ORGANIC LETTERS

2005
Vol. 7, No. 4
677−680

Indol-2-one Intermediates: Mechanistic Evidence and Synthetic Utility. Total Syntheses of (±)-Flustramines A and C

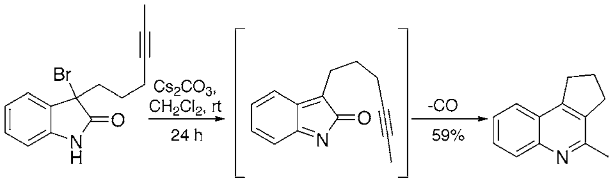
James R. Fuchs and Raymond L. Funk*

Department of Chemistry, Pennsylvania State University,
University Park, Pennsylvania 16802

rlf@chem.psu.edu

Received December 1, 2004

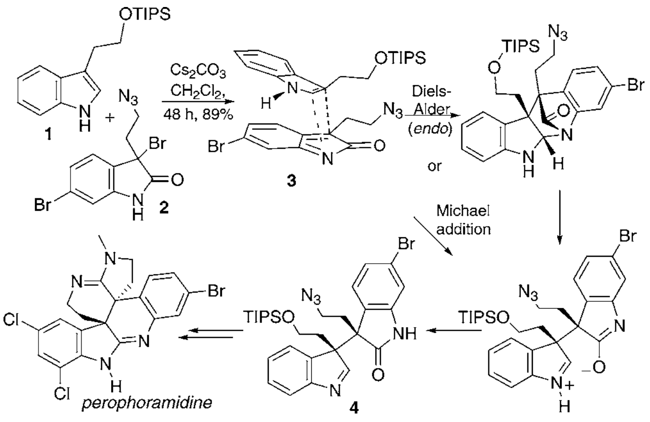
ABSTRACT



A variety of 3,3-disubstituted 2-indolinones have been prepared by treatment of 3-bromo-3-alkyl-2-indolinones with dienophiles/nucleophiles in the presence of cesium carbonate. Application of this general strategy has facilitated the total syntheses of the reverse prenylated marine natural products (±)-flustramine A and (±)-flustramine C.

Recently, we reported the total synthesis of (±)-perophoramidine via a key base-promoted tryptamine “dimerization” reaction of indolin-2-one **2** with indole **1**.[1] We proposed that the transformation proceeded via a putative indol-2-one intermediate **3** through either a Diels−Alder cycloaddition[2] or Michael addition pathway to produce indolenine **4** (Scheme 1).[3] Our initial study of this reaction drew upon the seminal observations of Hinman and Bauman who reported the substitution reactions of 3-bromo-3-methylindolin-2-one with hetero nucleophiles (Scheme 2),[4] although the intermediacy of 3-methylindol-2-one was not advanced in these studies. Herein we report an extensive investigation of the base-promoted reactions of 3-alkyl-3-bromoindolin-2-ones with dienophiles/nucleophiles, further document the utility of this method in the construction of C(3) reverse prenylated pyrrolidinoindoline natural products, and provide evidence that suggests that transient indol-2-ones are indeed generated under these conditions.

Scheme 1



---

(1) Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 5068.

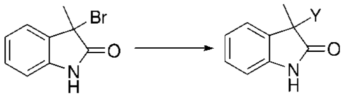
(2) For the generation and Diels−Alder cycloaddition of the related 2-azacyclopenta-2,4-dien-1-one with polymer-supported acetylene-dicarboxylate, see: (a) Gavina, F.; Costero, A. M.; Andreu, M. R.; Carda, M.; Luis, S. V. *J. Am. Chem. Soc.* **1988**, *110*, 4017. (b) Yokotsuji, D. L. S.; Dailey, W. P.; Kende, A. S.; Birzan, L.; Liu, K. *J. Phys. Chem.* **1995**, *99*, 15870.

(3) Alternative pathways for the formation of indolenine **4** were also envisaged, including direct displacement and transfer alkylation.

