Effective Catalytic Activity of the Hydrated Gold Catalyst NaAuCl₄·2H₂O To Construct Highly Fused Cyclopentenones

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Abstract: The rapid synthesis of various carbocycle-fused highly substituted cyclopentenones is described to occur via tandem 1,2-shift of pivaloate followed by carbocyclization under the catalysis of the hydrated gold catalyst NaAuCl₄·2H₂O.

Key words: cyclopentenones, carbocycles, gold catalysis, 1,2-pivaloate shift, Nazarov-type cyclization

Cyclopentenones are potent building blocks in organic synthesis. To date, a large number of innovative approaches have been reported for the construction of the cyclopentenone skeleton, which has been used as a key intermediate in the synthesis of various natural products and pharmaceutically valuable compounds. Although gold-catalyzed intramolecular carbocyclization has recently become an effective method for preparing a variety of structural motifs, the synthesis of the cyclopentenone skeleton by gold-catalyzed reactions is somewhat less documented.

Toste et al. reported an efficient methodology for generating cyclopentenones by a 1,2-shift of pivaloate and carbocyclization in the presence of Au(PPh₃)OTf and Au(PPh₃)SbF₆ as the catalyst in acetonitrile, although all these transformations require appreciably longer reaction times for completion. Later, Zhang et al. showed that the catalyst AuCl(PPh₃)/AgSbF₆ did not work well under anhydrous conditions in the synthesis of cyclopentenones from the corresponding enynyl acetates, whereas under wet conditions the desired cyclopentenone formed in excellent yield by 1,3-shift of pivaloate and Nazarov-type cyclization in the presence of the same catalyst.

Initially, we concentrated on the optimization of the gold-catalyzed cyclopentenone formation (Table 1). We commenced our study with substrate 1d, which on treatment with 5 mol% of AuCl(PPh₃)/AgSbF₆ in 1,2-dichloroethane afforded the desired cyclopentenone 4d in 66% yield within 15 hours (Table 1, entry 1). The activity of gold(III) bromide was very similar (entry 2). Notably, gold(III) chloride proved to be a better catalyst, providing 4d in better yield (72%) within seven hours.

 Gratifyingly, remarkable catalytic activity was observed in the case of the hydrated gold(III) catalyst NaAuCl₄·2H₂O (entry 4). When 1d was treated with 5 mol% of NaAuCl₄·2H₂O in 1,2-dichloroethane at room temperature, the reaction time reduced dramatically to two hours, and product 4d was obtained in excellent yield (85%). Unfortunately, 1d remained unchanged even after prolonged treatment (15 h) with BINAP–gold(I) chloride (1:1) in acetonitrile (entry 5). On the other hand, when the reaction was carried out with the same catalyst in conjunction with silver(I) hexafluoroantimonate as cocatalyst under similar conditions, complete conversion resulted within 15 hours, affording 4d in 68% yield (entry 6). Other catalysts such as silver(I) hexafluoroantimonate and platinum(IV) chloride were found to be ineffective for this conversion (entries 7 and 8).

In light of these fruitful findings, we became interested in exploring the synthetic potential of the catalyst NaAuCl₄·2H₂O to construct structurally similar substrates (Table 2). During our comprehensive experimentation, we found that cyclohexenylpropargyl pivaloates 1a,b (Table 2, entries 1 and 2) on treatment with NaAuCl₄·H₂O underwnt smooth and clean cyclization to furnish the corresponding cyclohexane-fused cyclopentenones 4a,b in good yields (60–75%) within short reaction times (2–4 h) at ambient temperature. The time that sterically hindered 1b required to convert into the corresponding cyclopentenone 3b (4 h) was longer than that needed by 1a (2 h). Next, we investigated the scope of cyclization of the cyclohexenylpropargyl pivaloate dimer 1c (entry 3). Interestingly, when the reaction was carried out at slightly higher temperature (70 °C), cyclization proceeded smoothly at the two termini of 1c to construct the propylene-tethered cyclohexane-fused cyclopentenone dimer 4c in 78% yield within a short time (3 h) (entry 3). Cycloheptenyl-fused cyclopentenone 4d is the core structure of natural products such as cyperenone and sugeonol acetate, as mentioned above (Figure 1). Methyl-substituted cycloheptenylpropargyl pivaloate 1d, as stated earlier, on treatment with the same catalyst afforded a cis/trans mixture (1:1) of 4d in excellent yield (85%) (entry 4). We further succeeded in synthesizing various cyclooctyl-fused cyclopentenones 4e–g in good to excellent yields (70–80%) from the corresponding cyclooctenylpropargyl pivaloates 1e–g with different substituents at the alkyne end (entries 5–7), employing similar reaction conditions [NaAuCl₂·H₂O (5 mol%), r.t., 3–4 h]. From these results, it was apparent that substitution at the alkyne end influenced the rate as well as the yield of the gold-catalyzed cyclization.

The first report on the construction of cyclopentenones by this type of rearrangement was by Rautenstrauch, using a palladium catalyst. Recently, Lera et al. reported on a detailed mechanistic study of such a type of tandem gold-catalyzed 1,2-shift of pivaloate followed by Nazarov-type carbocyclization of the ene–yne tethered pivaloates leading to cyclopentenones. Due to the extraordinary alkynophilicity of gold, gold(I) or gold(III) forms a complex with the alkyne, which induces the intramolecular nucleophilic attack by the carbonyl oxygen of the pivaloate at the electron-deficient sp-hybridized carbon (position 2 in C) to generate the cationic vinyl–gold intermediate D (Scheme 2). According to their energy calculations, intermediate D then converts into gold-coordinated...
allyl cation E, which, on Nazarov-type carbocyclization, transforms into cyclopentenyl cation F. They argued that the electron-donor properties of gold favored the ionic cyclization. Although it is not clearly distinguished whether this mechanistic mode is pericyclic or ionic, their calculation supports the ionic mechanism. Intermediate F, on simple protodemetalation, furnishes the pivaloyloxy-substituted cyclopentadiene G, which on hydrolysis smoothly converts into cyclopentenone H. It is noteworthy that all the transition states of this transformation are cationic. From our investigation, it seemed to us that in the presence of a catalytic amount of a polar protic molecule such as water, all the cationic transition states are stabilized to some extent and, consequently, such a conversion requires a short reaction time.

