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Synthesis of bis(indolyl)methanes Catalyzed by Triethylborane

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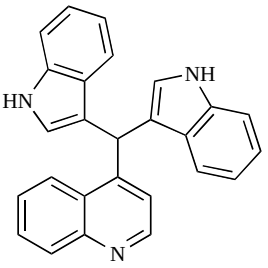
Abstract: Triethylborane (TEB) was found to be a mild, efficient, and acid catalyst in electrophilic substitution reaction of indoles with aldehydes compounds to afford the corresponding bis(indolyl)methanes. Vibrindole A (**5**) and bis(indolyl)methanes derivatives **16** and **18** were synthesized using this methodology. Compound **16** is an intermediary in the synthesis of the natural bisindoles arsindoline B (**2**) and streptindole (**6**). The structure of vibrindole A (**5**) was unequivocally confirmed by a single crystal X-ray diffraction analysis.

Keywords: Arsindoline B, bis(indolyl)methanes, indole, streptindole, triethylborane.

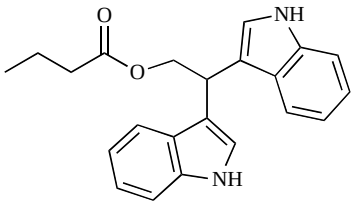
INTRODUCTION

The indole nucleus, referred to as a "privileged structure" by some authors, [1] is very important in pharmaceutical products, biological systems, and in the field of materials science. Moreover, the indole nucleus is present in many natural products isolated from marine and terrestrial organisms. These products are a rich source of antitumor agents.

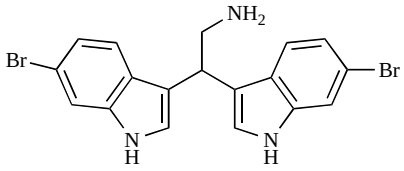
There are several reports related to the isolation, characterization, and biological evaluation of indole. Among them, arsindoline A (**1**) and B (**2**) were isolated from a marine-derived bacterium strain CB101 identified as *Aeromonas sp* (Fig. **1**) [2,3]. 2,2-Bis(6-bromo-3-indolyl)ethylamine (**3**) was isolated from the Californian tunicate *Didemnum candidum* [4]. However, there are no reported biological studies on the promising antitumor potential of these indole alkaloids (Fig. **1**). On the other hand, there are several natural bioactive products that share a common bis(indolyl)methane molecular unit. Arundine (**4**), isolated from the root of *Arundo donax*, which exhibits potent carcinogenicity [5]; vibrindole A (**5**), a



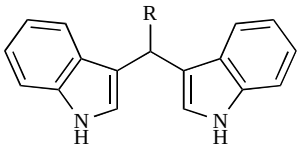
Arsindoline A (**1**)



Arsindoline B (**2**)



2,2-Bis(6-bromo-3-indolyl) ethylamine (**3**)



R = H Arundine (**4**)
R= CH_3 Vibrindole A (**5**)
R= CH_2OAc Streptindole (**6**)

Fig. (1). BIMs from the natural source.

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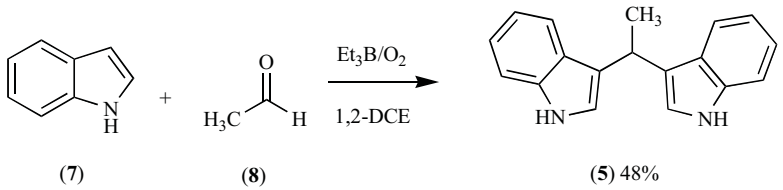


(**7**) (**8**) (**5**) 48%

Scheme 1.

metabolite of the marine *Vibrio parahaemolyticus*, shows antibacterial activity against *Staphylococcus aureus*, *Staphylococcus albus* and *Bacilus subtilis* [6], and streptindole, (**6**) isolated from the intestinal bacterium *Streptococcus faecium* IB 37, demonstrate DNA-damaging activity and genotoxicity (Fig. **1**) [7].

In this context, bis(indolyl)methanes (BIMs) have attracted considerable interest in recent years [8]. An increasing number of naturally occurring bioactive BIMs have shown cytotoxic activity against several cancer lines. Consequently, numerous protocols for the synthesis of BIMs derivatives have been reported [9,10].

