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One-Pot Construction of 3,3′-Bisindolylmethanes through Bartoli Indole Synthesis

Takumi Abe,[†] Shuuhei Nakamura,[†] Reiko Yanada,[‡] Tominari Choshi,[§] Satoshi Hibino,[§] and Minoru Ishikura*,[†]

School of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan, Faculty of Pharmaceutical Sciences, Hiroshima International University, Hirokoshingai, Kure, Hiroshima 737-0112, Japan, and Faculty of Pharmacy and Pharmaceutical Sciences, Fukuyama University, Fukuyama, Hiroshima 729-0292, Japan

ishikura@hoku-iryo-u.ac.jp

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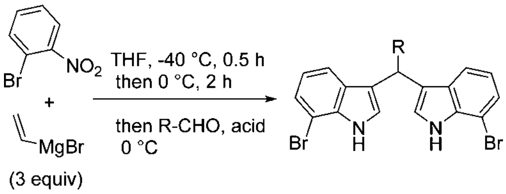
ABSTRACT



A one-pot approach to 3,3′-bisindolylmethane derivatives from nitrobenzene derivatives through the Bartoli indole synthesis was developed, in which the acid used to quench the reaction markedly affected its outcome. Quenching the reaction with concd HCl produced 3,3′-bisindolylmethane in contrast to the formation of 7-substituted indole by quenching with NH_4Cl.

The search for natural products from terrestrial and marine sources has led to the isolation of novel 3,3′-bisindolylmethane alkaloids with biological activities and intriguing structures (Figure 1). For example, arundine (**1**),[1] isolated from the root of *Arundo donax* in 1994, exhibits potent carcinogenicity, and vibrindole A (**2**),[2] isolated from the culture medium of the marine bacterium *Vibrio parahemolyticus* in 1994, shows antibacterial activity. Research has focused on developing efficient synthetic methods[3] and evaluating biological activity for 3,3′-bisindolylmethane derivatives.[4] The majority of synthetic methods depend on the condensation of indoles with carbonyl compounds or their synthetic equivalents in the presence of acid or base. Recently, metal-catalyzed processes have been reported,[5] such as the Pd-catalyzed benzylic substitution of gramine with an indole,[6] the Pt-catalyzed bisindolylation of allene,[7] and the Re-catalyzed addition of indoles to a terminal alkyne.[8]

Bartoli indole synthesis is one of the shortest and most flexible methods for accessing 7-substituted indoles.[9] After

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[†] Health Sciences University of Hokkaido.

[‡] Hiroshima International University.

[§] Fukuyama University.

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1-chloro-2-nitrobenzene (**8a**) was treated with vinylmagnesium bromide (3 equiv) in THF at −40 °C for 0.5 h and then at 0 °C for 2 h, quenching the reaction by adding aqueous NH_4Cl solution produced 7-chloroindole (**9**) in 60% yield (Table 1, entry 1). However, on quenching the reaction with 10% HCl instead of NH_4Cl, the reaction mixture changed immediately from pale yellow to dark red, and to our surprise, bisindolylmethane **10a** was isolated in 26% yield along with **9** in 22% yield (entry 4). An aqueous $KHSO_4$ solution produced **10a** in 34% yield along with **9** in 8% yield, whereas AcOH was virtually ineffective for producing **10a** (entries 2 and 3). Furthermore, when concentrated HCl was used, **10a** was obtained in 55% yield without **9** (entry 5), and **10b** and **10c** were obtained from **8b** and **8c** in 60 and 41% yields, respectively (entries 6 and 7). Moreover, subjecting the other nitrobenzene derivatives **8d**, **8e**, and **8f** to the same reaction conditions provided **10d**, **10e**, and **10f** in 50%, 20%, and 32% yields, respectively (entries 8−10).

