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Gold-catalysed Cyclisation of *N*-Propargylic *β*-enaminones to Form 3-Methylene-1-pyrroline Derivatives†‡

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Kommuru Goutham,[a,b] N. S. V. M. Rao Mangina,[a,b] Surisetti Suresh,[c] Pallepogu Raghavaiah,[d] and Galla V. Karunakar*[a,b]

Gold (I) catalysed reaction of *N*-propargylic *β*-enaminones and arynes was developed to access 3-methylene-1-pyrrolines. The title compounds were obtained in 57-78% yields. This reaction is useful for the generation of substituted 1-pyrrolines exhibiting significant molecular complexity.

Heterocyclic molecules have received much attention in organic synthesis.[1] Among various heterocycles, nitrogen-containing heterocycles have attained greater importance.[2] Also they are worthy in different applications in various fields such as crop protection, human health care and functional materials.[3] 1-Pyrrolines (3,4-dihydro-2*H*-pyrrolines) have received considerable attention—they are exhibiting important role in several applications such as semiochemicals,[4a] flavouring agent for various food products,[4b] natural products,[4c,] alkaloids,[4d] high-affinity radioligands,[4e] and therapeutic compounds (Figure-1).[5]

More significantly, 1-pyrrolines were proven as building blocks for synthesis of several pharmaceutically active molecules.[6] For example 1-pyrrolines were used for synthesis of (i) *β*-lactam derivatives, which are showing inhibitory activity against *Mycobacterium tuberculosis*,[7] (ii) diarylpyrrolizine acetic acid derivatives, which show anti-inflammatory, antiplatelet activities,[8] (iii) cyclic enaminone esters, have been investigated in mice testing for anticonvulsant activity,[9] (iv) fluoroquinolone analogs were exhibiting antibacterial acivity,[10] and (v) pyrrolidino enaminone carboxylic derivatives were investigated for inhibition of enzymes cyclooxygenase.[11]

Search for versatile building blocks, new synthetic strategies and exploration of new methods to construct nitrogen heterocyclic compounds is limitless frontier. Enaminones are known as potential intermediates in synthetic organic chemistry because they exhibit both nucleophilic character and electrophilic character exerted by the enamine and the enone functional groups, respectively.[12] We have undertaken efforts to study the reactivity of *N*-propargylic *β*-enaminones **1**, which are diversified chemical substrates having several distinct functional groups such as alkyne, alkene, enamine, enone, enaminone and propargylamine.

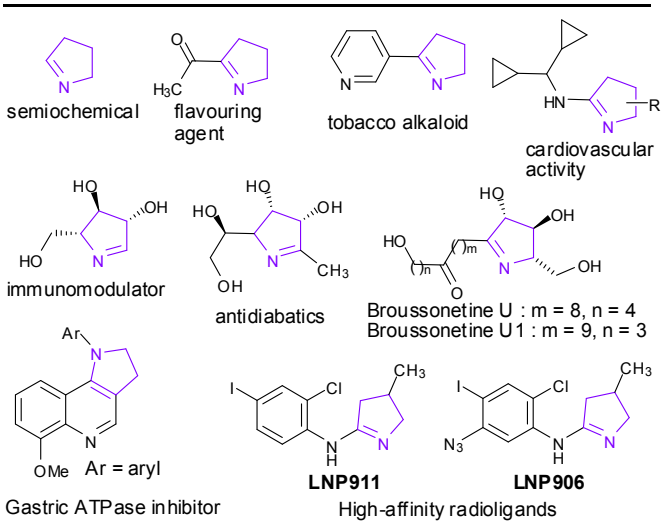


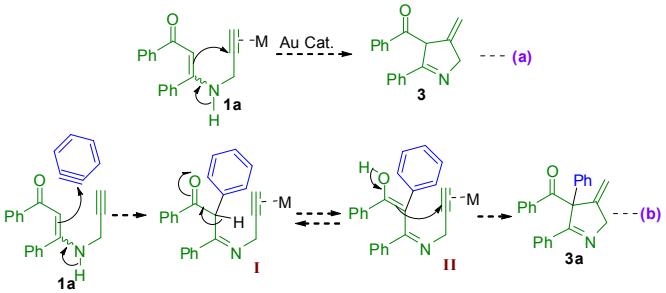
Figure 1 Selected examples containing 1-pyrroline core skeleton in important molecules and their applications

