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# Three component tandem reactions involving protected 2-amino indoles, disubstituted propargyl alcohols, and $I_2$/ICl: iodo-reactant controlled synthesis of dihydro-α-carbolines and α-carbolines via iodo-cyclization/iodo-cycloelimination ☆

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ABSTRACT

Two simple, highly efficient three component tandem reactions for the synthesis of diversified $N^a$ $N^b$ dicarbamate-4,9-dihydro-3-iodo-α-carbolines and $N^a$-carbamate-3-iodo-α-carbolines have been described. The strategy involves one-pot condensation of bis-carbamate protected 2-amino indoles with disubstituted propargyl alcohols and $I_2$/ICl. The salient feature of the reaction involves iodocyclo-elimination of $N^b$-linked carbamate under mild condition in the final step.

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α-Carbolines (pyrido[2,3-*b*]indoles) are structural units found in an array of natural products: Dendrodoine A, grossularines-1, and -2, metabolites isolated from the tunicate *Dendrodoa grossularia*,[1] indoloquinoline alkaloid neocryptolepine from *Cryptolepis sanguinolenta*[2] kapakahines from the marine sponge *Cribrochalina olemda*[3] and mescengricin, isolated from *Streptomyces griseoflavus*.[4] Besides, α-carbolines are also formed as pyrolysis product (2-amino-alpha-carboline; mutagenic, and carcinogenic)[5] during the high temperature cooking of food/burning of tobacco and as bioactive molecules with antitumor[6] and antiviral[7] properties. Such important pharmacological activities[5–7] have made the molecules of significant synthetic targets and, therefore, have resulted in sustained interest in developing new methods for the preparation of highly diversified α-carbolines. However, despite being an attractive synthetic target, a multicomponent reaction for the direct synthesis of these tricyclic class of compounds is scarce.[8] In addition to this, most of the syntheses[9] reported in the literature for α-carbolines are low yielding and require several steps from starting materials that are not commercially available.

In recent years one-pot multicomponent reactions (MCR) involving condensation of three or more monomers either in a single step or in tandem have become an integral part of drug discovery program.[10] In either situation inherent formation of several bonds occurs without the isolation of the intermediate formed. All or most of the parts of the participating monomers contribute to the formation of a new molecule assembled in situ following a cascade of irreversible chemical pathways. Thus, using simple and readily available components in a highly diverse array, libraries of small molecules inspired either from natural products or from other target structures of therapeutic interest has been reported in the literature.[11]

In continuation of our studies aiming at the efficient construction of indole-based polyheterocycles[12] involving multistep/multicomponent reaction format, we herein report one-pot three component tandem reactions involving protected 2-aminoindoles, disubstituted propargyl alcohols, and $I_2$/ICl leading to the synthesis of highly diversified 3-iodo-α-carboline derivatives. Although the use of $I_2$/ICl has been documented in the literature for multistep synthesis, their application in multicomponent format as reactant is limited.[13]

In the first instance we subjected 2-aminoindole hydrochloride to three component reaction by treating it with benzaldehyde and

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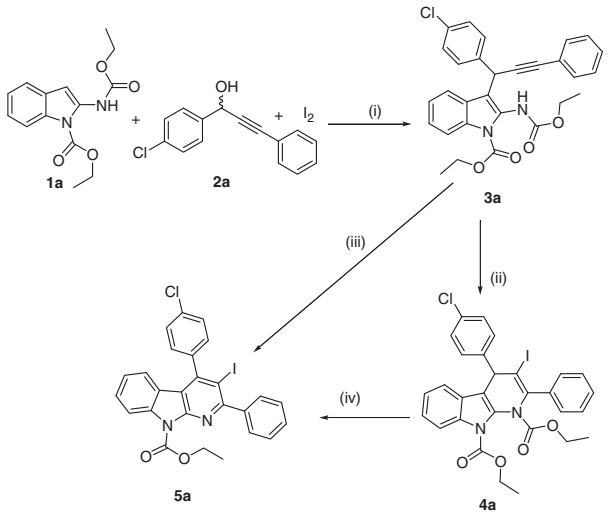
a terminal alkyne as the other two components in one pot. However, despite exploring reactions both with hydrochloride salt and with free base generated in situ under a series of experimental conditions, we failed to observe the formation of α-carboline. This can be attributed to poor stability[14] of 2-amino indole as free base which prompted us to use protected 2-amino-indole derivative. Initial attempts to use acid-labile amine protecting group, such as *t*-Boc-reported earlier by us[11e] for the synthesis of δ-carbolines from *N*-Boc-3-amidoindole in multicomponent format, was not feasible since in our hand synthesis of *N*-Boc-2-amidoindole using $(Boc)_2O$ was obtained in poor yields (<10%).

