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Gold-catalyzed [4+3]- and [4+2]-annulations of 3-en-1-ynamides with isoxazoles *via* novel 6π -electrocyclizations of 3-azahepta trienyl cations[†]

New gold-catalyzed [4+3]-annulations of 3-en-1-ynamides with isoxazoles afford 4*H*-azepines efficiently; this process involves 6π electrocyclizations of gold-stabilized 3-azaheptatrienyl cations. In the presence of Zn(OTf)₂, the resulting 4*H*-azepines undergo skeletal rearrangement to furnish substituted pyridine

derivatives. We subsequently develop new catalytic [4+2]-annulations between the same 3-en-1-

ynamides and isoxazoles to deliver substituted pyridine products using Au(1)/Zn(11) catalysts. This work

reports the first success of the 6π electrocyclizations of heptatrienyl cations that are unprecedented in

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Introduction

Electrocyclizations of acyclic conjugated π -motifs are powerful tools to access five-, six- and seven-membered carbocycles;¹ prominent examples include Nazarov cyclizations of pentadienyl cations² and 6π electrocyclizations of trienes,³ which have found widespread applications in organic synthesis.

literature reports.



Scheme 1 Electrocyclizations of conjugated π -motifs.

In the context of seven-carbon π -motifs, heptatrienyl anions I undergo facile 8π electrocyclizations *via* rapid interconversions among various anion configurations (Scheme 1).⁴ In contrast, heptatrienyl cations III⁵ exclusively undergo Nazarov reactions because of the difficulties of forming all σ -*cis* configured cations V that have a high energy state.^{5b} 1-Aza- and 1-oxaheptatrienyl cations⁶ were also reported to follow Nazarov cyclizations. The realization of a 6π electrocyclization of conjugated seven-membered cations is formidable but challenging. This work reveals the first success of such seven-membered cyclizations of gold-stabilized 3-azaheptatrienyl cations V' to form azacyclic products 3–4 *via* a new C–C bond formation.

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The advent of gold catalysis has inspired new annulations between alkynes and poor nucleophiles.⁷ N–O containing nucleophiles serve as useful building blocks to construct valuable azacyclic frameworks.⁷ Ye and Hashmi reported interesting [3+2]-annulations of isoxazoles or benzisoxazoles with electron-

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rich ynamides, yielding substituted pyrrole derivatives through aza-Nazarov cyclizations of the key intermediate [eqn (1)].^{7,8} These [3+2]-annulations were extensively expanded to other N–O heterocycles including benzisoxazoles, 1,2,4-oxadiazoles, 1,4,2-dioxazoles and 4,5-dihydro-1,2,4-oxadiazoles, yielding additional five-membered azacycles as depicted in [eqn (1)].⁹ Here, we report two distinct [4+3]- and [4+2]-annulations between 3-en-1-ynamides and isoxazoles using varied catalysts. An Au(1) catalyst alone delivers 4*H*-azepines 3–4 through 6π electrocyclizations of intermediates V' [eqn (2)] whereas a combined action of Au(1)/Zn(π) on the same reactants furnishes highly functionalized pyridines 5 [eqn (3)]. With our convenient synthesis, the synthetic utility of new 4*H*-azepines 3–4 is also reported.¹⁰

Results and discussion

We examined the reactions of 3-methyl-3-en-1-ynamide **1a** with 3,5-dimethylisoxazole **2a** using various gold catalysts. Heating this mixture (1a/2a = 1 : 2 ratio) in hot DCE with 5 mol% LAuCl/AgNTf₂ [L = $p(t\text{-Bu})_2(o\text{-biphenyl})$ and IPr] afforded a [4+3]-annulation product, 4*H*-azepine **3a**, in 64% and 75% yields respectively (Table 1, entries 1–2). Under these conditions, a low loading (1.2 equiv.) of 3,5-dimethylisoxazole **2a** gave **3a** in a decreased yield, *ca.* 62% (entry 3). With a 10 mol% catalyst, IPrAuCl/AgNTf₂ gave a clean reaction, yielding desired **3a** up to 91% (entry 4). We tested other phosphine ligands such as PPh₃ and P(OPh)₃, yielding desired **3a** in satisfactory yields (78-81%, entries 5–6). Other counter anions such as OTf⁻ and SbF₆⁻ were also effective in producing **3a** in 85–88% yields (entries 7–8). AgNTf₂ alone was not active at all (entry 9).



