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Gold-catalysed Cycloisomerisation Reactions of 2-(2-Propynyl)pyridine N-Oxides Leading to Indolizinones

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Gold(I)-catalysed tandem oxygen-transfer/cycloisomerisation reaction of 2-(2-propynyl)pyridine N-oxides provides an atom-economic route to indolizinoone frameworks.

Indolizinones, the structure of which are closely related to that of indolizines which exhibit strong anti-inflammatory, anti-HIV, and anti-leukemia, have been exploited as privileged structural motifs in the development of biologically active molecules. Development of efficient and selective constructions of these heterocycles with different substitution patterns from readily available starting materials under mild conditions remains an important task in synthetic chemistry. In this regard, transition metal-catalysed cycloisomerisation reaction of heteroatom-functionalized alkynes has received considerable attention, since they provide a wide variety of complexed heterocycles with high atom-efficiency. π-Alkyne metal complexes are key intermediates capable of undergoing a wide range of reactions. Perhaps most commonly, they induce the addition of internal nucleophiles with a suitable length of tethers leading to zwitterion (or metallocarbenoid) intermediates. A variety of oxygen species may serve as the nucleophiles: carbonyl (C=O), epoxides, amine N-oxides (R_N=O), nitrones, nitro, and sulfoxides have been employed with various transition-metal catalysts. In line with our recent interests in the development of facile and efficient cycloisomerisation reactions leading to heterocycles, we applied oxygen transfer from pyridine N-oxide to alkynes activated with transition metals A to the generation of zwitterions B or metallocarbenoids C (Scheme 1). Since resulting metallocarbenoids C possess reactive pyridyl groups, they might be further converted into nitrogen-containing heterocycles. Herein, we wish to report gold-catalysed cycloisomerisation of 2-(2-propynyl)pyridine N-oxides leading to indolizinoones via acyl[(2-pyrindyl)methyl]-carbenoid complexes.

We reported the atom-economical generation of (2-furyl)carbene complexes using carbonyl-ene-yne compounds as their precursors. In the course of our continuing studies on such reactive intermediates, we have found the novel method for the generation of carbene complexes bearing a pyridyl group from pyridine N-oxides having alkyl moieties. When, pyridine N-

Scheme 1 Transition Metal-induced Oxygen-transfer in Pyridine N-Oxides Involving an Alkyne Moiety.

oxide 1a was treated with 5 mol% of AuCl(P^Bu_3)/AgSbF_6 in CICH_2CH_2Cl at rt (Scheme 2), β-pyridylenone 2 (E:Z = 92:8) and indolizinoone 3a were obtained in 59% and 41% yields, respectively. The relative stereochemistry of 3a was established by X-ray crystallography. When the reaction was carried out at 50 °C, the total yield of 2 was decreased to 25%, whereas the yield of 3a was raised up to 75%. These results indicate that 3a might be formed by the cycloisomerisation of 2 under the reaction conditions.

Scheme 2 Gold(I)-catalysed Cycloisomerisation of 1a.

This interesting result stimulated us to optimize conditions for the cycloisomerisation of 1a leading to indolizinoone 3a. The results are summarized in Table 1. First, reactions of 1a in the presence of other gold catalysts were examined. While reactions were generally sluggish in the presence of neutral gold catalysts, such as AuCl, AuCl_3, and AuCl(P^Bu_3) (entries 1-3), cationic gold species prepared in situ from the reaction of equimolar amounts of gold and silver salts exhibited much higher catalytic activity (entries 4-5). The combination of AuCl(P^Bu_3)/AgSbF_6 was the catalyst of choice for this cycloisomerisation and the yield of 3a was improved to 86% when the reaction temperature was increased to 80 °C (entry 6). Furthermore, we found that reducing the catalyst loading to 2 mol% did not influence the selectivity and efficiency of the reaction (entry 7). The use of
other metal catalysts including \([\text{Rh(OAc)}_2]\), which was the most effective catalyst for the generation of (2-furyl)carbene complexes from carbonyl-ene-yne compounds, decreased the reaction efficiency.\textsuperscript{16} Screening of solvents also identified \(\text{CICH}_2\text{CH}_2\text{Cl}\) as optimal.\textsuperscript{17} It is noteworthy that the \((Z)\)-isomer of \(\beta\)-pyridylenone 2 was obtained in 14\% yield as a by-product under the optimized reaction condition (entry 7).