Using an alternative strategy, we then hypothesized that protecting the amine with the acid resistant acyl type protecting group followed by condensation with 1,3-disubstituted propargyl alcohol derivatives may furnish intermediate that could then be subjected to intramolecular electrophilic (6-*endo*) cyclization in the presence of iodo-reactant as electrophilic reagent to furnish iodo-α-carbolines. Initial experiments to acylate 2-amino indole hydrochloride with acetic anhydride/acetyl chloride furnished complex mixture comprising mono-, di-, and tri-acylated (one of them being Friedal–Craft acylated product) indoles arising from the acylation of $N^a$, *C*-2-$N^bH_2$, and *C*-3. We next protected the amino function in the 2-amino indole hydrochloride with ethoxycarbonyl chloride, which is relatively less electrophilic due to the presence of $C_2H_5O$ group attached to the –C=O than $CH_3$–C=O in the acetyl chloride and may preclude C-acylation at the 3-position of the indole. Pleasingly, reaction of the 2-amino indole hydrochloride[15] with ethoxycarbonyl chloride in the presence of $NaHCO_3$ furnished regioselective 2-ethoxycarbonylamino-indole-1-carboxylic acid ethyl ester **1a**[16] (hitherto not reported in the literature) as the only product in quantitative yield. Bis-ethoxy carbonylated compounds have been reported[17] for amidines bearing structural resemblance to 2-amino-indole. Next, the resulting indole derivative **1a** was treated with 1-(4-chloro-phenyl)-3-phenyl-prop-2-yn-1-ol **2a**[15] at 0 °C to rt in the presence of iodine as an electrophilic reagent (Scheme 1). The progress of the reaction was monitored by TLC and within 30 min a new spot appeared which remained unchanged even after extended stirring for 2 h at rt. After work-up, instead of isolating α-carboline, we observed formation of **3a**[18] as a *C*-3 nucleophilic substituted[19] product of propargyl alcohol in quantitative yields. This led us to believe that although iodine promoted nucleophilic substitution of 1-(4-chloro-phenyl)-3-phenyl-prop-2-yn-1-ol resulting in **3a**, it failed to facilitate the subsequent intramolecular electrophilic cyclization to furnish α-carbolines. We then screened several electrophilic reagents, with the view to promote intramolecular electrophilic cyclization of the intermediate **3a** and the results have been summarized in Table 1. As observed, best results were obtained when cyclization of **3a** was carried out in the presence of ICl, furnishing $N^a$-ethoxycarbonyl-3-iodo-α-carboline derivative **5a** in 85% isolated yield. Analogous iodo-cyclization using NIS produced **5a** in 23% yield; in contrast, bromocyclization using $Br_2$/NBS and application of Bronsted acids/metals failed to promote cyclizations. The most interesting observation of our optimization studies was isolation of $N^a$, $N^b$-diethoxycarbonyl-4,9-dihydro-3-iodo-α-carboline **4a**[17] as a single product in the presence of $I_2/K_2CO_3$ in 61% isolated yield instead of **5a** (Scheme 1). Compound **4a** appeared to be the precursor of **5a** and to support this we treated **4a** with ICl in $CH_3CN$ at 0 °C for 45 min. Since ICl is known to behave both as electrophilic reagent (with ability to iodinate) and as oxidizing agent, formation of **5a** from **4a** occurred in 88% isolated yield via concomitant oxidative aromatization and elimination of $N^b$-carbamate (Scheme 1). This gets support from a single report in the literature demonstrating elimination of N-linked ethoxycarbonyl group in dihydropyridines, where aromatization was affected under a stream of oxygen.[20] A plausible mechanism for the formation of **5** from **3** is illustrated in Figure 1.

