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Cascade Electrophilic Iodocyclization: Efficient Preparation of 4-Iodomethyl Substituted Tetrahydro-β-carbolines and Formal Synthesis of Oxopropaline G

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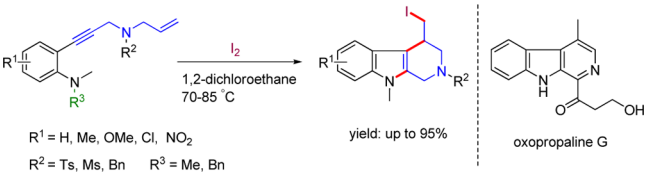
ABSTRACT



4-Iodomethyl substituted tetrahydro-β-carbolines, the core structure of numerous natural products and bioactive molecules, are readily prepared via I_2-promoted cascade electrophilic cyclization. The reactivity differences of olefins and alkynes ensure that the reaction proceeds smoothly. This methodology was successfully applied to the formal synthesis of oxopropaline G.

Carbolines and tetrahydrocarbolines are common structural motifs in natural products and pharmaceuticals,[1] of which β-carboline and its saturated analog are particularly prevalent.[2] 4-Substituted β-carbolines and tetrahydrocarbolines are important motifs in many important natural products, such as the lavendamycin, (−)-(*S*)-brevicolline, oxopropaline D and G, and neonaucleoside C (Figure 1), all of which are attractive synthetic targets because of their biological activities and synthetically challenging structures.

Various strategies have been developed for the construction of β-carbolines and tetrahydrocarbolines, including the Pictet−Spengler reaction,[3a] electrocyclic reactions,[3b] palladium-catalyzed iminoannulation of internal alkynes,[3c] Pd-catalyzed direct dehydrogenative annulation of indolecarboxamides with alkynes,[3d] Fisher indolization,[3e] catalytic nitrene insertion into C−H bonds,[3f] metal catalyzed domino reactions,[3g] and [2 + 2 + 2] cycloaddition of *o*,*N*-dialkynyl-*N*-tosylanilides and nitriles.[3h] However, the development of a general synthetic method for the rapid synthesis of 4-substituted β-carbolines and tetrahydrocarbolines in a single operation remains a great challenge.

Cascade reactions constitute a fascinating branch of organic chemistry[4] that offer atom economy,[5] as well as economies of time, labor, resource management, and waste generation. During the past few years a rapid increase of interest in halogen-atom-promoted electrophilic heteroatom cyclization has occurred, and it has now become an

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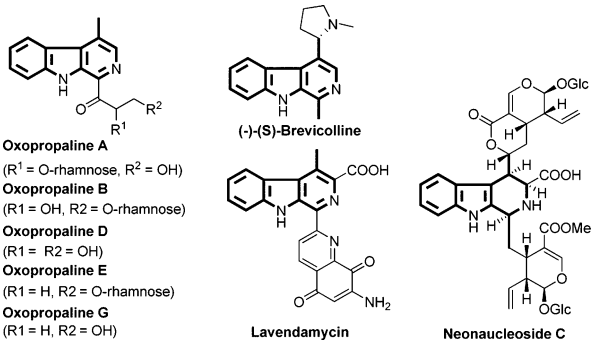
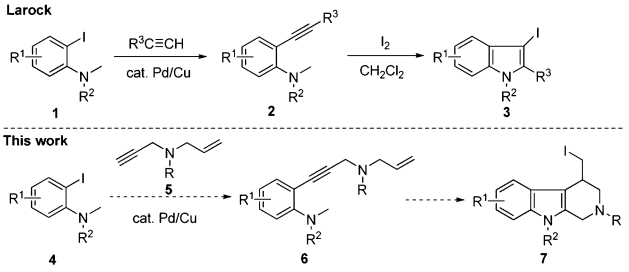


Figure 1. Selected examples of 4-substituted carboline alkaloids and tetrahydrocarboline alkaloids.

Scheme 1. Iodine-Mediated Cascade Cyclization of Enynes to Iodinated Tetrahydro-β-carbolines

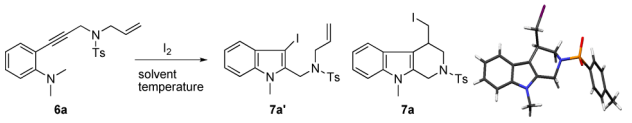


extremely active and original field of heterocycle synthesis.[6] Larock et al. reported an iodocyclization process used in the synthesis of indoles.[6a] We were curious whether an iodine-mediated domino electrophilic cyclization reaction of alkynes and alkenes could be applied for the preparation of 4-iodomethyl substituted tetrahydro-β-carbolines (Scheme 1). The electrophilic cyclizations of olefins are more difficult compared with the reactions of alkynes. While, the difference can be used to generate the indole ring preferentially, herein, we present first results on the synthesis of 4-iodomethyl substituted tetrahydro-β-carbolines via a cascade electrophilic iodocyclization reaction of enynes.

