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Three-Component Domino Process for the Pyrrolizine Skeleton via [3 + 2]-Cycloaddition–Enamine Cyclization Triggered by a Gold Catalyst

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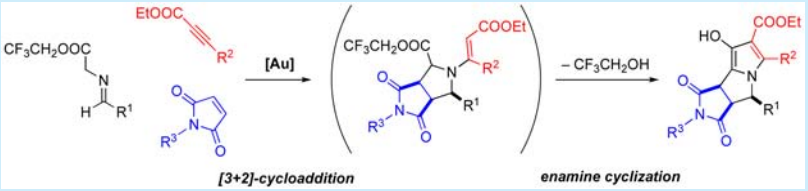
Supporting Information



ABSTRACT: Pyrrolizines are bicyclic fused azaheterocycles with a bridgehead nitrogen contained in a core skeleton and are often found in biologically active compounds. Despite their importance, there have been few reports on concise and flexible syntheses of pyrrolizines. A novel one-pot, convergent method is described for pyrrolizines by simple mixing of iminoesters, acetylenes, and dipolarophiles in the presence of a cationic gold catalyst and an acid additive. This domino process affords multisubstituted pyrrolizines without handling unstable intermediates.

Pyrrolizines are an important class of heterocycles that have a bicyclic 5–5 fused ring system with one nitrogen atom on the bridgehead position. They are widespread in naturally occurring biologically active compounds.[1] For example, antitumor alkaloid retronecine, which was isolated from *Senecio* and *Crotalaria* species, has a partially reduced pyrrolizine core.[1c] Myrmicarins from the poison gland secretions of *Myrmicaria* ants are tricyclic alkaloids containing a fused pyrrolizine skeleton.[2] The structural features of such skeletons attract much attention from medicinal chemists and have been installed in several drugs such as Ketorolac[3] and potential thrombin inhibitors[4] (Figure 1).

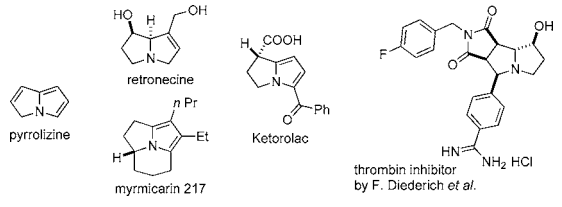
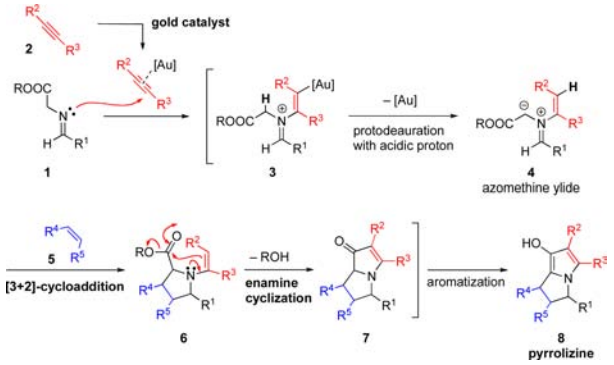


Figure 1. Biologically active pyrrolizines.

As a result of fruitful synthetic endeavors on natural and unnatural pyrrolizines, a number of approaches to such skeletons has been established.[1] Whereas various modes of bond formation could be potentially applied for pyrrolizine syntheses, most of the previous strategies employed monocyclic pyrrolidine derivatives as starting materials and suffered from circuitous reaction steps including protection–deprotection stages for the reactive nitrogen atom. Thus, development of more atom[5] and step economical[6] strategies has been a critical problem for pyrrolizine syntheses. To comply with such requirements, we designed a novel, gold-catalyzed domino reaction[7−9] involving simultaneous formation of four covalent bonds, which enables multicomponent assembly without isolation of any intermediates in a one-pot manner[10] (Scheme 1).