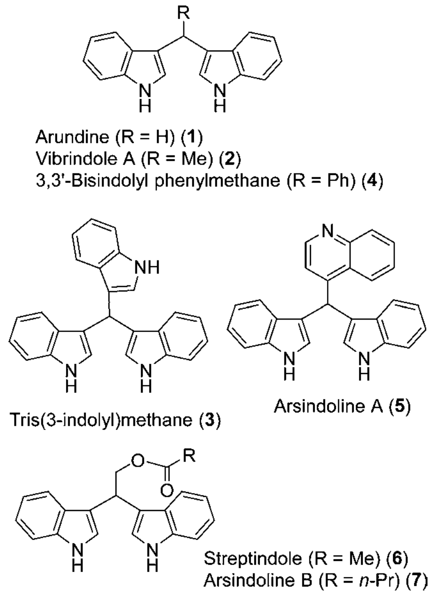
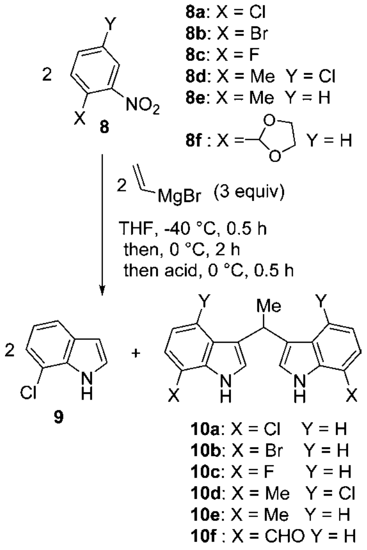


Figure 1. 3,3′-Bisindolylmethanes.

Scheme 1 illustrates a plausible reaction path in accordance with the usual Bartoli reaction mechanism,[10] involving the *in situ* generation of indoline intermediate **12** from **8a** and vinylmagnesium bromide. Typically, indole **9** was produced from **12** through quenching the reaction mixture with NH_4Cl. In contrast, the production of **10a** apparently resulted from the condensation of 2 equiv of **9** with acetaldehyde. The first step of the Bartoli reaction is presumed to involve the interaction of the nitro group of **8a** with vinylmagnesium bromide, to produce nitroso benzene **11** and vinyloxymagnesium bromide. Thus, the presence of acetaldehyde can be explained by the rapid hydrolysis of vinyloxymagnesium bromide under strongly acidic conditions, which may support the existence of the proposed vinyloxymagnesium bromide species in the Bartoli reaction. However, **10a** was not observed as a product of the reaction of indole **9** with acetaldehyde in the presence of concentrated HCl and $MgBr_2$, and 7,7′-dichloro-2,3-dihydro-2,3′-bisindole was isolated instead. Therefore, the simple assumption that **9**, which was derived from **12**, underwent condensation with acetaldehyde appears inconsistent with these observations. The details of the reaction path are under investigation.

Table 1. Reaction of **8** with Vinylmagnesium Bromide



entry	8	acid	10 (%)[a]
1	**8a**	NH_4Cl	–[b]
2	**8a**	AcOH	**10a** (10)[c]
3	**8a**	$KHSO_4$	**10a** (34)[d]
4	**8a**	10% HCl	**10a** (26)[e]
5	**8a**	concd HCl	**10a** (55)
6	**8b**	concd HCl	**10b** (60)
7	**8c**	concd HCl	**10c** (41)
8	**8d**	concd HCl	**10d** (50)
9	**8e**	concd HCl	**10e** (20)
10	**8f**	concd HCl	**10f** (32)

[a] Isolated yield based on **8a**. [b] **9** (60%). [c] **9** (35%). [d] **9** (8%). [e] **9** (22%).

