JOC*Note*

New Palladium-Catalyzed Reaction Pathway to the *Erythrina* Skeleton

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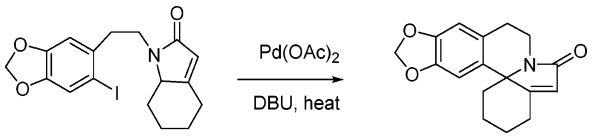
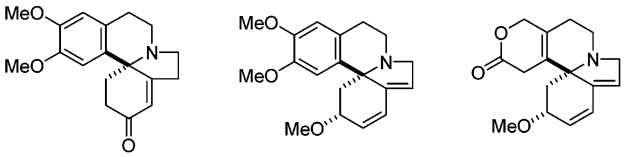


Palladium-catalyzed arylation of α,β-unsaturated γ-lactam, which could be prepared by condensation of amines and keto-esters, has been carried out to make the core structure of *Erythrina* alkaloids.

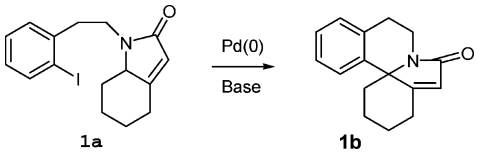
Erythrina alkaloids display a variety of biological activity including hypnotic and CNS activity.[1] The pharmacological effects associated with the distinctive skeleton have drawn attraction for the synthesis of the alkaloids and their derivatives over the years, and some of the recent strategies on the construction of the core spirocyclic structure include intramolecular cyclization reactions such as radical cyclizations,[2] electrophilic substitution cyclizations on *N*-acyliminium intermediates or Pummerer-induced cyclizations,[3] Heck reactions,[4] and anionic substitution reactions.[5]



13-Demethoxyerythratidinone | Erysotramidine | β-Erythroidine

To develop a novel route to the skeleton, we have focused on the application of the recent palladium-catalyzed arylation reaction of ketone enolates[6] for the core quarternary center of the molecule. In this paper, we describe the first examples, to our knowledge, of the palladium-catalyzed arylation of α,β-unsaturated γ-lactam enolate for a concise pathway to the core structure. We thought that the condensed products of arylamine and keto-ester intermediates[3c] would be eligible for arylation, and they could be prepared by reaction of 2-iodo-arylamines and ethyl 2-oxocyclohexaneacetate under reflux in toluene in the presence of TsOH in about 40−90% yields (Scheme 1).[3d]

TABLE 1. Optimization of Palladium-Catalyzed Cyclization of 1a

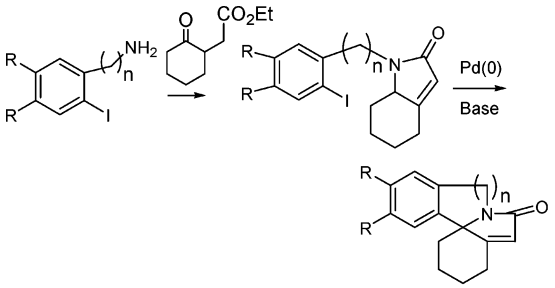


1a 1b

entry	solvent/base	palladium	temp (°C)	time (h)	yield (%)[b]
1	DMF/DBU(5 equiv)	$Pd(OAc)_2$	140	14	23
2	toluene/DBU(5 equiv)	$Pd(OAc)_2$	140	14	20
3	DBU	$Pd(PPh_3)_4$	140	14	42
4	DBU	$Pd(OAc)_2$	100	14	27
5[a]	DBU	$Pd(OAc)_2$	140	14	72

[a] The reaction was carried out in a pressure tube. [b] Isolated yields after purification by silica gel column chromatography.

SCHEME 1



In the context of our interests in the development of the arylation reaction, we first focused on the reaction feasibility by using $Pd(OAc)_2$ in THF with some bases at various temperatures. No sign of progress was detected, even under reflux. However, heating over 100 °C in DMF with base and palladium catalyst enabled the process in moderate yields. A number of palladium sources including $Pd(OAc)_2$, $Pd_2(dba)_3$, $Pd(PPh_3)_4$, $PdCl_2$, and $PdCl_2(PPh_3)_2$ have been found to provide 20−42% yields. Any C−O bond formation product, pyrrole moiety, was not detected. Treatment of 5 mol % of $Pd(OAc)_2$ was selected as a most practical use. We envisioned that a strong base as well as heating should be required for the effective enolate formation of the α,β-unsaturated γ-lactam. Among various bases examined, DBU was found to be best. Addition of ligands did not significantly improve yields. Heating the reaction mixture in DBU in a pressure tube with 5 mol % $Pd(OAc)_2$ at 140 °C was selected as an optimum condition (Table 1).

