Organic LETTERS

Letter

pubs.acs.org/OrgLett

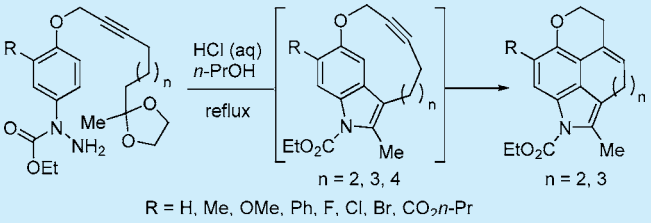
Intramolecular Fischer Indole Synthesis in Combination with Alkyne Hydroarylation: Synthesis of Tetracyclic Chromeno-indoles

Jun Park, Sun-Young Kim, Ji-Eun Kim, and Cheon-Gyu Cho*

Department of Chemistry, Hanyang University, Seoul 131-791, Korea

Supporting Information

ABSTRACT: Aryl hydrazides bearing a carbonyl function connected through an alkyne tether underwent an intramolecular Fischer indolization and alkyne hydroarylation in a tandem fashion to afford novel tetracyclic chromeno-indoles. The accompanying isomerization of the 2*H*-chromene double bond can be avoided by stopping the tandem process at the indolophane stage and conducting the alkyne-hydroarylation reaction separately in the absence of a proton source.



Indole is arguably the most frequently found structural motif in nature.[1] The intriguing biological properties and molecular architechtures of indole based natural products continue to pose challenges and motivations for the synthesis.[2] Recently, polycyclic indole alkaloids with a 3,4-fused tricyclic indole core have emerged as the target system of interest in the same vein (Figure 1).[3]

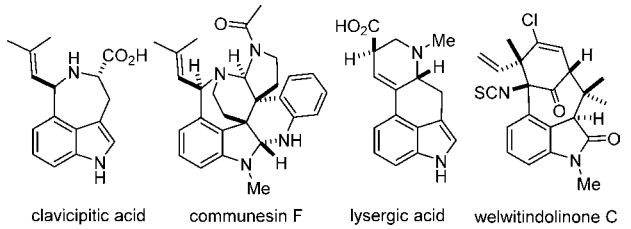
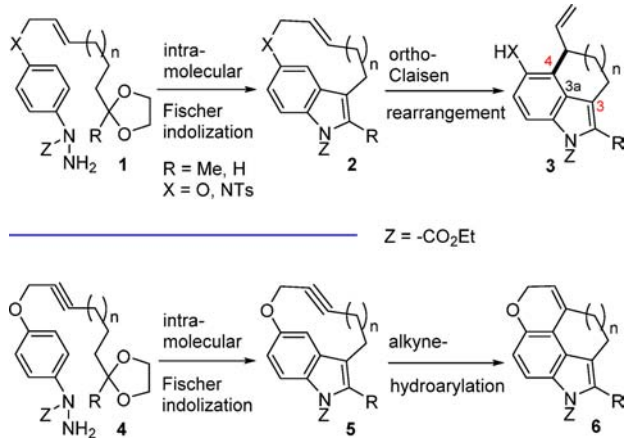


Figure 1. Selected examples of polycyclic indole alkaloids with a 3,4-fused tricyclic indole core.

However, their synthesis can often be difficult due to the lack of a general synthetic method that paves the way to such 3,4-fused tricyclic indoles. We have previously demonstrated that the intramolecular Fischer indole synthesis (IMFIS)[4] coupled with an aromatic [3,3]-sigmatropic rearrangement can be an effective synthetic entry to the 3,4-fused tricyclic indole **3** (Scheme 1).[5] In this reaction sequence, aryl hydrazide **1** with a carbonyl function attached to the para-position of the aryl hydrazide undergoes an intramolecular Fischer indolization to first give indolophane intermediate **2**. Subsequent engagement with an aromatic [3,3]-sigmatropic rearrangement reaction affords 3,4-fused tricyclic indole **3** due to the deliberate insertion of the C−C double bond in the tether. As an extension, we set out to investigate the similar tandem reaction of aryl hydrazide incorporating a C−C triple bond in the tether. In this contest, the aromatic [3,3]-sigmatropic rearrangement would be followed by aromatization, a [1,5]-hydrogen shift, and 6π-electrocyclization to give novel tetracyclic 2*H*-chromeno-indole **6**.[6] Ozonolysis or an equivalent reaction of the 2*H*-chromene double bond would then provide ketone function in the center ring for further derivatization.

