Trifluoromethanesulfonic Acid-Catalyzed Tandem Semi-Pinacol Rearrangement/Alkyne-Aldehyde Metathesis Reaction of Arylpropargylsulfonamide-Tethered 2,3-Epoxycyclohexan-1-ols to Spiropiperidines

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Abstract: A simple and efficient trifluoromethanesulfonic acid-catalyzed cycloisomerization of arylpropargylsulfonamide-tethered 2,3-epoxycyclohexan-1-ols is described. The cyclization proceeds via tandem semi-pinacol rearrangement/alkyne-aldehyde metathesis to afford spiropiperidines under mild reaction conditions.

Keywords: alkyne/aldehyde metathesis; semi-pinacol rearrangement; spiropiperidines; tandem reactions; triflic acid

The construction of azaspiro cyclic building blocks is an important synthetic goal because such ring skeletons are present in numerous natural products of biological interest. [1] Because the availability of functionalized azaspiro cyclic building blocks could greatly facilitate the elaboration of more structurally complex compounds, the design of expedient and efficient synthetic routes to such intermediates has been actively pursued. [2] Many synthetic methods, as the key step, have been developed in pursuit of this structure, including the platinum(II)-catalyzed intramolecular cyclization of cyclic enesulfonamides bearing an alkyne tether; [2a] the ene-type cyclization of cyclic 1,7-enynes with tethered alkynes catalyzed by the cationic palladium complex; [2b] the samarium(II)-mediated cyclization of unsaturated ketolactams; [2c] the intramolecular radical cyclization of cyclic enamines carrying an alkyl bromide [2d] and the palladium-catalyzed transformation of 3,4-di hydro-2-pyridinones carrying a (2-bromophenyl)ethyl substituent. [2e] Although a transition metal-catalyzed process is a useful protocol to obtain azaspirocycles, most of the catalytic approaches involve addition of nucleophiles to metal-activated carbon-carbon multiple bonds. From both economical and environmental points of view, the development of metal-free catalytic processes is desirable for the synthesis of functionalized azaspirocycles. We have now demonstrated that trifluoromethanesulfonic (triflic) acid (TfOH) can be applied, in a catalytic fashion, to a series of various arylpropargylsulfonamide-tethered 2,3-epoxycyclohexan-1-ols allowing the synthesis of functionalized spiropiperidines. In this transformation, a TfOH-induced semi-pinacol-type rearrangement [3] of the six-membered ring epoxy alcohols occurs to generate the ring contraction 2-hydroxycyclopentane-carbaldehyde derivatives. A subsequent TfOH-promoted intramolecular alkyne-aldehyde metathesis [4] then takes place to afford the spiropiperidines in good to high yields under mild reaction conditions.

The requisite arylpropargylsulfonamide-tethered 2,3-epoxycyclohexan-1-ols 1 were prepared starting from the addition of lithiated dimethyl sulfide to 3-isobuty oxycyclohex-2-en-1-one in THF at room temperature to produce 3-(methylthio)methyl)cyclohex-2-en-1-one. Treatment of the resulting thioether with methyl iodide in CH₂Cl₂ at 40°C afforded 3-(iodomethyl)cyclohex-2-en-1-one. Reaction of the corresponding arylpropargylsulfonamide with 3-(iodomethyl)cyclohex-2-en-1-one in acetone at room temperature followed by reduction of the resulting enones with NaBH₄ in MeOH at 0°C and subsequent epoxidation with mCPBA in CH₂Cl₂ at room temperature provided 1 in 41–62% overall yields. [5] Due to the fact that cationic phosphine gold(I) complexes have emerged as versatile catalysts for electrophilic activation of alkenes toward a variety of nucleophiles under mild reaction conditions [6] we first screened reaction condi-
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In order to facilitate analysis and shorten reaction times, the reaction temperature was increased to 50°C. The parent compound 1a did cyclosomizerize smoothly at 50°C and a 91% isolated yield of the expected spiropiperidine 2a was obtained after 40 min at 50°C (Table 1, entry 6). The investigation of various solvents in the presence of the TiOH catalyst revealed that dichloromethane, THF, toluene and CH3CN were less effective and afforded 2a in moderate yields (33–64%, Table 1, entries 7–10). Thus, the use of TiOH (10 mol%) in DCE at 50°C was found to be the most efficient and was chosen as the standard reaction conditions. A similar catalytic condensation reaction of electron-rich arenes with aldehydes using various Lewis acids, for example, AuCl3, Hg(ClO4)2, Ti(ClO4)3, and Brønsted acids has been reported.²⁷

