Three-Component Coupling of Aldehydes, Homoallylic Alcohols, and Trimethylsilyl Azide: A Facile Synthesis of 4-Azidotetrahydropyrans via the Prins Cyclization

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Abstract: The coupling of aldehydes, homoallylic alcohols, and trimethylsilyl azide has been achieved in the presence of phosphomolybdic acid (PMA) in dichloromethane to produce 4-azidotetrahydropyran derivatives in high yields with all cis selectivity. The use of a heteropoly acid makes this procedure simple, convenient, and cost effective.

Keywords: Prins cyclization, sodium azide, homoallylic alcohol, 4-azidotetrahydropyrans

Multicomponent, one-pot reactions are gaining importance in organic synthesis because of their wide range of application in pharmaceutical chemistry for the production of structural scaffolds and combinatorial libraries for drug discovery.1 Substituted tetrahydropyrans are important targets because of their presence in many natural products.2 In particular, the 4-aminotetrahydropyran nucleus is a core structure in various natural products such as ambruticins VS, glycamino acid, and others.3,4 Tetrahydropyran derivatives are generally prepared by Prins cyclization using acid catalysis.2b,5,6 Recently, azido compounds have been somewhat popularized due to their pivotal role in the emerging field of ‘click chemistry’7 and in particular, since the discovery of the copper(I)-catalyzed Huisgen cycloaddition8 between organic azides and terminal alkynes.9 This powerful and reliable bond-forming process has found widespread application, e.g., in combinatorial drug discovery,10 material science,11 and bioconjugation.12,13 Therefore, the introduction of an azido functionality into an organic molecule is a challenging task. Furthermore, the development of a simple and more versatile approach for the direct preparation of 4-azidotetrahydropyrans would be very useful for the synthesis of natural products possessing a 4-aminotetrahydropyran framework.

In continuation of our research on the Prins cyclization,14 we report a simple and convenient method for the preparation of 4-azidotetrahydropyrans via a three component coupling (3CC) involving the condensation of a homoallylic alcohol 2 with an aldehyde 1 and trimethylsilyl azide. The three-component-coupling reaction was carried out in the presence of 10 mol% phosphomolybdic acid (PMA).

Initially, we studied the three component coupling of 2-naphthaldehyde, but-3-en-1-ol (2a), and trimethylsilyl azide using 10 mol% phosphomolybdic acid in dichloromethane. The reaction was complete within six hours at room temperature and the product, 4-azido-2-(2-naphthyl)tetrahydro-2H-pyran (3a), was isolated in 85% yield with cis selectivity (Table 1, entry 1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-naphthyl</td>
<td>5.0</td>
<td>3a</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>4-ClC6H4</td>
<td>6.0</td>
<td>3b</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>4-MeC6H4</td>
<td>5.5</td>
<td>3c</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>4-MeOC6H4</td>
<td>5.5</td>
<td>3d</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>4-O2NC6H4</td>
<td>6.5</td>
<td>3e</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>i-Pr</td>
<td>3.0</td>
<td>3f</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>Cy</td>
<td>4.0</td>
<td>3g</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>(CH3)2Ph</td>
<td>3.5</td>
<td>3h</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>(CH3)3Me</td>
<td>4.5</td>
<td>3i</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>(E)-CH=CHPh</td>
<td>3.5</td>
<td>3j</td>
<td>82</td>
</tr>
</tbody>
</table>

All products were characterized by 1H NMR, IR, and MS.

Isolated and unoptimized yield.