Scheme 1. Tandem IMFIS/ortho-Claisen Rearrangement vs IMFIS/Alkyne Hydroarylation



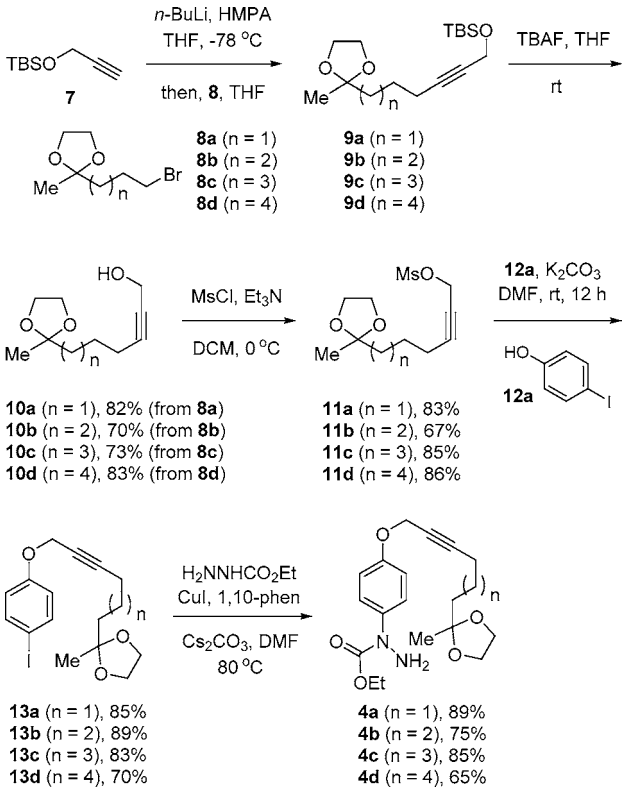
At the outset of its synthetic utility, this elaboration raises a few fundamental questions such as whether IMFIS would ever be possible, as it needs to go through indolophane **5** that has a much higher strain energy than indolophane **2**, and whether the indolophane **5**, even if formed, can undergo an intramolecular alkyne-hydroarylation reaction that usually requires an extremely high reaction temperature (200−250 °C)[7] or a metal catalyst.[8] Also, the effect of tether length on this tandem process needs to be addressed. The potential synthetic value together with the aforementioned basic issues prompted us to investigate the tandem IMFIS/alkyne-hydroarylation reactions of aryl hydrazides **4** with alkyne tethers of varying lengths.

Received: November 2, 2013
Published: December 5, 2013

dx.doi.org/10.1021/ol4031638 | *Org. Lett.* 2014, 16, 178−181

Aryl hydrazides **4a**–**4d** were prepared from TBS propargyl ether **7** via the route described in Scheme 2. Deprotonation

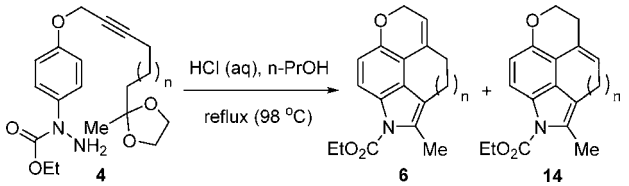
Scheme 2. Synthesis of Aryl Hydrazide 4a–4d