It is presumed that initially the alkyne in the intermediate **3** probably forms an iodonium complex in the presence of ICl thereby enhancing the electrophilicity of the alkyne to generate intermediate **A**. The activated (electron-deficient) triple bond then undergoes nucleophilic attack by the nitrogen attached to the *C*-2 of the indole thereby facilitating intramolecular 6-*endo* (electrophilic cyclization) to furnish $N^a$, $N^b$-dicarbamte-4,9-dihydro-3-iodo-α-carboline as protonated intermediate **B**. Latter undergoes deprotonation leading to the formation of **4a** by releasing HCl. Finally, spontaneous oxidative aromatization of **4a** via elimination of the $N^b$-linked carbamate results in the formation of $N^a$-carbamte-3-iodo-α-carbolines **5**. Encouraged by the above findings that offered opportunity for the selective multistep synthesis of either **4** or **5**, we next laid emphasis on their synthesis in multicomponent format (Scheme 2).

In the first instance we developed synthesis of 4,9-dihydro-α-carboline **4a** in a multicomponent tandem format by treating a mixture of **1a** and **2a** with $I_2$ for 30 min at 0 °C followed by addition of $K_2CO_3$ and stirring the reaction mixture at rt for 2 h. The crude product so obtained was purified by column chromatography furnishing **4a** in 61% isolated yield. We demonstrated the utility of the method by synthesizing four additional dihydro-α-carboline deriv-




**Scheme 1.** Optimized reaction conditions for the synthesis of **4a** and **5a** via iodocyclization/iodocyclo-elimination. Reagents and conditions: (i) $CH_3CN$, 0 °C to rt, 30 min; (ii) $I_2/K_2CO_3$, $CH_3CN$ 2 h, rt; (iii) ICl, $CH_3CN$ 0 °C, 1 h; (iv) ICl, 0 °C, $CH_3CN$, 45 min.

**Table 1**
Optimization of reaction conditions for the conversion of **3a** to **5a**

| Entry | Electrophilic reagent | Temp (°C) | Time (h) | Yield of **4a**/**5a** (%) |
|---|---|---|---|---|
| 1 | Iodine in $CH_3CN$ | 0 to rt | 1 | 0/0 |
| 2 | Iodine in $CH_3CN$ | rt | 12 | 15/0 |
| 3 | Iodine/$K_2CO_3$ in $CH_3CN$ | rt | 2 | 61/0 |
| 4 | *N*-Iodosuccinimide in $CH_3CN$ | rt | 12 | 0/23 |
| 5 | Bromine in $CH_3CN$ | rt | 12 | 0/0 |
| 6 | *N*-Bromosuccinimide in $CH_3CN$ | rt | 12 | 0/0 |
| 7 | Iodine monochloride in $CH_3CN$ | 0 | 1 | 0/85 |
| 8 | *p*-TsOH in $CH_3CN$ | 80 | 12 | 0/0 |
| 9 | Copper iodide in $CH_3CN$ | 80 | 16 | 0/0 |