Scheme 1. Strategy for One-Pot, Three-component Pyrrolizine Synthesis via Domino Reaction



Although the various types of gold-catalyzed dipole generation have been reported,[11] we selected iminoesters as a precursor of dipole azomethine ylide for our task. The nitrogen atom on imine **1** attacks the triple bond in **2** activated by the gold catalyst. While vinylgold species usually regenerate the

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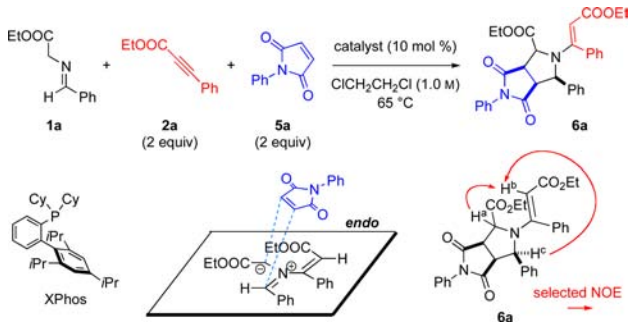
gold catalyst by protodeauration with an acidic proton remaining on the nucleophilic atom, the resulting vinylgold **3**, having no proton on the nitrogen, generates an azomethine ylide **4** and the gold catalyst by protodeauration with the most acidic α-proton of the ester. Ylide **4**, the first reactive intermediate, is immediately captured by dipolarophile **5** via [3 + 2]-cycloaddition, which then generates the second reactive intermediate **6**. Next, the nucleophilic enamine moiety in **6** attacks the pendant ester to cause cyclization with release of ROH, leading to the five-membered vinylogous lactam **7**. Finally, aromatization produces the bicyclic pyrrolizine skeleton **8**. Thus, our blueprint for a domino-type construction of the pyrrolizine skeleton is characterized by two consecutive stages: (1) gold-catalyzed azomethine ylide formation via intermolecular coupling reaction between an iminoester and acetylene, followed by [3 + 2]-cycloaddition; (2) enamine cyclization and subsequent aromatization. The present study revealed optimal reaction conditions for the first stage, and we successfully extended the results for completion of the planned domino process including the second stage to provide multisubstituted pyrrolizines.

We started our investigations using easily prepared and relatively stable benzylidene iminoester **1a**, ethyl phenylpropiolate (**2a**),[12] and *N*-phenylmaleimide (**5a**) as three-component substrates in dichloroethane with catalytic amounts of $(Ph_3P)AuCl$ and AgOTf (Table 1, entry 1). The main

Table 1. Three-Component Coupling between Iminoester 1a, Acetylene 2a, and *N*-Phenylmaleimide (5a)



entry	catalyst	additive (2 equiv)	time (h)	yield (%)
1	$(Ph_3P)AuCl/AgOTf$	–	4	46
2	(XPhos)AuCl/AgOTf	–	3	14
3	$(Ph_3P)Au(NTf_2)$	–	8.5	22
4	$(Ph_3P)AuCl/AgPF_6$	–	4.5	26
5	$(Ph_3P)AuCl/AgBF_4$	–	5.5	34
6	AgOTf	–	4.5	10
7	none	–	11.5	0
8	$(Ph_3P)AuCl/AgOTf$	EtOH	3	29
9	$(Ph_3P)AuCl/AgOTf$	benzoic acid	1.5	69
10	$(Ph_3P)AuCl/AgOTf$	TFA	2.5	0

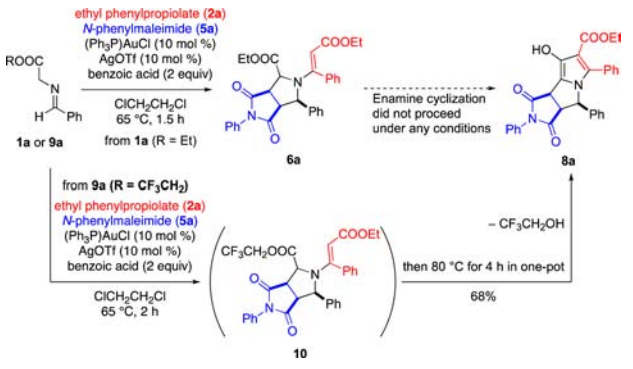
product isolated in 46% yield was the *endo* [3 + 2]-cycloadduct **6a**,[13] the precursor for the desired pyrrolizine. The geometry of enamine in **6a** was determined as the (*E*)-configuration on the basis of NOE experiments between structurally key protons (H^a, H^b, and H^c). Because the second enamine cyclization did not proceed under these conditions, we for a while pursued optimal conditions for the first cyclization stage giving the adduct **6a** triggered by the gold catalyst. With bulkier ligands, the yields of **6a** were reduced significantly (entry 2). Although the counteranion of the cationic gold species was changed to $^-NTf_2$, $^-PF_6$, and $^-BF_4$, the reaction yield did not increase (entries 3–5). The possibility that AgOTf served as the actual catalyst in this reaction was excluded (entry 6), and no desired product was obtained without the catalyst (entry 7). These observations indicated that the cationic gold served as the active catalyst in this transformation.[11d]