It must be mentioned that attempts to separate the mixture of two diastereomeric isomers of 2a using flash column chromatography on silica gel failed. Oxidation of the mixture with 2-iodoxybenzoic acid (IBX) in refluxing acetone for 6 h gave 9-benzoyl-7-tosyl-7-azaspiro[4.5]dec-9-en-1-one (3a) in nearly quantitative yield from 2a (Figure 1). The structure elucidation of 3a was achieved by X-ray crystallography.²⁸

With the optimal reaction conditions, we next examined the substrate scope of the TiOH-catalyzed transformation. The results of the TiOH-catalyzed cycloisomerization reaction of the arylpropargylsulfonamide-tethered 2,3-epoxycyclohexan-1-ols 1a–1l to produce spiropiperidines 2a–l are listed in Table 2. Electron-neutral and electron-rich arenes at the alkyne terminus were proven to be good substrates, as the yields of desired spiropiperidines 2a–f as a mixture of diastereomers ranged from 66% to 91% (entries 1–6, Table 2). The crude mixture of diastereomeric isomers of 2c was separated in a ratio of 2:1 using flash column chromatography on silica gel. The ¹H NMR spectrum of the major isomer exhibited a singlet at δ = 6.33 assigned to the vinyl H, a broad singlet at δ = 4.18 assigned to the H at the carbinol carbon, and two doublets, centered at δ = 4.26 and 3.73, assigned to the two diastereotopic methylene protons at the allylic carbon. The ¹H NMR spectrum of the minor isomer exhibited a singlet at δ = 6.58 assigned to the vinyl H, a broad singlet at δ = 4.21 assigned to the H at the carbinol carbon, and two doublets, centered at δ = 4.11 and 3.69, assigned to the two diastereotopic methylene protons at the allylic carbon. However, substrates with a bromine atom at the phenyl ring, for example, 1g–k, were less effective and required prolonged reaction times to provide spiropiperidines 2g–k in 14% to 56% isolated yields (Table 2, entries 7–11). Moreover, substrate 11 having a methyl group at

Table 1. Optimization of the reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>t</th>
<th>Yield [%]</th>
<th>Diastereoisomeric ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5% PPh₃Au/AgOTf</td>
<td>DCM</td>
<td>24</td>
<td>10 h</td>
<td>33 (58:42)</td>
<td>2:1</td>
</tr>
<tr>
<td>2</td>
<td>10% BF₃·OEt₂</td>
<td>THF</td>
<td>24</td>
<td>2.0 h</td>
<td>46 (52:48)</td>
<td>2:1</td>
</tr>
<tr>
<td>3</td>
<td>10% AgSbF₆</td>
<td>DCE</td>
<td>24</td>
<td>3.0 h</td>
<td>60 (48:52)</td>
<td>2:1</td>
</tr>
<tr>
<td>4</td>
<td>10% NHTf₂</td>
<td>DCE</td>
<td>24</td>
<td>0.5 h</td>
<td>83 (87:13)</td>
<td>2:1</td>
</tr>
<tr>
<td>5</td>
<td>10% TiOH</td>
<td>DCE</td>
<td>24</td>
<td>3.5 h</td>
<td>86 (49:51)</td>
<td>2:1</td>
</tr>
<tr>
<td>6</td>
<td>10% TiOH</td>
<td>DCE</td>
<td>50</td>
<td>40 min</td>
<td>91 (76:24)</td>
<td>2:1</td>
</tr>
<tr>
<td>7</td>
<td>10% TiOH</td>
<td>DCM</td>
<td>50</td>
<td>2.0 h</td>
<td>64 (73:27)</td>
<td>2:1</td>
</tr>
<tr>
<td>8</td>
<td>10% TiOH</td>
<td>THF</td>
<td>50</td>
<td>2.5 h</td>
<td>82 (63:37)</td>
<td>2:1</td>
</tr>
<tr>
<td>9</td>
<td>10% TiOH</td>
<td>toluene</td>
<td>50</td>
<td>2.0 h</td>
<td>57 (37:63)</td>
<td>2:1</td>
</tr>
<tr>
<td>10</td>
<td>10% TiOH</td>
<td>MeCN</td>
<td>50</td>
<td>4.0 h</td>
<td>33 (69:31)</td>
<td>2:1</td>
</tr>
</tbody>
</table>

Diastereoisomeric ratio.

