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A Gold(I)-Catalyzed Hydroamination/Cycloisomerization Cascade: Concise Synthesis of (±)-seco-Antofine and (±)-Septicine

Guilong Tian, Liangliang Song, Zhenghua Li, Koen Robeyns, Luc Van Meervelt, and Erik V. Van der Eycken*

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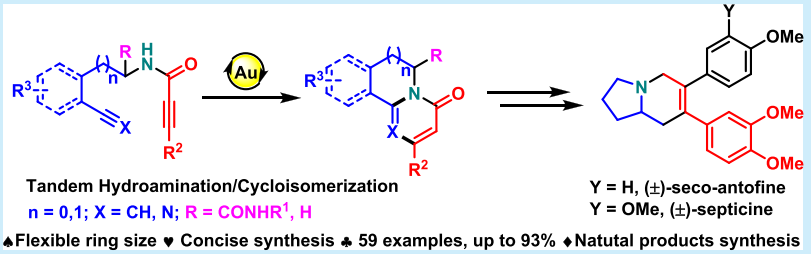

ABSTRACT: A concise and flexible procedure for the synthesis of highly functionalized N-heterocyclic 1,6-annulated 2-pyridones and 2,3-annulated 4-pyrimidinones has been elaborated through a gold-catalyzed tandem hydroamination/cycloisomerization cascade. This novel and highly efficient method allows the rapid construction of these diverse N-heterocyclic scaffolds starting from readily available building blocks, and shows a wide scope and good functional group tolerance. The total synthesis of (±)-seco-antofine and (±)-septicine were realized employing this strategy.

Natural products as the inspiration and the starting point of novel drugs have attracted medicinal chemists' attention.[1] However, many initial drug development studies with natural products failed, because of their poor solubility and unpredictable toxicity.[2] Molecules with the same key scaffold potentially have similar biological or physicochemical activity.[3] As a consequence, the development of practical methods for the synthesis of scaffolds present in pharmacologically potent compounds led to the successful finding of novel drug candidates.[4]

The 1,6-annulated 2-pyridone and 2,3-annulated 4-pyrimidinone skeletons are common in bioactive natural products[5] and many pharmacologically potent compounds.[6] They show a diversity of bioactive properties such as antitumor, antimicrobial, anti-inflammatory, cardiotonic, antiviral, and antimalarial activity.[7] These scaffolds are also important intermediates in many organic transformations.[8] A series of methods have been developed for the synthesis of 1,6-annulated 2-pyridones and 2,3-annulated 4-pyrimidinones[9] such as intramolecular nucleophilic substitution, radical cyclization, intramolecular alkenylation, and intramolecular Heck reaction. Most of these methods involve the modification of 2-pyridone or 4-pyrimidinone derivatives limiting the synthetic potential of these scaffolds. Moreover, most of the reported procedures need multiple steps, and only in a few cases the direct synthesis of the 1,6-annulated 2-pyridone and the 2,3-annulated 4-pyrimidinone scaffolds is described from scratch.[10] Therefore, new concise and flexible methods for the synthesis of these scaffolds, from simple starting materials, are highly desirable.

Recently, homogeneous gold catalysis has been successfully applied for the construction of C−C(hetero) bonds.[11] Furthermore, the arsenal of tandem cyclization protocols to synthesize structurally complex molecules and natural products has been expanded tremendously through the employment of gold catalysis.[12] In this regard, our research group has explored new effective strategies based on the combination of multicomponent reactions and tandem gold catalysis, for the diversity-oriented construction of various *N*-heterocyclic scaffolds, starting from readily available building blocks.[13]

Based on our knowledge and experience in this field, we combined a gold-catalyzed tandem cyclization for the synthesis of 1,6-annulated 2-pyridones and 2,3-annulated 4-pyrimidinones, as outlined in Scheme 1b. An intramolecular tandem hydroamination/cycloisomerization process is envisaged, starting from diverse precursors which can be easily prepared by Ugi four-multicomponent reaction (Ugi-4CR) or the condensation of alkynoic amine and propiolic acid.[14]