To test the feasibility of this concept, compound **6a** was initially prepared. When **6a** was treated with 2 equiv of iodine in dichloromethane for 4 h at room temperature, the iodinated indole **7a′** was obtained in 30% yield solely (Table 1, entry 1). By extending the reaction time to 24 h, the desired tetrahydrocarboline (**7a**) was obtained in less than 5% yield (Table 1, entry 2). When the mixture was heated at reflux, it gave the tetrahydrocarboline in 15% yield (Table 1, entry 3), which meant that a higher temperature was favorable for tetrahydrocarboline yield.

(6) (a) Benhur, G.; Ricardo, F. S.; Gilson, Z. *Chem. Rev.* **2011**, *111*, 2937. (b) Larock, R. C. *Org. Lett.* **2004**, *6*, 1037. (c) Chen, C. C.; Yang, S. C.; Wu, M. J. *J. Org. Chem.* **2011**, *76*, 10269. (d) Ferrara, G.; Jin, T. N.; Akhtaruzzaman, M.; Islamc, A.; Han, L. Y.; Jiang, H.; Yamamoto, Y. *Tetrahedron Lett.* **2012**, *53*, 1946.

Table 1. Optimization of the Reaction Conditions[a]



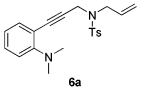
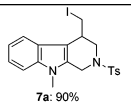
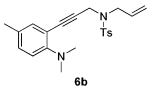
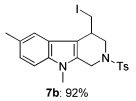
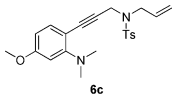
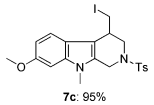
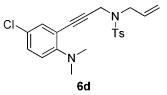
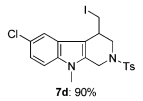
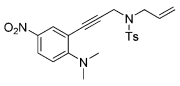
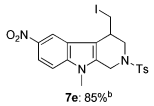
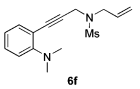
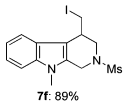
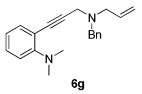
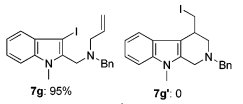
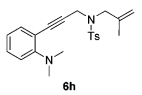
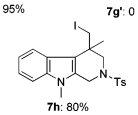
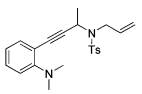
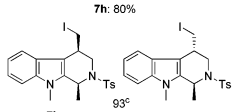
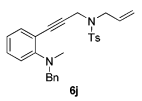
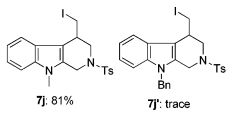
entry	solvent	ratio (**6a**/I_2)	temp (°C)	t (h)	**7a′**	**7a**
1	DCM	1:2	rt	4	30%	–
2	DCM	1:2	rt	24	58%	trace
3	DCM	1:2	40	12	60%	15%
4	**DCE**	**1:2**	**70**	**4**	–	**90%**
5	DCE	1:1.5	70	4	85%	10%
6	DCE	1:1	70	4	92%	trace
7	acetonitrile	1:2	70	12	60%	trace
8	toluene	1:2	70	12	80%	10%

[a] DCM = dichloromethane, DCE = 1,2-dichloroethane.

Gratifyingly, the tetrahydrocarboline was obtained in 90% yield when dichloromethane was replaced by 1,2-dichloroethane, and the mixture was heated at 70 °C for 4 h (Table 1, entry 4). It was necessary to use a 2-fold amount of iodine to ensure the target compound was obtained in a high yield. When the amount of iodine was reduced to 1.5-fold or a molar equivalent, the reaction gave mainly the indole compound **7a′** (Table 1, entries 5 and 6). The solvent also greatly influenced the outcome. It was found detrimental to generate the carboline compounds when the solvent was acetonitrile or toluene, even when the reactions were conducted at the same temperature and reaction time (Table 1, entries 7 and 8).