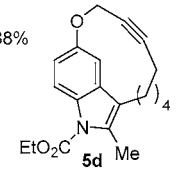
with *n*-BuLi and the substitution reaction with alkyl bromides **8a**–**8d** furnished silyl propargyl ethers **9a**–**9d** which were desilylated with TBAF to give alcohols **10a**–**10d** in good overall yield (70%–83%). The resulting alcohols **10a**–**10d** were then mesylated into **11a**–**11d** for the reaction with *p*-iodophenol **12a**. Simple mixing in the presence of potassium carbonate at rt afforded aryl propargyl ethers **13a**–**13d** in good overall yields (70%–89%). Finally, Cu(I)-catalyzed coupling reactions with ethyl carbazate were conducted on iodides **13a**–**13d** to provide the corresponding aryl hydrazides **4a**–**4d**.[9] Aryl hydrazides **4a**–**4d** were then heated under reflux in *n*-PrOH containing a small amount of HCl (aq), with the conditions previously optimized for the tandem process of **1** (Table 1).

As shown above, aryl hydrazide **4a** (n = 1) afforded no desired product, but a complex mixture of unidentifiable products (entry 1). Varying the reaction conditions (temperature, solvent) or the type of acid catalyst gave no improvement. Fortunately, the desired tandem IMFIS/alkyne-hydroarylation reaction was realized when the tether was elongated by one carbon unit. Thus, aryl hydrazide **4b** (n = 2) gave an inseparable mixture of tetracyclic 2*H*-chromeno-indole **6b** and its double bond isomerization product **14b** (1:10) in 88% total yield after 24 h (entry 2). Aryl hydrazide **4c** with a one-carbon longer tether (n = 3) also underwent the tandem reaction at a much faster rate. In this case, the initially formed tandem product was completely isomerized into **14c** in 83% yield after 4 h (entry 4). However, aryl hydrazide with one-carbon further extended tether **4d** (n = 4) gave no tandem reaction products (**6d** or **14d**). The reaction was found to stop at the Fischer indole stage, furnishing indolophane **5d** in 81%

Table 1. Tandem Reactions of Aryl Hydrazides 4a–4d



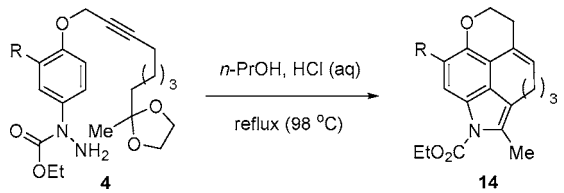
entry	4	time	results
1	**4a** (n = 1)	4 h	decomposition
2	**4b** (n = 2)	24 h	**6b**+**14b** (1:10), 88%
3	**4c** (n = 3)	19 h	**14c**, 83%
4	**4d** (n = 4)	4 h	**5d**, 81%
5	**4d** (n = 4)	3 d	**5d**, 82%



yield after 4 h (entry 4). Increasing the reaction time up to 3 days had little effect on the reaction (entry 5). Apparently, this tandem process is strongly dependent on the tether length, and the tethers employed in aryl hydrazides **4b** and **4c** (n = 2 and 3) appeared to be adequate. Evidently, the alkyne tether in aryl hydrazide **4a** (n = 1) is too short to furnish the required indolophane intermediate **5a**. On the other hand, the tether in aryl hydrazide **4d** (n = 4) would be too long to give the conformation needed for the ensuing aromatic [3,3]-sigmatropic rearrangement, after the formation of the indolophane intermediate **5d**. It is worth noting that the reactions described in entries 2 and 3 represent the first nonmetal catalyzed intramolecular alkyne-hydroarylation reaction of aryl propargyl ether to proceed at temperatures as low as the refluxing temperature for *n*-propyl alcohol. The ring strain in the corresponding indolophane intermediate **5b** and **5c** is believed to be the main driving force. With the above-mentioned results in hand, we set out to investigate the tandem IMFIS/alkyne-hydroarylation process of the aryl hydrazide that contains a substituent next to the phenolic oxygen of the aromatic ring (Table 2).

