New Efficient Synthesis of 6,7,8,9-Tetrahydro-benzothieno[2,3-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-ones via a Tandem Aza-Wittig/Heterocumulene-Mediated Annulation

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Abstract: The carbodiimides 2, obtained from aza-Wittig reactions of iminophosphorane 1 with aromatic isocyanates, reacted with hydrazine to give selectively 3-amino-2-arylamino-5,6,7,8-tetrahydro-benzothieno[2,3-d]-[4(3H)]-ones 4. Reactions of 4 with triphenylphosphine, hexachloroethane and Et3N produced iminophosphoranes 5. A tandem aza-Wittig reaction of iminophosphorane 5 with isocyanate, acyl chloride or CS2 generated 6,7,8,9-tetrahydro-benzothieno[2,3-d]-[1,2,4-triazolo][1,5-a]pyrimidin-10(3H)-ones 7, 9 or 11 in satisfactory yields.

Key words: aza-Wittig reaction, benzothieno[2,3-d]pyrimidin-4(3H)-one, benzothieno[2,3-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-ones, triazole, iminophosphorane

The derivatives of thienopyrimidine are of great importance because of their remarkable biological properties. For example, some thienopyrimidinones show significant antifungal and antibacterial activities.1,2 Whereas others exhibited good anticonvulsant and angiotensin II or H2 receptor antagonist activities.3-5 On the other hand, heterocycles containing 1,2,4-triazole nucleus also exhibit various biological activities; several of them have been used as fungicidal, bactericidal, insecticidal, antitumor and anti-inflammatory agents.6-10 The introduction of a triazole ring to the thienopyrimidine system is expected to influence the biological activities significantly. In fact, some 6,7,8,9-tetrahydro-benzothieno[2,3-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-ones have been reported to display good antibacterial and anticonvulsant activities.11,12 The methods described so far for the preparation of some representative derivatives of this ring system involve either reaction of 3-arylamino-5,6,7,8-tetrahydro-benzothieno[2,3-d]pyrimidin-4(3H)-ones with triethyl orthoformate or acetic anhydride at refluxing temperature,11,12 or cyclization of 3-arylamino-5,6,7,8-tetrahydro-benzothieno[2,3-d]pyrimidin-4(3H)-ones with carboxylic acids or isothiocyanates.13 However, these methods often require relatively harsh acid or the heating at high temperature. Recently we have been interested in the synthesis of triazoloquinazolinones, thienopyrimidinones and imidazolinones via aza-Wittig reaction, with the aim of evaluating their fungicidal activities.14-18

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Here we wish to report a new efficient synthesis of various 2-substituted 6,7,8,9-tetrahydro-benzothieno[2,3-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-ones from easily accessible iminophosphorane 1. Iminophosphorane 1 reacted with aromatic isocyanates to give carbodiimides 2, which were allowed to react with hydrazine to give selectively 2-arylamino-3-amino-5,6,7,8-tetrahydro-benzothieno[2,3-d]pyrimidin-4(3H)-ones 4 in 74–87% yields at room temperature (Scheme 1). The formation of 4 can be rationalized in terms of an initial nucleophilic addition of hydrazine to give the guanidine intermediate 3 which cyclizes to give 4 across the strong nucleophilic hydrazine group rather than the arylamino one. Although 4 have been obtained from prolonged heating of corresponding thioureido derivatives with hydrazine hydrate in 48–50% yields,11 our synthetic method of 4 has the advantage of good yields, mild condition and easy separation of the product by simple filtration. Compounds 4 were further converted to novel functionalized iminophosphoranes 5 via reaction with triphenylphosphine, hexachloroethane and Et3N in good yields (76–84%, Scheme 1).