Figure 1. Structures of 3a and 4.
Table 2. Synthesis of spiropiperidines 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>t</th>
<th>Product[a]</th>
<th>Yield [%] of 2 (df)</th>
<th>Yield of 3 [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>phenyl</td>
<td>40 min</td>
<td>2a</td>
<td>91 (76:24)</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>4-methoxyphenyl</td>
<td>10 min</td>
<td>2b</td>
<td>84 (54:46)</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>4-methylphenyl</td>
<td>30 min</td>
<td>2c</td>
<td>76 (67:33)</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>4-phenylphenyl</td>
<td>15 min</td>
<td>2d</td>
<td>81 (58:42)</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>1-naphthyl</td>
<td>10 min</td>
<td>2e</td>
<td>86 (57:43)</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>9-phenanthryl</td>
<td>15 min</td>
<td>2f</td>
<td>66 (50:50)</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>4-bromophenyl</td>
<td>4 h</td>
<td>2g</td>
<td>56 (38:62)</td>
<td>53</td>
</tr>
<tr>
<td>8</td>
<td>1h</td>
<td>2-bromophenyl</td>
<td>3 h</td>
<td>2h</td>
<td>48 (44:56)</td>
<td>43</td>
</tr>
<tr>
<td>9</td>
<td>1i</td>
<td>2-ethoxycarbonylphenyl</td>
<td>2 h</td>
<td>2i</td>
<td>28 (52:48)</td>
<td>26</td>
</tr>
<tr>
<td>10</td>
<td>1j</td>
<td>3-ethoxycarbonylphenyl</td>
<td>2 h</td>
<td>2j</td>
<td>51 (52:48)</td>
<td>48</td>
</tr>
<tr>
<td>11</td>
<td>1k</td>
<td>4-nitrophenyl</td>
<td>8 h</td>
<td>2k</td>
<td>14 (44:56)</td>
<td>13</td>
</tr>
<tr>
<td>12</td>
<td>1l</td>
<td>CH₃</td>
<td>30 h</td>
<td>2l</td>
<td>21 (29:71)</td>
<td>20</td>
</tr>
<tr>
<td>13</td>
<td>1m</td>
<td>H</td>
<td>1 h</td>
<td>2m</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] All products 2 were subjected to IBX oxidation and characterized as 9-aryloyl-7-tosyl-7-azaspiro[4.5]dec-9-en-1-ones 3.

The alkynyl terminus lowered the catalytic activity of TfOH and the yield of 2l was diminished to 21% (Table 2, entry 12). Unfortunately, the reaction of the substrate with a terminal alkyne, for example, 1m, resulted in decomposition of the starting substrate (Table 2, entry 13). It is worthy of mention that substrates bearing a geminal dimethyl group at C-5 of the ring, for example, 1n, 1o, do not interfere with the catalytic activity of TfOH as shown by the fact that the yields of their corresponding spiropiperidines 2n and 2o were 86% and 93%, respectively. However, the reaction was sluggish with the substrate bearing an methyl group at the C-2 position of the ring, for example, 1p, and the cyclization produced spiropiperidine 2p in only 43% yield (Figure 2).

On the basis of the experiment results, a possible reaction pathway for the observed TfOH-catalyzed cycloisomerization of 1a to provide 2a is suggested in Scheme 1. Protonation of the epoxide of 1a with TfOH led to the oxiranium ion 5, which promoted a semi-pinacol rearrangement to give the phenylpropylsulfonamide-tethered 2-hydroxycyclopentanecarbaldehyde 4 as a mixture of diastereomers. It must be mentioned that the usual semi-pinacol rearrangement of 2,3-epoxycyclohexan-1-ols gives 2-hydroxycyclopentane-carbaldehyde 6 (Figure 3), which led to the formation of cyclopentene-1-carbaldehyde derivatives after dehydration.[3a] The formation of 2-hydroxycyclopentanecarbaldehyde 4 demonstrated that the preferred reaction pathway for the semi-pinacol rearrangement of 5 proceeded via migration of the hydroxyalkyl group to the tertiary carbocation. The similar unusual semi-pinacol rearrangement had previously been observed with an α-silyloxyethyl epoxide having both allylic and tertiary centers.[3c] The following TfOH-catalyzed intramolecular alkyne-aldehyde metathesis started with protonation of the formyl group of 4 to give the oxonium species 7, which produced oxete 8 via [2 + 2]cycloaddition. The intermediate 8 then underwent [2 + 2]cycloreversion to afford spiropiperidine 2a and regenerated the acid in the catalytic cycle.