Encouraged by these initial results, the substrate scope of this reaction was next examined using different sets of 2-(3-(allylamino)prop-1-ynyl)aniline (their preparation can be found in the Supporting Information). The transformation was found to be very widely applicable, and the desired 4-iodomethyl substituted tetrahydro-β-carbolines were obtained in reasonable yields. First, the electronic effect of substituents on the benzene ring moiety was investigated (Table 2, entries 1−5). Anilines bearing methyl or methoxy groups (Table 2, entries 3 and 4) as well as nitro or chloro groups (Table 2, entries 4 and 5) all produced the tetrahydro-β-carbolines in good-to-excellent yields. The substituents on the allylamino group had a crucial impact on the electrophilic cyclization of the olefin (Table 2, entries 1, 6, 7). Just like compound **6a**, the allylamino-containing methanesulfonamide **6f** underwent electrophilic cyclization smoothly and the total conversion was almost quantitative (Table 2, entry 6). However, when the substituent was changed to benzyl, **6g** converted to iodinated indole **7g** completely, without affording the target tetrahydrocarboline (**7g′**). Compound **7g** decomposed when the reaction time was prolonged (Table 2, entry 7). The substrate with a sterically hindered olefin (**6h**) was also converted into the target tetrahydrocarboline (**7h**) smoothly (Table 2, entry 8). The reaction did not exhibit

Table 2. Preparation of 4-Iodomethyl Substituted Tetrahydro-β-carbolines by Iodine-Mediated Domino Electrophilic Cyclization of Substituted 2-(3-(Allylamino)prop-1-ynyl)anilines[a]

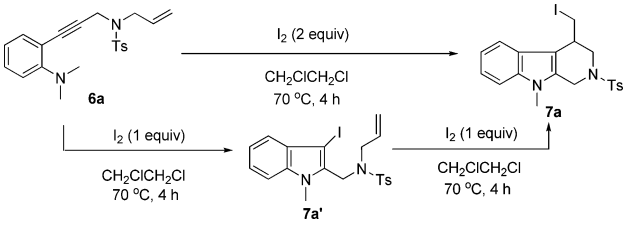
entry	alkyne	t (h)	product[d]
1	 **6a**	4	 **7a**: 90%
2	 **6b**	3	 **7b**: 92%
3	 **6c**	2	 **7c**: 95%
4	 **6d**	6	 **7d**: 90%
5	 **6e**	24	 **7e**: 85%[b]
6	 **6f**	3	 **7f**: 89%
7	 **6g**	1	 **7g**: 95% **7g'**: 0
8	 **6h**	6	 **7h**: 80%
9	 **6i**	3	 **7i** 93[c] (37:63) **7i'**
10	 **6j**	6	 **7j**: 81% **7j'**: trace

[a] Experimental procedure is given in the Supporting Information. [b] The reaction mixture was heated to reflux for 24 h. [c] The ratio of the compounds **7i** and **7i'** was determined by ^{1}H NMR, and the determination of the relative configuration was given in the Supporting Information. [d] The yields given in the table are isolated yields.

significant stereoselectivity (Table 2, entry 9). Alkyne **6j**, with two different alkyl groups (a methyl and benzyl group) on the nitrogen of the aniline, gave rise to interesting selectivity. Due to the different leaving abilities of the methyl and benzyl groups in an S_N2 reaction, the *N*-methyl product **7j** was obtained with high selectivity (Table 2, entry 10).

In order to study the process of the domino electrophilic cyclization reaction, control experiments were performed. As mentioned in Table 1 (entries 6) and Scheme 2, **6a** was reacted with 1 equiv of iodine at 70 °C for 4 h to give the iodinated indole **7a'** exclusively. Then, when **7a'** was reacted under the same conditions, by adding another equivalent amount of iodine, it transformed to the tetrahydrocarboline **7a** smoothly. This finding suggested that the indole

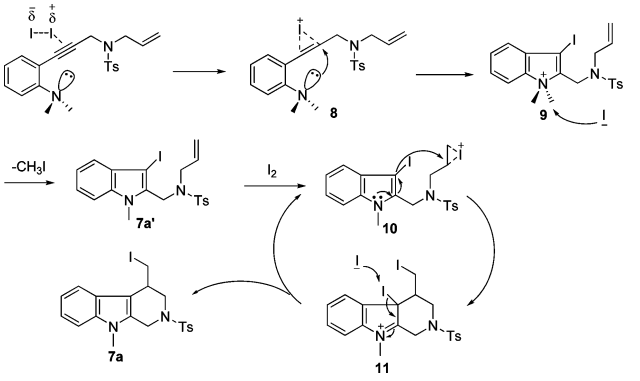
Scheme 2. Control Experiment



compound **7a'** was more readily generated and that the target compound **7a** was indeed transformed from the indole compound **7a'** rather than generated from **6a** directly. Furthermore, when the reaction time was increased to 7 h, **6a** could transform to the target compound **7a** exclusively, with a 1.5-fold amount of iodine (Table 1, entry 5). Thus the second cyclization is a catalytic process.

