FIRST EVIDENCE OF 1,3-BIS-INDOLYLALLENES: 
GENERATION BY A SEQUENTIAL DOUBLE 
NUCLEOPHILIC PROCESS FROM YNONES

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GRAPHICAL ABSTRACT

Abstract The first examples of 1,3-bis-indol-3-ylallenes (1,3-BIAs) are described. They have been generated by addition of a 3-lithioindole reactant to tetramethylsilane-protected mono- and di-alkynyl ketones. The one-pot preparation of 1,3-BIAs is enabled by both the double electrophilic character of the ynone substrates and the double nucleophilic character of the lithio-enamine function of the indolyl moiety, leading to a transient azafulvenium intermediate.

Keywords Allene; bisindole; indole; lithioenamine; ynone

INTRODUCTION

The indole motif is largely found in nature, especially in C3-substituted derivatives of tryptophan. Several isolated or bio-inspired representatives exhibit remarkable biological activities, in particular as pharmaceuticals[1] and have motivated methodological studies of their synthesis[2] and functionalization.[3] Bioactive bis-indolyl compounds such as directly connected 3,3′-bis-indoles[4] or

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bis(indol-3-yl)methanes (BIMs, where the two indole motifs are linked to the same $sp^3$ carbon atom) were also isolated from natural sources and targeted by total synthesis. Beyond bis-indol-3-yl ketones (BIK), where two indole motifs are linked to the same $sp^2$ carbon atom, few examples of $gem$-bis-indolylethene analogues ($gem$-BIEs) have been described (Fig. 1). The vic-BIEs isomers, where the two indolyl moieties are separated by two $sp^2$ C atoms, have been more widely exemplified. The particular case of bis-indolylmaleimides with various $\omega$-aminoalkyl substituents $R_n$ at indolic N atoms (BIM-$n$, $n = 1, 2, 3, 8$, and bis-indolylfurandione analogs), where the ethendiyl bridge is included inside a maleimide or furandione ring, is largely documented for potent proteine kinase inhibition activities.

Within a logical prospect, the next representatives of the bis-indole series are 1,3-bis-indolylallenes (BIAs), where the two indolyl C3 atoms are separated by two $sp^2$ and one central $sp$ carbon atoms (Fig. 1). To the best of our knowledge, no example of BIA molecules has ever been reported and evidence of formation of the first representatives is described hereafter.

RESULTS AND DISCUSSION

Because of the limited stability of the secondary enamine function, especially under acidic conditions, derivatization/functionlization of the indole core often requires substitution of the nitrogen atom, which also induces an enhanced nucleophilicity of the C3 atom located at the "tautomeric" position. Bis-indol-3-ylallene targets could be thus envisaged in one pot from the 3-bromo-5-methoxy-1,2-dimethyl-1$H$-indole substrate $1a$, where the $\pi$-donating ($+M$) character of the N atom is further enhanced by a para-methoxy substituent,$^{[10]}$ and where the N and C2 positions are substituted by methyl groups. The N-methyl-3-bromoindole $1a$ was thus prepared from commercially available 2-methyl-5-methoxy-1$H$-indole using known procedures,$^{[11]}$ and in spite of a poor stability (see the Supporting Information) could be used as the starting core.
While BIMs are generally prepared from unsubstituted indole nucleophiles and C1 electrophiles, or alternatively via formyl-indoles under acidic conditions, the reactivity of 1a was investigated with ynones as C3 dielectrophiles. The indolylithium reactant 1b was generated in situ by treatment of a freshly prepared sample of 1a with 1 equivalent of n-butyllithium, and then reacted with the phenyl and trimethylsilyl-lethynyl ketones 2\textsuperscript{[12]} and 3\textsuperscript{[13]} to give the BIAs 4 and 5, respectively (Scheme 1). The study was completed by the reaction of 1a with benzophenone.