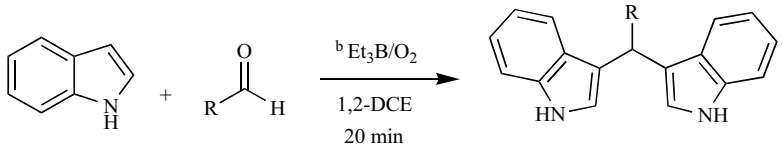
Common methodologies for the synthesis of BIMs involve the condensation of indoles with several aldehydes or ketones in the presence of protic acids or Lewis acids [11-15]. These methodologies are well documented as useful routes to a large variety of BIMs. As a continuation of our research on the synthesis of heterocyclic compounds, herein are described preliminary results of the Friedel-Crafts alkylations using TEB as a catalyst. Through this methodology, the synthesis of vibrindole A (**5**) and BIM derivatives **16** and **18** was carried out in short time reaction. Compound **16** is an intermediary in the synthesis of the natural bisindoles arsindoline B (**2**) and streptindole (**6**).

RESULTS AND DISCUSSION

First, we carried out the reaction of indole with acetaldehyde and triethylborane in 1,2-dichloroethane at room temperature. Corresponding bis(indolyl)methane was formed (TLC) in a short reaction time (Scheme **1**).

To prove the generality of the protocol, the reaction was then extended towards a variety of aldehydes and the results are summarized in Table **1**.

Table 1. Et_3B catalyzed synthesis of bis(indolyl)methanes.[a]



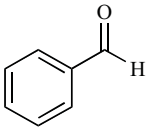
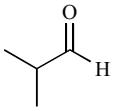
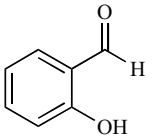
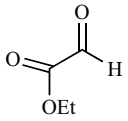
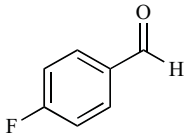
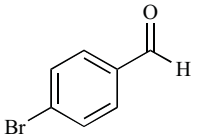
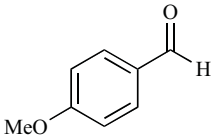
Entry	Aldehyde	Product	Yield (%)[c]	References
1	 (**9**)	10	**32**	**[16,17]**
2	 (**11**)	12	**28**	**[18,19]**
3	 (**13**)	14	**12**	**[20]**

Table 1. contd…

Entry	Aldehyde	Product	Yield (%)[c]	References
4	 (**15**)	16	**92**	**[19,7]**
5	 (**17**)	18	**52**	**[17]**
6	 (**19**)	20	**12**	**[13,21]**
7	 (**21**)	22	**10**	**[18,19]**

[a] All reactions were carried out with 1 equiv. of aldehyde and 2 equiv. of indole in 1,2-DCE at room temperature for 20 min. [b] Reaction was carried out with (0.05 mL) de Et_3B. [c] Yields refer to pure, isolated products.

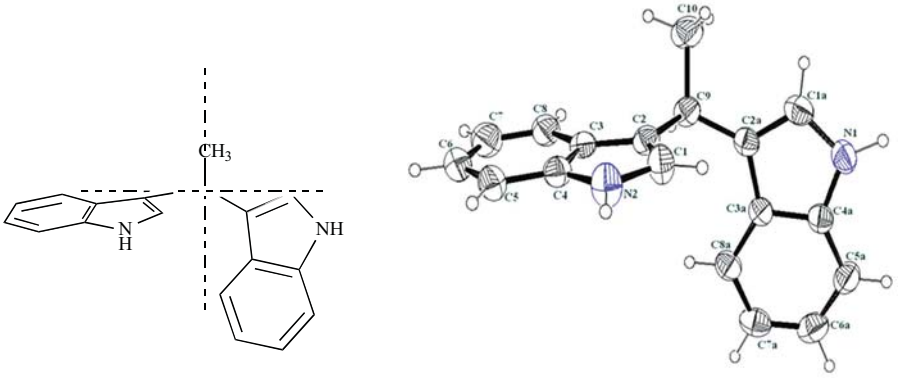


Fig. (2). Molecular structure of vibrindole A (**5**). Thermal ellipsoids at 30% probability level.