We started our investigation using *N*-(2-ethynylbenzyl)-propiolamide **1aa** as a model substrate, which is readily furnished through Ugi-4CR of 2-ethynylbenzaldehyde, ammo-

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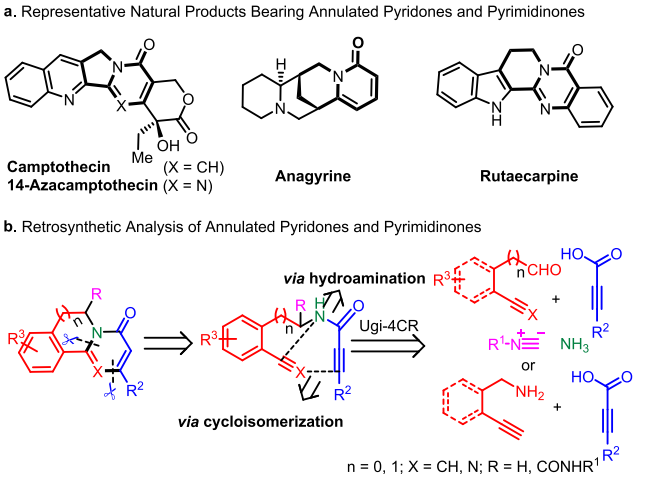
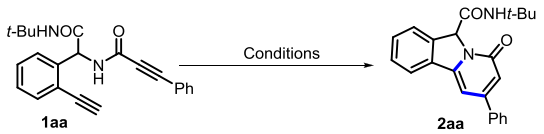
Scheme 1. Representative Natural Products and Retrosynthetic Analysis for the Core Scaffolds



nia, *tert*-butyl isocyanide, and phenylpropiolic acid. Initially, the screening of various gold catalysts such as AuCl, $AuCl_3$, and *in situ* generated $Ph_3PAuOTf$, IPrAuOTf, and JohnPhosAuOTf (Table 1, entries 1−5) showed that IPrAuOTf gave the desired

Table 1. Optimization of Reaction Condition[a]



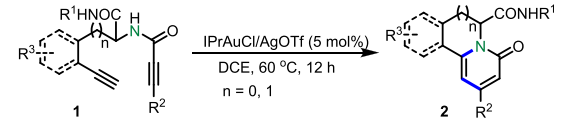
entry	catalyst	solvent	T (°C)	t (h)	yield of **2aa** (%)[b]
1	AuCl	DCE	60	12	26
2	$AuCl_3$	DCE	60	12	<10
3	$Ph_3PAuCl/AgOTf$	DCE	60	12	39
4	**IPrAuCl/AgOTf**	**DCE**	**60**	**12**	**75**
5	JohnPhosAuCl/AgOTf	DCE	60	12	56
6	IPrAuCl/AgOTf	Toluene	60	12	42
7	IPrAuCl/AgOTf	MeCN	60	12	55
8	IPrAuCl/AgOTf	Dioxane	60	12	31
9	IPrAuCl/AgOTf	THF	60	12	21
10	IPrAuCl/AgOTf	DCM	60	12	50

[a]Unless otherwise stated, all reactions were run with 0.05 mmol of Ugi adduct **1aa**, 5 mol % of catalyst, and 1.0 mL of solvent in a sealed flask. [b]Isolated yields. DCE = 1,2-dichloroethane; OTf = trifluoromethanesulfonate; IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; JohnPhos = (1,1′-biphenyl-2-yl)di*tert*-butylphosphine.

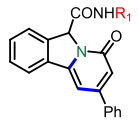
1,6-annulated 2-pyridone **2aa** in the highest yield of 75% (Table 1, entry 4). No amelioration was observed when changing the solvent to toluene, MeCN, dioxane, THF, or DCM (Table 1, entries 6−10).

