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Copper(I) mediated facile synthesis of potent tubulin polymerization inhibitor, 9-amino-α-noscapine from natural α-noscapine

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ABSTRACT

Facile synthesis of natural α-noscapine analogue, 9-amino-α-noscapine, a potent inhibitor of tubulin polymerization for cancer therapy, is achieved via copper(I) iodide mediated in situ aromatic azidation and reduction of 9-bromo-α-noscapine (obtained by bromination of natural α-noscapine) with NaN_3 in DMSO at 130 °C in the presence of L-proline as an amino acid promoter. The protocol developed here avoided isolation of 9-azido-α-noscapine and did not cleave the sensitive C–C bond between two heterocyclic phthalide and isoquinoline units.

α-Noscapine **1** (also known as Narcotine, Nectodon, Nospen, and Anarcotine) is a naturally occurring phthalide isoquinoline alkaloid isolated from plants of the Papaveraceae family.[1] It has been used orally as antitussive agent and displays a favorable toxicity profile.[2] It has also been known for some time that α-noscapine can act as anticancer agent through the disruption of tubulin steady state dynamics.[3] Although it is weak inhibitor of microtubule polymerization, it is not toxic at tumor suppressive doses. With excellent oral bioavailability and low cost, allow this natural product for further exploratory medicinal chemistry.[3] Derivatized analogues of noscapine, such as 9-fluoro, 9-bromo, 9-chloro and 9-iodo α-noscapinoids have shown to increase anticancer activity than the parent α-noscapine.[4] Recently 9-amino-α-noscapine **5** [(*S*)-3-((*R*)-9-amino-4-methoxy-6-methyl-5,6,7 ,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)-6,7-dimethox- yisobenzofuran-(3*H*)-one] was identified as potent inhibitor of tubulin polymerization for cancer theraphy.[5]

Computational methods predicted that 9-amino-α-noscapine binds to tubulin at a site overlapping with colchicine-binding site and possess better anti-tumor activity than the parent compound **1**.[6] 9-Amino-α-noscapine **5** was also derivatized to its folate analogue and evaluated for anti-tumor activity.[7] In view of the increased utility of 9-amino-α-noscapine in anticancer evaluations, it is desirable to develop an efficient method for the synthesis of 9-amino-α-noscapine **5**. Continuing our programme[8] on the synthesis of natural products and its analogues for bio-evaluations, we herein report a facile synthesis of 9-amino-α-noscapine **5** from 9-bromo-α-noscapine **3** via copper(I) mediated in situ aromatic azidation and reduction. The reaction conditions adopted here avoided isolation of 9-azido-noscapine **4** and did not affect the sensitive C–C bond between two heterocyclic phthalide and isoquinoline units.

The general synthetic approaches for the preparation of 9-amino-α-noscapine are depicted in Scheme 1. To the best of our knowledge, only two methods are in the patent literature[7,9] for the synthesis of 9-amino-α-noscapine. The first route is a two step method involving nitration of natural α-noscapine using silver nitrate, excess of trifluoroacetic anhydride in acetonitrile,[9a] followed by Pd/C catalyzed hydrogenation. The second method[9b] is a three step route involving aromatic bromination using aq HBr/Br_2–H_2O; azidation using NaN_3 in DMF and selective reduction of 9-azido-α-noscapine **4** to 9-amino-α-noscapine **5** using $SnCl_2$/PhSH/Et_3N/THF. During our attempts on nitration of natural α-noscapine using concentrated nitric acid at low temperatures (0 °C), we noticed an acid catalyzed hydrolysis of C–C bond between two heterocyclic lobs leading to the formation of Cotarnine (92%) and Opianic acid (89%) as major products (Scheme 2) along with 9-nitro-α-noscapine **2** (3%). Further attempts with $AgNO_3$, excess