^{*a*} [**1a**] = 0.15 M. ^{*b*} Product yields are reported after separation from a silica column. ^{*c*} L = $p(t-Bu)_2(o-biphenyl)$. ^{*d*} IPr = 1,3-bis(diisopropylphenyl)-imidazol-2-yildene. Ms = methanesulfonyl, DCE = 1,2-dichloroethane, and Tf = trifluoromethanesulfonyl.



(11) (**3**I, 2.5 h, 48%, **x-ray**) (**6**I, 43%, *E/Z*= 3.3:1) (12) (**3**m, 14 h, 16%) (**6**m, 73%, **x-ray**)

 a^{a} [1] = 0.15 M. b^{b} Product yields are reported after separation from a silica column. EWG = electron withdrawing group.

 Table 3
 [4+3]-Annulations with various isoxazoles

الله ۱b ^a	$ \begin{array}{c} $	10 n IPrAuC DCE, ti	nol % I/AgNTf ₂ .70 °C me R ²	N Ts R ¹ 4 ^b 7a'	
Entry	(R^1, R^2)	2	Time [h]	Yield [%]	4
1)	н, н	2b	4	84 8	4a (X-ray) 7a'
2)	H. Me	2d	3	8 75	4b
3)	Me, H	2c	3	87	4c
4)	Et, Et	2e	6	85	4d
5)	<i>n</i> -Bu, <i>n</i> -Bu	2 f	7	81	4e
6)	Me, <i>n</i> -Bu	2g	3	82	4 f
7)	<i>n</i> -Bu, <i>c</i> -Pr	2h	2	77	4g
8)	Ph, <i>n</i> -Bu	2i	4	69	4h
9)	Ph, Ph	2j	6.5	61	4i
				30	5i (X-ray)
10)	Me, Ph	2k	4	71	4j
	Ph 0 R ¹ N	F N ^{Ts F}	R ¹ = Ph (5i) R ¹ = Me (5j)	15	5j

 $^{a}\left[\mathbf{1b}\right]=0.15$ M. b Product yields are reported after separation from a silica column.

Suitable substituents of 3-en-1-ynamides **1** are crucial to achieve 6π cyclizations of 3-azaheptatrienyl cations **V**' [eqn (2)]. We tested the reactions on 3-en-1-ynes **1b–1m** bearing a C(3)-substituent to circumvent aza-Nazarov cyclizations as reported in Ye's work.⁷ Herein, only entries 9 and 10 showed the presence of 3-azanorcaradienes **3'**. We examined these [4+3]-annulations on 3-methyl-3-en-1-ynamides **1b–1e** bearing various sulfon-amides NTsR⁴ (R⁴ = Me, cyclopropyl, benzyl and N(*n*-C₄H₉) ($-SO_2Bu$)), affording the desired 4*H*-azepines **3b–3e** in high yields (84–90%, Table 2, entries 1–4). Nevertheless, this new annulation becomes less efficient for 3-en-1-ynamide **1f** bearing an oxazolidin-2-one to yield product **3f** in 64% yield (entry 5).

