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Construction of Polycyclic Spiroindolines via an Intramolecular Oxidative Coupling/Cyclization Cascade Reaction Process

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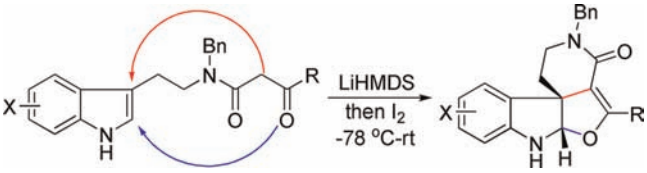
ABSTRACT



An efficient protocol for assembling a polycyclic spiroindoline scaffold is developed, which involves an intramolecular oxidative coupling of dianions derived from indole-embodied β-ketoamides using iodine as the oxidant, and subsequent attack of oxygen anion to the resultant imine moiety. A number of tetracyclic spiroindolines are prepared with moderate to good yields.

A polycyclic spiroindoline is a complex molecular skeleton that often exists in both natural products and pharmaceutical molecules with potent biological activities.[1,2] Its synthesis through novel and practical methodologies has been extensively pursued.[3,4] One of most attractive methods would be developing a reaction cascade from simple starting materials that can construct multiple rings and create several stereocenters in a single step. Such a methodology would be particularly valuable for medicinal chemistry because it could provide a convenient approach to access a library of polycyclic spiroindolines.

Oxidative coupling of carbon anions is one of the most direct methods for forming C−C bonds.[5,6] However, this

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(3) Examples of total synthesis of *strychnos* alkaloids: (a) Bonjoch, J.; Sole, D. *Chem. Rev.* **2000**, *100*, 3455. (b) Sirasani, G.; Paul, T.; Dougherty, W.; Kassel, S.; Andrade, R. B. *J. Org. Chem.* **2010**, *75*, 3529. (c) Martin, D. B. C.; Vanderwal, C. D. *Chem. Sci.* **2011**, *2*, 649. (d) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183.

(4) Examples of total synthesis of communesin alkaloids: (a) Yang, J.; Wu, H.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129*, 13794. (b) Liu, P.; Seo, J. H.; Weinreb, S. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2000. (c) Zuo, Z.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2010**, *132*, 13226. (d) Zuo, Z.; Ma, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 12008. For reviews, see: (e) Siengalewicz, P.; Gaich, T.; Mulzer, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 8170. (f) Zuo, Z.; Ma, D. *Isr. J. Chem.* **2011**, *51*, 434. (g) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447.

(5) Selected examples for oxidative homocoupling: (a) Ivanoff, D.; Spassoff, A. *Bull. Soc. Chim. Fr.* **1935**, *2*, 76. (b) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 4605. (c) Brocksom, T. J.; Petragnani, N.; Rodrigues, R.; La Scala-. Teixeira, H. *Synthesis* **1975**, *6*, 396. (d) Frazier, R. H.; Harlow, R. L. *J. Org. Chem.* **1980**, *45*, 5408. (e) Belletire, J. L.; Fry, D. F. *J. Org. Chem.* **1987**, *45*, 2549. (f) Renaud, P.; Fox, M. A. *J. Org. Chem.* **1988**, *45*, 3745. (g) Quermann, R.; Maletz, R.; Schafer, H. J. *Liegigs Ann. Chem.* **1993**, *11*, 1219. (h) Kise, N.; Tokioka, K.; Aoyama, Y. *J. Org. Chem.* **1995**, *60*, 1100. (i) Langer, T.; Illich, M.; Felmchen, G. *Tetrahedron Lett.* **1995**, *36*, 4409. (j) Kim., J. W.; Lee, J. J.; Lee, S.-H.; Ahn, K.-H. *Synth. Commun.* **1998**, *28*, 1287.

