ORGANIC LETTERS

2013
Vol. 15, No. 13
3464–3467

Dearomatization Strategy of β-Enamino Ester: Construction of Indenoazepines via Tandem Michael Addition/Polycyclization

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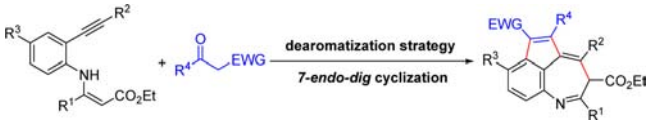
Received June 3, 2013

ABSTRACT



A dearomatization strategy of β-enamino esters was developed to construct indenoazepine derivatives. The oxidative dearomatization was combined with a base-promoted tandem Michael addition/polycyclization and an acid-catalyzed aromatization. The nonaromatic structure of the Michael adducts might be essential to the realization of the 7-*endo-dig* cyclization.

The rapid and economic construction of architecturally complex molecules from simple aromatic compounds using a dearomatization strategy has been intensively explored and utilized by organic chemists.[1] Recently, dearomatization of aniline derivatives has drawn significant attention.[2] The Kerr,[3] Quideau,[4] and Canesi[5] groups have developed a variety of dearomatization methods to convert anilines into useful molecules. In our previous works, we developed a dearomatization strategy to convert *N*-Ts protected *o*-alkynylanilines to 3,4-dihydro-cyclopenta[*c*,*d*] indoles.[6] Polycyclization is the key step to build the tricyclic structure.[7] In this current study, we have sought to further extend the utility of this process by exploring the dearomatization of β-enamino esters **1**.[8] In particular, we were interested in the selectivity of the reaction between the generated cyclohexadienimine intermediate **2** and activated methylene compounds **3** (Scheme 1).

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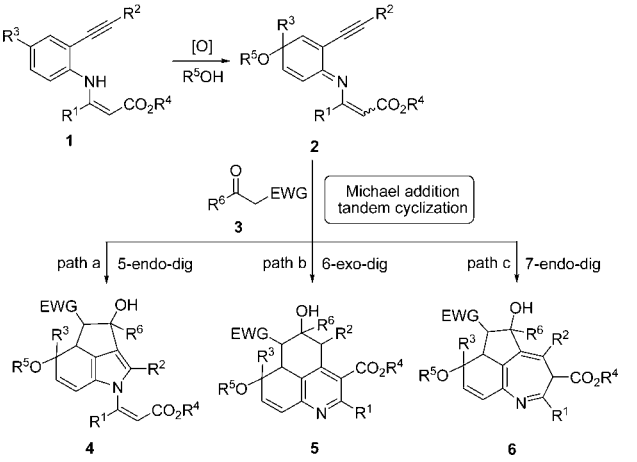
10.1021/ol401553n
Published on Web 06/24/2013

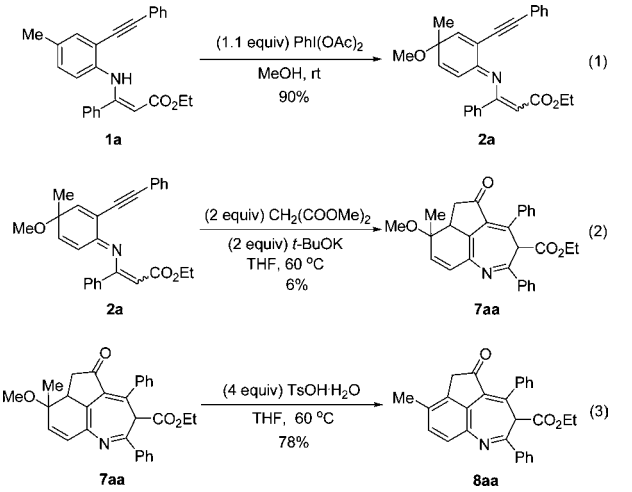
According to our experience,[9] the attack of the activated methylene compounds to cyclohexadienimine might occur at the C-3 position to form a Michael adduct. This intermediate contains two nucleophilic centers in the β-enamino ester moiety: the nitrogen atom and the α-carbon of the α,β-unsaturated system. Potentially, it might undergo a polycyclization via a 5-*endo-dig*,[10] a 6-*exo-dig*,[11] or a 7-*endo-dig* manner to generate compound **4**, **5**, or **6**. Normally, compared with the 5-*endo* or the 6-*exo* cyclization, the 7-*endo* cyclization is often hindered by entropic factors and transannular interactions.[12] Interestingly, in the course of this study, a 7-*endo* process was preferred over the 5-*endo* or the 6-*exo* process.