The 1H NMR spectra of the crude reaction mixtures were not explicitly informative of the reaction outcome, but the BIAs 4 and 5 were the sole products isolated after chromatography over silica gel. The poor isolated yields (15% for 4, 18% for 5) remained the same whatever the quantity of the indolylithium salt used (1 or 2 equivalents), and this could be attributed to the poor stability of either the indolylithium reagent, reaction intermediates, or the unprecedented BIA products. Several experimental conditions were tested (different temperatures and reaction times) without improvement of the isolated yields in 4 and 5. For each BIA, 1H and 13C NMR spectroscopy evidenced two sets of signals for the two nonequivalent indole moieties, and signals at 209.9 and 216.7 ppm provided definite evidence of the allene moieties in 4 and 5, respectively. X-ray diffraction analysis of a single crystal of 4, deposited from a Et2O/DCM solution at 4°C, allowed confirmation of the bis-indolylallene structure, and indicated a π-π stacking interaction between two ortho centers of the two quasiparallel anisole rings (C9–C24 = 3.41 Å, Fig. 2).

Upon reaction of the lithium salt of 1a with benzophenone (Scheme 1), the monoindolyl carbinol 6 was obtained as main product (in 85–90% crude yield estimated by 1H NMR spectroscopy), while the BIM 7 was not observed. This result is at least consistent with previous reports describing the synthesis of BIMs by reactions.

Scheme 1. Reaction of the lithium salt 1b of the indole 1a with ynones and benzophenone.
of aldehydes or ketones with indole derivatives in the presence of Lewis acids (and not in a basic medium as here). The absence of BIM product can also be attributed to the steric crowding at the central carbon atom of benzophenone, preventing addition of two indolyl moieties. After a tedious purification process by multistep chromatography, 6 was finally isolated in 51% yield.

The formation of the bis-indolylallenes 4 and 5 can be accounted for by a mechanism involving previously invoked processes (Scheme 2). The indolylithium 1b, generated from the 3-bromo-indole 1a, would first attack at the carbonyl center of the mono- or bis-propargylic ketone 2 or 3, giving the corresponding lithium alkoxide intermediate 8. The enamine lone pair of 8 would then expell the LiO⁻ nucleofuge while affording an azafulvenium cation 9, as previously proposed for the formation of BIM products under acidic conditions. Such a cleavage of C—OLi bonds had also been previously reported to occur in the presence of FeCl₃. Then, the conjugated enyne moiety of 9 would undergo an attack by a second equivalent of 1b, thus giving the allenic moieties of 4 and 5.

Reaction of 1b with benzophenone lead to the mono-adduct 6 only (Scheme 1), likely because of the steric crowding of the corresponding gem-diphenyl-azafulvenium.
cation, the electrophilicity of which is also decreased by extended delocalization of the positive charge over the two phenyl substituents.

A bifunctional version of 3 under the form of the macrocyclic bis-propargylic diketone 10, a [6]pericyclynedione,[18] was recently reported to react with an indolyl lithium salt 2b (generated from the corresponding bromide 2a) to give the bis-monoadduct 11 (Scheme 3).[19] The formation of 11 required a short reaction time at low temperature to prevent the appearance of side products, which could be tentatively assigned to endo-macrocyclic BIA double adducts of type 12. The hydrolysis products of 11 and triple adducts of type 12 could not be isolated, but after direct treatment of the crude mixture with the reductive SnCl2/HCl system, the isolation

Scheme 2. Proposed mechanism, enabled by the double nucleophilic character of the lithio-enamine moiety, for the one-pot preparation of the BIAs 4 and 5 (Scheme 1).

Scheme 3. Outcome of the addition of an indol-3-yl lithium to the [6]pericyclynedione 10.[19]
of the bis-indolyl-carbo-benzene 13 confirmed the structure of its precursor 11.\[^{20}\]
Beyond the global poor yield, the absence of evidence for the formation of a triple adduct of type 12 can be attributed to either an intrinsic instability and/or to the steric hindrance of the electrophilic \(sp\)-C centers (the “Michael positions”) in 11 (Scheme 3).\[^{19}\]

CONCLUSION

The first experimental evidence and full characterization of bis-indolylallenes (BIAs) have been obtained using a synthetic route based on the double nucleophilic behaviour of a 3-lithio-indolyl reactant toward doubly electrophilic silyl-protected ynone substrates. The moderate stability of the BIA products and indole precursor did not allow us to perform a systematic study, but improvement and generalization of their preparation will rely on the optimization of the structural compatibility between the ynone electrophile and 3-lithioindole nucleophile.