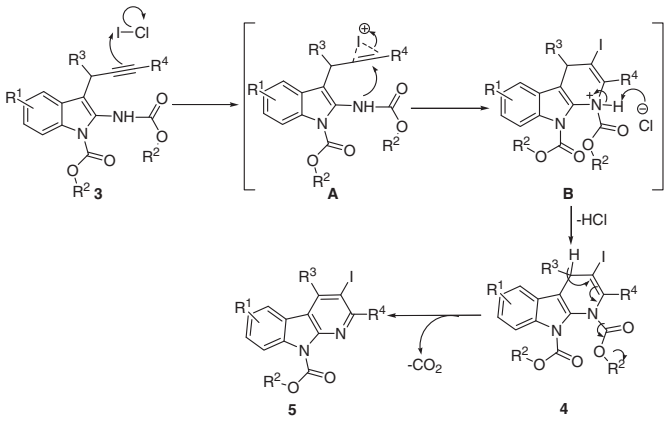
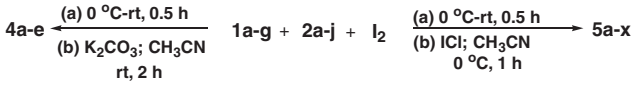


**Figure 1.** A plausible mechanism for the formation of α-carbolines **5** via iodo-cyclo-elimination from **3**.



**Scheme 2.** Three component tandem reactions in one pot for the synthesis of **4** and **5**.

atives **4b–e** as summarized in Table 2. No further attempt was made to optimize the conditions to improve the yield for **4** instead we continued with our main objective for synthesizing α-carboline derivatives **5** in a multicomponent format.

For the synthesis of **5** in multicomponent format, condensation of bis-*N*-carbamate protected indole derivative **1a** with **2a** was effected either in the presence of a mixture $I_2$ and ICl or in the presence of ICl alone, however, both the conditions failed to furnish the compound **5a**. This prompted us to carry out the multicomponent reaction in tandem format for the one-pot synthesis of α-carboline derivatives **5**. Accordingly, **1a** was initially treated with **2a** in the presence of iodine from 0 °C to rt for 30 min followed by addition of ICl at 0 °C to yield 3-iodo-α-carboline derivative **5a** in 86% yield within 60 min (Scheme 2). On comparing the two multicomponent tandem reactions, it is evident that whereas for the synthesis of **4** iodine remains source for the iodo group at position 3, the ICl remains source for the iodo group at position 3 in compound **5**.

The scope and limitation of the optimized reaction conditions were examined by studying the effect of different substituent on the indole ($R^1$ and $R^2$) and on the propargyl alcohols ($R^3$ and $R^4$). In the indole derivatives, on one hand ethoxy carbonyl group in **1a** has been replaced with isobutoxy- and benzyloxy-carbonyl groups and on the other hand, substitution ($R^1$) has been introduced in the phenyl ring of the indole. The resulting substrates **1a–g**[15] were subjected to multicomponent tandem reaction by treating them with structurally diverse **2** (The requisite propargyl derivatives can be readily prepared in quantitative yields using

**Table 2**
Synthesis of dihydro-α-carbolines **4** from **1**, **2** and $I_2/K_2CO_3$ in three-component tandem formats

| Entry | 1 | $R^1$ | $R^2$ | 2 | $R^3$ | $R^4$ | Product | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | H | $CH_2CH_3$ | **2a** | 4-$ClC_6H_4$ | $C_6H_5$ | **4a** | 61 |
| 2 | **1a** | H | $CH_2CH_3$ | **2j** | 4-$EtOC_6H_4$ | 4-$CH_3C_6H_4$ | **4b** | 73 |
| 3 | **1e** | F | $CH_2CH_3$ | **2c** | 2,3-di$ClC_6H_3$ | $C_6H_5$ | **4c** | 75 |
| 4 | **1e** | F | $CH_2CH_3$ | **2i** | 4-$CH_3C_6H_4$ | 4-$(CH_3)_3CC_6H_4$ | **4d** | 69 |
| 5 | **1g** | $CF_3$ | $CH_2CH_3$ | **2c** | 2,3-di$ClC_6H_3$ | $C_6H_5$ | **4e** | 72 |

