Efficient Synthesis of a 5α-Reductase Inhibitor, 3-(Tetrazol-5-yl)-3,5-pregnadien-20-one through Allylic Rearrangement of Cyanophosphates

Hiroki Yoneyama
Yoshihide Usami
Shinya Harusawa*
Osaka University of Pharmaceutical Sciences, 4-20-1 Nasahara, Takatsuki, Osaka 569-1094, Japan
harusawa@gly.oups.ac.jp

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Abstract We describe the use of allylic rearrangements of cyanophosphates for the efficient and practical synthesis of 3-(tetrazol-5-yl)-3,5-pregnadien-20-one, which is a potent 5α-reductase inhibitor (IC50: 15.6 nM), from pregnene-3,20-dione in 92% overall yield in four steps.

Key words synthesis, DEPC, cyanophosphates, allylic rearrangement, 3-(tetrazol-5-yl)-3,5-pregnadien-20-one, 5AR inhibitor

Androgens play a vital role in benign prostatic hyperplasia (BPH) and cancer growth in the prostate.1 5α-Reductase (5AR) catalyzes the conversion of testosterone into more potent dihydrotestosterone (DHT). DHT stimulates several growth factors that drive cellular proliferation in the human prostate. Therefore, the inhibition of 5AR has been considered as a valid therapeutic target. There are two main isozymes, 5AR-1 and 5AR-2, with different tissue distribution patterns and distinct biochemical and pharmacological properties.2 The most commonly used 5AR inhibitor in BPH treatment is finasteride (1), which was the first 5AR inhibitor approved in the U.S. for the treatment of BPH (Figure 1).3,4 However, its limited activity and side effects, which are related to sexual function, have prompted the development of new 5AR inhibitors.5

Kumar and co-workers recently reported a series of steroidal tetrazole derivatives; 3-(tetrazol-5-yl)-3,5-pregnadien-20-one (TzPD, 2) showed the most potent 5AR-2 inhibition with an IC50 of 15.6 nM, while that of clinically used drug finasteride is 40 nM (Figure 1).5 Compound 2 also showed significant 5AR-1 inhibition with an IC50 547 nM, whereas that of finasteride is IC50 453 nM.

Kumar et al. prepared TzPD 2 in 67% yield through treatment of diene nitrile 4 with sodium azide and triethylamine hydrochloride (Scheme 1).6 However, the yields of the two steps (bromination and cyanation)7 for the preparation of 4 from pregn-4-ene-3,20-dione (progesterone, 3) were not reported.

α-Cyanophosphates (CPs)8 have been widely utilized as synthetic intermediates in organic synthesis.9 In 1985, we reported that CPs derived from α,β-unsaturated ketones were transformed into diene nitriles through a BF3·OEt2-catalyzed allylic rearrangement, as shown in Scheme 2.10 In the case of 6-methylbicyclo[4,4,0]dec-1-en-3-one (5),10a treatment with diethyl phosphorocyanidate (DEPC)9 in the
presence of lithium cyanide afforded CP 6, bearing a 3α-cyano-3β-diethyolphosphoxy group. Subsequent treatment of 6 with BF₃·OEt₂ afforded diene nitrile 8 (94%) through allylic rearrangement to give phosphate 7 and subsequent elimination of (EtO)₂P(O)OH. It has been considered that the rearrangement is a suprafacial [3,3]-sigmatropic rearrangement.11

Scheme 2  Formation of diene nitrile 8 through allylic rearrangement of CP 6

In a continuation of our recent program on the utilization of CPs, we were encouraged to look once again for a practical synthetic method to access key intermediate 4 for TzPD 2. Herein, we report the efficient and practical synthesis of potent 5AR-2 inhibitor 2 by using the allylic rearrangement of CPs.

Starting from progesterone 3, the synthesis of precursor 4 towards target tetrazole 2 was carried out through the allylic rearrangement of CPs followed by dephosphorylation, as illustrated in Scheme 3. Reaction of 3 with DEPC (4.0 equiv) in the presence of LiCN (2.0 equiv) easily afforded C₁₂₂₀-bis-CP 9. Compound 9 was subsequently treated with BF₃·OEt₂ (3.0 equiv) in benzene at room temperature (rt) for 1 hour (h) to give diene nitrile 10; C₂₀-CP was left unchanged. Subsequent hydrolysis of 10 with a solution of 20% NaOH produced diene nitrile 4 in 94% overall yield in three steps from starting compound 3. Furthermore, it should be noted that the CP group also plays a significant role as a protecting group for the C₂₀-ketone.