As a part of our current research program, we were driven to investigate the reactivity of *N*-propargylic *β*-enaminones **1** with alkynes. Despite their interesting structure, studies aimed towards the synthetic applications, *N*-propargylic *β*-enaminones **1** have

[a]*Crop protection Chemicals Division, CSIR-Indian Institute of Chemical Technology, Hyderabad, 500007, India.* gallavk@iict.res.in
[b]*Academy of Scientific and Innovative Research, New Delhi, 110001, India*
[c]*Organic and Biomolecular Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad, 500007, India.*
[d]*School of Chemistry, University of Hyderabad, Hyderabad, 500046, India.*
†Dedicated to Professor Mariappan Periasamy, on the occasion of his 60th birthday.
‡Electronic Supplementary Information (ESI) available: CCDC 932648. For ESI and crystallographic data CIF or other electronic format see DOI:10.1039/c000000x/

received much less attention.[13] Recently, Ramtohul *et al.* reported that *β*-enaminone esters react with arynes to produce the corresponding C-arylated *β*-enaminone derivatives.[13c] Hashmi *et al.* have reported gold catalyzed formal 1,6-acyloxy migrations utilizing suitably substituted homopropargylic enaminones.[14]

We envisaged the synthesis of 1-pyrrolines **3** through gold catalyzed[15] cyclisation of **1a** (Scheme 1a). Accordingly, we have performed a reaction to convert **1a** to 2,4-dihydro pyrrole **3** as a product, in the presence of $AuCl_3/AgSbF_6$ (10:15 mol %). However, this reaction did not yield the desired product instead the *N*-propargylic *β*-enaminone **1a** was recovered. We have also performed few more reactions using $AuClPEt_3$ and $AuClPEt_3/CsF$ for this transformation. None of these reactions were successful. The reasons may be attributed to the poor nucleophilicity of enaminone or weak electrophilic character of propargylic functionality under gold catalysis.



Scheme 1 Strategies for conversion of *N*-propargylic *β*-enaminone **1a** to 1-pyrroline **3**/**3a** via gold catalysis

Hence we thought of tuning the nucleophilicity of enaminone moiety or employing a reactive external alkyne substrate like an aryne[16] to enable the cyclisations as depicted in Scheme 1b. We have then conducted experiments by reacting **1a** with benzyne, generated *in situ* by the reaction of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **2a** (1 equiv.) and CsF (3 equiv.), in the presence of gold catalyst $AuCl_3/AgSbF_6$ (5/15 mol%). To our delight we have observed the formation of 3-methylene-3,4-dihydro-2*H*-pyrrole **3a** in 32% yield (Table 1, entry 1). The structure of the product **3a** was further confirmed by X-ray crystal structure analysis (Figure 2).

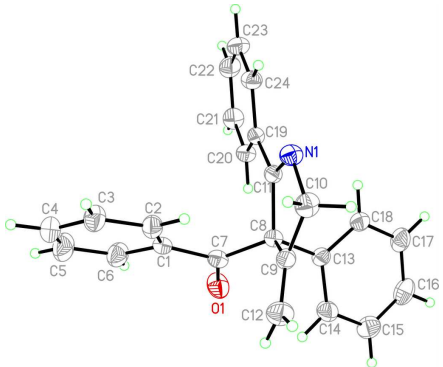
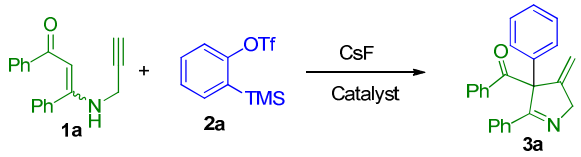


Figure 2 ORTEP representation of 3-methylene-3,4-dihydro-2*H*-pyrrole **3a** [CCDC 932648]

It was revealed from the X-ray crystal structure analysis that mono substitution took place on the benzyne intermediate and the product **3a** was formed with a quaternary stereocenter and an exocyclic double bond.