**Table 3**
Synthesis of α-carbolines **5** from **1**, **2** and $I_2$/ICl in three-component tandem formats

| Entry | 1 | $R^1$ | $R^2$ | 2 | $R^3$ | $R^4$ | Product | Yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | H | $CH_2CH_3$ | **2a** | 4-$ClC_6H_4$ | $C_6H_5$ | **5a** | 86 |
| 2 | **1a** | H | $CH_2CH_3$ | **2c** | 2,3-di$ClC_6H_3$ | $C_6H_5$ | **5b** | 88 |
| 3 | **1a** | H | $CH_2CH_3$ | **2d** | 4-$BrC_6H_4$ | $C_6H_5$ | **5c** | 85 |
| 4 | **1b** | H | $CH_2CH(CH_3)_2$ | **2d** | 4-$BrC_6H_4$ | $C_6H_5$ | **5d** | 81 |
| 5 | **1b** | H | $CH_2CH(CH_3)_2$ | **2g** | 4-$EtOC_6H_4$ | $C_6H_9$ | **5e** | 72 |
| 6 | **1b** | H | $CH_2CH(CH_3)_2$ | **2h** | 4-$CH_3C_6H_4$ | $C_6H_9$ | **5f** | 68 |
| 7 | **1c** | H | $CH_2C_6H_5$ | **2g** | 4-$EtOC_6H_4$ | $C_6H_9$ | **5g** | 78 |
| 8 | **1c** | H | $CH_2C_6H_5$ | **2h** | 4-$CH_3C_6H_4$ | $C_6H_9$ | **5h** | 65 |
| 9 | **1c** | H | $CH_2C_6H_5$ | **2i** | 4-$CH_3C_6H_4$ | 4-$(CH_3)_3CC_6H_4$ | **5i** | 83 |
| 10 | **1c** | H | $CH_2C_6H_5$ | **2j** | 4-$EtOC_6H_4$ | 4-$CH_3C_6H_4$ | **5j** | 90 |
| 11 | **1d** | $CH_3$ | $CH_2CH_3$ | **2a** | 4-$ClC_6H_4$ | $C_6H_5$ | **5k** | 80 |
| 12 | **1d** | $CH_3$ | $CH_2CH_3$ | **2b** | 2-$ClC_6H_4$ | $C_6H_5$ | **5l** | 81 |
| 13 | **1d** | $CH_3$ | $CH_2CH_3$ | **2c** | 2,3-di$ClC_6H_3$ | $C_6H_5$ | **5m** | 87 |
| 14 | **1d** | $CH_3$ | $CH_2CH_3$ | **2d** | 4-$BrC_6H_4$ | $C_6H_5$ | **5n** | 83 |
| 15 | **1d** | $CH_3$ | $CH_2CH_3$ | **2f** | 2-$ClC_6H_4$ | $C_6H_{13}$ | **5o** | 50 |
| 16 | **1d** | $CH_3$ | $CH_2CH_3$ | **2e** | 2-$BrC_6H_4$ | $C_5H_{11}$ | **5p** | 46 |
| 17 | **1e** | F | $CH_2CH_3$ | **2a** | 4-$ClC_6H_4$ | $C_6H_5$ | **5q** | 84 |
| 18 | **1e** | F | $CH_2CH_3$ | **2b** | 2-$ClC_6H_4$ | $C_6H_5$ | **5r** | 80 |
| 19 | **1e** | F | $CH_2CH_3$ | **2c** | 2,3-di $ClC_6H_3$ | $C_6H_5$ | **5s** | 86 |
| 20 | **1e** | F | $CH_2CH_3$ | **2d** | 4-$BrC_6H_4$ | $C_6H_5$ | **5t** | 82 |
| 21 | **1f** | $CF_3$ | $CH_2CH_3$ | **2b** | 2-$ClC_6H_4$ | $C_6H_5$ | **5u** | 85 |
| 22 | **1f** | $CF_3$ | $CH_2CH_3$ | **2c** | 2,3-di$ClC_6H_3$ | $C_6H_5$ | **5v** | 87 |
| 23 | **1f** | $CF_3$ | $CH_2CH_3$ | **2d** | 4-$BrC_6H_4$ | $C_6H_5$ | **5w** | 78 |
| 24 | **1g** | $CF_3$ | $CH_2CH(CH_3)_2$ | **2f** | 2-$ClC_6H_4$ | $C_6H_{13}$ | **5x** | 50 |

