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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.

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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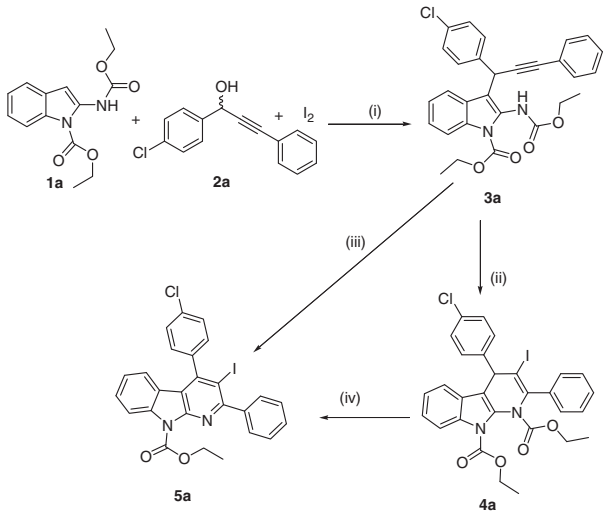
a terminal alkyne as the other two components in one pot. However, despite exploring reactions both with hydrochloride salt and with free base generated in situ under a series of experimental conditions, we failed to observe the formation of α-carboline. This can be attributed to poor stability[14] of 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