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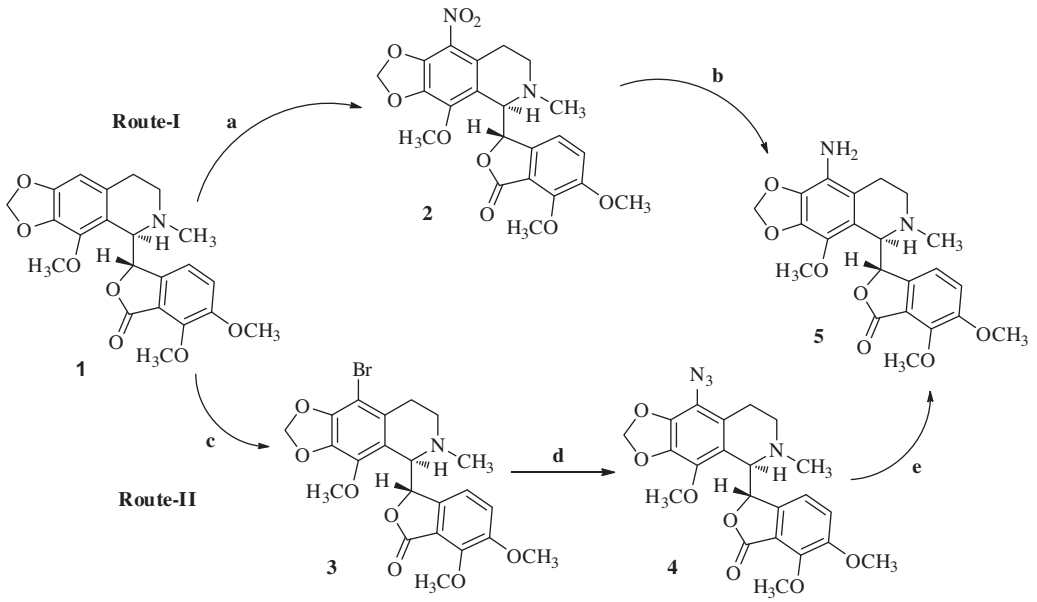
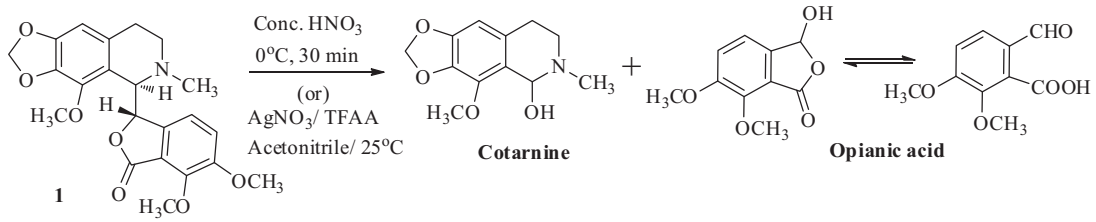
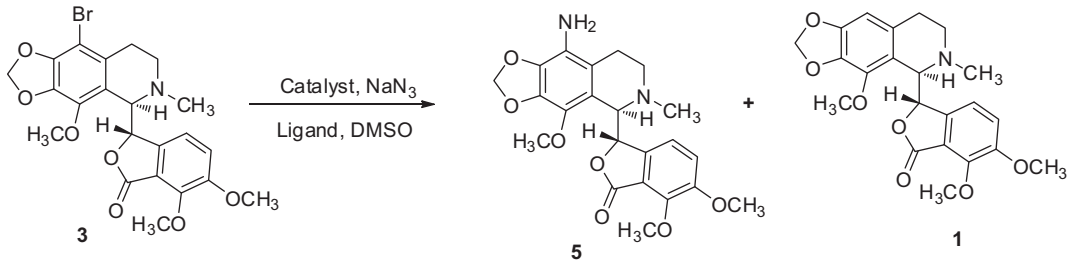


Scheme 1. Synthetic approaches for the preparation of 9-amino-α-noscapine. (a) $AgNO_3$, TFAA, acetonitrile, 25 °C, 18%; (b) Pd/C, H_2, 83%; (c) HBr/Br_2–H_2O, 25 °C, 82%; (d) NaN_3/NaI/DMF/ 80 °C 74%; (e) $SnCl_2$/PhSH/Et_3N/THF/ 25 °C, 83%.