procedure published in the literature[21]) and ICl. In all cases, the substrates efficiently underwent intramolecular electrophilic cyclization to furnish 24 compounds in good to excellent yields (Table 3). In general reactions were not sensitive either to the electronic properties of the substituent on the phenyl ring of the indole or to the nature of the carbamate group. Use of substituted phenyl ring $R^3$ in **3** with both electron-donating and withdrawing groups had no effects on the yield of α-carbolines. Similarly, employing phenyl ring as $R^4$ had no effect on the yield 78–90% but employing aliphatic as $R^4$ moiety reduced the yield of α-carbolines to 46–78%. As described elsewhere[19], propargyl alcohol ($R^3 = R^4 = H$; unstablized[22]) failed to undergo nucleophilic substitution by *C*-3 of the indoles to form **3**.

In summary, we have developed two simple and highly efficient multicomponent tandem reactions for the selective synthesis of $N^a$ $N^b$ dicarbamate-4,9-dihydro-3-iodo-α-carbolines and $N^a$-carbamate-3-iodo-α-carbolines via iodo-cyclization/iodo-cyclo-elimination in good to excellent yields. Haloheterocycles have been documented to play a central role as intermediates in organic synthesis, due to their ability to undergo numerous palladium-catalyzed reactions for the substitution of halide atom. Studies to extend the scope of the procedure to other iodoheterocycles via iodocyclization of substrates containing carbamate-protected amino groups are in progress in our laboratory and results will be published elsewhere.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.147.

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18. *General procedure for the three component tandem synthesis of 4,9-dihydro-3-iodo α-carbolines* **4**: To a solution of 2-ethoxycarbonylamino-indole-1-carboxylic acid ethyl ester **1a** (0.200 g, 0.73 mmol) and 1-(4-chloro-phenyl)-3-phenyl-prop-2-yn-1-ol **2a** (0.175 g, 0.73 mmol) in acetonitrile (10 ml), iodine (0.920 g, 3.62 mmol) was added and stirred for 0.5 h at 0 °C to rt. Next, $K_2CO_3$ (0.250 g, 1.81 mmol) was added to the reaction mixture at 0 °C and the reaction mixture was allowed to stir at room temperature for 1 h. After completion of the reaction as analyzed by TLC, it was diluted with saturated sodium thiosulphate solution and extracted with EtOAc (20 mL × 3). The organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The crude product so obtained was purified on a silica gel column using hexane: ethyl acetate (1:9, v/v) as eluent to afford dihydro-α-carbolines **4**.
*General procedure for the one-pot three-component tandem reaction leading to the synthesis of 3-iodo-α-carbolines* **5**: To a solution of 2-ethoxycarbonylamino-indole-1-carboxylic acid ethyl ester **1a** (0.200 g, 0.73 mmol) and 1-(4-chloro-phenyl)-3-phenyl-prop-2-yn-1-ol **2a** (0.175 g, 0.73 mmol) in acetonitrile (10 ml), iodine (0.920 g, 3.62 mmol) was added and stirred for 0.5 h at 0 °C to rt. Next, ICl (1 M solution in DCM, 3.4 ml) was added to the reaction mixture at 0 °C and the reaction mixture was allowed to stir at room temperature for 1 h. After completion of the reaction as analyzed by TLC, it was diluted with saturated sodium thiosulphate solution and extracted with EtOAc (20 mL × 3). The organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The crude product so obtained was purified on a silica gel column using hexane: ethyl acetate (1:19, v/v) as eluent to afford α-carbolines **5**.
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