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Fatih Sirindil, Stéphane Golling, Raphaël Lamare, Jean-Marc Weibel, Patrick Pale, et al.. Synthesis of Indolizine and Pyrrolo[1,2- a]azepine Derivatives via a Gold(I)-Catalyzed Three-Step Cascade. Organic Letters, 2019, 10.1021/acs.orglett.9b03402 . hal-02347330

HAL Id: hal-02347330

<https://hal.science/hal-02347330>

Submitted on 5 Nov 2019

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Synthesis of Indolizine and Pyrrolo[1,2-a]azepine Derivatives via a Gold(I)–Catalyzed 3-Step Cascade

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Supporting Information Placeholder

ABSTRACT: Linear *N*-alkenyl or alkynyl *N*-sulfonyl 1-aminobut-3-yn-2-ones are converted into bicyclic indolizines and pyrrolo[1,2-*a*]azepine-type alkaloids upon gold(I) catalysis (17 examples, 10-85%). The reaction cascade allowed to form C-N, O-S and C-C bonds via a cycloisomerization/sulfonyl migration/cyclization process using 10 mol % of [(2-biphenyl)di-*tert*-butylphosphine]gold(I) triflimide complex in dichloromethane.

Alkaloids constitute a huge family of natural products. Among them, indolizines and their saturated analogs are commonly distributed in nature, especially in plants (Figure 1).¹ These alkaloids exhibit numerous biological activities and have thus been the focus of various synthetic studies and numerous analogs have been produced.² Rosabulin (STA-5312)³ or rhazinilam⁴ are typical examples, developed as anticancer agents possessing a microtubule inhibitor activity. Isolated from the poison gland secretions of *Myrmecaria* ants, the poisonous myrmecarin alkaloid family represent another example.⁵

Figure 1. Representative natural and bioactive products with hydroindolizine or pyrrolo[1,2-*a*]azepine scaffolds.

Although analogs to indolizine derivatives, pyrrolo[1,2-*a*]azepine derivatives are far less represented in nature. Such motif can be found in the large family of *Stemona* alkaloids,⁶ isolated from *Stemonaceae* plants. Used in traditional Chinese medicine to treat bronchitis, tuberculosis

and parasite-induced illness, these alkaloids exhibit diverse physiological properties, as with the antiparasitic parvistemonine A⁷ or the insecticidal dihydrotuberostemonine⁸.

Scheme 1. Synthetic Strategies Towards Ring-Fused Pyrroles via Gold-Catalyzed Cyclisation/*N*-to-*O* Sulfonyl Migration.

Previous work:

This work:

The gold-catalyzed⁹ cyclization-sulfonyl migration cascade¹⁰ we recently developed offers a unique opportunity to design a new synthetic route to indolizine and azepine type alkaloids. This cascade could indeed provide a mild and efficient access to sulfonylated pyrroles (Scheme 1, top) and if the nitrogen atom of the latter carries an unsaturated chain, gold may promote a third step. A cyclization involving the newly created pyrrole and this activated unsaturation would furnish 1-azabicyclo[*n*.3.0]alkane derivatives (*n* = 4 or 5), depending on the chain length (Scheme 1, bottom). Furthermore, the so-formed motif should carry a sulfonate group, allowing for direct modification through Suzuki-Miyaura-type coupling reaction.^{10b}

We report here the implementation of this gold(I)-catalyzed cascade toward the synthesis of substituted and/or functionalized hydroindolizines or pyrrolo[1,2-*a*]jzepines **2** from linear *N*-alkenyl or alkynyl *N*-sulfonyl 1-aminobut-3-yn-2-ones **1**.

Table 1. Optimization of the Reaction Conditions.

Mbs = 4-methoxybenzenesulfonate

entry	catalyst (mol %)	yield 2a+3a (%) ^a	ratio 2a:3a ^b
1	Ph ₃ PAuNTf ₂ (5)	57	0:100
2	(C ₆ F ₅) ₃ PAuNTf ₂ (5)	13	0:100
3	[(2,4- <i>t</i> BuPhO) ₃ P Au(MeCN)]NTf ₂ (5)	18	0:100
4	IPrAuNTf ₂ (5)	44	33:67
5	[IPrAu(MeCN)] [PMo ₁₂ O ₄₀][H ₂] (5)	27	100:0
6	XPhosAuNTf ₂ (5)	19	100:0
7	CyJohnPhosAuNTf ₂ (5)	55	90:10
8	JohnPhosAuNTf ₂ (5)	72	90:10
9	JohnPhosAuCl/AgSbF ₆ (5)	24	100:0
10	JohnPhosAuNTf ₂ (10)	81	100:0

^aCalculated yield from ¹H NMR integration relative to an internal standard (dimethyl terephthalate). ^bThe ratio was determined from the ¹H NMR spectrum of crude reaction.