When solutions of iminophosphoranes 5 in anhydrous CH2Cl2 were treated with aromatic isocyanate at room temperature, the color of the reaction mixture quickly turned red, disappearing after few minutes, and 2-arylamino-6,7,8,9-tetrahydro-benzothieno[2,3-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-ones 7 were isolated as crystalline solids in excellent yields (81–92%, Table 1, Scheme 2). Presumably, the conversion of 5 into 7 involves initial aza-Wittig reaction between the iminophosphorane 5 and the isocyanate to give a carbodiimide 6 as highly reactive intermediate, which easily undergoes ring closure across the arylamino group to give the otherwise not readily available 2-arylamino substituted 6,7,8,9-tetrahydro-benzothieno[2,3-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-ones 7. It is noteworthy that the reaction can be easily carried out at room temperature under mild neutral condition and the separation of 7 from the reaction mixture was also easily carried out by simple filtration.

Iminophosphoranes 5 reacted with acyl chlorides in the presence of Et3N in CH2Cl2 at room temperature to give 2-substituted 6,7,8,9-tetrahydro-benzothieno[2,3-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-ones 9 in good yields (68–83%, Table 1, Scheme 3). The formation of 9 can be
viewed as an initial aza-Wittig reaction between the iminophosphorane 5 and acyl chloride in presence of Et₃N affording the intermediate imidoyl chloride 8, which undergoes cyclization to give 9.

Scheme 3

Table 1  Preparation of Compounds 4, 5, 7, 9 and 11

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th>Conditions</th>
<th>Yield (%) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>Ph</td>
<td></td>
<td>r.t./10 min</td>
<td>87</td>
</tr>
<tr>
<td>4b</td>
<td>4-Cl-C₆H₄</td>
<td></td>
<td>r.t./10 min</td>
<td>74</td>
</tr>
<tr>
<td>5a</td>
<td>Ph</td>
<td></td>
<td>r.t./4 h</td>
<td>84</td>
</tr>
<tr>
<td>5b</td>
<td>4-Cl-C₆H₄</td>
<td></td>
<td>r.t./6 h</td>
<td>76</td>
</tr>
<tr>
<td>7a</td>
<td>Ph</td>
<td>4-Me-C₆H₄</td>
<td>r.t./2 h</td>
<td>86</td>
</tr>
<tr>
<td>7b</td>
<td>Ph</td>
<td>3-Me-C₆H₄</td>
<td>r.t./2 h</td>
<td>84</td>
</tr>
<tr>
<td>7c</td>
<td>Ph</td>
<td>Ph</td>
<td>r.t./1 h</td>
<td>91</td>
</tr>
<tr>
<td>7d</td>
<td>Ph</td>
<td>4-Cl-C₆H₄</td>
<td>r.t./1 h</td>
<td>92</td>
</tr>
<tr>
<td>7e</td>
<td>4-Cl-C₆H₄</td>
<td>4-Me-C₆H₄</td>
<td>r.t./2 h</td>
<td>81</td>
</tr>
<tr>
<td>7f</td>
<td>4-Cl-C₆H₄</td>
<td>3-Me-C₆H₄</td>
<td>r.t./2 h</td>
<td>83</td>
</tr>
<tr>
<td>7g</td>
<td>4-Cl-C₆H₄</td>
<td>Ph</td>
<td>r.t./1 h</td>
<td>90</td>
</tr>
<tr>
<td>7h</td>
<td>4-Cl-C₆H₄</td>
<td>4-Cl-C₆H₄</td>
<td>r.t./1 h</td>
<td>86</td>
</tr>
<tr>
<td>9a</td>
<td>Ph</td>
<td>Ph</td>
<td>r.t./3 h</td>
<td>83</td>
</tr>
<tr>
<td>9b</td>
<td>Ph</td>
<td>Me</td>
<td>r.t./4 h</td>
<td>68</td>
</tr>
<tr>
<td>11</td>
<td>Ph</td>
<td></td>
<td>40 °C/18 h</td>
<td>88</td>
</tr>
</tbody>
</table>

a Isolated yields.
In summary, we have developed an efficient synthesis of 2-substituted 6,7,8,9-tetrahydro-benzothieno[2,3-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-ones via aza-Wittig reactions. This method utilizes easily accessible starting material and allows mild reaction conditions, straightforward product isolation and good yields. We think that the synthetic approach discussed here in many cases favorably compares with other existing methods.