EXPERIMENTAL

Tetrahydrofuran (THF) was dried and distilled over sodium/benzophenone. All other reagents were used as commercially available. In particular, commercial solutions of \(n\)-BuLi were 2.5 M in hexane. All reactions were carried out under an argon atmosphere using Schlenk and vacuum line techniques. Column chromatography was carried out on silica gel (60 P, 70–200 mm). Silica gel thin-layer chromatographic (TLC) plates (60F254, 0.25 mm) were revealed by treatment with an ethanolic solution of phosphomolybdic acid (20%). The following analytical instruments were used: \(^1\)H and \(^{13}\)C NMR, Bruker DPX 300, Avance 300, Avance 400, Avance 400WB, or Avance 500 spectrometers; and mass spectrometry, Quadrupolar Nermag R10-10H spectrometer. Most of the NMR spectra were recorded in CDCl\(_3\) solutions. NMR chemical shifts \(\delta\) are given in parts per million (ppm), with positive values to high frequency relative to the tetramethylsilane (TMS) reference; coupling constants \(J\) are in hertz. IR used a 0.1-mm CaF\(_2\) cell, Perkin-Elmer GX FTIR. 3-Bromo-5-ethyl-1,2-dimethyl-1\(H\)-indole 1a,\[^{11}\] 1-phenyl-3-(trimethylsilyl)prop-2-yn-1-one,\[^{12}\] and trimethyl[3-oxo-5-(trimethylsilyl)penta-1,4-diyn-1-yl]silane \[^{13}\] were prepared following described procedures.

Crystallographic Data for BIA 4

Intensity data were collected at 100 K on a Gemini Agilent diffractometer using a Cu Ka radiation source and equipped with an Oxford Cryosystems Cryostream Cooler device. The structure was solved by SUPERFLIP\[^{21}\] and refined by full-matrix least-squares procedures on \(F\), using the programs of the PC version of CRYSTALS.\[^{22}\] Atomic scattering factors were taken from the international tables for x-ray crystallography.\[^{23}\] All nonhydrogen atoms were refined anisotropically. Hydrogen atoms were refined using a riding model. Absorption corrections were introduced using the MULTISCAN program.\[^{24}\]

Crystal data for 4: \(C_{34}H_{38}N_2O_2Si\), 2(CH\(_2\)Cl\(_2\)), \(M = 704.64\) g mol\(^{-1}\), triclinic, \(a = 11.7650(4)\), \(b = 12.2770(4)\), \(c = 13.2538(7)\) Å, \(\alpha = 84.895(3)\), \(\beta = 71.579(4)\),
\[
\gamma = 80.329(3)^\circ, \quad V = 1789.15(14) \text{ Å}^3, \quad T = 100 \text{ K}, \quad \text{space group } P-1, \quad Z = 2, \quad \mu(\text{Mo-K}\alpha) = 3.594 \text{ mm}^{-1}, \quad 22420 \text{ reflections measured, 5593 unique (}R_{\text{int}} = 0.022\text{)}, \quad 5048 \text{ reflections used in the calculations [}I > 3\sigma(I)\text{], 406 parameters, } R_1 = 0.0452, \quad wR_2 = 0.0581.
\]

**General Experimental Procedure**

\(n\)-BuLi (290 µl, 0.73 mmol) was added to a solution of 3-bromo-5-methoxy-1,2-dimethyl-1\(^H\)-indole 1a (200 mg, 0.8 mmol) in THF (5 mL) under stirring at \(-78^\circ\text{C}\). The reaction mixture was stirred over 1 h at \(-78^\circ\text{C}\) before addition of a solution of the ketone substrate (0.66 mmol) in THF (3 mL). The temperature was allowed to increase slowly up to 0 °C over 3 h. The mixture was then quenched with saturated aqueous NH\(_4\)Cl. The aqueous layer was extracted with diethyl ether, and the combined organic layers were washed with brine, dried over MgSO\(_4\), and concentrated to dryness under reduced pressure. The residue was purified by silica-gel chromatography (pentane/EtOAc).

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**SUPPLEMENTAL MATERIAL**

Full experimental details, \(^1\text{H}\) and \(^{13}\text{C}\) NMR, infrared, and mass spectra, and crystallographic data for 4 can be accessed on the publisher’s website.

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