With this result in hand, we have screened different catalysts, catalyst combinations and reaction conditions to improve the yields of **3a** (Table 1). It is noteworthy that this transformation did not occur in the absence of catalyst (Table 1, entry 2).

Table 1 Optimization of reaction conditions



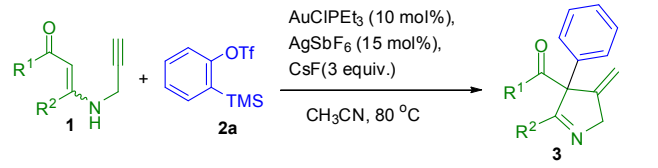
Entry	Catalyst (mol%)	Solvent	T (°C)	Time (h)	Yield (%)[a]
1	$AuCl_3/AgSbF_6$ (5/15)	CH_3CN	80	18	32
2	No catalyst	CH_3CN	80	24	nr
3	$AuCl_3/AgSbF_6$ (5/15)	DMF	100	20	nr
4	$AuCl_3/AgSbF_6$ (5/15)	Toluene	90	15	nr
5	$AuCl_3$ (10)	CH_3CN	80	18	16
6	$AgBF_4$ (10)	CH_3CN	70	12	nr
7	CuI (10)	CH_3CN	60	15	nr
8	$Zn(OTf)_2$ (10)	CH_3CN	70	10	57
9	$Zn(OTf)_2/AgBF_4$ (10/15)	CH_3CN	70	12	26
10	$Sm(OTf)_3$ (10)	CH_3CN	80	18	nr
11	$Sc(OTf)_3$ (10)	CH_3CN	80	30	10
12	$Yb(OTf)_3$ (10)	CH_3CN	60	18	54
13	$Eu(OTf)_3$ (10)	CH_3CN	80	30	nr
14	$AuClPEt_3$ (10)	CH_3CN	80	15	32
15	$AuClPEt_3/AgSbF_6$(10/15)	CH_3CN	80	15	78
16	$AuClPEt_3/Zn(OTf)_2$ (10/15)	Toluene	80	15	48
17	$AuClPEt_3/Zn(OTf)_2$ (10/15)	CH_3CN	80	24	53
18	$AgSbF_6$ (10)	CH_3CN	80	24	nr
19	$AuClPEt_3/AgSbF_6$ (5/7.5)	CH_3CN	80	36	21
20	$AuClPEt_3/AgOTf$ (10/15)	CH_3CN	80	36	6
21	$AuClPPh_3/AgOTf$ (10/15)	CH_3CN	80	36	19
22	$AuClPPh_3/AgSbF_6$ (10/15)	CH_3CN	80	30	8
23	$AuClPPh_3/AgBF_4$ (10/15)	CH_3CN	80	30	5
24	$IPrAuNTf_2/AgOTf$ (10/15)	CH_3CN	80	36	17