(4) (a) Hinman, R. L.; Bauman, C. P. *J. Org. Chem.* **1964**, *29*, 2431. For further examples of reactions that may occur via generation of indol-2-one intermediates, see: (b) Labroo, R. B.; Labroo, V. M.; King, M. M.; Cohen, L. A. *J. Org. Chem.* **1991**, *56*, 3637. (c) Rajeswaran, W. G.; Labroo, R. B.; Cohen, L. A.; King, M. M. *J. Org. Chem.* **1999**, *64*, 1369. (d) Kobayashi, M.; Aoki, S.; Gato, K.; Matsunami, K.; Kurosu, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1994**, *42*, 2449. For an example of an intramolecular displacement of a tertiary mesylate with inversion of stereochemistry, see: Monde, K.; Taniguchi, T.; Miura, N.; Nishimura, S.-I.; Harada, N.; Dukor, R. K.; Nafie, L. A. *Tetrahedron Lett.* **2003**, *44*, 6017.

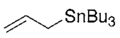
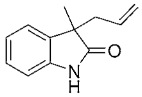
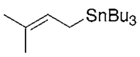
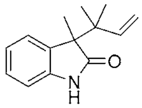
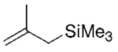
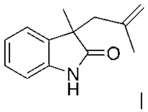
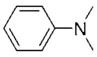
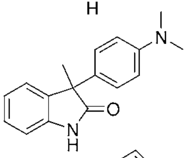
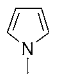
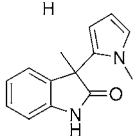
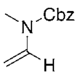
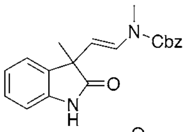
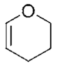
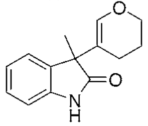
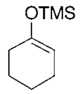
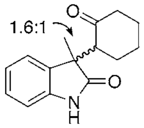
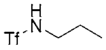
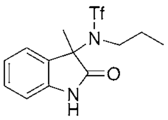
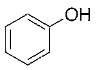
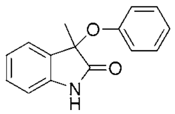
10.1021/ol047532v CCC: $30.25

Scheme 2



Y	conditions	yield
OH	$NaHCO_3$, H_2O *t*-BuOH, 22 h, rt	84 %
OCH_3	$NaHCO_3$, H_2O MeOH, 3 d, rt	85 %
SC_6H_5	NaOH, HSC_6H_5 *t*-BuOH, 15 min, rt	48 %
NC_5H_{10}	Et_2O, HNC_5H_{10}, 1.5 h, rt	91 %

Table 1. Intermolecular Addition of Nucleophiles to 3-Bromo-3-methylindolin-2-one

Entry	Nucleophile	Conditions	Product
1		Cs_2CO_3, CH_2Cl_2, rt 12 h, 79%	
2		Cs_2CO_3, CH_2Cl_2, rt 12 h, 75%	
3		Cs_2CO_3, CH_2Cl_2, rt 24 h, 81%	
4		Cs_2CO_3, CH_2Cl_2, rt 12 h, 84%	
5		Cs_2CO_3, CH_2Cl_2, rt 12 h, 60%	 3:1 + regio
6		Cs_2CO_3, CH_2Cl_2, rt 24 h, 70%	
7		Cs_2CO_3, CH_2Cl_2, rt 24 h, 45%	
8		Cs_2CO_3, CH_2Cl_2, rt 24 h, 75%	
9		Cs_2CO_3, CH_2Cl_2, rt 24 h, 73%	
10		Cs_2CO_3, CH_2Cl_2, rt 12 h, 63%	

We first surveyed the intermolecular reaction of various nucleophiles/dienophiles with 3-bromo-3-methylindolin-2-one (**1**, Table 1) using our standard reaction conditions (Cs_2CO_3, CH_2Cl_2, rt).[5] Allyl stannanes (entries 1 and 2) and methallyltrimethylsilane (entry 3) cleanly provided the 3-allyl-substituted oxindoles. However, the less nucleophilic allyltrimethylsilane[6] failed to provide any product. Electron-rich aromatic compounds such as *N*,*N*-dimethylaniline (Table 1, entry 4) and *N*-methylpyrrole (entry 5) also served as competent nucleophiles, whereas anisole and 1,3-dimethoxybenzene were unreactive. The examples shown in entries 6 and 7 demonstrate that enamides and cyclic enol ethers also react with the putative indol-2-one intermediate via Diels–Alder or Michael-type pathways eventually leading to products containing regenerated enamide/enol ether functionality. Nucleophiles that can be generated in situ by deprotonation with cesium carbonate proceed smoothly, as shown in entries 9 and 10. Much to our dismay, it was found that poor Michael donors, yet competent dienophiles, such as the electron-neutral 2-butyne or electron-poor diethyl fumarate/dimethyl acetylenedicarboxylate gave no product and resulted only in the decomposition of the starting 3-bromo-3-methylindolin-2-one.