Scheme 2. Nitration of α-noscapine **1**.

Table 1
Coupling of 9-bromo-α-noscapine **3** with sodium azide[a]



S. No.	Catalyst (equiv)	NaN_3 (equiv)	Solvent	Ligand (equiv)	Reaction time (h)	Temp (°C)	Product[b] (%)	
							5	**1**
1	CuI (1.0)	2.0	DMSO	Proline (1.3)	12	100	<1	3
2	CuI (1.0)	2.0	DMF	Proline (1.3)	12	100	<1	5
3	CuI (2.0)	2.0	DMSO	Proline (2.0)	12	100	<1	5
4	CuI (2.0)	2.0	DMSO	Proline (3.0)	12	110	5	8
5	CuI (2.0)	2.0	DMSO	Proline (3.0)	12	120	9	12
6	CuI (2.0)	2.0	DMSO	Proline (3.0)	4	140	Decomposed	
7	CuI (2.0)	2.0	DMSO	Proline (3.0)	4	130	30	22
8	CuI (2.0)	3.0	DMSO	Proline (3.0)	3	130	48	19
9	CuI (2.0)	2.0	DMSO	Proline (4.0)	3	130	62	15
10	CuI (3.0)	4.0	DMSO	Proline (4.0)	3	130	58	16
11	CuI (2.0)	4.0	DMSO	Proline (6.0)	3	130	60	16
12	CuI (2.0)	4.0	DMF	Proline (4.0)	3	130	55	16
13	CuI (2.0)	4.0	2-Propanol	Proline (4.0)	3	Reflux	8	20
14	Cu_2O(2.0)	4.0	DMSO	Proline (4.0)	3	130	~2	~3

Table 1 (*continued*)

S. No.	Catalyst (equiv)	NaN_3 (equiv)	Solvent	Ligand (equiv)	Reaction time (h)	Temp (°C)	Product[b] (%)	
							5	**1**
15	CuCl (2.0)	4.0	DMSO	Proline (4.0)	3	130	~2	~2
16	—	4.0	DMSO	Proline (4.0)	3	130	—	—
17	CuOTf(2.0)	4.0	DMSO	Proline (4.0)	3	130	45	22
18	CuBr (2.0)	4.0	DMSO	Proline (4.0)	3	130	26	10
19	CuI (2.0)	4.0	DMSO	DMEDA (4.0)	3	130	6	5

[a] 9-Bromo-α-noscapine **3** (1 mmol), solvent (4 mL) were used.
[b] Isolated yields.