Yields observed in Table **1** are moderate and in some cases lower, except for entry 4. In the presence of weak activating groups, the reaction proceeds in yields from 28% to 48% (Scheme **1**, Entry 1 and 2); unexpectedly, a general trend in low yields with the electron rich aldehydes is observed (Entry 3 and 7) while the aldehydes with electron withdrawing group (Entry 4 and 5) gave the best results in terms of yield. In the case of entry 6, the yield also was low. In this context, though bromine is considered as electron withdrawing group, its electronegativity is lower compared with fluorine. To the best of our knowledge, condensation of indole with aldehydes in the presence of triethylborane as Lewis acids has not been reported yet.

Suitable crystals for X-ray analysis of the vibrindole A (**5**) were obtained from its solution in a mixture of hexane-ethyl acetate (7:3) by slow evaporation of the solvent, crystallizing in the triclinic system, space group P1. The X-ray crystal structure analysis (Fig. **2**) showed that the dihedral angle between the five membered rings N(2)→C(4) and N(1)→C(4a) is 85.98 (19)°, and the dihedral angle between the aromatic rings C(3)→C(8) and C(3a)→C(8a) was 89.33(16)°. In the ORTEP diagram, an indole fragment is perpendicular to the second indole substituent (Fig. **2**). In the crystal, molecules are linked *via* X-H···π interactions (Fig. **3**).

CONCLUSION

In summary, we have developed an efficient method for the synthesis of vibrindole A (**5**) and BIMs derivatives **16** and **18**. Compound **16** is an intermediate for the synthesis of

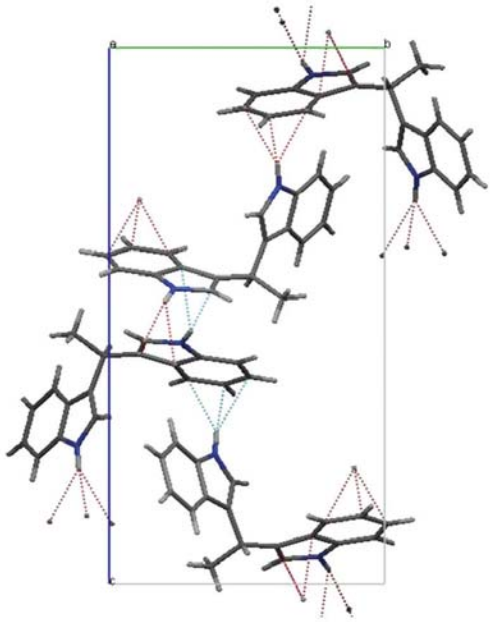


Fig. (3). The crystal packing of the title compound, viewed along the *c* axis. The dashed lines indicate the X-H···π interactions.

the natural bisindoles arsindoline B (**2**) and streptindole (**6**). The structure of vibrindole A (**5**) was unequivocally established by single-crystal X-ray diffraction. The reaction is simple, non-toxic, easy to handle, and with shorter reaction times. The triethylborane catalyzed C3-selective Friedel-Crafts alkylation of indoles with aldehydes. Work along these lines is underway.

EXPERIMENTAL

IR spectra were acquired on a Perkin Elmer TF-IR System 2000 using KBr pellets ($\overline{\upsilon}$, cm^{-1}). NMR spectra (^1H, ^{13}C, HETCOR and COSY) were determined on JEOL Eclipse +400 spectrometer, and chemical shifts are stated in ppm (δ) and are referred to the residual ^1H signal (δ = 7.27) or to the central ^{13}C triplet signal (δ = 77.0) for $CDCl_3$. The products were separated by chromatography over silica gel (70-230 mesh). Crystals of **5**, suitable for X-ray analysis, were obtained from hexane-ethyl acetate 7:3 by slow evaporation of the solvent at room temperature. The X-ray measurement was performed at 293 K on a Bruker SMART CCD diffractometer with Mo Kα-radiation, γ = 0.71073 Å. The structure was solved by direct methods (SHELXS-86) and refined using SHELXL-97. All non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were included at calculated positions with the use of a riding model. CCDC 1050231 contained crystallographic data for this publication. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Crystal Data for Compound 5