Incorporation of the substituent R makes the aryl hydrazide unsymmetrical and thus may invoke a regioselectivity issue depending on the direction the Fischer indolization proceeds

Table 2. Tandem Reactions of Substituted Aryl Hydrazides



entry	4	time (h)	14 (yield)
1	**4e** (R = Me)	13	**14e** (73%)[a]
2	**4f** (R = OMe)	13	**14f** (50%)[b]
3	**4g** (R = Ph)	13	**14g** (74%)
4	**4h** (R = F)	13	**14h** (70%)
5	**4i** (R = Cl)	13	**14i** (89%)
6	**4j** (R = Br)	13	**14j** (78%)
7	**4k** (R = CO_2Pr)	14	**14k** (40%)

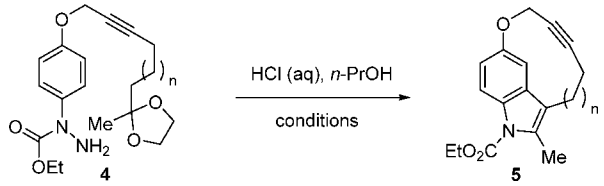
[a]Yield was calculated from iodide **13e** (two steps), because hydrazide **4e** was difficult to purify. [b]Yield was calculated from iodide **13f** (two steps), because hydrazide **4f** was difficult to purify.

dx.doi.org/10.1021/ol4031638 | *Org. Lett.* 2014, 16, 178–181

(clockwise vs counter-clockwise). Despite the concern, however, all the alkyne tethered substituted aryl hydrazides were wrapped around one direction (clockwise) to afford tetracyclic chromeno-indoles **6**, in good yield, after double bond isomerization. The substituent R appeared to provide sufficient steric bias forcing the intramolecular Fischer indolization reaction at a distance. The electronic nature of the substituent R has little effect on the reaction, as the product yield for the aryl hydrazide **4f** bearing an electron-donating methoxy group (entry 2) is essentially identical to that for **4h** with an electron-withdrawing fluorine group (entry 4). However, a significant drop in the product yield was observed with the aryl hydrazide **4k** that contains strongly electron-withdrawing ester functionality (entry 7).

For the installation of the ketone function in the central ring, we need to suppress the double bond migration process. Toward this, we opted to disintegrate the tandem process into the individual reactions by stopping the reaction at the indolophane intermediate stage and conducting the intramolecular alkyne-hydroarylation reaction separately in the absence of proton sources. Thus, the intramolecular Fischer indolization reactions were carried out at lower temperatures (Table 3). In the case of aryl hydrazide **4b** (n = 2), lowering the

Table 3. Interruption of the Tandem Reaction at the Fischer Indolization Stage



4 5

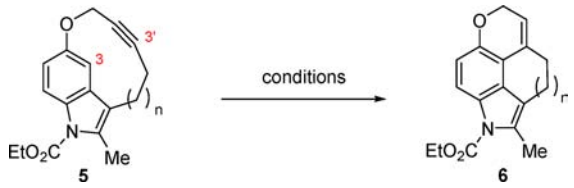
entry	4	conditions	5
1	**4b** (n = 2)	60 °C, 3 h	trace[a]
2	**4b** (n = 2)	rt, 24 h	trace[b]
3	**4c** (n = 3)	60 °C, 12 h	**5c**, 88%

[a]A mixture of **6b** and **14b** (1:10) was obtained in 62% total yield. [b]A mixture of **6b** and **14b** (1:10) was obtainedin 5% total yield.

reaction temperature to 60 °C had little influence as the reaction proceeded all the way to afford a mixture of **6b** and **14b** (1:10) in 62% total yield after 3 h (entry 1). When performed at room temperature, the reaction slowed down quite a bit to give a mixture of **6b** and **14b** (ratio: 1:10) in 5% total yield after 24 h. At this low conversion, there was no noticeable indolophane **5b** formed (entry 2). On the other hand, the reaction of aryl hydrazide **4c** (n = 3) effectively stopped at the Fischer indolization stage, when performed at 60 °C, providing the indolophane **5c** in 88% yield after 12 h (entry 3).