Despite making great efforts on the optimization of ligands and counteranions of the gold catalyst, the chemical yield of **6a** still remained moderate. During our investigations, we noticed that the turnover of the gold catalyst was sluggish. Therefore, we noted recent reports on gold-adduct formation, which revealed that nucleophilic enamines easily formed a stable enamine–gold complex.[14] According to these reports, the enamine moiety in our cycloadduct **6a** might inhibit the catalytic turnover. To circumvent such drawbacks in our system, we examined acid additives having various pK_a values aiming at decomposition of the supposed enamine–Au complex (entries 8–10). Finally, benzoic acid was found to be the most effective additive, giving the highest yield of 69% (entry 9).

Thus, we optimized the reaction conditions for the azomethine ylide formation followed by [3 + 2]-cycloaddition (the first stage). However, the enamine cyclization (the second stage) has not been realized thus far. In fact, the enamine product **6a**, isolated from the reaction of **1a** and **2a**, could not participate in further cyclization to form **8a** under any circumstances such as acidic, basic, or heating conditions. To overcome such difficulties, we envisioned that more activated enamino-esters with a highly electron-withdrawing ester moiety could serve as a suitable intermediate for the desired enamine cyclization step. After considerable attempts, we found that utilization of trifluoroethyl iminoester **9a** was critical for our final goal.[15] The reaction of **9a**, **2a**, and **5a** under the optimal conditions for the first stage produced the activated enamino-ester intermediate **10**, which was too unstable for efficient isolation.[16] However, we found that the desired enamine cyclization reaction from **10** efficiently proceeded to furnish the target pyrrolizine skeleton **8a**, simply by raising the reaction temperature to 80 °C from 65 °C. This transformation worked the best in a one-pot manner, and **8a** could be produced in 68% yield from **9a** without isolation of the unstable enamine intermediate **10** (Scheme 2).[17]

Encouraged by our success in the second enamine cyclization employing a trifluoroethyl active ester in a one-pot manner, we examined the three-component domino reaction leading to the pyrrolizine skeleton **8** using various combinations of substrates. As summarized in Scheme 3, the high generality of the one-pot

Scheme 2. Successful Transformation into Pyrrolizine



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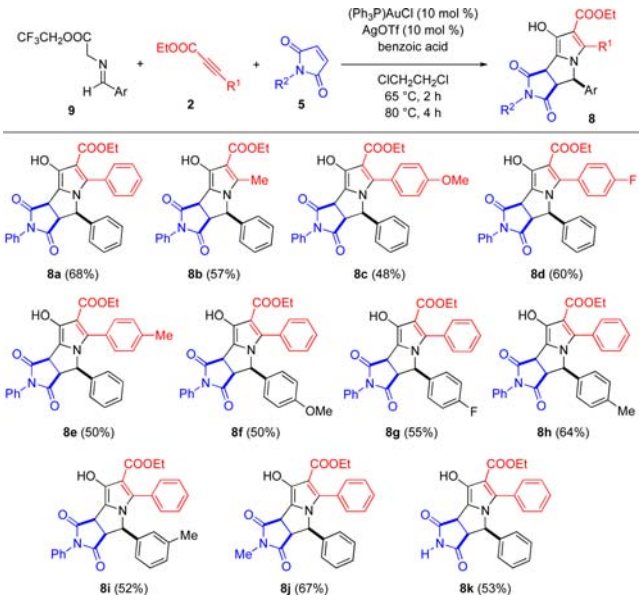
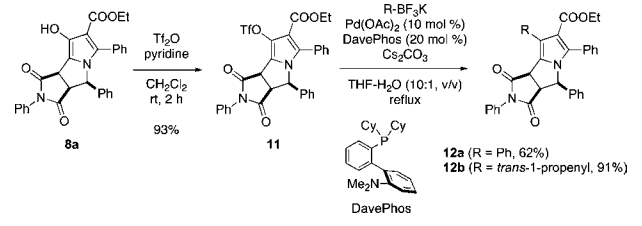
Scheme 3. One-Pot, Three-Component Domino Pyrrolizine Synthesis