For the screening of the reaction conditions, we selected the *N*-pent-4-enyl *N*-4-methoxybenzenesulfonyl 1-aminobut-3-yn-2-one **1a**, readily prepared in 4 steps from methyl glycinate (see Supporting Information). **1a** was submitted to different gold complexes as catalyst (Table 1). Previously reported to promote the cyclization-sulfonyl migration reaction,¹⁰ the Gagosz catalyst¹¹ only provided the pyrrole intermediate **3a** in dichloromethane at 40°C (entry 1). The more electron withdrawing tri-(fluorophenyl)phosphine analog as well as a phosphite analog also gave the sole pyrrole **3a**, but in low yields (entries 2-3). Gold carbene complexes allowed reversing the selectivity, with a surprisingly dramatic effect of the counterion. Indeed, with a triflimide, a mixture of pyrrole **3a** and the expected bicyclic product **2a** was produced in a 1:2 ratio, while with a polyoxometalate as anion,¹² only the expected bicyclic product was observed, unfortunately in modest yield along with degradation products (entry 4 vs 5). Shifting to Buchwald-type ligand also reversed the selectivity but with more interesting results. The large XPhos ligand promoted the sole formation of the bicyclic product **2a**, but again with modest yield (entry 6). Using the less hindered CyJohnPhos ligand increased the reactivity and the overall yield but with a slightly lower selectivity (entry 7 vs 6). Switching to JohnPhos ligand with different steric parameter¹³ rewardingly provided even higher reactivity and yield, in favor of the expected bicyclic product **2a**, but again not fully selectively (entry 8). Changing the NTf₂ anion to SbF₆ increased the selectivity, with only the

bicycle formed, but to the detriment of yields (entry 9). Unfortunately, the compounds **2a** and **3a** were inseparable by chromatography. Therefore, we tried to improve the selectivity by performing the reaction with 10 mol % of JohnPhosAuNTf₂ catalyst (entry 10) and we were pleased to obtain **2a** with a total selectivity and with high yield. This catalyst was thus used for exploring the scope of this reaction.

With the optimized conditions in hand, various substrates carrying *N*-alkenyl or *N*-alkynyl chain were prepared **1a-p** (see Supporting Information) and engaged in the new gold-catalyzed cycloisomerization-sulfonyl migration-cyclisation cascade (Scheme 2).

Scheme 2. Reaction Scope of the Cascade with Terminal *N*-Alkenyl or Alkynyl *N*-Sulfonyl 1-Aminobut-3-yn-2-one Derivatives **1**.^a

^aReactions run at 40°C for *N*-alkenyl derivatives or at room temperature for *N*-alkynyl derivatives, c = 0.1 mol/L. ^bIsolated along 10% of pyrroles intermediate **3d** (See Supporting Information). ^cCalculated yield from ¹H NMR integration relative to an internal standard (dimethyl terephthalate). ^dPartial degradation occurs during purification. ^eDegradation occurs. ^fCumulative yield with the exo-methylene product.

Considering the importance of the sulfonyl group for the migration step,^{10a,14} its influence was first examined. As shown with *N*-pent-4-enyl substrates **1a-c**, the *para*-methoxybenzenesulfonate (Mbs) gave the best result, providing the expected bicycle **2a** in high yield. In contrast, the tosylate (Ts) and mesylate (Ms) derivatives **1b-c** furnished, after 20 h at 40 °C, mostly the bicyclic products **2b**

and **2c** in an average yield of 60% but together with 5% of pyrrole intermediates **3**. The Mbs sulfonate was thus used to explore functional compatibility.

With a phenyl group as substituent of the alkyne, the cascade proceeded as well, but the conjugation of this group to the formed pyrrole **3d** lowered the nucleophilicity of this pyrrole, and thus some pyrrole was left, lowering the yield of the expected bicyclic product **2d**. The substrates **1e** and **1f**, possessing respectively electron withdrawing (Cl) or donating (OMe) groups on the aryl part, were more problematic. Indeed, the tetrahydroindolizine **2e** was only obtained in low yield along with many degradation products, while compound **2f** proved highly instable and could only be isolated in modest yield, despite a clean reaction observed by NMR.