This result provided incentive for further study with various aromatic aldehydes. Interestingly, substituted arylaldehydes such as 4-chlorobenzaldehyde, 4-methylbenzaldehyde, 4-methoxybenzaldehyde, and 4-nitrobenzaldehyde underwent smooth coupling with but-3-en-1-ol (2a) to furnish the corresponding 2,4-disubstituted tetrahydropyrans 3b–e in high yields (Table 1, entries 2–5). Aliphatic aldehydes such as isobutyraldehyde, cyclohexane carboxaldehyde, 3-phenylpropanaldehyde, and decanal also participated in this reaction (Table 1, entries 6–9). Furthermore, acid sensitive cinnamaldehyde also under-
went smooth cyclization with but-3-en-1-ol (2a) and tri-methylsilyl azide to give 4-azidopyran (3j) in 82% yield (Table 1, entry 10). Next, we examined the coupling of substituted homoallylic alcohols with aldehydes to produce 2,4,6-trisubstituted tetrahydropyran derivatives 4a–c (Table 2). Thus, treatment of benzaldehyde with 1-phenylbut-3-en-1-ol (2b) gave the symmetric 4-azido-2,6-diphenyltetrahydro-2H-pyran (4a) with all cis configuration (Table 2, entry 1).

Table 2 Preparation of 2,6-Disubstituted 4-Azidotetrahydropyrans

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Ph</td>
<td>6.5</td>
<td>4a</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>Cy</td>
<td>Ph</td>
<td>6.0</td>
<td>4b</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>Cy</td>
<td>Cy</td>
<td>4.0</td>
<td>4c</td>
<td>91</td>
</tr>
</tbody>
</table>

a All products were characterized by 1H NMR, IR and MS.

b Isolated and unoptimized yield.

Similarly, the coupling of cyclohexanecarbaldehyde with 1-cyclohexylbut-3-en-1-ol (2c) afforded the symmetrical 4-azido-2,6-dicyclohexyltetrahydro-2H-pyran (4c) under identical conditions (Table 2, entry 3). However, no reaction was observed in the absence of a catalyst even after an extended reaction time (15 h). As solvent, dichloromethane appeared to give the best results. In all cases, the reactions proceeded rapidly at room temperature unromethane appeared to give the best results. In all cases, an extended reaction time (15 h).

In conclusion, we have developed a novel method for the synthesis of highly substituted 4-azidotetrahydropyran derivatives via the Prins cyclization and azidation sequence using phosphomolybdic acid as a solid acid catalyst. This method provides an access to 2-substituted and 2,6-disubstituted 4-azidotetrahydropyran in a single step. The use of a heteropoly acid makes this procedure quite simple, convenient and practical.

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. 1H NMR spectra were recorded on Varian unity 300 spectrometer in CDCl₃ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

2-Substituted and 2,6-Disubstituted 4-Azidotetrahydropyrans 3 and 4; General Procedure

A mixture of TMSN₃ (2 mmol) and PMA (10 mol%) in CH₂Cl₂ (3 mL) was stirred at 23 °C for 30 min. Then a solution of homoallylic alcohol (1.0 mmol) and aldehyde (1.0 mmol) in CH₂Cl₂ (3 mL) was added at 0 °C and allowed to stir at 23 °C for the specified time (Tables 1 and 2). When the reaction was complete (TLC), the mixture was quenched with H₂O and extracted with CH₂Cl₂ (2 × 10 mL). The combined organic layers were washed with brine and dried (anhyd Na₂SO₄). Removal of the solvent followed by purification on silica gel (Merck, 100–200 mesh, EtOAc–hexane, 1:9) gave the pure 4-azidotetrahydropyran. The products thus obtained were characterized by IR, NMR, and MS.

4-Azido-2-(2-naphthyl)tetrahydro-2H-pyran (3a)

Dark yellow liquid.

IR (KBr): 3055, 2923, 2850, 2095, 1499, 1364, 1253, 1145, 1083, 1008, 787, 716 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.74 (m, 4 H), 7.41 (m, 3 H), 4.43 (dd, J = 1.6, 11.7 Hz, 1 H), 4.23 (dd, J = 4.7, 11.7 Hz, 1 H), 3.70–3.56 (m, 1 H), 3.60 (dt, J = 2.4, 11.7 Hz, 1 H), 2.32–2.17 (m, 1 H), 2.03–1.86 (m, 1 H), 1.86–1.52 (m, 2 H).