domino process was demonstrated with a concise experimental technique, including simply mixing the reagents and then heating at 65 °C for 2 h and then at 80 °C for an additional 4 h. Aromatic and aliphatic propiolates such as alkyne **2**, trifluoroethyl iminoester **9** derived from various aromatic aldehydes, and *N*-substituted and unsubstituted maleimides as dipolarophiles **5** were proven to be applicable for the domino reaction with moderate to good yields.[18] It is important to note that key unstable intermediates involved in this domino process, namely azomethine ylides **4** and activated enaminoesters **10**, are transiently generated and efficiently adopt a tandem bond formation triggered by gold catalysis in a step-by-step manner, without requiring isolation, in the same reaction medium.

Furthermore, we successfully demonstrated that densely carbon-substituted pyrrolizines could be elaborated via versatile carbon−carbon bond formation within a few steps by our strategy. Suzuki−Miyaura coupling of triflate **11**, which was smoothly prepared from pyrrolizine **8a**, with trifluoroborates[19] was quite effective to introduce phenyl- or *trans*-1-propenyl groups on the pyrrolizine core to furnish pyrrolizines **12** (Scheme 4).

Scheme 4. Derivatization of Pyrrolizine 8a



In summary, we achieved a one-pot, convergent, and stereoselective synthesis of multisubstituted pyrrolizines triggered by gold catalysis. This one-pot approach worked quite efficiently to accomplish the atom and step economical domino process without the need to handle unstable intermediates. This method potentially enables flexible installation of substituents on the pyrrolizine core by judicious selection of the three-component combination, namely, easily accessible iminoesters, acetylenes, and dipolarophiles. Further applications of this method for stereoselective syntheses of natural and unnatural biologically active compounds are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectral data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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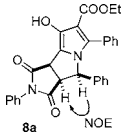
(12) Since Momose and co-workers reported that a electron-rich pyrrole ring with a hydroxy group was highly unstable, we chose acetylene carboxylates for the installation of an electron-withdrawing group on the final pyrrole core. See: Momose, T.; Yanaka, T.; Yokota, T.; Nagamoto, N.; Yamada, K. *Chem. Pharm. Bull.* **1979**, *27*, 1448.

(13) Relative stereochemistries in **6a** were tentatively assigned as shown in Table 1 based on the NOE experiments on **8a** obtained by further cyclization. See ref 16. The relative configuration of the ethoxycarbonyl group on the pyrrolidine ring in **6a** has not been unambiguously determined.

(14) For an enamine−gold complex, see: (a) Liu, X.-Y.; Guo, Z.; Dong, S. S.; Li, Z.-H.; Che, C.-M. *Chem.—Eur. J.* **2011**, *17*, 12932. Unexpected (*E*)-enamine **6a** would be produced by isomerization of (*Z*)-enamine (**6** in Scheme 1) through this enamine−gold complex formation reaction. An enol ether−gold complex was isolated and characterized by X-ray crystallography. (b) Zhu, Y.; Day, C. S.; Jones, A. C. *Organometallics* **2012**, *31*, 7332.

(15) Pentafluorophenyl, *p*-nitrophenyl, and phenyl iminoesters were also examined, but none of them could be synthesized because of their instability.

(16) Because of its instability, relative stereochemistries of **10** were speculated from those of **8a**.



8a

(17) When the whole process was conducted at 80 °C, the reaction was sluggish and gave no desired product **8a**.

(18) The reactions with maleic anhydride, DMAD, and acrylic acid derivatives as a dipolarophile did not give satisfactory results.

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