We next turned to the intramolecular variant of this reaction, namely, the cyclization of appropriately substituted 3-alkyl-3-bromoindolin-2-ones (Table 2). For example, the triflamide shown in entry 1 (prepared through NBS-mediated oxidation of the corresponding indole) gave rise to the spirocyclic indolin-2-one upon treatment with cesium carbonate. Entry 2 suggests that electrophilic aromatic substitution reactions with electron-rich aromatic rings can indeed be accomplished if performed intramolecularly,[7] albeit in low yield. Finally, the silyl enol ether shown in entry 3 reacted in the presence of base to provide a mixture of the corresponding *E*/*Z* exocyclic silyl enol ether products that was subsequently hydrolyzed to provide a 1.5:1 mixture of the diastereomeric aldehydes.

It was hoped that convincing evidence for an indol-2-one intermediate might be obtained by subjecting the 3-(4-hexynyl)indolin-2-one **7** to our standard reaction conditions (Scheme 3). However, the preparation of this substrate necessitated the development of a strategy that avoided the relatively harsh brominating conditions (NBS, *t*-BuOH/THF (1:1), rt, 1 h) employed in our standard procedure, halooxidation of 3-substituted indoles. To that end, the dianion of oxindole (**5**) was alkylated with the 6-iodo-2-hexyne according to the procedure of Kende.[8] Subsequent formation of the dianion of the alkylated oxindole **6** and treatment with NBS at low temperature led to the formation of the 3-alkyl-3-bromoindolin-2-one **7**. It should be noted that the 3-alkyl-3-bromoindolin-2-ones shown in entries 2 and 3 of Table 2,

---

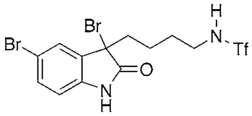
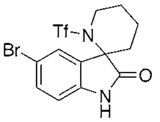
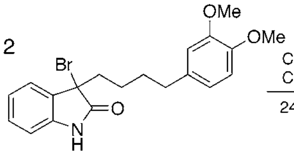
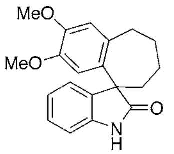
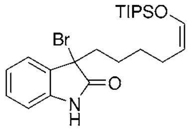
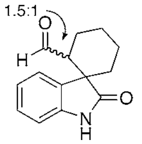
(5) These conditions had been previously employed for the generation of *N*-acyl and *N*-sulfonyl-aza-*ortho*-xylylenes. Steinhagen, H.; Corey, E. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1928.

(6) For a reference scale of π-nucleophilicity, see: (a) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66. (b) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500.

(7) Previous studies have suggested that the seven-membered ring closure is preferred geometrically in internal electrophilic aromatic substitution reactions. Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3349.

(8) Kende, A. S.; Hodges, J. C. *Synth. Commun.* **1982**, *12*, 1.

Table 2. Intramolecular Addition of Nucleophiles

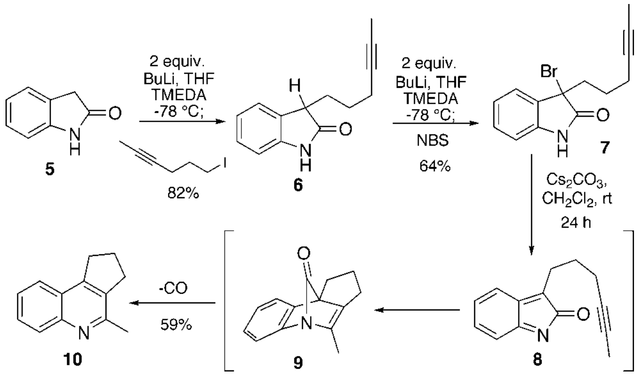
Entry	Substrate	Conditions	Product
1		Cs_2CO_3, CH_2Cl_2, rt 12 h, 85%	
2		Cs_2CO_3, CH_2Cl_2, rt 24 h, 13%	
3		Cs_2CO_3, CH_2Cl_2, rt 24 h, 78%	

which possess more labile substituents, were also prepared using this mild and direct route.