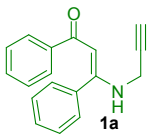
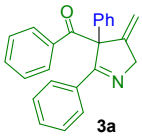
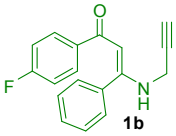
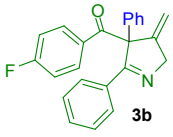
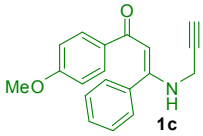
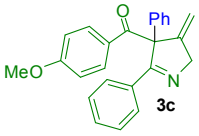
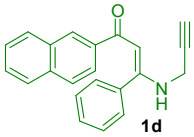
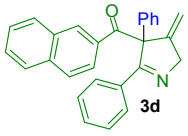
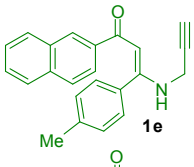
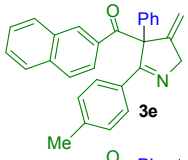
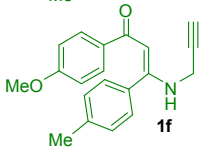
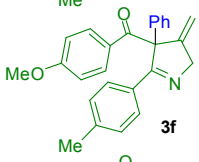
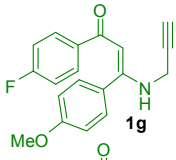
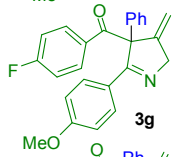
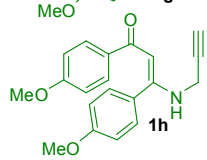
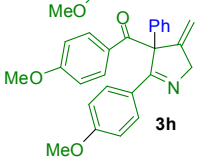
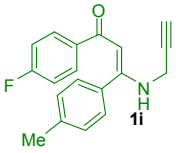
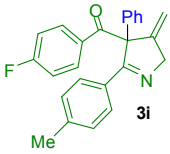
[a] Reaction conditions: 1a (0.4 mmol), 2a (0.4 mmol), CsF (1.2 mmol), solvent (3 mL); [b] Oil bath temperature; [c] Isolated yields; nr: no reaction. All reactions were conducted under nitrogen atmosphere.

When the above reaction was performed in the presence of $Zn(OTf)_2$ and $Yb(OTf)_3$ moderate (57% and 54%) yields of **3a** was obtained (Table 1, entries 8 and 12). In the case of $AuClPEt_3$ only 32% of **3a** was observed (Table 1, entry 14).

Impressive yield (78%) of **3a** was obtained while utilizing the combination of $AuClPEt_3$ (10 mol%) and $AgSbF_6$ (15 mol%) in CH_3CN solvent at 80 °C (Table 1, entry 15). Two experiments were conducted by utilizing $AuClPEt_3/Zn(OTf)_2$ in toluene and acetonitrile solvents (Table 1, entries 16 and 17) that gave **3a** in 48% and 53% yields, respectively.

Table 2 Scope of the synthesis of 3-methylene-3,4-dihydro-2*H*-pyrroles.



Entry	Substrate	Product	Yield (%)
1			78
2			58
3			66
4			67
5			64
6			67
7			57
8			72
9			55

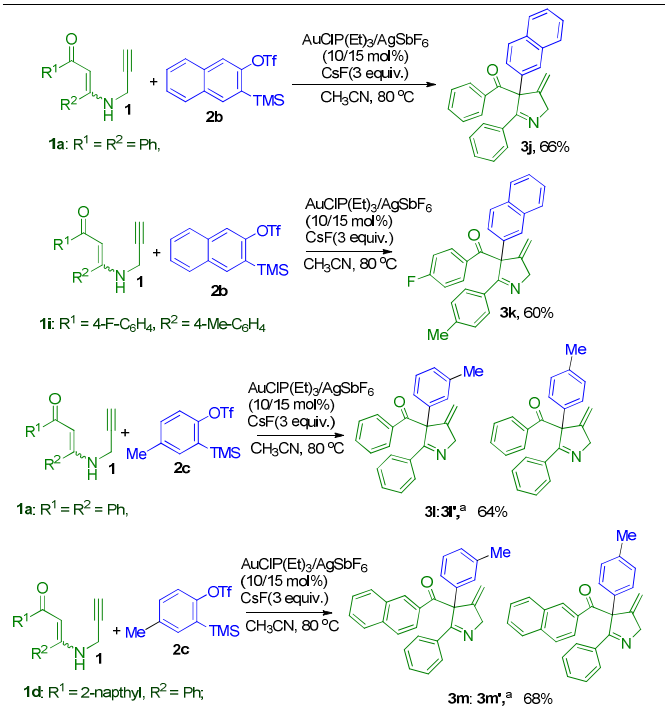
Reaction conditions: **1** (0.4 mmol), **2a** (0.4 mmol), CsF (1.2 mmol), CH_3CN (3 mL); $AuClPEt_3/AgSbF_6$ (10/15 mol%); Yields are for isolated products. All the reactions were carried out under nitrogen atmosphere.