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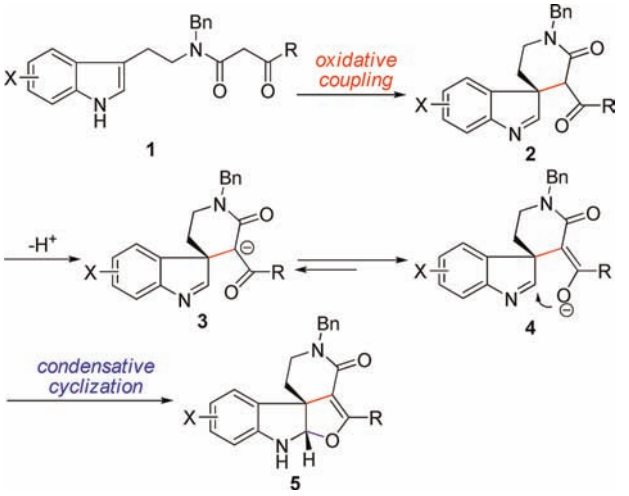
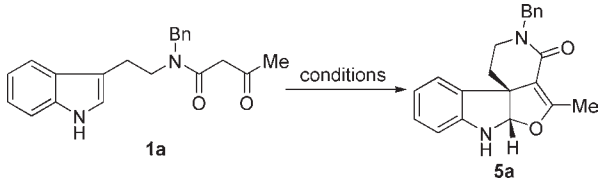
method was rarely applied in the total synthesis of complex natural products due to the lack of selectivity (homocoupling versus heterocoupling).[6] Recently, oxidative coupling of enolates experienced a renaissance due to its applications in alkaloid synthesis. For example, Baran and co-workers have achieved the total synthesis of fischerindole, hapalindole, and welwitindolinone through intermolecular oxidative coupling of ketone-derived enolates with indoles.[7] The Overman group has employed an intramolecular oxidative coupling as a key step in the total synthesis of actinophyllic acid.[8] Quite recently, we finished the first enantioselective total synthesis of (−)-communesin F[4c] and communesin A and B[4d] via an intramolecular oxidative coupling reaction between indole and amide-derived enolate, and subsequent annulation of the resulting indoline with an apendant aniline. In the synthesis of (−)-communesins,[4c,d] we had to utilize a stepwise strategy to establish their polycyclic ring framework due to the lack of reactivity of the potential cascade reaction precursor. We thus hypothesized that if the oxidative cyclization precursors possessed functionalities that are tolerant under conditions of oxidative coupling and are further capable of a second ring closure, an efficient reaction cascade could be developed for preparing complex polycyclic spiroindolines. Accordingly, we were interested in using β-ketoamides **1** (Scheme 1) as the substrates for an oxidative coupling reaction. We speculated that intramolecular oxidative coupling of **1** would initially afford spiroindolines **2**, which should undergo further deprotonation to provide enolates **4**, and the resultant oxygen anion would attack the imine moiety to produce tetracyclic spiroindolines **5**.

Scheme 1



With this idea in mind, an intramolecular oxidative coupling reaction of **1a** was examined under various conditions. To our delight, treatment of **1a** under our previous conditions (LiHMDS then iodine, THF, −78 °C to rt)[4c,d] delivered spiroindoline **5a** with 74% yield (Table 1, entry 1). Its structure was unambiguously confirmed by X-ray crystallography analysis. Only one isomer was determined in this case, presumably because a *cis*-fused ring system is more stable. Interestingly, the other conditions we tested all gave poor results. For example, decreased yields were observed when LiHMDS was replaced with LDA and KHMDS (entries 2 and 4), although NaHMDS gave a similar result (entry 3). Inorganic oxidants like $Fe(acac)_3$, $Cu(OTf)_2$, and $Cu(2\text{-ethylhexate})_2$, which have provided the best results in the intermolecular oxidative coupling of indole and enolate,[6d] were totally ineffective in our transformation (entries 5−7). Other solvents such as ether, toluene, and DME gave inferior results (entries 8−10). Furthermore, we found that it was necessary to raise the reaction temperature after the addition of iodine to obtain a good yield (compare entries 1 and 11). These results indicated that the present transformation is quite sensitive to the base, solvent, oxidant, and reaction temperature used.

Table 1. Condition Screening for Formation of **5a** from β-Ketoamide **1a**



entry	conditions	yield (%)[c]
1	standard conditions[a]	74
2	LDA instead of LHMDS	46
3	NaHMDS instead of LHMDS	72
4	KHMDS instead of LHMDS	36
5	$Cu(2\text{-ethylhexate})_2$ instead of I_2	—[b]
6	$Cu(OTf)_2$ instead of I_2	—[b]
7	$Fe(acac)_3$ instead of I_2	—[b]
8	Et_2O instead of THF	15
9	Toluene instead of THF	18
10	DME instead of THF	40
11	−78 °C instead of rt	48

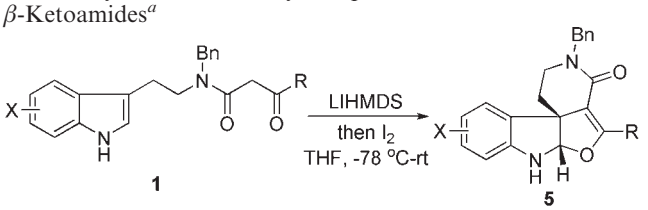
[a] Standard conditions: **1a** (0.2 mmol), LiHMDS (0.44 mmol), THF (3 mL), −78 °C, 30 min, then addition of iodine (0.22 mmol), −78 °C, then rt, 30 min. [b] No oxidative coupling occurred. [c] Isolated yield.