According to the above experimental results, a proposed reaction mechanism is outlined in Scheme 3. First, the iodine, serving as a Lewis acid, coordinates to the triple bond to promote cyclization which produces the intermediate **9**. Then, one of the alkyl groups is removed by iodide via an S_N2 reaction; this occurs rapidly. Subsequently, the second cyclization is promoted by the excess iodine which coordinates to the double bond of the iodoindole **7a'** to produce an iminium **11**. The iodide could attack **11** in the manner indicated to give the target compound **7a** and iodine which can then participate in the next catalytic cycle (Scheme 3).

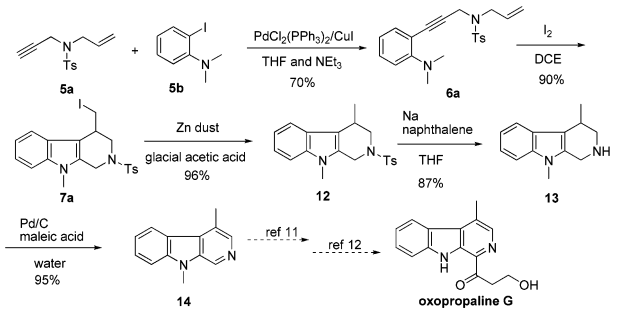
Scheme 3. Proposed Mechanism



To probe the utility of our method, we used it for a rapid formal synthesis of the natural product oxopropaline G, which was isolated from *Streptomyces* sp. G 324 by Abe and co-workers in 1993.[2] Compound **6a** was readily prepared by Sonogashira coupling of the corresponding **5a** and **5b** in 70% yield (Scheme 4).[7] Treatment of **6a** under our optimized reaction conditions successfully afforded the desired 4-iodomethyl substituted tetrahydro-β-carboline **7a** in 90% yield. The iodine was reduced by zinc

(7) Rubin, M.; Trofimov, A.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10243.

Scheme 4. Formal Synthesis of Oxopropaline



dust in glacial acetic acid to give **12** in 96% yield.[8] Deprotection of the *N*-tosyl group using sodium/naphthalene at −78 °C in anhydrous THF provided **13** in 87% yield.[9] Tetrahydrocarboline **13** was oxidized using in the Pd/C–maleic acid system in water[10] to give *β*-carboline **14** in 95% yield, which could be converted to oxopropaline G according to reported literature.

(8) Smith, E. C.; Barborak, J. C. *J. Org. Chem.* **1976**, *41*, 1433.
(9) Kim, Y. H.; Choi, J. Y. *Tetrahedron Lett.* **1996**, *37*, 5543.
(10) Akabori, S.; Saito, K. *Beriche der Deutschen Cheischen Gesellschaft (A and B Series)* **1930**, *63*, 2245.
(11) Rosenau, T.; Hofinger, A.; Potthast, A.; Kosma, P. *Org. Lett.* **2004**, *6*, 541.
(12) Choshi, T.; Kuwada, T.; Fukui, M.; Matsuya, Y.; Sugino, E.; Hibino, S. *Chem. Pharm. Bull.* **2000**, *48*, 108.

In summary, we have developed a new and general strategy for the construction of 4-iodomethyl substituted tetrahydro-*β*-carbolines by an iodine-promoted cascade electrophilic iodocyclization reaction. This strategy includes two electrophilic iodocyclization reactions on the alkyne and alkene successively in one pot. The reactive differences of olefins and alkynes ensure that the reaction proceeds smoothly. The utility of this method was demonstrated by a formal synthesis of oxopropaline G. 4-Iodomethyl substituted tetrahydro-*β*-carbolines containing different substituents can be prepared by using this method.

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Supporting Information Available. Detailed experimetal procedures, copies of ^{1}H and ^{13}C NMR spectra for compounds **6a**–**6j**, **7a**–**7j**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.