We altered the C(3)-substituents as in substrates **1g–1i**; their resulting products **3g–3h** (\mathbb{R}^1 = isopropyl and cyclopropyl) were obtained in 74–79%, and **3i** (\mathbb{R}^1 = Ph) with only 58% yield (entries 6–8). Notably, when a long *n*-butyl group was present as in species **1j** and **1k**, their corresponding reactions afforded compounds **3j/3j'** = 5/1 and **3k/3k'** = **11.1 : 1**, respectively, in 55% and 68% yields (entries 9–10). For *E*-configured trisubstituted 3-en-1-yne **1l** (\mathbb{R}^1 = Me, \mathbb{R}^2 = Ph and \mathbb{R}^3 = H), 4*H*-azepine **3l**



Scheme 2 New functionalization of 4*H*-azepines.

and pyrrole **6l** were obtained in equal proportions (entry 11). When a cyclohexenyl group was present for alkene as in species **1m**, pyrrole product **6m** was dominant over azepine **3m** (entry 12). Accordingly, preferable 3-en-1-ynes comprise a small R^2 or R^3 substituent whereas R^1 must be substituted. Herein, the structures of 4*H*-azepines **3b** and **3l**, and pyrrole species **6m** were confirmed with X-ray diffraction.¹¹

Isoxazoles of a wide scope are compatible with these [4+3]annulations, as depicted in Table 3. The reaction of unsubstituted isoxazole 2b with model 3-en-1-ynamide 1b afforded the desired 4*H*-azepine 4a in 84% yield, together with pyrrole 7a' in only 8% yield (entry 1). Mono-substituted 3-methyl or 5-methyl isoxazoles 2c and 2d are also suitable for these annulations to afford compounds 4b and 4c in 75% and 87% yields, respectively (entries 2–3). We prepared additional 3,5-disubstituted isoxazoles 2e–2i with R^1 = alkyl and phenyl, and R^2 = alkyl; their annulations proceed smoothly to produce desired 4d–4h in 69– 85% yields (entries 4–8). For di-substituted isoxazoles 2j and 2k bearing R^2 = Ph, 4*H*-azepines 4i and 4j were obtained in 61% and 71% yields respectively, together with their rearrangement products 5i and 5j in 15–30% yields (entries 9–10). Compounds 4a and 5i were characterized by X-ray diffraction.¹¹

Our convenient synthesis of 4*H*-azepines provides new synthetic utilities; several new functionalizations are depicted in Scheme 2. NaBH₄-reduction of species **3b** delivered an alcohol derivative **7a** in 84% yield. Selective hydrogenation of the same species afforded 2-aza-1,3-dien-5-one **7b** in 71% yield. A final treatment of 4*H*-azepine **3b** with NBS in acetone afforded compound **7c**, of which the molecular structure was determined by ¹H NOE spectra.

The Lewis-catalyzed rearrangement of 4*H*-azepines **3–4** to substituted pyridines **5** [eqn (3)] is unprecedented in 4*H*-azepine chemistry.¹⁰ We undertook such novel [4+2]-annulations

Table 4 [4+2]-Annulations between 5-en-1-ynamides and isoxazo	Table 4	[4+2]-Annulations	between 3-en-1-	vnamides and	isoxazoles
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Entry	(R^1, R^2, EWG)	1	(R^3, R^4)	2	Time [h]	Yield [%]	5
(1)	Me, Me, Ts	1b	Me, Me	2a	19	73 (35) ^c	5a (X-ray)
(2)	<i>n</i> -Bu, Me, Ts	1k	Me, Me	2a	33	64	5b
(3)	<i>c</i> -Pr, Me, Ts	1h	Me, Me	2a	20	56	5c
(4)	<i>i</i> -Pr, Me, Ts	1g	Me, Me	2a	15	51	5 d
(5)	Me, <i>n</i> -Bu, Ms	1a	Me, Me	2a	28	63	5e
(6)	Me, Me, Ts	1b	<i>n</i> -Bu, <i>n</i> -Bu	2 f	19	78	5f
(7)	Me, Me, Ts	1b	Et, Et	2e	16	69	5g
(8)	Me, Me, Ts	1b	<i>n</i> Bu, <i>c</i> -Pr	2h	20	75	5ĥ
(9)	Me, Me, Ts	1b	Ph, Ph	2j	24	80	5i (X-ray)
(10)	Me, Me, Ts	1b	Me, Ph	2k	30	75	5j Š

a [1] = 0.15 M. b Product yields are reported after separation from a silica column. c The value in parentheses is reported using a mixture of IPrAuCl/AgNTf₂ (10 mol%) and Zn(OTf)₂ (20 mol%) in hot DCE (70 °C, 48 h); **3b** was also isolated in 28% yield.