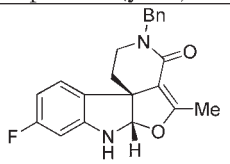
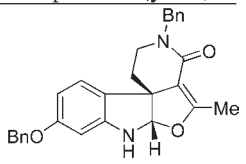
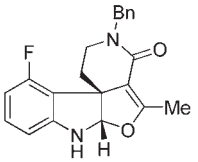
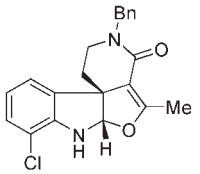
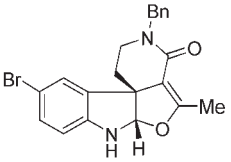
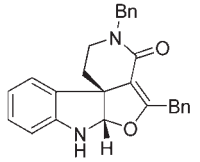
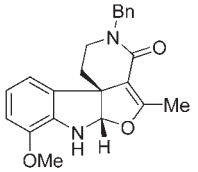
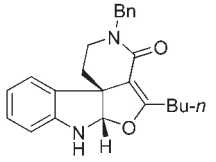
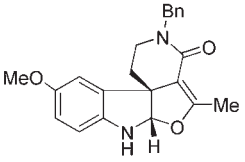
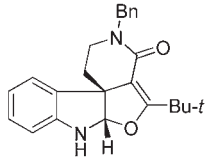
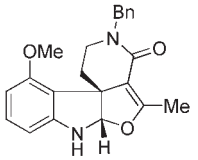
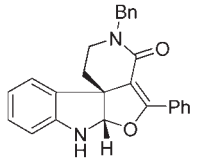
(6) Selected examples for oxidative heterocoupling: (a) Ito, Y.; Konoike, T.; Harada, T.; Saegusa, T. *J. Am. Chem. Soc.* **1977**, *99*, 1487. (b) Baran, P. S.; Richter, J. M.; Lin, D. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 609. (c) Baran, P. S.; DeMartino, M. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 7083. (d) Richter, J. M.; Whitefield, B.; Maimone, T. J.; Lin, D. W.; Castroviejo, P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857. (e) Richter, J. M.; Whitefield, B.; Maimone, T. J.; Lin, D. W.; Castroviejo, P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857. (f) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546.

(7) (a) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450. (b) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394. (c) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404. (d) Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 17938.

(8) (a) Martin, C. L.; Overman, L. E.; Rohde, J. A. *J. Am. Chem. Soc.* **2010**, *132*, 4894. (b) Martin, C. L.; Overman, L. E.; Rohde, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 7568.

Table 2. Synthesis of Tetracyclic Spiroindolines from Different β-Ketoamides[a]



entry	product (yield)[b]	entry	product (yield)[b]
1	 **5b** (87%)	7	 **5h** (76%)
2	 **5c** (66%)	8	 **5i** (78%)
3	 **5d** (75%)	9	 **5j** (42%)
4	 **5e** (80%)	10	 **5k** (63%)
5[c]	 **5f** (51%)	11[e]	 **5l** (20%)
6[d]	 **5g** (38%)	12	 **5m** (48%)

[a] Reaction conditions: **1a** (0.2 mmol), LiHMDS (0.44 mmol), THF (3 mL), −78 °C, 30 min, then addition of iodine (0.22 mmol), −78 °C, then rt, 30 min. [b] Isolated yield. [c] 15% starting material was recovered. [d] 22% starting material was recovered. [e] Simple oxidative coupling product was isolated in 37% yield.

Next, we turned our attention to exploring the scope and limitations of this transformation. Thus, a number of β-ketoamides with different substituents at either the indole ring or the γ-position of the amide were examined. We were pleased to find that substrates with both electron-rich and -deficient indole moieties worked well under our standard conditions, providing the corresponding products with moderate to good yields (Table 2, entries 1−8). When β-ketoamides with 4-substituted indoles were used, poorer yields were obtained in comparison to their regioisomers (compare entries 1 and 2, and 5 and 6). This could be ascribed to steric reasons which can be seen from the crystallography of **5a**. The H4 of the indole was very close to the newly formed piperidine ring. When this proton was substituted with other groups, the steric interaction between the piperidine ring and the group on C4 should slow down the oxidative coupling reaction. Further attempts revealed that changing the γ-substituents of the β-ketoamides was possible to give the desired products **5j**−**5m** (entries 9−12). However, their reaction yields were considerably lower than that observed for a γ-methyl substituted β-ketoamide. This problem might result from the poor conversion in the condensative cyclization, because the simple oxidative coupling product was isolated in ~37% yield in the case of the formation of **5l**. This result indicated that dihydrofuran ring formation is sensitive to the steric hindrance of γ-substituents.

In summary, an oxidative coupling/cyclization cascade reaction process for preparing polycyclic spiroindolines from simple β-ketoamides was developed. This method features the creation of two new rings and one quaternary carbon center in a single step. Application of this method in the synthesis of bioactive compounds is being actively pursued, and the results will be disclosed in due course.

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Supporting Information Available. Experimental procedures and copies of ^{1}H and ^{13}C NMR spectra for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.