Based on these results, we expected that a one-pot reaction containing an additional aldehyde should provide various substituted bisindoles **10**. We treated **8b** with vinylmagnesium bromide (3 equiv) in THF at −40 °C for 0.5 h and then at 0 °C for 2 h and added propanal (2 equiv) to the reaction mixture. The mixture was then immediately

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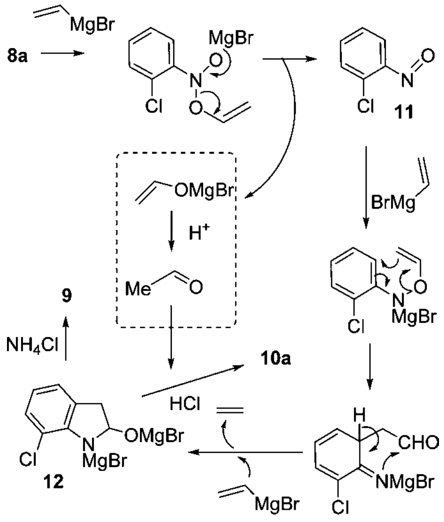
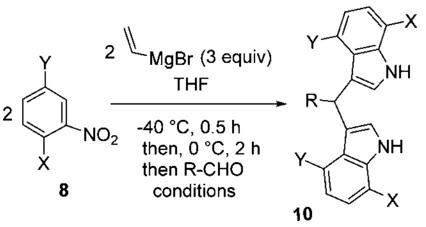
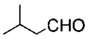
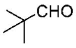
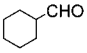
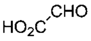
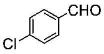
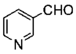
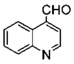
Scheme 1. A Plausible Reaction Path



quenched with concentrated HCl at 0 °C for 0.5 h. This produced **10g** in a 70% yield (Table 2, entry 1). Having established a one-pot protocol for the formation of **10g**, the scope of the one-pot reaction was examined. Table 1 shows that the yield of **10b** was improved to 75% by using additional acetaldehyde (entry 4). Compound **10j** was obtained by using paraformaldehyde or aqueous HCHO solution (entries 5 and 6). The reaction with isovaleraldehyde and cyclohexanecarboxaldehyde gave **10k** and **10l** in 66 and 37% yields, respectively, whereas only 8-bromoindole was isolated from the reaction with sterically hindered pivalaldehyde in 70% yield (entries 7−9). In addition, glyoxalic acid produced **10m** in 55% yield (entry 10). Aqueous $KHSO_4$ was suitable for quenching the reaction involving aromatic aldehydes, whereas the reaction with concentrated HCl resulted in a complex mixture of products (entries 11−14).

Table 2. Formation of 3,3′-Bisindolylmethanes **10**



entry	8	R-CHO	conditions	10 (%)[a]
1	**8b**	EtCHO	concd HCl 0 °C, 0.5 h	70 (**10g**)
2	**8d**	EtCHO	concd HCl 0 °C, 0.5 h	63 (**10h**)
3	**8e**	EtCHO	concd HCl 0 °C, 0.5 h	46 (**10i**)
4	**8b**	MeCHO	concd HCl 0 °C, 0.5 h	75 (**10b**)
5	**8b**	HCHO[b]	concd HCl 0 °C, 0.5 h	63 (**10j**)
6	**8b**	$(CH_2O)_n$	concd HCl 0 °C, 0.5 h	65 (**10j**)
7	**8b**	 CHO	concd HCl 0 °C, 4 h	66 (**10k**)
8	**8b**	 CHO	concd HCl 0 °C, 72 h	---[c]
9	**8b**	 CHO	concd HCl 0 °C, 24 h	37 (**10l**)
10	**8b**	 HO_2C CHO	concd HCl 0 °C, 4 h	55 (**10m**)
11	**8b**	Ph-CHO	$KHSO_4$, 0 °C, 16 h	50 (**10n**)
12	**8b**	 Cl CHO	$KHSO_4$, 0 °C, 16 h	55 (**10o**)
13	**8b**	 CHO N	$KHSO_4$, 0 °C, 48 h	44 (**10p**)
14	**8b**	 CHO N	$KHSO_4$, 0 °C, 48 h	48 (**10q**)

[a] Isolated yield based on **8**. [b] 37 wt % solution in water. [c] 7-Bromoindole in 70% yield.