The isolated Fischer product **5c** was then subjected to the various conditions to execute the intramolecular alkyne-hydroarylation reaction (Table 4). When heated in xylene under reflux, **5c** was cleanly converted into tetracyclic 2*H*-chromeno-indole **6c** in quantitative yield after 1 h, with no detectable double bond isomerization product **14c** (entry 1). The reaction was also found to proceed at lower temperature, affording the same product **6c** in 83% yield after 22 h in refluxing toluene (entry 2). Running the reaction in lower boiling benzene resulted in a substantial decrease in the conversion (32% yield after 8 days, entry 3). The strain

Table 4. Alkyne Hydroarylation Reactions of 5c and 5d



5 6

entry	5	conditions	results
1	**5c** (n = 3)	xylene, reflux, 1 h	**6c** (99%)
2	**5c** (n = 3)	toluene, reflux, 22 h	**6c** (83%)
3	**5c** (n = 3)	benzene, reflux, 8 d	**6c** (32%)[a]
4	**5c** (n = 3)	InI_3, CH_2CI_2, 0 °C, 10 min	**6c** (99%)
5	**5d** (n = 4)	xylene, reflux, 1 h	decomposition
6	**5d** (n = 4)	InI_3, CH_2CI_2, rt, 5 d	no reaction

[a]Starting indolophane **5c** was recovered in 65% yield.

embedded in the indolophane **5c** together with the favorable entropy effect enabled the reaction to proceed at temperatures much lower than required for the acyclic cases. In the presence of InI_3,[8a] the reaction went to completion within 10 min at 0 °C to provide **6c** in essentially quantitaive yield (entry 3). Unfortunately, **5d** gave no hydroarylation product under either thermal or metal-catalyzed conditions (entries 4 and 5). A simple molecular modeling study indicated that the distance between the two reacting carbon temini (C3 and C3′) is a little too far (3.09 Å for **5c** vs 3.20 Å for **5d**) for appropriate orbital overlapping to occur.

In summary, we have found that aryl hydrazide connected to the carbonyl function through an alkyne tether can undergo an intramolecular Fischer indolization and cycloisomerization reaction to afford novel tetracyclic 2*H*-chromeno-indoles. The accompanying double bond migration can be avoided by stopping the tandem process at the Fischer indolization stage and conducting the alkyne-hydroarylation reaction separately in the absence of a proton source. This conceptually new approach may find further uses in the synthesis of macrocyclic or polycyclic indoles of pharmacological interest.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectral data for new polycyclic indole compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ccho@hanyang.ac.kr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a grant from the National Research Foundation of Korea (2011-0022343).

■ REFERENCES

(1) (a) Eicher, T.; Hauptmann, S. In *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications*, 2nd ed.; Wiley-VCH: Weinheim, 2003. (b) Indole and its Derivatives. *A. Joule in Science of Synthesis: Methods of Molecular Transformations (Houben-Weyl)*, Cat. 2, Vol. *10*; Thomas, E. J., Ed.; Thieme: Stuttgart, 2000; p 361. (f) Saxton,

J. E. *The Chemistry of Heterocyclic Compounds*; Wiley: New York, 1983; Vol. 25, Part IV. (e) Rahman, A. *Indole Alkaloids*; Harwood Academic Publisher: Amsterdam, 1998. (f) Raffauf, R. F. *A Handbook of Alkaloids and Alkaloid-containing Plants*; Wiley-Interscience: New York, 1970. (g) Manske, R. H. F.; Holmes, H. L. *The Alkaloids: The Ergot Alkaloids*; Academic Press: New York, 1965; Vol. *8*, p 725.

(2) (a) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Org. React.* **2012**, *76*, 281. (b) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195. (c) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (d) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (e) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.