(1) (a) Tanaka, H.; Tanaka, T.; Etoh, H.; Goto, S.; Terada, Y. *Heterocycles* **1999**, *51*, 2759−2764. (b) Dyke, S. F.; Quessy, S. N. *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic Press: New York, 1981; Vol. 18.

(2) (a) Miranda, L. D.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 1135−1138. (b) Chikaoka, S.; Toyao, A.; Ogasawara, M.; Tamura, O.; Ishibashi H. *J. Org. Chem.* **2003**, *68*, 312−318 and references therein.

(3) (a) Allin, S. M.; Streetley, G. B.; Slater, M.; James, S. L.; Martin, W. P. *Tetrahedron Lett*. **2004**, *45*, 5493−5496. (b) Allin, S. M.; James, S. L.; Elsegood, M. R. J.; Martin, W. P. *J. Org. Chem.* **2002**, *67*, 9464−9467. (c) Padwa, A.; Lee, H. I.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2004**, *69*, 8209−8218 and references therein. (d) Katritzky, R. A.; He, H.-Y.; Jiang, R. *Tetrahedron Lett*. **2002**, *43*, 2831−2833.

(4) (a) Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834−7835. (b) Rigby, J. H.; Deur, C.; Heeg, M. J. *Tetrahedron Lett*. **1999**, *40*, 6887−6890.

(5) Dréau, M.-A.; Desmaële, D.; Dumas, F.; d'Angelo, J. *J. Org. Chem.* **1993**, *58*, 2933−2935.

(6) For reviews on palladium-catalyzed α-arylation of carbonyl compounds, see: (a) Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 953−955. (b) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res*. **2003**, 36, 234−245.

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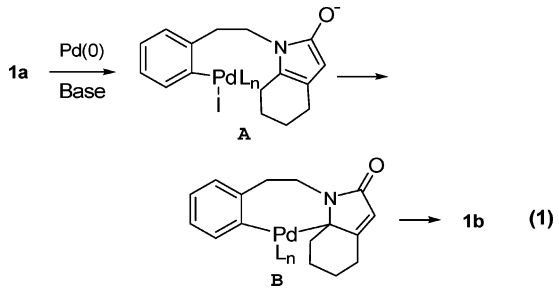
A plausible mechanism is depicted in eq 1 and involves the formation of complex **A** of Pd and α,β-unsaturated γ-lactam enolate as well as insertion to complex **B** followed by reductive elimination to afford **1b**.[7] However, the possibility of exo-Heck type cyclization on intermediate **A** followed by reductive elimination cannot be excluded.[4a]

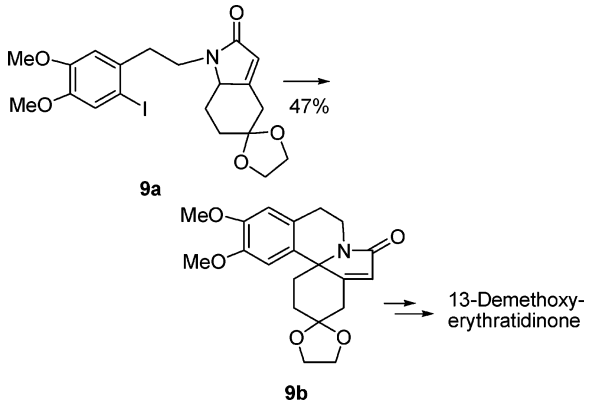


Under the optimized condition, the scope of the palladium-catalyzed cyclization was explored using several α,β-unsaturated γ-lactams (Table 2).

The cyclization reaction afforded moderate to good yields in the case of either aryl iodide or bromide in the formation of five- or six-membered ring compounds. The pathway to the skeleton seemed to be promising in terms of concise preparation of the starting precursors and effective cyclization.

For the synthetic application, we prepared intermediate **9a** from the known starting material[3c] and applied the same condition, which yielded the known precursor **9b** for 13-demethoxyerythratidinone[8] in 47% yield (Scheme 2).