For the purpose of our investigation, we examined the oxidative dearomatization of β-enamino ester **1a**, which was prepared from the corresponding β-keto ester and 2-alkynyl aniline. When 1.1 equiv of $PhI(OAc)_2$ was used as the oxidant,[13] the dearomatization in methanol gave rise to cyclohexadienimine **2a** in a 90% isolated yield (Scheme 2, eq 1). When the dearomatization was conducted in other organic solvents in the presence of 5 equiv of methanol, cyclohexadienimine **2a** was produced in much lower yields (< 30%). The initial test on the reaction of cyclohexadienimine **2a** with dimethyl malonate using methanol as the solvent and sodium methoxide as the base failed to give any desired annulation products. When THF was used as the solvent, although a complex reaction was observed, the isolated compound was identified as product **7aa** (Scheme 2, eq 2). This product was supposed to be formed from a decarboxylation of the expected product **6aa**. Treatment of compound **7aa** with 4 equiv of 4-methylbenzenesulfonic acid led to an indenoazepine[14] derivative **8aa** (Scheme 2, eq 3). The structure of compound **8aa** was confirmed by its single-crystal diffraction analysis (Figure 1).[15]

Scheme 1. Dearomatization Strategy of β-Enamino Esters



Scheme 2



In an attempt to make this approach more efficient, the tandem Michael addition/polycyclization and the aromatization reaction were combined in one pot. Various bases were used to promote the formation of compound **7aa** (Table 1, entries 1−5). While inorganic bases such as potassium *tert*-butoxide, cesium carbonate, or sodium hydride exhibited higher activities, no reaction was observed when organic bases such as triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were used. For the aromatization reaction, a variety of Brønsted acids or Lewis acids were examined, and $BF_3\cdot Et_2O$ proved to be the best catalyst (Table 1, entries 6−12). A screening of solvents revealed that 1,4-dioxane was the best reaction media for this two-step/one-pot procedure (Table 1, entries 13−17). The best ratio of compound **2a**, dimethyl malonate, sodium hydride, and $BF_3\cdot Et_2O$ was 1:4:3:4, increasing the yield to 83% (Table 1, entry 19).

A possible intermediate was isolated and identified as the Michael adduct **9aa**. When compound **9aa** was treated

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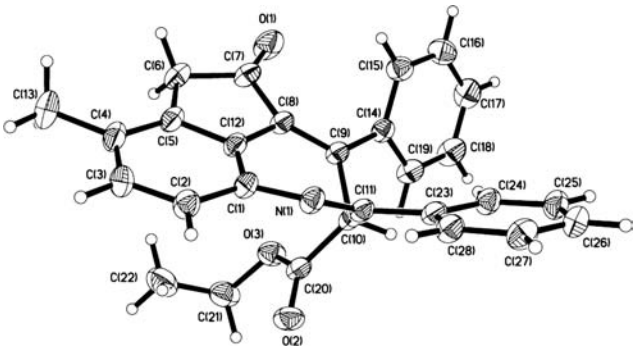
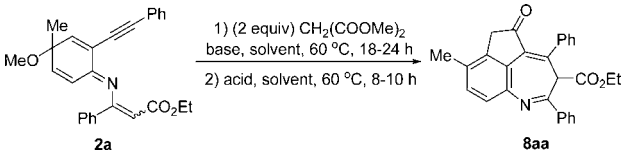


Figure 1. X-ray diffraction structure of compound **8aa**.

Table 1. Evaluation of Conditions for the Two-Step/One-Pot Procedure[a]