Next, various *N*-alkynic 2-ynamides **1** assembled by Ugi-4CR were subjected to the optimal conditions for the evaluation of the scope and limitations (Table 2). First, the effect of the R^1-substituent resulting from the isonitrile was evaluated. While employing bulky groups like adamantyl and 1,1,3,3-tetramethylbutyl (TMB), the tandem process performed smoothly and gave the 1,6-annulated 2-pyridone **2ab** and **2ac** in good yields. However, slightly lower yields were observed in the case of less bulky groups like cyclohexyl, naphthyl, and benzyl (**2ad**−**af**).

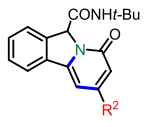
Table 2. Scope of Tandem Cyclization Process for the Synthesis of 1,6-Annulated 2-Pyridones[a]



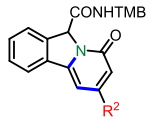
n = 0



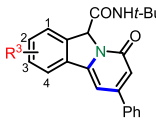
2ab, R^1 = admantyl, 91%
2ac, R^1 =TMB, 86%
2ad, R^1 = Cy, 72%
2ae, R^1 = Nap, 74%
2af, R^1 = Bn, 62%



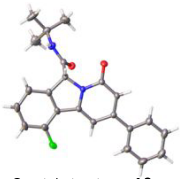
2ag, R^2 = H, 25%
2ah, R^2 = Me, 31%
2ai, R^2 = Et, 42%
2aj, R^2 = *n*-Pr, 56%
2ak, R^2 = *n*-Pentyl, 61%
2al, R^2 = 2-Thiophene, 72%



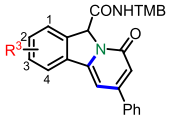
2am, R^2 = H, 42%
2an, R^2 = Me, 51%
2ao, R^2 = Et, 66%
2ap, R^2 = *n*-Pr, 72%
2aq, R^2 = *n*-Pentyl, 77%
2ar, R^2 = *p*-MePh, 93%
2as, R^2 = *p*-ClPh, 73%
2at, R^2 = 2-Thiophene, 82%



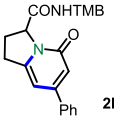
2au, R^3 = 1-F, 69%
2av, R^3 = 2-F, 71%
2aw, R^3 = 3-F, 66%
2ax, R^3 = 4-F, 70%
2ay, R^3 = 2-Cl , 66%
2az, R^3 = 2-Br, 61%
2ba, R^3 = 2-OMe, 56%
2bb, R^3 = 2,3-di-OMe, 32%
2bc, R^3 = 2,3-OCH_2O-, 46%



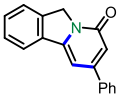
Crystal structure of **2ax**



2bd, R^3 = 1-F, 82%
2be, R^3 = 2-F, 80%
2bf, R^3 = 3-F, 84%
2bg, R^3 = 4-F, 79%
2bh, R^3 = 2-Cl, 89%
2bi, R^3 = 2-Br, 85%
2bj, R^3 = 2-OMe, 75%
2bk, R^3 = 2,3-di-OMe, 46%
2bl, R^3 = 2,3-OCH_2O-, 61%

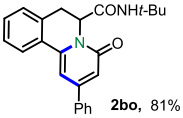


2bm, 61%

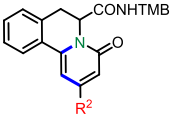


2bn, 85%

n = 1



2bo, 81%



2bp, R^2 = Ph, 85%
2bq, R^2 = *p*-MePh, 89%
2br, R^2 = *n*-Pr, 71%
2bs, R^2 = *n*-Pentyl, 78%
2bt, R^2 = 2-Thiophene, 80%

[a]Unless otherwise stated, all reactions were run with 0.1 mmol of **1ab**-**bt**, 5 mol % of IPrAuCl/AgOTf, and 2.0 mL of DCE at 60 °C in a sealed flask for 12 h; all yields are isolated yields. TMB = 1,1,3,3-tetramethylbutyl; Nap = naphthalenyl.