In conclusion, we have shown that the gold-catalyzed tandem 1,2-shift of pivaloate and carbocyclization of the ene–yne-tethered pivaloates could be achieved rapidly and efficiently in the presence of the hydrated gold catalyst NaAuCl₄·2H₂O. We also investigated the scope of the formation of various carbocycle-fused highly substituted cyclopentenone derivatives under mild conditions. Some of the products could have the potential to be valuable precursors for the total synthesis of some important natural products and medicinal compounds.

### Table 2  Gold(III)-Catalyzed Synthesis of Different Carbocycle-Fused Cyclopentenones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>4a</td>
<td>25 °C, 2 h</td>
<td>75 (20:1)</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>4b</td>
<td>25 °C, 4 h</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>4c</td>
<td>70 °C, 3 h</td>
<td>78 (5:1)</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>4d</td>
<td>25 °C, 2 h</td>
<td>85 (1:1)</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>4e</td>
<td>25 °C, 3 h</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>4f</td>
<td>25 °C, 4 h</td>
<td>70 (5:1)</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>4g</td>
<td>25 °C, 4 h</td>
<td>76 (10:1)</td>
</tr>
</tbody>
</table>

*a Isolated yield of products 4a–g. The values in parentheses are the diastereomeric ratios, as determined by ¹H NMR spectroscopy of the crude products.

Scheme 2  Proposed mechanism for gold-catalyzed cyclopentenone formation
Cyclization of Alkynes 1a–g To Form Fused Cyclopentenones 4a–g: General Procedure

A clean and dry 5-mL test tube containing a magnetic stirrer bar was charged with a soln of one of 1a–g (0.2 mmol) in DCE (0.2 M in substrate). To the resulting soln, NaAlH4·2H2O (5 mol%) was added at 0 °C. The reaction mixture was then allowed to attain r.t. and stirred at the temperature and for the amount of time shown in Table 2 (e.g., with 1c, the reaction mixture was stirred at 70 °C for 3 h) and monitored periodically by TLC. Upon completion of the reaction, the mixture was quenched with a drop of Et3N and concentrated under reduced pressure, after which the residue was loaded directly onto a silica gel column, and chromatographed with the appropriate hexanes–EtOAc mixture; this gave the corresponding cyclized products 4a–g.

6-tert-Butyl-1,4,5,6,7,7a-hexahydro-2H-inden-2-one (4a)

1H NMR (400 MHz, CDCl3): δ = 5.82 (s, 1 H), 2.86 (dt, J = 18.4, 2.8 Hz, 1 H), 2.67–2.56 (m, 3 H), 2.30–2.19 (m, 2 H), 2.09–2.04 (m, 1 H), 1.99 (dd, J = 18.4 Hz, 1 H), 1.38–1.31 (m, 1 H), 1.23–1.13 (m, 1 H), 0.89 (s, 9 H).

13C NMR (100 MHz, CDCl3): δ = 209.37, 185.03, 126.63, 47.35, 42.85, 42.14, 36.21, 32.69, 31.06, 28.26, 27.83.


1-Phenyl-1,4,5,6,7,7a-hexahydro-2H-cyclopenta[8]annulen-2-one (4f)

1H NMR (400 MHz, CDCl3): δ = 7.34–7.11 (m, 5 H), 6.02 (s, 1 H), 3.41 (d, J = 3.6 Hz, 1 H), 3.01 (d, J = 3.2 Hz, 1 H), 2.89–2.83 (m, 1 H), 2.46–2.39 (m, 1 H), 2.22–2.14 (m, 1 H), 2.03–1.97 (m, 1 H), 1.80–1.58 (m, 6 H), 1.53–1.43 (m, 1 H), 1.39–1.31 (m, 1 H).

13C NMR (100 MHz, CDCl3): δ = 205.18, 187.36, 139.12, 129.23, 128.75, 128.26, 126.90, 57.41, 53.63, 30.95, 30.76, 25.53, 23.88, 24.47.

HRMS (ESI): m/z calcd for C13H12NaO: 263.1412; found: 263.1414.

1-Butyl-1,4,5,6,7,8,9,9a-octahydro-2H-cyclopenta[8]annulen-2-one (4g)

1H NMR (400 MHz, CDCl3): δ = 5.89 (s, 1 H), 2.79–2.74 (m, 1 H), 2.63 (br s, 1 H), 2.40–2.33 (m, 1 H), 2.19–2.12 (m, 2 H), 1.97–1.91 (m, 1 H), 1.79–1.72 (m, 2 H), 1.71–1.50 (m, 7 H), 1.48–1.28 (m, 5 H), 0.90 (s, J = 5.8 Hz, 3 H).

13C NMR (100 MHz, CDCl3): δ = 211.14, 187.07, 129.76, 50.76, 50.36, 30.73, 30.46, 30.44, 29.44, 27.05, 25.90, 25.63, 24.77, 22.89, 13.96.


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References