Crystal data for compound **5**: $C_{18}H_{16}N_2$, colorless prisms, 0.2 mm × 0.18 mm × 0.19 mm, formula weight M = 260.33, triclinic, P1, a = 6.562 Å, b = 9.977 Å, c = 21.357 Å, α=β=γ = 90°, V = 1398.2 $Å^3$, Z = 4, Dx = 1.237 Mgm^{-3}, μ = 0.073 mm^{-1}, $F(000)$ = 552. Collected reflections: 10165 within a theta range of 1.91-27.07°. Unique reflections: 1794. Observed reflections: 1794 with F>4σ(F) the absorption correction was not applied. Refinement: (refinement on F^2), final R = 0.0494, wR^2 = 0.1302, goodness-of-fit = 0.976, 1794 reflections, 190 parameters, maximum and minimum difference electron densities were 0.183 $eÅ^{-3}$ and -0.118 $eÅ^{-3}$, respectively.

Typical Procedure for the Preparation of bis(indolyl) methanes

A solution of indole (0.2 g, 3.4 mmol) and aldehyde (0.07 g, 1.7 mmol) in $ClCH_2CH_2Cl$ (0.5 mL) was treated with Et_3B (0.05 mL) and the resulting reaction mixture was stirred at room temperature for 20 min. The solvent was removed *in vacuo* and the resulting mixture was purified by flash column chromatography eluting with hexane-ethyl acetate 7:3 or 9:1. The spectral data of some of the bis(indolyl)methanes are summarized below.

***3,3'-Bis(indolyl)-2-(hydroxyphenyl)methane (Entry 3, 14)*:** IR (ν, cm^{-1} KBr): 3382, 3226, 2918, 2849, 1735, 1664, 1619, 1459, 1376, 1268, 1195, 1108, 749. NMR ^1H 400 MHz ($CDCl_3$), δ: 7.80 (1H, s, NH), 7.40 (1H, d, H-5, J = 7.7Hz), 7.31 (1H, d, H-8, J = 8.1Hz), 7.20 (3H, m, H-12, H-13 y H-14), 7.04 (1H, td, H-6, J = 0.7, 7.3 Hz), 6.87 (2H, d, H-2, H-7, H-15, J =2.2 Hz), 6.63 (1H, s, H-2), 5.9 (1H, s, H-3′), 5.48 (1H, s broad, OH). NMR ^{13}C 100 MHz ($CDCl_3$), δ: 154.5, (C-10), 136.9 (C-3), 130.1 (C-12), 129.2 (C-10), 128.1 (C-13), 126.8 (C-9), 123.8 (C-2), 122.4 (C-14), 120.9 (C-15), 120.0 (C-5), 119.9 (C-4), 119.6 (C-6), 117.1 (C-11), 116.6 (C-7), 111.4 (C-8), 35.9 (C-3′).

***3,3'-Bis(indolyl)-4-(bromophenyl)methane (Entry 6, 20)*:** IR (ν, cm^{-1} KBr): 3417, 2918, 2849, 1618, 1482, 1455, 1414, 1199, 1033, 742, 541. NMR ^1H 400 MHz ($CDCl_3$), δ: 7.78 (1H, s, NH), 7.39 (2H, m, H-5 y H-11), 7.33 (1H, d, J = 8.8 Hz, H-8), 7.20 (1H, t, H-6, H-12, J = 8.2 Hz), 7.04 (1H, d, H-7, J = 8.2 Hz), 6.56 (1H, s, H-2), 5.85 (1H, s, H-3′). NMR ^{13}C 100 MHz ($CDCl_3$), δ: 143.22 (C-10), 136.79 (C-14), 131.41 (C-3), 130.59 (C-4), 126.98 (C-13), 123.70 (C-6), 123.01 (C-9), 122.19 (C-2), 120.02 (C-7), 119.90 (C-5), 119.48 (C-12), 119.16 (C-11), 111.25 (C-8), 39.81 (C-10).

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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