With a protected hydroxy group, the cascade was very effective, only giving the corresponding bicycle **2g** in high yield, but only when this functional group is remote from the alkyne moiety. When such functional group is at the propargylic position, degradation occurred (**2h** vs **2g**).

N-Alkynyl chains were then evaluated. Substrates carrying such chain proved more reactive and the reactions were conducted at room temperature. The *N*-pent-4-ynyl chain induced a 6-*exo-dig* cyclization in good yield with the Mbs derivative **1i**, but in modest yield with the *N*-tosyl analog **1j**. Structural analysis of these products revealed that the resulting double bond in such products was internal to the newly created cycle, despite *exo*-cyclization. This could be the result of double bond migration, probably assisted by the catalyst. Interestingly, the longer *N*-hex-4-ynyl chain also allowed *exo-dig* cyclization, which provided in good yields dihydropyrrolo[1,2-*a*]azepine compounds **2k-p**, here again after double bond migration. As in the *N*-alkenyl series, changing the tosylate or mesylate for the *para*-methoxybenzenesulfonate improved the cyclization efficiency and yield (**2k** vs **2l-m**). Modification of the ynone was perfectly tolerated as attested by the good yields obtained for bicyclic products **2n-p**. It is worth noticing that in this *N*-alkynyl series, the bicyclic products contain a double bond, which can be further functionalized.

The influence of the chain length as well as the substitution of the alkene or alkyne function were then investigated (Scheme 3). With a shorter *N*-but-4-enyl chain, the substrates **1q** and **1r** still provide the tetrahydroindolizine system, although in modest yields. The cyclization still proceeded, but in a 6-*endo-trig* process instead of the 6-*exo-trig* cyclisation observed with the *N*-pent-4-enyl chain. With the longer *N*-hex-4-enyl chain (**1s**) or with substituted alkene such as in the (*E*)-*N*-(hex-4-en-1-yl) chain (**1t**), the cascade stopped at the pyrrole stage and no bicyclic product could be detected.

The *N*-but-4-ynyl chain (**1u**) also allowed a 6-*endo-dig* cyclization, but in very low yield mostly due to the high instability of the so-formed dihydroindolizine **2u**. However, the cascade was efficiency restored with internal alkynes (**1v-w**), as showed by the formation of the expected dihydroindolizines **2v** and **2w** in good yields.

Scheme 3. Synthesis of Indolizine Derivatives from Linear *N*-Enyl or Ynyl *N*-Sulfonyl 1-Aminobut-3-yn-2-ones **1q-v** and Limitations.^a

^a*c* = 0.1mol/L. ^bCumulative yield of inseparable **2q** and **3q** derivatives. ^cDegradation occurs. ^dCalculated yield from ¹H NMR integration relative to an internal standard (dimethyl terephthalate).

The mechanism of this cascade was postulated to begin by the π -activation of the ynone substrate **1** by gold(I) catalyst (Scheme 4). Intramolecular ammonium formation of the alkyne¹⁵ could then occur leading to the transient vinylgold ammonium intermediate **A**. At this stage, the intramolecular sigmatropic *N*-to-*O* migration of the sulfonyl group took place affording the sulfonylated pyrrole intermediate **B**.¹⁰ Finally, the nucleophilic addition of the electron-rich pyrrole motif to the remaining unsaturation activated by gold furnished the bicyclic product **2**.¹⁶ Further isomerization of the double bond also occurred when starting from *N*-alkynyl substrates.

Scheme 4. Proposed Mechanism for the Formation of Indolizine and Pyrrolo[1,2-*a*]azepine via Gold(I)-Catalyzed Cascade.

In conclusion, we developed a new 3 step gold-catalyzed cascade from readily available compounds derived from glycine. The cycloisomerization of *N*-alkenyl or alkynyl *N*-sulfonyl 1-aminobut-3-yn-2-ones followed by a *N*-to-*O* sulfonyl migration provided *N*-alkenyl or alkynyl pyrrolyl sulfonates and a further cyclization afforded functionalized

indolizines or pyrrolo[1,2-a]azepines in good to high yields.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.
Experimental details, copies of spectra (PDF).

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We gratefully acknowledge the French Ministry of Research and the CNRS for financial support. The authors thank Delphine Hatey (Institut de Chimie, University of Strasbourg) for the preparation of compound **1p**. F. S. thanks the French Ministry of Research for PhD fellowship.

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