Scheme 3 A plausible reaction mechanism.

between 3-en-1-ynamides 1 and isoxazoles 2 using Au(I)/Zn(II) in a relay series, as depicted in Table 4. In the reactions of various 3-substituted 3-en-1-ynamides 1 (\mathbb{R}^1 = methyl, *n*-butyl, cyclopropyl and isopropyl) with 3,5-dimethylisoxazole 2a, substituted pyridines 5a-5d were obtained in satisfactory yields (51-73%, entries 1-4). In entry 1, if the reaction was performed with combined Au(I)/Zn(II) catalysts in a non-relay operation, compounds 5a and 3b were isolated in 35% and 28% yields respectively. For 3-en-1-ynamide 1a bearing a NMs(n-butyl), the corresponding product 5e was obtained in 63% yield (entry 5). We tested the reactions on 3,5-disubstituted isoxazoles 2e-2f & 2h bearing all alkyl substituents, producing desired 5f-5h in good yields (69-78%, entries 6-8). For such disubstituted isoxazoles bearing $R^4 = Ph$, the reactions afforded the desired pyridine derivatives 5i and 5j in 75-80% yields (entries 9-10). The molecular structures of compounds 5a and 5i were characterized by X-ray diffraction.11

Scheme 3 rationalizes the crucial roles of substituents of 3en-1-ynamides in the chemoselectivity that relies on two conformational structures D versus D'. The N-attack of isoxazole at gold- π -ynamide A is expected to form a gold-carbene D', which can be visualized as a gold-stabilized cycloheptatrienyl cation. Conformation **D** is favorable with R = H, which prefers aza-Nazarov reactions.¹² When a C(3)-substituent is present (R = alkyl and aryl), all σ -*cis* configured species **D**' are the preferable geometry to induce novel 6π electrocyclizations. This ring closure is expected to proceed through an attack of enamide at the alkenylgold moiety that is also visualized as a goldstabilized cation. Additional C(4)-substituents render the formation of cations D' difficult, thus yielding pyrrole 6 as byproducts. A loss of an acidic proton from seven-membered cations E is expected to yield azepines 3-4. 4H-Azepines 3-4 bear an enone conjugated with a triene; this extensive conjugation is very stable to impede a 6π electrocyclization of their triene moieties unless a Lewis acid is present. Zn(OTf)₂ likely coordinates with the carbonyl of 4H-azepine 3 to generate a 2azapentadienyl cation F bearing a zinc enolate, further enabling an intramolecular cyclization to generate species G. A 1,2-acyl shift¹⁴ of species G delivers the observed product 5.¹³

Conclusions

In summary, this work describes new gold-catalyzed [4+3] annulations¹⁵ of 3-substituted 3-en-1-ynamides with isoxazoles to form 4*H*-azepines. A relay catalysis is also developed with Au(1)/Zn(II) catalysts to achieve [4+2] annulations from the same reactants. The mechanisms of gold-catalyzed [4+3] annulations involve unprecedented 6π electrocyclizations of 3-azacycloheptatrienyl cations to form 4*H*-azepines **3**–**4** efficiently. Control experiments confirm that 4*H*-azepines **3**–**4** are catalyzed by Zn(OTf)₂ to undergo new rearrangement reactions to form substituted pyridine derivatives.

Conflicts of interest

The authors declare no conflict of interest.

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