Then, the effect of the R^2-substituent on the 2-ynamide was examined. Switching a small hydrogen (**2ag** and **2am**) into a larger alkyl or aryl substituent (**2ah**−**al** and **2an**−**at**) resulted in an increase of the yield. The application of electron-rich (hetero)arene groups such as phenyl or thiophene (**2al** and **2ar**−**at**) conjugated with the 2-ynamide resulted in reasonable good yields.

Examination of the effect of the R^3-substituent on the benzene ring of the phenylacetylene fragment revealed no significant influence in the case of halides (**2au**−**az** and **2bd**−**bi**) while the employment of electron-rich groups yielded the compounds **2ba**−**bc** and **2bj**−**bl** in decreased yields. The structure of compound **2ax** was confirmed by X-ray diffraction. The substrate **1bm** derived from 4-pentynal successfully underwent the tandem cyclization resulting in the formation of the 1,6-annulated 2-pyridone **2bm** in 61% yield. In addition, the

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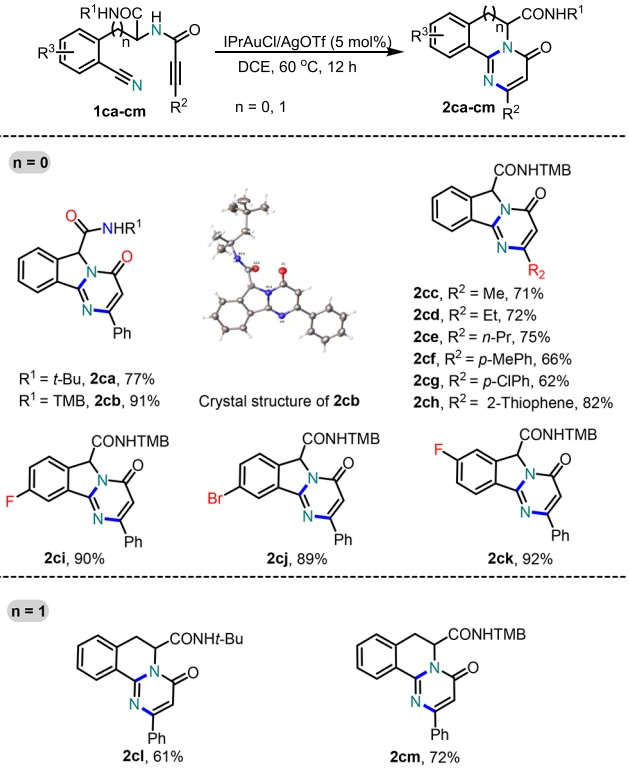
substrate **1bn** lacking the amide chain provided the 1,6-annulated 2-pyridone **2bn** in 85% yield. Then this gold-catalyzed hydroamination/cycloisomerization process was also applied to the Ugi adducts **1bo−bt** derived from 2-(2-ethynylphenyl)acetaldehydes with the aim of constructing a library of pyrido[2,1-*a*]isoquinolin-4-ones (*n* = 1, Table 2). To our satisfaction, this process worked well with various aliphatic and aromatic substituents on the 2-ynamide moiety, affording the targeted 1,6-annulated 2-pyridones **2bo−bt** in good yields of 71−89%.

For the synthesis of diverse 2,3-annulated 4-pyrimidinones, we next planned to use the Ugi adducts **1ca−cm** assembled from 2-formylbenzonitrile and 2-(2-oxoethyl)benzonitrile. As summarized in Table 3, treatment of various substrates under the

Table 3. Scope of Tandem Cyclization Process for the Synthesis of 2,3-Annulated 4-Pyrimidinones[a]

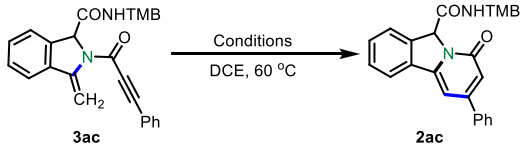


[a]Unless otherwise stated, all reactions were run with **1ca−cm**, (0.1 mmol), 5 mol % of IPrAuCl/AgOTf, and 2.0 mL of DCE at 60 °C in a sealed flask for 12 h; all yields are isolated yields. TMB = 1,1,3,3-tetramethylbutyl.