Reductive debromination of **10b**, **10j**, **10n**, and **10q** was then carried out using n-Bu_3SnH in the presence of a catalytic amount of AIBN in refluxing toluene[11] to give arundine (**1**),[1] vibrindole A (**2**),[2] 3,3′-bisindolylphenylmethane (**4**),[3f,12] and arsindoline A (**5**).[13] Herein, we present the first synthesis of arsindoline A (**5**). Streptindole (**6**)[14] and arsindoline B (**7**)[13]

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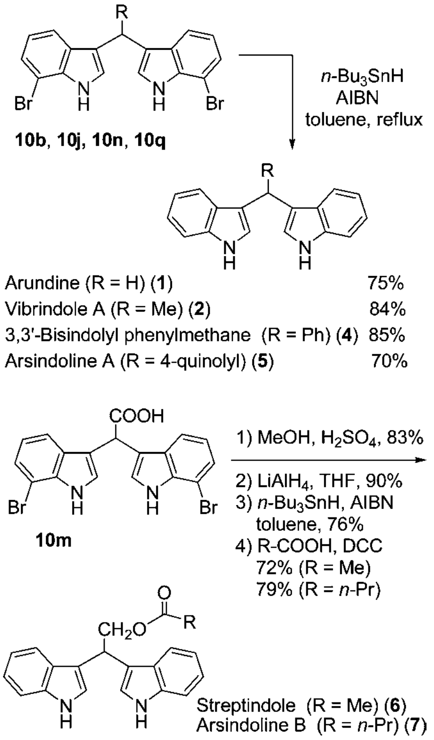
Scheme 2. Conversion of **10** to Alkaloids

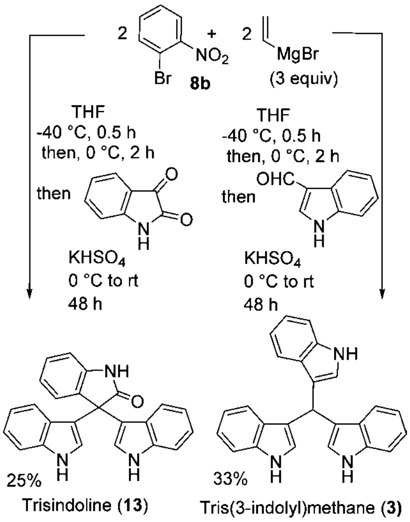


were derived from **10m** through esterification, reduction, debromination, and acylation (Scheme 2).

Notably, the one-pot synthesis of tris(3-indolyl)methane (**3**)[12,15] was achieved through the reaction of **8b** with vinylmagnesium bromide in the presence of indole-3-carboxaldehyde (−40 °C, for 0.5 h, 0 °C, for 2 h, then addition of indole-3-carboxaldehyde and $KHSO_4$). An unexpected debromination at the 7-position of the indole ring was observed. In addition, the reaction with isatin under the same conditions produced trisindoline (**13**)[16] with the same debromination (Scheme 3).

In summary, we have demonstrated that the Bartoli reaction of nitrobenzene **8a** with vinylmagnesium bromide produced 3,3′-bisindolylmethane **10a** when the reaction was quenched with HCl. In contrast, 7-chloroindole (**9**) was formed by quenching the reaction with NH_4Cl. The production of **10a** from indoline **12** was caused by the capture of acetaldehyde, which was generated from vinyloxymagnesium bromide during the treatment with HCl. Moreover, various derivatives of **10** were obtained from the one-pot reaction in the presence of an additional aldehyde. This protocol was developed for synthesizing several natural products. We are currently conducting further studies to explore the scope of this reaction.

Scheme 3. One-Pot Formation of **3** and **13**



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Supporting Information Available. Experimental procedures and characterization data for products and isolated intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.