SCHEME 2

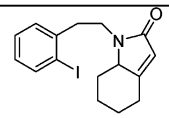
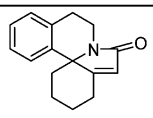
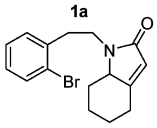
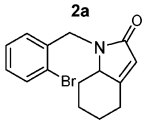
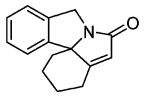
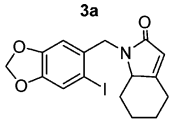
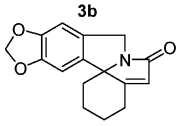
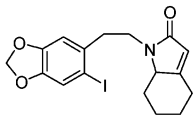
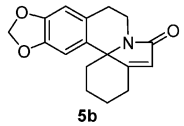
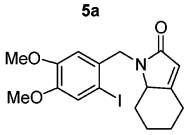
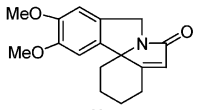
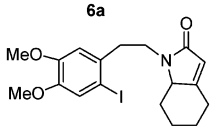
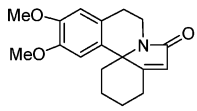
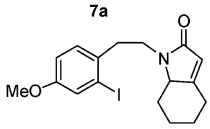
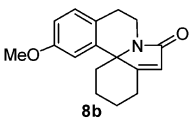


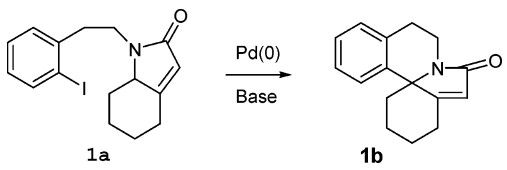
In conclusion, we have described a new palladium-catalyzed cyclization method for the construction of the *Erythrina* alkaloid azaspiro skeleton from α,β-unsaturated γ-lactam intermediates. The intermediates could be prepared readily by condensation of the corresponding amine and cyclic keto-ester. Further application of this reaction for related alkaloid compounds is under study.

Experimental Section

Palladium-Catalyzed Cyclization of 1a. A 15-mL pressure tube was charged with a solution of **1a** (0.165 g, 0.415 mmol) in 4 mL of DBU and $Pd(OAc)_2$ (4.5 mg, 0.020 mmol). After the resulting solution was stirred at 140 °C for 14 h, the reaction mixture was diluted with 15 mL of $CHCl_3$ and washed with 5 mL of 1 N HCl solution three times. The organic layer was then dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography on silica gel (elution with hexane/EtOAc = 1:1 first, then hexane/EtOAc = 1:3) provided 0.081 g (72%) of a yellow oil.

TABLE 2. Cyclization of α,β-Unsaturated γ-Lactam Using $Pd(OAc)_2$

entry	substrate	yield[b]	product
1	 **1a**	72%	 **1b**
2	 **2a**	60%	**1b**
3	 **3a**	71%	 **3b**
4	 **4a**	54%	 **4b**
5	 **5a**	64%	 **5b**
6	 **6a**	56%	 **6b**
7	 **7a**	57%	 **7b**
8	 **8a**	70%	 **8b**



Spectral data for 1b: IR (KBr) 1684, 1558, 1374, and 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, 1H, J = 6.8 Hz), 7.26−7.23 (m, 3H), 5.92 (s, 1H), 4.02 (q, 1H, J = 6.6 Hz), 3.54 (q, 1H, J = 6.6 Hz), 3.06−2.88 (m, 3H), 2.45−2.42 (m, 1H), 2.17 (m, 2H), 1.70 (m, 2H), and 1.58−1.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 164.1, 137.8, 134.5, 129.5, 127.1, 125.7, 125.2, 121.2, 66.8, 41.3, 36.6, 29.6, 28.5, 27.9, and 21.1; MS (EI)

(7) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 5816−5817.

(8) Ishibashi, H.; Sato, T.; Takahashi, M.; Hayashi, M.; Ikeda, M. *Heterocycles* **1988**, *27*, 2787−2790.

m/*z* 239 (M^+, 100); EI-HRMS calcd for $C_{16}H_{17}NO$ 239.1310, found 239.1305.

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Supporting Information Available: Spectral data of **3b**, **4b**, **5b**, **6b**, **7b**, **8b**, and **9b**; copies of ^{1}H NMR and ^{13}C NMR spectra of **1b**, **3b**, **4b**, **5b**, **6b**, **7b**, and **8b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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