optimal conditions smoothly produced the desired fused 2,3-annulated 4-pyrimidinones **2ca−cm** in moderate to good yields. In particular, substrates bearing an alkyl or an aryl substituent on the 2-ynamide are compatible, yielding the products **2cc−ch** in 62−82%. A high tolerance for halides (F and Br) on the benzonitrile moiety was observed (**2ci−ck**). The substrates **1cl** and **1cm** derived from the 2-(2-oxoethyl)benzonitrile, successfully gave **2cl** and **2 cm** in 61% and 72% yield, respectively. The structure of compound **2cb** was confirmed by X-ray crystallography.

We propose compound **3ac** is an intermediate for the tandem cyclization. To shed light on the reaction process, treatment of compound **3ac** with IPrAuCl/AgOTf (5 mol %) in DCE (1,2-dichloroethane) at 60 °C for 12 h delivered the desired product **2ac** in 92% yield (Scheme 2). This indicates that the first step of this tandem process is a hydroamination of the alkyne or cyanide

Scheme 2. Mechanism Study[a]



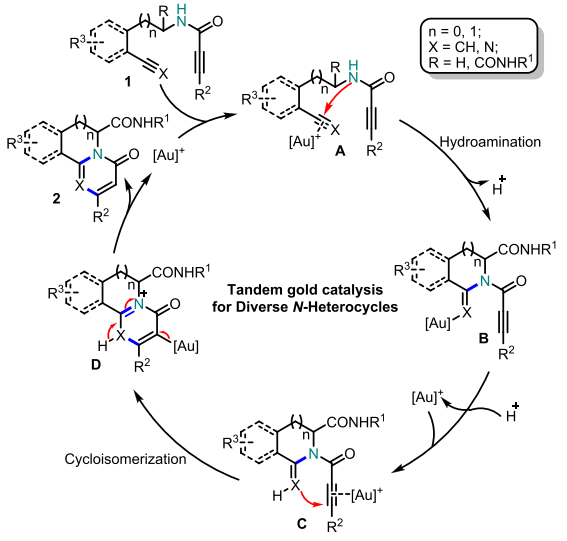
Condition **A**: IPrAuCl/AgOTf (5 mol%)	92%[b]
Condition **B**: AgOTf (5 mol%)	43%[b]
Condition **C**: IPrAuCl (5 mol%)	0
Condition **D**: HOTf (5 mol%)	0
Condition **E**: NaOTf (5 mol%)	0
Condition **F**: none	0

[a]The reaction was run on a 0.05 mmol scale. [b]Isolated yield. TMB = 1,1,3,3-tetramethylbutyl.

and the compound **3ac** is an intermediate of the tandem process. When AgOTf was utilized as a catalyst, the reaction delivered **2ac** in only a moderated yield (Condition **B**). No conversion was observed when IPrAuCl was utilized as catalyst (Condition **C**). Neither HOTf (5 mol %) nor NaOTf (5 mol %) can catalyze the reaction (Condition **D**, **E**). These results indicate that the cationic gold catalyst is the real catalyst for the cycloisomerization.

Based on these observations and previous reports,[15,16] a plausible mechanism for this gold(I)-catalyzed tandem hydroamination/cycloisomerization process is depicted in Scheme 3.

Scheme 3. Plausible Mechanism of Gold(I)-Catalyzed Hydroamination/Cycloisomerization Process



First, the intramolecular hydroamination of the gold π- activated terminal alkyne (X = CH) or nitrile group (X = N) occurs in an *exo*-dig fashion producing the isoindoline (*n* = 0) or isoquinolinone (*n* = 1) intermediate **B**, which upon protodeauration gives *N*-alkenyl or *N*-(iminomethyl) alkynylamide intermediate **C**.[11] Subsequently, the second annulation of the newly formed double bond with the cationic gold π-activated alkyne of the 2-ynamide occurs, delivering iminium intermediate **D**,[12] which after isomerization and protodeauration affords 1,6-annulated 2-pyridones or 2,3-annulated 4-pyrimidinones.