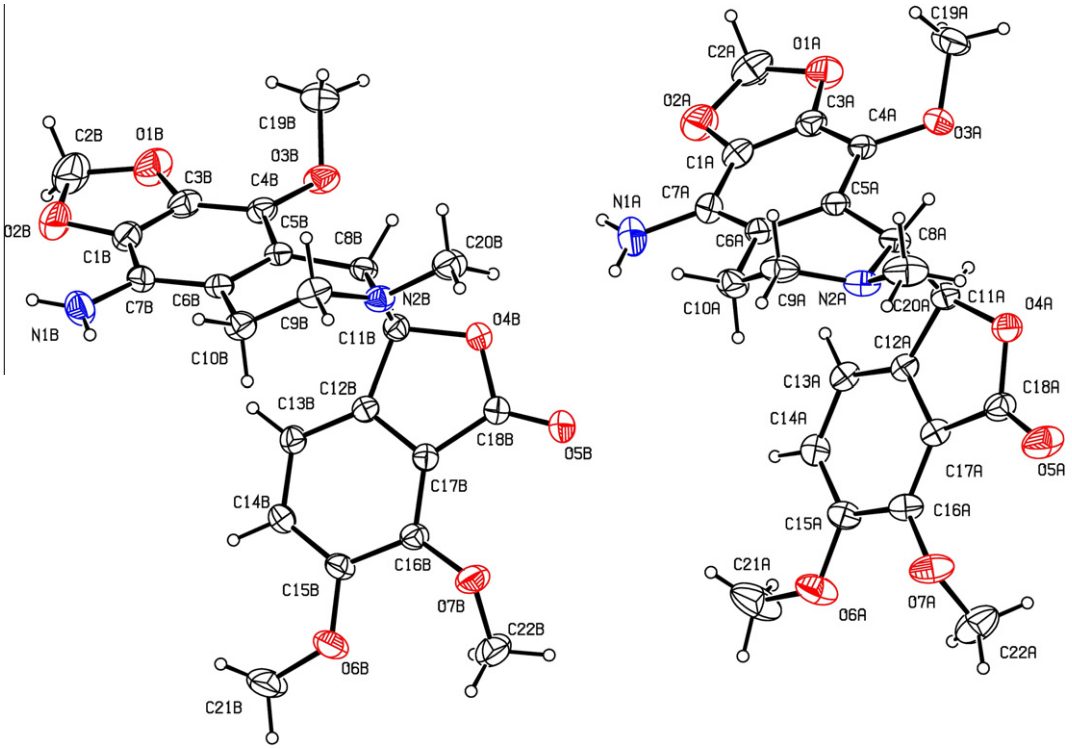


Figure 1. ORTEP representation of 9-amino-α-noscapine **5** with thermal displacement ellipsoids drawn at the 30% probability level and H atoms are represented by circles of arbitrary radii.

trifluoroacetic anhydride (TFAA) in acetonitrile at 25 °C resulted 9-nitro-α-noscapine **2** in low yields (18%) along with the formation of Cotarnine (65%) and Opianic acid (58%).[18] Such C–C bond hydrolysis is also consistent with literature precedents.[10] Further catalytic hydrogenation of 9-nitro-α-noscapine is also sluggish leading to a mixture of unidentified products. Next, we focused our attention on second route (Scheme 1) for the synthesis of 9-amino-α-noscapine **5**. As a starting point of the study, 9-bromo-α-noscapine **3** required was synthesized in excellent yield (90%) from natural α-noscapine **1** using bromine water in 48% aqueous HBr modifying the reaction conditions described in literature.[4g] Bromo noscapine **3** obtained was fully characterized by IR, ^1H & ^{13}C NMR and Mass (ESI and HRMS) spectra data. Following the sequence, conversion of **3** with sodium azide/sodium iodide was attempted in DMF at 80–85 °C. Contrary to our expectation, the reaction did not proceed in our hands and after prolonged reaction time (48 h) gave only poor yield (~3%) of 9-azido-α-noscapine **4**. Repeated reactions under various conditions like changing mole ratio of sodium azide/sodium iodide, temperature, time and solvent are also not fruitful. As a result, we are forced to search for alternate method for the preparation of compound **4** and then **5.**

Previously it was reported[11] that use of sodium azide in aromatic substitution reactions of bromo aromatics consists of a variety of results, with respect to whether the starting compounds are electron rich or electron poor and the products formed are azides or amines.[11,12] Most of these reports[11–14] use modified conditions of Ullmann type coupling wherein the reaction was carried out using CuI, NaN_3 and amino acid additives in basic medium. During the synthesis of 9-amino-α-noscapine we realize the work of Helquist and co-workers[13] in the conversion of bromo aromatics to primary aryl amines under neutral conditions. They reported that the reaction is facilitated by combining sodium azide and copper reagents along with proline in excellent yields via in situ reduction of aromatic azides. A similar approach was applied in our study for the conversion of 9-bromo-α-noscapine **3** to 9-amino-α-noscapine **5**.