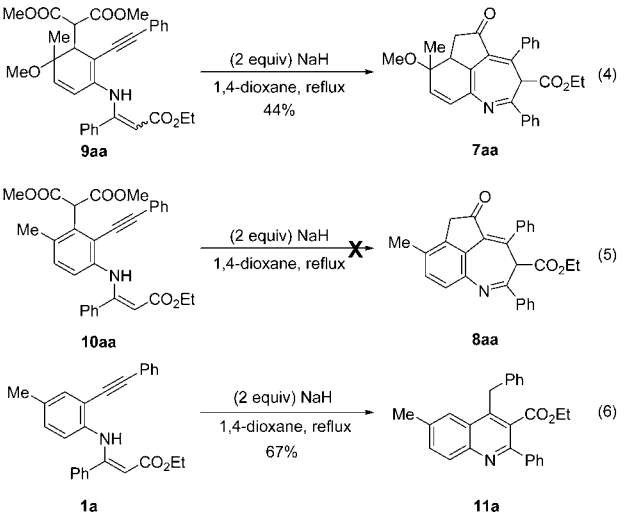
entry	base (equiv)	acid (equiv)	solvent	**8aa** (%)[b]
1	*t*-BuOK (2)	$TsOH·H_2O$ (4)	THF	28
2	Cs_2CO_3 (2)	$TsOH·H_2O$ (4)	THF	43
3	NaH (2)	$TsOH·H_2O$ (4)	THF	44
4	Et_3N (2)	$TsOH·H_2O$ (4)	THF	–[c]
5	DBU (2)	$TsOH·H_2O$ (4)	THF	–[c]
6	NaH (2)	TfOH (4)	THF	12
7	NaH (2)	CH_3COOH (4)	THF	–[d]
8	NaH (2)	$Cu(OTf)_2$ (0.2)	THF	–[d]
9	NaH (2)	$Zn(OTf)_2$ (0.2)	THF	–[d]
10	NaH (2)	AgOTf (0.2)	THF	–[d]
11	NaH (2)	$Bi(OTf)_3$ (0.2)	THF	–[d]
12	NaH (2)	$BF_3·Et_2O$ (2)	THF	53
13	NaH (2)	$BF_3·Et_2O$ (2)	$ClCH_2CH_2Cl$	23
14	NaH (2)	$BF_3·Et_2O$ (2)	toluene	42
15	NaH (2)	$BF_3·Et_2O$ (2)	DMSO	–[e]
16	NaH (2)	$BF_3·Et_2O$ (2)	DMF	–[e]
17	NaH (2)	$BF_3·Et_2O$ (2)	1,4-dioxane	59
18[f]	NaH (2)	$BF_3·Et_2O$ (2)	1,4-dioxane	64
19[f,g]	NaH (3)	$BF_3·Et_2O$ (4)	1,4-dioxane	83

[a] General reaction conditions: reactions performed on 0.2 mmol scale in *t*-BuOH (2 mL). [b] Isolated yield. [c] No reaction was observed, and compound **2a** was recovered. [d] The aromatization was not observed, and compound **7aa** was isolated. [e] The reaction was complex, the formation of compound **7aa** was not observed. [f] The reaction was conducted at reflux. [g] 4 equiv of dimethyl malonate was used.

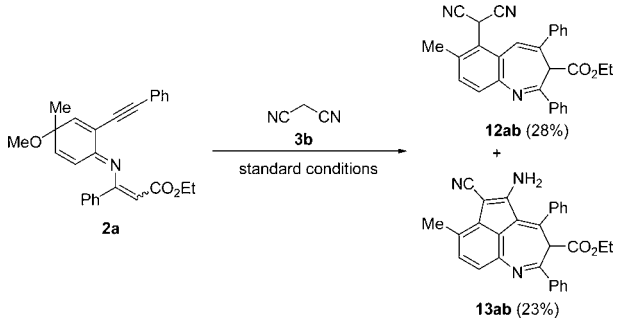
with sodium hydride under the optimized reaction conditions, it could be converted to compound **7aa** (Scheme 3, eq 4). However, its aromatization product **10aa** could not be converted to the desired compound **8aa** under the same conditions (Scheme 3, eq 5). This reaction was complex, and all isolated compounds did not have a seven-membered ring structure. As a control experiment, the cyclization of β-enamino ester **1a** only gave rise to a 6-*exo-dig* cyclization product **11a** (Scheme 3, eq 6).

Moreover, to specify the influence of the second ring closure on the 7-*endo-dig* C-cyclization, malononitrile was used instead of dimethyl malonate. The reaction produced two 7-*endo-dig* cyclization products, benzoazepine **12ab** and indenoazepine **13ab** (Scheme 4). The above results indicated that the nonaromatic structure of the corresponding Michael addition product might be essential to the realization of the 7-*endo-dig* C-cyclization.