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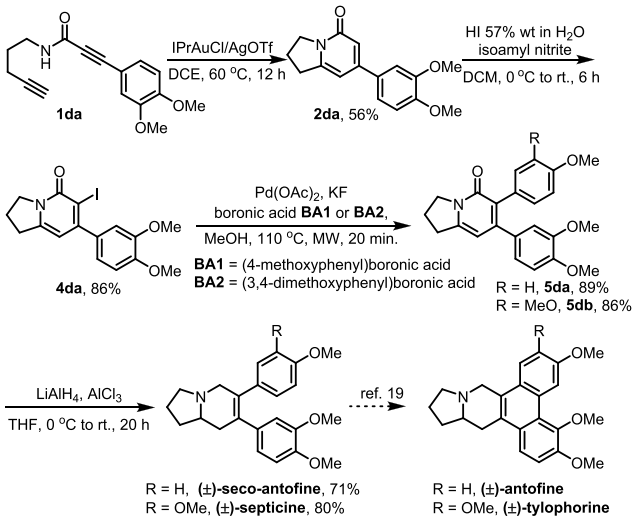
The alkaloids (±)-seco-antofine and (±)-septicine have interesting physiological effects on the respiratory system as well as antibiotic, antileukemic, and anticancer activity (Scheme 4).[17] To demonstrate the utility of our method, we prepared

Scheme 4. Total Synthesis of (±)-seco-Antofine and (±)-Septicine



these alkaloids using the tandem cyclization as a key step. 1,6-Annulated 2-pyridone **1da** was synthesized in 56% yield employing the optimized conditions. Selective iodination of the 2-pyridone ring and subsequent Suzuki cross-coupling generated intermediates **5da** and **5db** in good yields. Reduction under Moore's conditions delivered (±)-seco-antofine and (±)-septicine, respectively.[18] These two alkaloids could be converted into (±)-antofine and (±)-tylophorine as described in the literature.[19]

In conclusion, we have designed a novel and highly efficient tandem process for the synthesis of diverse 1,6-annulated 2-pyridones and 2,3-annulated 4-pyrimidinones. First, the Ugi-4CR, which generates diversity into the molecule from readily available starting materials, is performed. Next, an efficient gold(I)-catalyzed tandem hydroamination/cycloisomerization process leads to the formation of highly functionalized *N*-heterocyclic scaffolds. The wide substrate scope, the high functional group tolerance, and the operational simplicity of this protocol render this method an attractive way to generate these interesting scaffolds. Further, we utilized this tandem cyclization process as the key step for the synthesis of (±)-seco-antofine and (±)-septicine in a concise way.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03062.

Experimental procedures, characterization data, and copies of NMR spectra for all compounds (PDF)

Accession Codes

CCDC 1850841 and 2007686 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Erik V. Van der Eycken − *Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC) Department of Chemistry, KU Leuven, B-3001 Leuven, Belgium; Peoples' Friendship University of Russia (RUDN University), Moscow 117198, Russia;* orcid.org/0000-0001-5172-7208; Email: erik.vandereycken@kuleuven.be

Authors

Guilong Tian − *Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC) Department of Chemistry, KU Leuven, B-3001 Leuven, Belgium*

Liangliang Song − *Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC) Department of Chemistry, KU Leuven, B-3001 Leuven, Belgium*

Zhenghua Li − *Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC) Department of Chemistry, KU Leuven, B-3001 Leuven, Belgium*

Koen Robeyns − *IMCN, Molecules Solids and Reactivity division (MOST), Université Catholique de Louvain, B-1348 Louvain-la-Neuve, Belgium*

Luc Van Meervelt − *Biomolecular Architecture, Department of Chemistry, KU Leuven, B-3001 Leuven, Belgium;* orcid.org/0000-0003-2186-5209

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c03062

Notes

The authors declare no competing financial interest.

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