We next investigated the transformation of diene nitrile 4 into TzPD 2 by using two reagent systems: sodium azide (NaN₃) in the presence of triethylamine hydrochloride (Et₃N·HCl) (Table 1, entries 1–3) and the system described in Wittenberger’s method, namely trimethylsilyl azide (TMSN₃) in the presence of a catalytic amount of Bu₂SnO (entries 4–6). Although the reaction of 4 with NaN₃/Et₃N·HCl gave diene tetrazole 2 in low yields in tetrahydrofuran (THF) and N,N-dimethylformamide (DMF) (entries 1 and 2), compound 4 was converted into 2 in 93% yield under microwave (MW) irradiation conditions in DMF at 130 °C (entry 3). Alternatively, it was found that 4 was transformed favorably into the corresponding tetrazole 2 in 98% yield when heated at reflux with 2 equivalents of TMSN₃ in the presence of Bu₂SnO (0.1 equiv) in toluene for 24 h (entry 6). Therefore, the synthesis of target molecule 2 from progesterone 3 was completed successfully in 92% overall yield in four steps, as summarized in Scheme 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>RN₃ (equiv)</th>
<th>Solv.</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaN₃ (3)</td>
<td>Et₃N·HCl (3)</td>
<td>THF</td>
<td>reflux</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>NaN₃ (3)</td>
<td>Et₃N·HCl (3)</td>
<td>DMF</td>
<td>24</td>
<td>130</td>
</tr>
<tr>
<td>3</td>
<td>NaN₃ (3)</td>
<td>Et₃N·HCl (3)</td>
<td>DMF</td>
<td>2</td>
<td>MW, 130</td>
</tr>
<tr>
<td>4</td>
<td>TMSN₃ (1)</td>
<td>Bu₂SnO (0.1)</td>
<td>toluene</td>
<td>reflux</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>TMSN₃ (1)</td>
<td>Bu₂SnO (0.1)</td>
<td>toluene</td>
<td>24</td>
<td>reflux</td>
</tr>
<tr>
<td>6</td>
<td>TMSN₃ (2)</td>
<td>Bu₂SnO (0.1)</td>
<td>toluene</td>
<td>24</td>
<td>reflux</td>
</tr>
</tbody>
</table>
In conclusion, we have described the efficient and practical synthesis of TzPD 2 from progesterone (3) by using an allylic rearrangement in CP 9. The present method for the synthesis of 2 is experimentally straightforward and it is suitable for the synthesis of some steroidal 5AR inhibitors. The present study also helps increase the diversity of available CPs. In addition, application of this method involving CPs to the synthesis of many biologically important substrates is under investigation in our laboratory.

Reactions were carried out under an Ar atmosphere. Anhydrous solvents (THF, benzene, and toluene) were purchased from Wako Chemical Company. Solvents were dried over Na2SO4, and removed on a rotary evaporator under reduced pressure. Fuji Silysia FL-60D silica gel was added NaOH (2.0 g, 50 mmol). After being stirred for 1 h at r.t., the reaction mixture was evaporated to give a residue, which was diluted with EtOAc/hexane (1:1), washed with H2O and brine, and dried over Na2SO4. After filtration, the solvent was evaporated to give a residue, which was purified using column chromatography (EtOAc/hexane, 3:1) to give 4.

Yield: 1678 mg (94%); white powder.

1H NMR (CDCl3, 400 MHz): δ = 6.66 (d, J = 2.4 Hz, 1 H), 5.78 (t, J = 3.6 Hz, 1 H), 2.55 (t, J = 8.8 Hz, 1 H), 2.06–2.44 (m, 4 H), 2.14 (s, 3 H), 1.63–1.72 (m, 6 H), 1.16–1.52 (m, 6 H), 1.02–1.10 (m, 1 H), 0.93 (s, 3 H), 0.66 (s, 3 H).

13C NMR (CDCl3, 100 MHz): δ = 209.3, 143.2, 139.8, 132.4, 120.3, 106.6, 63.5, 56.7, 47.6, 44.0, 38.6, 34.4, 32.7, 32.0, 31.5 (31.51), 31.5 (31.45), 243 (24.29), 243 (24.28), 22.8, 20.9, 18.9, 13.3.


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Supporting Information
Supporting Information for this article is available online at https://doi.org/10.1055/s-0037-1612060. Included are investigations of the reaction mechanism for the transformation of enone CPs into dienes, and 1H and 13C NMR spectra for compounds 2 and 4.

References
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(11) In connection with this study, the reaction mechanism for the transformation of enone CPs into diene nitriles was reinvestigated (see Supporting Information).


(13) Progesterone (3) was purchased from TCI Co., Ltd.