Melting points are uncorrected. MS were measured on a Finnigan Trace MS spectrometer. IR spectra were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm\(^{-1}\). NMR spectra were recorded in CDCl\(_3\) on a Varian Mercury 400 spectrometer and resonances are given in ppm (\(\delta\)) relative to TMS. Elementary analyses were taken on a Vario EL III elementary analysis instrument.

**3-Amino-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidin-4(3H)-ones 4; General Procedure**

To a solution of iminophosphorane 1\(^{10}\) (2.42 g, 5 mmol) in anhyd CH\(_2\)Cl\(_2\) (15 mL) was added aromatic isocyanate (5 mmol) under N\(_2\) at r.t. After the reaction mixture was allowed to stand for 6–12 h at 0–5 °C, the solvent was removed under reduced pressure and Et\(_2\)O-petroleum ether (1:2, 20 mL) was added to precipitate triphe-nylphosphine oxide. The reaction mixture was filtered and the solution was washed with water and dried over anhyd MgSO\(_4\). The orange-yellow oil was distilled under reduced pressure and the residue was recrystallized from CH\(_2\)Cl\(_2\)-EtOH to give iminophosphoranes 5; General Procedure

**4a**
White crystals; mp 227–229 °C (Lit.\(^{11}\) mp 230–232 °C).

**4b**
White crystals; mp 253–254 °C (Lit.\(^{11}\) mp 254–256 °C).

**N-(2-Arylamino-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidin-4(3H)-on-3-yl)iminophosphoranes 5; General Procedure**

To a mixture of 4 (8 mmol), PPh\(_3\) (3.14 g, 12 mmol) and C\(_6\)Cl\(_6\) (2.84 g, 12 mmol) in anhyd CH\(_2\)Cl\(_2\) (40 mL), Et\(_3\)N was added dropwise (2.42 g, 24 mmol) at r.t. The color of the reaction mixture quickly turned to yellow. After stirring for 4–6 h, the solvent was removed under reduced pressure and the residue was recrystallized from EtOH to give iminophosphoranes 5.

**5a**
White crystals; mp 279–280 °C.

<table>
<thead>
<tr>
<th>IR (KBr): 3284 (NH), 1649 (C=O), 1539, 1110 cm(^{-1}).</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^1)H NMR (400 MHz, CDCl(_3)): (\delta = 9.52) (s, 1 H, NH), 7.77–7.02 (m, 20 H, ArH), 2.67–2.60 (m, 4 H, 2 × CH(_2)), 1.78–1.65 (m, 4 H, 2 × CH(_2)).</td>
</tr>
</tbody>
</table>

**MS:** m/z (%) = 572 (65) [M\(^{+}\)], 312 (19), 262 (100), 183 (99), 108 (76).

**Anal. Calcd for C\(_{35}\)H\(_{26}\)ClN\(_5\)O: C, 66.81; H, 4.63; N, 9.31.**

**5b**
White crystals; mp 241–242 °C.

<table>
<thead>
<tr>
<th>IR (KBr): 3244 (NH), 1648 (C=O), 1541, 1113 cm(^{-1}).</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^1)H NMR (400 MHz, CDCl(_3)): (\delta = 9.52) (s, 1 H, NH), 7.77–7.26 (m, 19 H, ArH), 2.67–2.60 (m, 4 H, 2 × CH(_2)), 1.76–1.67 (m, 4 H, 2 × CH(_2)).</td>
</tr>
</tbody>
</table>

**MS:** m/z (%) = 608 (7) [M\(^{+}\)], 606 (20) [M\(^{+}\)], 278 (31), 262 (100), 183 (93), 108 (34).

**7a**
White crystals; mp 279–280 °C.

<table>
<thead>
<tr>
<th>IR (KBr): 3258 (NH), 1664 (C=O), 1578, 1401 cm(^{-1}).</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^1)H NMR (400 MHz, CDCl(_3)): (\delta = 7.62–7.05) (m, 9 H, ArH), 6.47 (s, 1 H, NH), 3.09–2.70 (m, 4 H, 2 × CH(_2)), 2.27 (s, 3 H, CH(_3)), 1.92–1.80 (m, 4 H, 2 × CH(_2)).</td>
</tr>
</tbody>
</table>

