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

![Fig. (1). BIMs from the natural source.](image-url)
A new index for the estimation of the aromatic character

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A metabolite of the marine Vibrio parahaemolyticus, shows antibacterial activity against Staphylococcus aureus, Staphylococcus albus and Bacillus 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 BIM 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 arsinindoline 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. Et3B catalyzed synthesis of bis(indolyl)methanes.*

| Entry | Aldehyde | Product | Yield (%)www | 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 (%)<sup>c</sup> | References |
|-------|----------|---------|----------------------|------------|
| 4     | \( \text{H} \text{O} \text{Et} \odot \) | 16      | 92                   | [19,7]     |
| 5     | \( \text{H} \text{O} \text{F} \odot \) | 18      | 52                   | [17]       |
| 6     | \( \text{H} \text{O} \text{Br} \odot \) | 20      | 12                   | [13,21]    |
| 7     | \( \text{H} \text{O} \text{MeO} \odot \) | 22      | 10                   | [18,19]    |

<sup>a</sup> 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. <sup>b</sup> Reaction was carried out with (0.05 mL) de Et₃B. <sup>c</sup> Yields refer to pure, isolated products.

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 was also 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)<sup>o</sup>, and the dihedral angle between the aromatic rings C(3)→C(8) and C(3a)→C(8a) was 89.33(16)<sup>o</sup>. 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...
EXPERIMENTAL

IR spectra were acquired on a Perkin Elmer TF-IR System 2000 using KBr pellets (\(\delta\), cm\(^{-1}\)). NMR spectra (\(^1H\), \(^13C\), HETCOR and COSY) were determined on JEOL Eclipse +400 spectrometer, and chemical shifts are stated in ppm (\(\delta\)) and are referred to the residual \(^1H\) signal (\(\delta = 7.27\)) or to the central \(^13C\) triplet signal (\(\delta = 77.0\)) for CDCl\(_3\). The IR spectra of some of the bis(indolyl)methanes are summarized below.

3,3′-Bis(indolyl)-2-(hydroxyphenyl)methane (Entry 3, 14): IR (\(v\), cm\(^{-1}\) KBr): 3417, 2918, 2849, 1618, 1482, 1455, 1376, 1268, 1195, 1108, 749. NMR \(^1H\) 400 MHz (CDCl\(_3\)), \(\delta\): 7.80 (1H, s, NH), 7.40 (1H, d, H-5, \(J = 7.7\) Hz), 7.31 (1H, d, H-8, \(J = 8.1\) Hz), 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, OD). NMR \(^13C\) 100 MHz (CDCl\(_3\)), \(\delta\): 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 (\(v\), cm\(^{-1}\) KBr): 3417, 2918, 2849, 1618, 1482, 1455, 1414, 1199, 1033, 742, 541. NMR \(^1H\) 400 MHz (CDCl\(_3\)), \(\delta\): 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 \(^13C\) 100 MHz (CDCl\(_3\)), \(\delta\): 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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