(3) (a) Breazzano, S. P.; Poudel, Y. B.; Boger, D. L. *J. Am. Chem. Soc.* **2013**, *135*, 1600. (b) Rafferty, R. J.; Williams, R. M. *J. Org. Chem.* **2012**, *77*, 519. (c) Allan, K. M.; Kobayashi, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2012**, *134*, 1392. (d) Belmar, J.; Funk, R. L. *J. Am. Chem. Soc.* **2012**, *134*, 16941. (e) Huters, A. D.; Quasdorf, K. W.; Styduhar, E. D.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 15797. (f) Li, X.; Gong, X.; Zhao, M.; Song, G.; Deng, J.; Li, X. *Org. Lett.* **2011**, *13*, 5808. (g) Cheng, D.-J.; Wu, H.-B.; Tian, S.-K. *Org. Lett.* **2011**, *13*, 5636. (h) Feldman, K. S.; Ngernmeesri, P. *Org. Lett.* **2011**, *13*, 5704.

(4) For intramolecular Larock indole synthesis, see: (a) Breazzano, S. P.; Poudel, Y. B.; Boger, D. L. *J. Am. Chem. Soc.* **2013**, *135*, 1600. (b) Shimamura, H.; Breazzano, S. P.; Garfunkle, J.; Kimball, F. S.; Trzupek, J. D.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 7776. (c) Shan, D.; Gao, Y.; Jia, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 4902.

(5) Park, I.-K.; Park, J.; Cho, C.-G. *Angew. Chem., Int. Ed.* **2012**, *51*, 2496. In the report, the product **3** was mistakenly named tricyclic benzo[*cd*]indole and should be called 3,4-fused tricyclic indole.

(6) The reaction on the acyclic aryl propargyl ether system is known as intramolecular alkyne hydroarylation or cycloisomerization. For the first report, see: Zsindely, J.; Schmid, H. *Helv. Chim. Acta* **1968**, *51*, 1510.

(7) For a review, see: Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205.

(8) For a metal catalyzed alkyne hydroarylation of aryl propargyl ether, see: (a) Qiu, W.-W.; Surendra, K.; Yin, L.; Corey, E. J. *Org. Lett.* **2011**, *13*, 5893. (b) Efe, C.; Lykakis, I. N.; Stratakis, M. *Chem. Commun.* **2011**, *47*, 803. (c) Menon, R. S.; Findlay, A. D.; Bissember, A. C.; Banwell, M. G. *J. Org. Chem.* **2009**, *74*, 8901. (d) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (e) Nevado, C.; Echavarren, A. M. *Chem.—Eur. J.* **2005**, *11*, 3155.

(9) (a) Suh, S.-E.; Park, I.-K.; Lim, B.-Y.; Cho, C.-G. *Eur. J. Org. Chem.* **2011**, 455. (b) Lee, W.-J.; Kim, H.-Y.; Cho, C.-G. *Org. Lett.* **2007**, *9*, 3185. (c) Kim, H.-Y.; Lee, W.-J.; Kang, H.-M.; Cho, C.-G. *Bull. Korean Chem. Soc.* **2007**, *28*, 1821. (d) Kang, H.-M.; Kim, H.-Y.; Jung, J.-W.; Cho, C.-G. *J. Org. Chem.* **2007**, *72*, 679. (e) Kang, H.-M.; Lim, Y.-K.; Shin, I.-J.; Kim, H.-Y.; Cho, C.-G. *Org. Lett.* **2006**, *8*, 2047. (f) Lim, Y.-K.; Jung, J.-W.; Cho, C.-G. *J. Org. Chem.* **2004**, *69*, 5778. (g) Lim, Y.-K.; Choi, S.; Park, K. B.; Cho, C.-G. *J. Org. Chem.* **2004**, *69*, 2603. (h) Lee, K.-S.; Kim, K.-Y.; Shin, J.-T.; Cho, C.-G. *Tetrahedron Lett.* **2004**, *45*, 117. (i) Lim, Y.-K.; Pang, S.-J.; Paek, S.-U.; Lee, H.; Cho, C.-G. *Bull. Korean Chem. Soc.* **2003**, *24*, 543. (j) Lim, Y.-K.; Lee, K.-S.; Cho, C.-G. *Org. Lett.* **2003**, *5*, 979. (k) Lee, G.-S.; Lim, Y.-K.; Cho, C.-G. *Tetrahedron Lett.* **2002**, *43*, 7463.