**MS:** m/z (%) = 427 (100) [M\(^{+}\)], 399 (61), 294 (76), 214 (44), 77 (79).

**7b**
White crystals; mp >300 °C.

<table>
<thead>
<tr>
<th>IR (KBr): 3248 (NH), 1673 (C=O), 1568, 1494 cm(^{-1}).</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^1)H NMR (400 MHz, CDCl(_3)): (\delta = 7.66–6.81) (m, 9 H, ArH), 6.46 (s, 1 H, NH), 3.08–2.69 (m, 4 H, 2 × CH(_2)), 2.26 (s, 3 H, CH(_3)), 1.92–1.80 (m, 4 H, 2 × CH(_2)).</td>
</tr>
</tbody>
</table>

**MS:** m/z (%) = 427 (100) [M\(^{+}\)], 399 (78), 294 (76), 214 (44), 77 (79).

**7c**
White crystals; mp 282–283 °C.

<table>
<thead>
<tr>
<th>IR (KBr): 3244 (NH), 1673 (C=O), 1574, 1477 cm(^{-1}).</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^1)H NMR (400 MHz, CDCl(_3)): (\delta = 7.70–7.06) (m, 10 H, ArH), 6.31 (s, 1 H, NH), 3.11–2.71 (m, 4 H, 2 × CH(_2)), 1.94–1.80 (m, 4 H, 2 × CH(_2)).</td>
</tr>
</tbody>
</table>

**MS:** m/z (%) = 413 (100) [M\(^{+}\)], 385 (73), 294 (69), 207 (42), 77 (84).

**7d**
White crystals; mp 257–259 °C.

<table>
<thead>
<tr>
<th>IR (KBr): 3415 (NH), 1681 (C=O), 1577, 1476 cm(^{-1}).</th>
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</thead>
<tbody>
<tr>
<td>1(^1)H NMR (400 MHz, CDCl(_3)/TFA): (\delta = 7.74–7.24) (m, 9 H, ArH), 6.39 (s, 1 H, NH), 3.01–2.73 (m, 4 H, 2 × CH(_2)), 1.93–1.80 (m, 4 H, 2 × CH(_2)).</td>
</tr>
</tbody>
</table>

**MS:** m/z (%) = 449 (35) [M\(^{+}\)], 447 (100) [M\(^{+}\)], 419 (54), 294 (55), 152 (26), 77 (72).

**7e**
White crystals; mp 189–190 °C.

| IR (KBr): 3258 (NH), 1666 (C=O), 1574, 1476 cm\(^{-1}\). |

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To a solution of iminophosphorane midin-10(3) from CH2Cl2–EtOH to give trate was concentrated to dryness. The residue was recrystallized precipitated ammonium salt was separated by filtration and the filtrate was collected by filtration to give 9; General Procedure

white crystals; mp >300 °C.

IR (KBr): 3254 (NH), 1667 (C=O), 1571, 1475 cm–1.

White crystals; mp 294–296 °C.

MS: m/z (%) = 354 (49) [M+] , 326 (10), 293 (10), 146 (11), 40 (100).

Anal. Calcd for C17H14N4OS2: C, 57.61; H, 3.98; N, 15.81. Found:

7f

6.32 (s, 1 H, NH), 3.02–2.74 (m, 4 H, 2 CH2). 1H NMR (400 MHz, CDCl 3/TFA):

IR (KBr): 1689 (C=O), 1585, 1473, 1399 cm–1.

(37), 77 (100).

Anal. Calcd for C24H20ClN5OS: C, 62.40; H, 4.36; N, 15.16. Found:

131 (29), 91 (58).

Anal. Calcd for C24H20ClN5OS: C, 62.40; H, 4.36; N, 15.16. Found:

Anal. Calcd for C24H20ClN5OS: C, 62.40; H, 4.36; N, 15.16. Found:

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References