Initially, 9-bromo-α-noscapine **3** was treated with CuI, NaN_3 and proline as additive at 100 °C similar to the conditions reported in the literature[13] (Table 1, entry 1). Disappointingly, no reaction took place and bromo compound **3** was recovered quantitatively. Changing the mole ratio of CuI and proline additive did not give any fruitful reaction (Table 1, entries 2–5). These results prompted us to think that structurally, the aromatic ring bearing bromine may be in the influence of strong electron rich environment and

therefore may be preventing from the requisite substitution reaction. A report from Ma and co-workers[14] described to enhance rate of aromatic substitution reaction of electron-rich aryl bromides with copper catalysts by rising the reaction temperature. Taking this clue, the reaction temperature was enhanced incrementally. To our success, after series of experiments, 9-bromo noscapine **3** was successfully converted with CuI, NaN_3 and proline at 130 °C for 4 h to give moderate yield (30%) of 9-amino-α-noscapine **5** (Table 1, entry 7). At this stage we also observed debromination of bromo noscapine **3** to give 22% of natural noscapine **1**. The reaction was best progressed when 9-bromo-α-noscapine **3** was reacted with CuI (2.0 equiv), sodium azide (2.0 equiv) and proline (4.0 equiv) in DMSO at 130 °C for 3.0 h (Table 1, entry 9). The crude reaction mixture was purified by triethyl amine treated silica gel column chromatography to give 9-amino-α-noscapine **5** in 62% yield.

Noscapine **1** (15%) was also isolated from this reaction. Heating the bromo compound **3** at 130 °C in the absence of copper catalyst but in the presence of 4 equiv of sodium azide and proline in DMSO did not result any reaction (Table 1, entry 16), suggesting that the present transformation is truly copper mediated. Changing of solvent to DMF did show any significant changes in the course of reaction or product yield (Table 1, entry 12). Addition of cesium carbonate or potassium carbonate as base additive led to sluggish and decomposed reaction mixtures. 9-Amino-α-noscapine **5** obtained was fully characterized by IR, ^1H & ^{13}C NMR and Mass (ESI and HRMS) spectra data. [15] Single crystal X-ray analysis unambiguously confirmed the structure of 9-amino-α-noscapine **5** (Fig. 1).[16]

Although the exact mechanism for the conversion of 9-bromo-α-noscapine **3** to 9-amino-α-noscapine **5** is not clear, a plausible mechanism is devised with the fact that Cu(I) form complex with amino acid through carbonyl and amino groups (Fig. 2). The L-proline–copper complex may be undergoing Ullmann type reaction with 9-bromo-α-noscapine **3** to give stabilized oxidative addition intermediates **II** and **III**. In this chelated environment, the aromatic ring of noscapine may become somewhat electron deficient and undergoes nucleophilic attack with azide, followed by in situ reduction of azide to amine under the reaction conditions employed.

In conclusion, we described here a copper mediated synthesis of 9-amino-α-noscapine **5** from natural α-noscapine **1.** 9-Bromo-α-noscapine **3** obtained through bromination of natural α-noscapine **1,** was reacted with sodium azide, in the presence of CuI & L-proline at 130 °C in DMSO under neural conditions to give 9-amino-α-noscapine **5** in 62% yield. The protocol developed here avoided isolation of 9-azido-α-noscapine and did not affect the sensitive C–C bond between two heterocyclic units. Due to the ever present potential for explosions when working with azides, we recommend appropriate care and protection while using this method for large scale conversions. Nonetheless, in view of its importance in medicinal chemistry the method is highly valuable for small scale preparations of 9-amino-α-noscapine **5** for their onward use as potent inhibitor of tubulin polymerization in clinical studies.

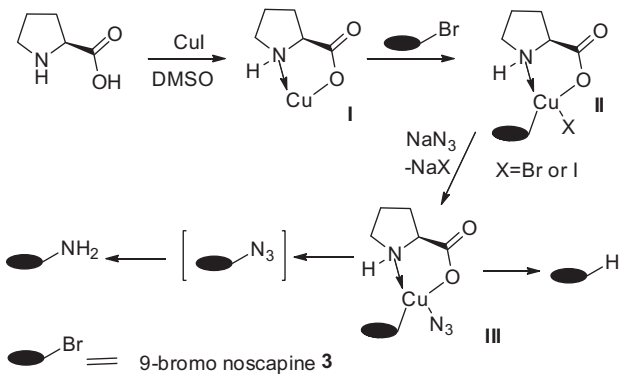


Figure 2. Plausible mechanism for the formation of 9-amino-α-noscapine **5**.