### Table 1. Transition Metal-catalysed Cycloisomerisation of \(1a\)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield of 3(a) (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{AuCl})</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>(\text{AuCl}_3)</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>(\text{AuCl}(\text{P}^3\text{Bu})_3)</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>(\text{AuCl}(\text{PPh})_3/\text{AgSbF}_6)</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>((\text{IPr})\text{AuCl}/\text{AgSbF}_6)</td>
<td>24</td>
</tr>
<tr>
<td>6\textsuperscript{c,d}</td>
<td>(\text{AuCl}(\text{P}^3\text{Bu})_3/\text{AgSbF}_6)</td>
<td>86</td>
</tr>
<tr>
<td>7\textsuperscript{e}</td>
<td>(\text{AuCl}(\text{P}^3\text{Bu})_3/\text{AgSbF}_6)</td>
<td>86</td>
</tr>
</tbody>
</table>

\(\textsuperscript{a}\) Reaction conditions: 1\(a\) (0.20 mmol) in \(\text{CICH}_2\text{CH}_2\text{Cl}\) (2.5 mL) was heated at 50 °C in the presence of catalyst (5 mol\%) for 17 h.

\(\textsuperscript{b}\) Isolated yields. \(\textsuperscript{c}\) At 80 °C. \(\textsuperscript{d}\) \((Z)\)-2 was obtained in 14\% yield. \(\textsuperscript{e}\) 2 mol\%. \(\text{IPr} = 1,3\)-bis(2,6-disopropylphenyl)imidazol-2-ylidene.

With the optimized reaction conditions in hand, we next examined the substrate scope of the present cycloisomerisation reaction. The results are summarized in Table 2. Both pivalate 1\(b\) and acetate 1\(c\) can serve as substrates for this reaction, affording the corresponding indolizinones 3\(b\) and 3\(c\) in 82\% and 71\% yields, respectively (entries 1 and 2). An excellent yield of the product was obtained in the reaction of ethyl group substituted pyridine \(N\)-oxide 1\(d\) (entry 3). The reaction of 1\(e\) and 1\(f\) having 2-naphthyl and butyl groups at the alkyne terminus produced the corresponding 9-benzyloxyindolizinones 3\(e\) and 3\(f\) in moderate yields, respectively (entries 4 and 5). In contrast, terminal alkyne 1\(g\) decomposed under the reaction conditions and no products being able to characterize were observed (entry 6).

The reaction of an alkyne-substituted 5,6,7,8-tetrahydroquinoline \(N\)-oxide 1\(h\) proceeded to give nitrogen-containing tricycle 3\(h\) in good yield (entry 7).

Interestingly, 1\(i\) which has a hydrogen atom at the propargyl position afforded \(\beta\)-pyridylenone 4 in 37\% yield as a mixture of stereoisomers without the formation of indolizinone (Scheme 3). The formation of 4 can be rationalized by invoking 1,2-hydride shift of the acyl(2-pyridyl)methyl)carbene complex generated from 1\(i\). This observation indicates that the migration of a benzyloxy group to the carbene carbon is essential in the cycloisomerisation of 1 leading to the indolizinone.

### Scheme 3 Gold(I)-catalysed Isomerisation of 1\(i\).

When the reaction of alcohols without a benzyloxy moiety was carried out, diketones 5\(a\) and 5\(b\) were obtained in 33\% and 31\% yields, respectively (Scheme 4). Diketones were formed via the domino process that includes the generation of carbene species and 1,2-rearrangement of \(H\) or \(Me\) followed by protodemetalation. This result supports that the present reaction proceeds through 6-endo-dig cyclization via the nucleophilic attack of the oxygen atom of pyridine \(N\)-oxides to alkyne moieties.