In summary, we have developed an efficient synthesis of 9-benzoyl-7-tosyl-7-azaspiro[4.5]dec-9-en-1-ols...
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aqueous Na2CO3 solution. The resulting mixture was ex-
room temperature and was treated with 5 mL of saturated
m
Aldehyde Metathesis
tions of these reactions are currently in progress.
mild reaction condition and the environmentally

advantages of this procedure are the
epoxycyclohexan-1-ols tethered an arylpropagylsulfo-
ment/alkyne-aldehyde metathesis reaction from 2,3-
Experimental Section
TfOH-catalyzed tandem semi-pinacol rearrange-
via

Scheme 1. Plausible reaction mechanism for the TfOH-cata-
yzed cycloisomerization of 1 to 2.

Figure 3. Structure of 6.

via TfOH-catalyzed tandem semi-pinacol rearrange-
ment/alkyne-aldehyde metathesis reaction from 2,3-
epoxycyclohexan-1-ols tethered an arylpropagylsulfo-
name. The advantages of this procedure are the

Experimental Section

General Procedure for Synthesis of 9-Benzoyl-7-tosyl-
7-azaspiro[4.5]dec-9-en-1-one (3) via TfOH-Cata-
ed Tandem Semi-Pinacol Rearrangement/Alkyne-
Aldehyde Metathesis

To an oven-dried, 10-mL round-bottom flask equipped with a stirrer bar and capped with a rubber septum was added 1a (103 mg, 0.25 mmol), TfOH (2.18 μL, 0.025 mmol) and DCE (1.25 mL) under nitrogen. The reaction mixture was stirred at 50°C for 40 min. The mixture was allowed to cool to room temperature and was treated with 5 mL of saturated aqueous Na2CO3 solution. The resulting mixture was extracted with dichloromethane (10×3 mL), and the combined extracts were washed with brine, dried (MgSO4), concentrat-
ed under reduced pressure to afford the crude product 2a as a yellow oil; yield: 93 mg. The crude 2a was used for the next oxidation step without further purification.

To an oven-dried, 10-mL round-bottom flask equipped with a stirrer bar and capped with a rubber septum was added 2a (93 mg, 0.23 mmol), 2-iodoxybenzoic acid (0.14 g, 0.5 mmol) and acetone (2.5 mL) under nitrogen. The reaction mixture was stirred at 55°C for 6 h. The reaction mixture was allowed to cool to room temperature and was filtered through a bed of Celite. The filtrate was concentrated under vacuum, and purified by flash column chromatography on silica gel (hexanes/ethyl acetate = 10:1) to give 3a as a colorless solid; yield: 89 mg (0.21 mmol, 87%); mp 197–198°C. 1H NMR (400 MHz, CDCl3): δ = 7.71 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 7.3 Hz, 2H), 7.53 (t, J = 7.3 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 6.28 (s, 1H), 4.43 (d, J = 16.6 Hz, 1H), 3.62 (d, J = 11.6 Hz, 1H), 3.48 (dd, J = 16.6, 2.0 Hz, 1H), 2.63 (d, J = 11.6 Hz, 1H), 2.44 (s, 3H), 2.41–2.28 (m, 3H), 2.12–2.00 (m, 3H); 13C NMR (100 MHz, CDCl3): δ = 216.8, 194.5, 144.1, 141.3, 137.0, 135.8, 133.0, 132.3, 129.9 (2C), 129.3 (2C), 128.4 (2C), 127.6 (2C), 53.2, 47.6, 44.4, 38.1, 34.8, 21.5, 19.3; IR (CH2Cl2): 3293, 1738, 1645 cm−1; HR-MS (EI): m/z = 432.1252, calcd. for C23H23NO4NaS (M+Na+): 432.1246. Crystals suitable for X-ray diffraction analysis were grown from CH2Cl2 and hex-

Supporting Information

Spectroscopic characterization and copies of 1H/13C NMR spectra of two diastereomers of 2c: 1H/13C NMR spectra of compounds 3a and 3o are available as Supporting Information.

Acknowledgements

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References


[8] Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 835096 (3a) and CCDC 835097 (3o). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (+ 44)-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk].

[9] All compounds 2 were subjected to IBX oxidation and fully characterized as 9-aryloxy-7-tosyl-7-azaspiro[4.5]deca-9-en-1-ones 3.