Acknowledgments

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Supplementary data

Complete experimental details, copies of ^1H, ^{13}C NMR and mass spectra (ESI and HR-MS) of synthesized products **3** and **5**; single crystal X-ray diffraction data for 9-amino-α-noscapine **5** (CCDC 854482) can be found free of charge from the Cambridge crystallographic data centre via www.ccdc.cam.ac.uk/data_request/cif.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2012.02.033.

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15. **(*S*)-3-((*R*)-9-amino-4-methoxy-6-methyl-5,6,7,8-tetrahydro[1,3]dioxo lo[4, 5-g]isoquinolin-5-yl)-6,7-dimethoxyisobenzofuran-1(3*H*)-one (5)**: 9-Bromo-α-noscapine **3** (1.0 g, 2.0 mmol) in dried and degassed DMSO (5 mL) were added CuI (0.387 g, 2.0 mmol), L-proline (0.936 g, 8.0 mmol) and sodium azide (0.264 g, 4.0 mmol) sequentially under argon atmosphere. The reaction mixture was stirred and heated at 130 °C under argon for 3 h (monitored by TLC), cooled to rt and saturated ammonium chloride solution was added. The mixture was filtered through celite pad; filtrate was extracted with dichloromethane (5 × 10 mL), organic layer was washed with water (2 × 5 mL), brine solution (10 mL), dried over anhydrous sodium sulphate and evaporated under reduced pressure. The crude residue was chromatographed over triethyl amine neutralized silica column eluted with ethyl acetate: hexane (2:3) to give pure 9-amino-α-noscapine **5** (0.540 g) as pale yellow solid. Yield: 62%; mp 156 °C; $[\alpha]_D^{25}$ −158.3 (*c* 1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (d, *J* = 8.3 Hz, 1H), 6.10 (d, *J* = *J* = 8.3 Hz, 1H), 5.93 (s, 2H), 5.53 (d, *J* = 3.77 Hz, 1H), 4.34 (d, *J* = 3.77, 1H), 4.07 (s, 3H), 3.90 (s, 3H), 3.85 (s, 3H), 3.25 (s, 2H), 2.70–2.59 (m, 1H), 2.53 (s, 3H), 2.47–2.20(m, 2H), 1.80–1.59(m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.07, 152.10, 147.69, 141.29, 135.34, 134.86, 133.80, 121.88, 119.88, 118.26, 117.94, 117.69, 117.19, 100.89, 81.70, 62.23, 60.79, 59.62, 56.77, 48.36, 45.53, 21.00. IR (KBr) 3437, 3362, 2924, 2853, 1750, 1652, 1615, 1494, 1459, 1388, 1265, 1159, 1115, 1036, 801, 711, 656, 514, 405. MS (ESI) *m*/*z*: 429 $[M+H]^+$; HR-MS (ESI) Calcd for $C_{22}H_{24}N_2O_7$ $[M+H]^+$: 429.1661, found:429.1673.
16. X-ray data for the compounds were collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) with ω-scan method [1]. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Integration and scaling of intensity data were accomplished using SAINT program.[17a] The structure was solved by direct methods using SHELXS97 [2] and refinement was carried out by full-matrix least-squares technique using SHELXL97.[17b] Anisotropic displacement parameters were included for all non-hydrogen atoms. All H atoms attached to C and N were located in difference Fourier maps and subsequently geometrically optimized and allowed for as riding atoms, with C–H = 0.93−0.97 Å, N–H = 0.86 Å, with $U_{iso}(H) = 1.5U_{eq}(C)$ for methyl H or $1.2U_{eq}$(C,N). The methyl groups were allowed to rotate but not to tip. In the absence of significant anomalous scattering effects, Fridels pairs were merged. The absolute configuration was known in advance for the procured material.
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18. Authors thank the referee for the suggestion. Nitration using $AcCl/AgNO_3$ also led to the cleavage of C–C bond between two heterocyclic lobes. Here we also noticed epimerization at chiral centers leading to formation of diasteromeric products.