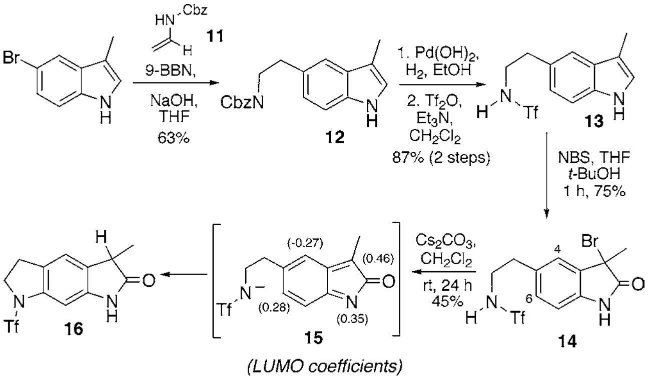
We were gratified to discover that treatment of the alkyne **7** with cesium carbonate resulted in the formation of quinoline **10** in good yield (Scheme 3). This transformation presumably occurs via cycloaddition of the *tethered* alkyne with the intermediate indol-2-one **8** to provide a strained bridged bicyclic lactam **9**.[2] The lactam then undergoes a retrocheleotropic reaction in situ to provide the quinoline **10**.

We have also examined the cyclization of a 3-bromoindolin-2-one possessing a nucleophilic substituent connected at C(5) rather than C(3) as found in the aforementioned examples. To that end, indole **12** was prepared via Suzuki coupling of enamide **11** employing the conditions reported by Overman.[9] The carbamate protecting group was then removed, and the resulting amine was converted to triflamide **13**. Subsequent halooxidation of the indole with *N*-bromosuccinimide provided the substituted 3-bromoindolin-2-one **14**. Treatment of this compound with cesium carbonate provided indoline **16** as the major product, presumably by intramolecular nucleophilic attack upon the indol-2-one intermediate **15** and subsequent rearomatization. An alternative S_N2' mechanism involving the direct addition of the triflamide anion to the aromatic ring seems less likely. The regiochemical preference of the reaction is consistent with the calculated LUMO coefficients of the carbons of the indol-2-one intermediate. The 3-methyl substituent may also act to sterically inhibit cyclization at C(4).

Scheme 3

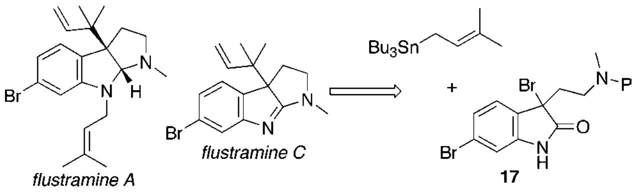


Scheme 4



Having delineated the scope and generality of this methodology, we turned to its application in natural product synthesis. The marine natural products flustramine A[10] and flustramine C[11] (Scheme 5) are particularly attractive targets since they embody a reverse prenylated substituent at C(3),[12] a functionality that is readily accessible using this methodology as previously demonstrated in entry 2 of Table 1. Thus, it was hoped that both of these natural products could be constructed from the product derived from 3-bromoindolin-2-one **17** and tributyl(3-methyl-2-butenyl)tin.

Scheme 5



We first directed our attention to the synthesis of flustramine A. To that end, 6-bromoindole **18** was treated with

---

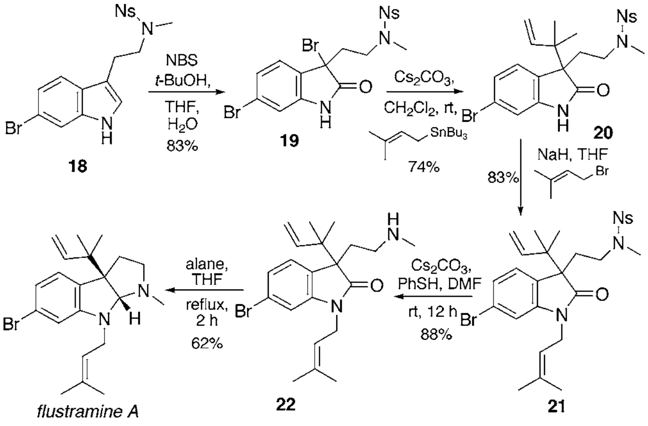
(9) Kamatani, A.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 8743.