13C NMR (75 MHz, CDCl₃): δ = 127.3, 40.7, 46.5, 67.1, 78.7, 123.9, 124.3, 125.8, 126.1, 127.6, 128.0, 128.1, 132.9, 133.3, 139.4.


4-Azido-2-(4-chlorophenyl)tetrahydro-2H-pyran (3b)

Yellow liquid.

IR (KBr): 2924, 2850, 2095, 1499, 1364, 1253, 1145, 1083, 1008, 821, 716 cm⁻¹.

Scheme 1

A Facile Synthesis of 4-Azidotetrahydropyrans

4-Azido-2-(2-phenylethyl)tetrahydro-2H-pyran (3c)
Light yellow liquid.
IR (KBr): 3028, 2954, 2924, 2854, 2809, 1461, 1358, 1250, 1149, 1087 cm⁻¹.
1H NMR (300 MHz, CDCl₃): δ = 7.58–7.08 (m, 5 H), 6.57 (d, J = 15.8 Hz, 1 H), 4.20–4.05 (m, 1 H), 4.00–3.81 (m, 1 H), 3.60–3.46 (m, 1 H), 3.50 (dt, J = 5.1, 12.0 Hz, 1 H), 2.15–2.02 (m, 1 H), 2.00–1.80 (m, 1 H), 1.78–1.34 (m, 2 H).
13C NMR (75 MHz, CDCl₃): δ = 131.2, 130.3, 129.5, 128.3, 127.4, 126.1, 77.3, 66.6, 58.0, 38.9, 32.9.
LC-MS: m/z (%) = 252 [M + Na].

4-Azido-2-(2-phenylvinyl)tetrahydro-2H-pyran (3i)
Colorless liquid.
IR (KBr): 2926, 2854, 1461, 1358, 1250, 1149, 1087 cm⁻¹.
1H NMR (300 MHz, CDCl₃): δ = 7.58–7.08 (m, 5 H), 6.57 (d, J = 15.8 Hz, 1 H), 4.20–4.05 (m, 1 H), 4.00–3.81 (m, 1 H), 3.60–3.46 (m, 1 H), 3.50 (dt, J = 5.1, 12.0 Hz, 1 H), 2.15–2.02 (m, 1 H), 2.00–1.80 (m, 1 H), 1.78–1.34 (m, 2 H).
13C NMR (75 MHz, CDCl₃): δ = 131.2, 130.3, 129.5, 128.3, 127.4, 126.1, 77.3, 66.6, 58.0, 38.9, 32.9.
LC-MS: m/z (%) = 252 [M + Na].

(2E)-4-Azido-2-(2-phenylvinyl)tetrahydro-2H-pyran (3j)
Yellow liquid.
IR (KBr): 2926, 2854, 2809, 1461, 1358, 1250, 1149, 1087 cm⁻¹.
1H NMR (300 MHz, CDCl₃): δ = 7.58–7.08 (m, 5 H), 6.57 (d, J = 15.8 Hz, 1 H), 4.20–4.05 (m, 1 H), 4.00–3.81 (m, 1 H), 3.60–3.46 (m, 1 H), 3.50 (dt, J = 5.1, 12.0 Hz, 1 H), 2.15–2.02 (m, 1 H), 2.00–1.80 (m, 1 H), 1.78–1.34 (m, 2 H).
13C NMR (75 MHz, CDCl₃): δ = 131.2, 130.3, 129.5, 128.3, 127.4, 126.1, 77.3, 66.6, 58.0, 38.9, 32.9.
LC-MS: m/z (%) = 252 [M + Na].
2-H). 314.2215. 1070, 1039, 996 cm–1. 4-Azido-2,6-dicyclohexyltetrahydro-2H-pyran (4b)
Pale yellow liquid. IR (KBr): 2923, 2848, 2093, 1488, 1369, 1154, 1085, 1010, 812 cm–1.

HRMS: m/z [M + Na] calcd for C17H17N3ONa: 302.1269; found: 302 [M + Na].

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References