### Scheme 4 Gold(I)-catalysed Isomerisation of Alcohols.

To obtain further insight into the reaction mechanism, the controlled reactions using the isolated \((Z)\)- and \((E)\)-2 were examined.\textsuperscript{18,19} It was found that indolizinone 3\(a\) was obtained quantitatively from the cycloisomerisation of \((E)\)-2 under the optimized reaction conditions, whereas \((Z)\)-2 behaved more sluggishly, being recovered intact even heated for prolonged reaction time. It is noteworthy that \((E)\)-2 remained untouched upon heating in the absence of \(\text{AuCl}(\text{P}^3\text{Bu})_3/\text{AgSbF}_6\) catalysts. This fact provides evidence for the participation of the gold catalyst in the cycloisomerisation of \((E)\)-2 leading to 3\(a\).

On the basis of the aforementioned observations, the most
plausible mechanism for the cycloisomerisation of 1a is proposed in Schemes 5 and 6. First, acyl[(2-pyridyl)methyl]carbene complex F is formed through 6-endo-dig cyclization via the nucleophilic attack of the oxygen atom of pyridine N-oxides to alkene moieties activated by the cationic gold catalyst followed by N–O bond cleavage (oxygen-transfer). Carbene complex F is then converted to (E)-β-pyryldienylene 2 through the migration of a benzoyloxy group onto the carbene center via the transient F". The fact that (E)-2 was obtained as a major isomer at room temperature can be explained by assuming the facile attack of a carbonyl moiety to a carbeneon center in a rotamer F (via transition state F") which is kinetically favoured (See also Scheme 2). On the other hand, the amount of (Z)-2 formed was slightly affected with the reaction temperature (5-8%), in which migration of a benzoyloxy group takes place via rotamer G and transient G". At further elevated temperature, (E)-2 only undergoes cycloisomerisation via the intramolecular attack of pyridyl nitrogen to the gold catalyst-activated carbonyl group to furnish indolizinozine 3a along with regeneration of the catalyst (Scheme 6).

In conclusion, we have demonstrated gold-catalysed oxygen-transfer and cycloisomerisation cascade of 2-(2-propynyl)pyridine N-oxides leading to 9-acyloxindolizinones. It is noted that gold catalyst serves as a π- and σ-acid catalyst. Further investigation of gold-catalysed tandem-type reactions as well as synthetic applications of the indolizinozine frameworks in bioactive discovery, are currently in progress in our laboratory.

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12. For rhodium-carbene complexes containing a pyridyl group, see: (a) H. M. L. Davies; R. J. Townsend, J. Org. Chem. 2001, 66, 6595; (b) S. Chuprakov; F. W. Hwang; V. Georgyvan, Angew. Chem. Int. Ed. 2007, 46, 4757; (c) S. Chuprakov; V. Georgyvan, Org. Lett. 2007, 9, 4463.
14. For X-ray crystal analysis data of 3a, see ESI (CCDC-869886).
15. When isolated 2Bu3P/AgSbF6 was used as a catalyst, 3a was obtained in 86% yield.
16. Other transition metal catalysts produced 3a in the following yields. AgSbF6: 15%, PdCl2: 17%, [Bu4N][OAc]: 8% [Ru(CO)3]: 0%.
17. 3a was obtained in 31% yield in MeCN and 50% yield in MeNO2, respectively, at 50 °C in the presence of 5 mol% of AuCl(PPh3)/AgSbF6.
Gold-catalysed isomerization of 1a at 0 °C selectively afforded (E)-2 in 12% yield without forming (Z)-2.

For X-ray crystal analysis data of (E)-2, see ESI (CCDC-869885).

The possibility that pyridylenones 2 are formed through 1,2-rearrangement of a benzoyloxy group followed by oxygen-transfer from pyridine N-oxide to the generated carbene complexes, or 1,3-rearrangement of a benzoyloxy group followed by oxygen-transfer from pyridine N-oxide to terminal position of the resulting allene cannot be ruled out completely. For the gold-catalysed allene formation and oxygen-transfer from sulfoxides to carbenes, see: (a) P. Mauleón; J. L. Krinsky; F. D. Toste, *J. Am. Chem. Soc.*, 2009, 131, 4513; (b) C. A. Witham; P. Mauleón; N. D. Shapiro; B. D. Sherry; F. D. Toste, *J. Am. Chem. Soc.*, 2007, 129, 5838.