(10) For the isolation from *Flustra foliacea* (L.), see: (a) Carle, J. S.; Christophersen, C. *J. Org. Chem.* **1980**, *45*, 1586. For the previous total synthesis, see: (b) Morales-Rios, M. S.; Suarez-Castillo, O. R.; Trujillo-Serrato, J. J.; Joseph-Nathan, P. *J. Org. Chem.* **2001**, *66*, 1186.

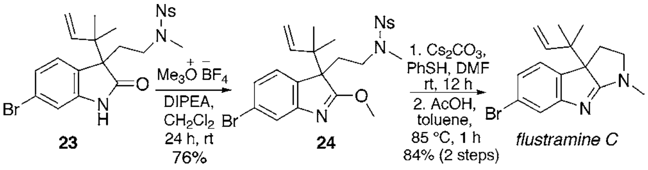
(11) For the isolation from *Flustra foliacea* (L.), see: (a) Carle, J. S.; Christophersen, C. *J. Org. Chem.* **1981**, *46*, 3440. For the previous total synthesis, see: (b) Kawasaki, T.; Terashima, R.; Sakaguchi, K.; Sekiguchi, H.; Sakamoto, M. *Tetrahedon Lett*. **1996**, *37*, 7525.

(12) For the total synthesis of related pyrrolidinoindoline alkaloids via reverse prenylation of putative *N*-acyl-aza-*ortho*-xylylenium ions, see: (a) Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143. (b) Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953. (c) Schiavi, B. M.; Richard, D. J.; Joullie, M. M. *J. Org. Chem.* **2002**, *67*, 620.

Scheme 6



Scheme 7



NBS to afford the key 3-alkyl-3-bromoindolin-2-one **19**. Treatment of the 3-bromoindolin-2-one with cesium carbonate in the presence of tributyl(3-methyl-2-butenyl)tin cleanly provided indolin-2-one **20**. *N*-Alkylation of the indolin-2-one with dimethylallyl bromide and subsequent deprotection of the secondary amine according to the protocol of Fukuyama[13] proved to be uneventful. Reduction of the resulting amine **22** with 2.5 equiv of alane led to formation of flustramine A as the minor product along with a substantial amount of fully reduced indoline byproduct resulting from reduction of the intermediate iminium ion (4:1 ratio). Fortunately, flustramine A could be obtained as the major product (3:1) by employing only 1.1 equiv of alane and decreasing the concentration of indolin-2-one **22** (0.2 → 0.05 M).

The reverse prenylated indolinone **23** was also easily converted to flustramine C. Thus, treatment of **23** with Meerwein's salt provided the cyclic imidate **24**. Removal of the nosylamide functionality of compound **24** under the Fukuyama conditions afforded none of the desired amidine. However, (±)-flustramine C could be obtained by heating the crude deprotected amine in toluene with an equivalent of acetic acid.

In conclusion, we have demonstrated that 3-alkyl-3-bromoindolin-2-ones undergo base-promoted reactions with a variety of dienophiles/nucleophiles to generate 3,3-disubstituted-2-indolinones and have thereby significantly expanded the initial studies of Hinman and Bauman.[4] Most importantly, we have provided substantive evidence for a pathway proceeding through heretofore unappreciated indol-2-one reactive intermediates. The concise total syntheses of (±)-flustramine A and (±)-flustramine C described herein further underscore the value of this methodology in natural product synthesis. Moreover, the discovery of a new strategy for the preparation of the requisite 3-alkyl-3-bromoindolin-2-ones that tolerates more nucleophilic substituents should pave the way for applications featuring intramolecular cyclizations of indol-2-one intermediates.

Acknowledgment. We appreciate the financial support provided by the National Institutes of Health (GM28553).

Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047532V

---

[13] Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.