indole-2-lithium salt.

Indigo (**3**) is known to give colorless and soluble leucoindigo (**4**) with proper recucing agents in an alkaline conditions, and this technique has been widely used for dyeing process from ancient days.[5] Various reductive methods of **3** were documented.[5,6] Trapping of desoxyindigo as 3-acetoxy-2,2'-bisindole (**5**) by Bergman and co-workers[3,6] is one of them, though its yield was no more than 19% yield. In spite of these discouraging background, reduction of **3** seems to be promising and straightforward synthetic method for **1**. We have now succeeded in simple syntheses of **1**, **5**, and 1-acetyl-2,3-dihydro-2,2'-bisindole (**6**) from **3**.

Based on the finding that acid sensitive **1** is tolerable to AcOH, we discovered, under argon atmosphere, direct reduction of **3** with a metal in AcOH-Ac_2O with vigorous stirring (ultra sound is recommended) produced **1**, **5**, and **6**. Typical examples are summarized in Table I. As can be seen from the Table, products were dependent on the metal and especially on the reaction temperatures. Zinc was the reagent of choice to obtain **1** and **6**. Under the reaction conditions in Entries 3 and 4, 34% yield of **1** and 82% yield of **6** were attained, respectively. Using iron, **5** was

Scheme 1



10	R¹	R²
a	H	Cl
b	Cl	Cl
c	H	H

14	R
a	$CH_2CH_2Ph(p\text{-}OMe)$
b	Me
c	$Ph(p\text{-}Me)$
d	$CH_2CH_2CH_3$

15	R
a	$CH_2CH_2Ph(p\text{-}OMe)$
b	Me
c	$Ph(p\text{-}Me)$

16	R
a	$CH_2CH_2Ph(p\text{-}OMe)$
b	Me

17	R¹	R²	R³
a	Br	H	H
b	H	Br	H
c	H	Br	Br
d	Br	Br	Br

obtained predominantly as shown in Entry 6. When Zn (Hg) was employed, 3-acetoxy-3'-acetyl- (**7**) and 3-acetoxy-1,3'-diacetyl-2,2'-bisindole (**8**) were generated instead of **1**, **5**, and **6** (Entry 7). Other metals, such as Al, Mg, Devarda's alloy (Cu, Al, Zn), Raney Ni, etc., were also extensively examined under similar reaction conditions, but none of the tested metals gave better yields of **5** and **6** or more selective product formation than the described metals in Table I. Reduction of **5** under argon atmosphere with zinc in AcOH at room temperature was also found to proceed slowly affording 2,3-dihydro-2,2'-bisindole (**9**) in 34% yield.

Table I. Reduction of Indigo (**3**) with Zinc and Iron

$$\mathbf{3} \xrightarrow[\text{AcOH-Ac}_2\text{O}]{\text{Ar, Metal}} \mathbf{1} + \mathbf{5} + \mathbf{6} + \mathbf{7} + \mathbf{8}$$

Entry	Metal (mol eq.)	Reaction Conditions Temp. (°C)	Time (h)	Yield (%) of **1**	**5**	**6**	**7**	**8**
1	Zn (20)	46-56	72	13	37	22	0	0
2	Zn (20)	64-65	2.5	18	58	trace	0	0
3	Zn (50)	48-52	8	34	14	14	0	0
4	Zn (50)	60-62	8	3	3	82	0	0
5	Zn (100)	62-65	2.5	6	7	68	0	0
6	Fe (20)	64-66	2.5	0	82	0	0	0
7	Zn (Hg) (20)	68-71	2.5	0	0	0	27	24

The following sequence of reactions was an alternative suitable method for the preparation of **1**. First, solvolysis of **6** with NaOMe in MeOH gave **9** in 86% yield. Subsequent oxidation of **9** with bubbling dioxygen[7] in MeOH in the presence of a catalytic amount of sarcomine produced **1** in 89% yield. Thus, **1** is now readily available in two ways, directly from indigo (**3**) or *via* **6**.

Treatment of **1** with chloroacetyl and dichloroacetyl chloride in refluxing AcOEt afforded 3-chloroacetyl- (**10a**) and 3-dichloroacetyl-2,2'-bisindole (**10b**) in 74 and 63% yields, respectively. The compound (**10b**) was alternatively prepared in 83% yield by reacting **1** with dichloroketene, generated *in situ* with $CHCl_2COCl$ and Et_3N. An attempt to obtain **11** or 12*H*-pyrido[1,2-*a* :3,4-*b*']diindole derivative (**12**) was made *in vain* by reacting **10a** with KOtBu resulting in the formation of unknown products. Radical cyclizations of **10a** and **10b** were also examined with (n-Bu)$_3$SnH but the desired products were not formed and the only isolable product was 3-acetyl-2,2'-bisindole (**10c**). According to our procedure,[2] **1** was converted to 5,6-dimethoxycarbonylindolo[2,3-*a*]carbazole (**13**) in 36% yield. Further treatment of **13** in DMF with amines, such as *p*-methoxyphenethylamine, methyl amine, toluidine, and propylamine, in the presence of the corresponding amine hydrochloride, afforded (**14a-d**) in 92, 90, 90, and 88%

yields, respectively. Reduction of **14a** with NaBH$_4$ in DMF-MeOH at room temperature produced 7-hydroxy-6-(4-methoxyphenethyl)indolo[2,3-a]pyrrolo[3,4-c]carbazole-5-(6*H*)one (**15a**) in 80% yield. Similarly, **15b** and **15c** were prepared in 67 and 69% yields, respectively, from **14b** and **14c**. Subsequent catalytic hydrogenation of **15a** and **15b** with 10% Pd/C gave **16a** and **16b** in 54 and 58% yields, respectively.

Bromination of **14b** (aglycon of AT 2433-B-1 and -B-2)[8] with NBS (1.0 mol eq.) in THF at room temperature afforded 1-bromo- (**17a**), 3-bromo- (**17b**), and 3,9-dibromo-6-methylindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-(6*H*)dione (**17c**) in 20, 37, and 13% yields, respectively, together with 27% yield of recovery (**14b**). When 1.5 mol eq. of NBS was used, tribromo derivative (**17d**) was formed in 3% yield in addition to **17a**, **17b**, and **17c** in 14, 11, and 12% yields, respectively. Interestingly, the more quantity of NBS was used, the lower the total yield of products except for tars.

In conclusion, we discovered a simple synthetic method for indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-(6*H*)dione and -5-(6*H*)one derivatives starting from readily available indigo (**3**). Synthetic applications of important building blocks, such as **1**, **6**, and **7**, and biological evaluations[9] of new compounds reported in this paper are currently in progress.

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