Scheme 3. Control Experiments

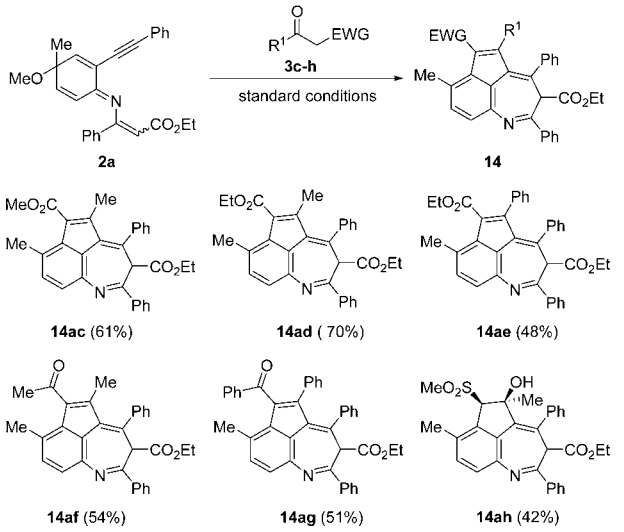


Scheme 4. Reaction between Cyclohexadienimine **2a** and Malononitrile



The reaction using other activated methylene compounds under the optimized conditions afforded the corresponding indenoazepine derivatives in moderate yields (Scheme 5). When acetoacetate or benzoylacetate was used, the second cyclization occurred at the ketone group. The structure of compound **14ah** was confirmed by its single-crystal diffraction analysis (Figure 2).[15] After a workup process to remove methanol and the generated acetic acid, the crude oxidative dearomatization product could be used in the two-step/one-pot reaction (Table 2). For most β-enamino esters, the reaction proceeded smoothly. When the R^2 group was a cyclopropyl group,

Scheme 5. Construction of Indenoazepine Derivatives from Cyclohexadienimine **2** and Activated Methylene Compounds



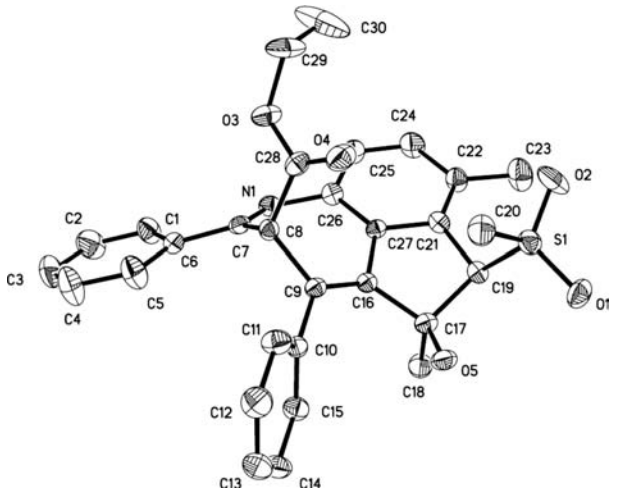
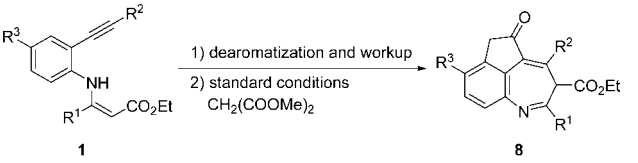


Figure 2. X-ray diffraction structure of compound **14ah**.

or when the R^3 group was a phenyl group, the oxidative dearomatization reaction proceeded well, but the corresponding reaction with dimethyl malonate was complex (Table 2, entries 11 and 14).

Table 2. Substrate Scope Investigation



entry	R^1	R^2	R^3	**8** (%)[a]
1	Ph	Ph	Me	**8aa** (75)
2	4-MeC_6H_4	Ph	Me	**8ba** (71)
3	4-$MeOC_6H_4$	Ph	Me	**8ca** (58)
4	4-ClC_6H_4	Ph	Me	**8da** (81)
5	4-BrC_6H_4	Ph	Me	**8ea** (69)
6	2-BrC_6H_4	Ph	Me	**8fa** (55)
7	CF_3	Ph	Me	**8ga** (40)
8	Ph	4-MeC_6H_4	Me	**8ha** (63)
9	Ph	4-$MeOC_6H_4$	Me	**8ia** (69)
10	Ph	4-ClC_6H_4	Me	**8ja** (45)
11	Ph	cyclopropyl	Me	**8ka** (0)
12	Ph	Ph	Et	**8la** (65)
13	Ph	Ph	*n*-Bu	**8ma** (63)
14	Ph	Ph	Ph	**8na** (0)

[a] Reported yields are of the isolated product based on compound **1**.

In conclusion, we have developed a method to construct indenoazepine derivatives from *β*-enamino esters using a dearomatization strategy. A 7-*endo-dig* polycyclization was the key step. Currently, efforts are focused toward extending its scope and exploring its reaction mechanism and possible synthetic applications, and these results will be reported in due course.

Acknowledgment. Financial support from National Natural Science Foundation of China (No. 21072033) and Shanghai Science and Technology Council (No. 12142200802) are gratefully acknowledged.

Supporting Information Available. Experimental procedures, characterization data, copies of ^1H and ^{13}C NMR of new compounds, and crystallographic data of compounds **8aa** and **14ah** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.