When the reaction was performed using 10mol% of $AgSbF_6$ only, the starting material was intact (Table 1, entry 18). It clearly indicates that $AgSbF_6$ alone did not have any effect on this reaction.

We have also conducted a reaction by taking the 5 mol% of $AuClPEt_3$ and 7.5 mol% of $AgSbF_6$, in this case only 21% of product **3a** was isolated (Table 1, entry 19). We have screened the combination of $AuClPPh_3$ with different silver catalysts such as AgOTf, $AgSbF_6$ and $AgBF_4$ for this transformation. However, only low yield of the product **3a** was observed under these reaction conditions (Table 1, entries 21-23). Another experiment was conducted using the combination of $IPrAuNTf_2$/AgOTf for this transformation and 17% of the product **3a** was isolated (Table 1, entry 24).

Based on the best optimized reaction conditions (Table 1, entry 15), the generality of this reaction and scope of the substrates was studied by using different substituted *N*-propargylic *β*-enaminones **1a-i** with benzyne precursor **2a** (Table 2).

Table 3 Scope of the aryne substrate for the synthesis of 3-methylene-3,4-dihydro-2*H*-pyrroles.



Reaction conditions 1a/ 1d/ 1i (0.4 mmol), 2b/ 2c (0.4 mmol), CsF (1.2 mmol), CH_3CN (3 mL); $AuClPEt_3/AgSbF_6$ (10/15 mol%); Yields are for isolated products. All the reactions were carried out under nitrogen atmosphere. [a]Inseparable mixtures of *m*-Me and *p*-Me isomers in 1:1 ratio for each pair of 3l:3l′and 3m:3m′ were formed.

Electron withdrawing substituted *N*-propargylic *β*-enaminones like **1b** reacted with **2a** to yield 58% of product **3b**. When the substrate **1d** reacted with **2a**, 67% yield of product **3d** was isolated. *N*-Propargylic *β*-enaminones having electron donating groups like **1c, 1e, 1f** and **1h** reacted with **2a** to give 66%, 64%, 67% and 72% yields of **3c, 3e, 3f** and **3h**, respectively. Substrates that are having both electron withdrawing and electron donating groups like **1g** and **1i** reacted with **2a** to give 57% and 55% yields of **3g** and **3i**, respectively. These results indicate nucleophilicity of enaminone has considerable effect on the yields of cyclisation product.

When the reaction was performed with **1a** and **1i** with benzyne precursor **2b** gave 66% and 60% yields of **3j** and **3k**, respectively.

Reaction of **1a** and **1d** with benzyne precursor **2c** gave 64% and 68% yields of inseparable mixtures of products **3l**:**3l′** and **3m**:**3m′**, respectively. The ^{1}H-NMR spectral data suggested that these mixtures were formed in 1:1 ratio of *m*-Me and *p*-Me isomers.[17]

In conclusion, we have developed a straight forward one pot synthesis of 3-methylne-1-pyrrolines having a quaternary stereocenter and an exocyclic double bond from the reaction of *N*-propargylic *β*-enaminones and arynes under gold(I) catalysis. Current research is focused further exploitation of reactivity of substituted *β*-enaminone derivatives.

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