A Solution-Phase Parallel Synthesis of 5-Substituted 3,6-Dihydro-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-ones

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5-Substituted 7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-ones (**4**) were rapidly prepared by a solution-phase parallel synthetic method, which includes aza-Wittig reaction of iminophosphorane (**1**) with phenyl isocynate to give carbodiimide (**2**) and subsequent reaction of **2** with various amine and alcohols in the presence of catalytic amount of sodium alkoxide in a parallel fashion.

Keywords aza-Wittig reaction, triazolo[4,5-*d*]pyrimidin-7-one, parallel synthesis, isocyanate

Introduction

7*H*-1,2,3-Triazolo[4,5-*d*]pyrimidin-7-ones, also named as 8-azaguanines, are of great importances because of their remarkable biological properties and their structural similarity with guanines. For example, some derivatives of them show significant antitumor, antiviral, and anti-HIV activities,[1-3] whereas others exhibited good fungicidal activities.[4] There are many known methods for the synthesis of 7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-ones,[5-8] however, there were few reports on the synthesis of 5-amino or 5-alkoxy substituted 7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-ones.[9]

Recently, combinatorial synthesis of libraries containing small organic molecules has become a rapid evolving area of research.[10-12] It includes solid-phase and solution-phase synthetic techniques. Solution-phase synthetic techniques have the advantages of nonlimiting scale and can be easily manipulated as well, but purification of the reaction products is difficult.

The aza-Wittig reactions of iminophosphoranes have received increased attention in view of their utility in the synthesis of nitrogen heterocyclic compounds.[13-15] Annelation of ring systems with *N*-heterocycles by means of an aza-Wittig reaction has been widely utilized because of the availability of functionalized iminophosphoranes. Here we wish to report a solution-phase parallel synthesis of some new derivatives of 5-substituted 7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-ones (**4**). By using this parallel synthetic method, **4** was rapidly obtained and the separation of **4** from the reaction mixture was easily carried out by simple recrystallization.

Exeperimental

Melting points were determined using a X-4 model apparatus (Beijing Taike Company) and were uncorrected. MS were measured on Finnigan Trace MS spectrometer. IR spectra were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. NMR were recorded in $CDCl_3$ on a Varian Mercury 400 spectrometer and resonances are given relative to TMS. Elementary analyses were taken on a Vario EL III elementary analysis instrument. Iminophosphorane (**1**) was prepared by the literature report.[16]

Parallel synthesis of 2-substituted 7*H*-1,2,3-triazolo-[4,5-d]pyrimidin-7-ones (4)

To a solution of iminophosphorane **1** (13.7 g, 26 mmol) in dry methylene dichloride (100 mL) was added phenyl isocyanate (3.09 g, 26 mmol) under nitrogen at r.t. After the reaction mixture was stood for 24 h, the solvent was removed off under reduced pressure and ether/petroleum ether (V ∶ V = 1 ∶ 2, 200 mL) was added to precipitate triphenylphosphine oxide. After filtration, the filtrate was condensed and methylene dichloride was added to make a solution of carbodiimide (**2**) (130 mL), which was divided into thirteen parts (10 mL every part). To each part of **2** prepared above (10 mL) was added separately di-*n*-propylamine (0.20 g, 2 mmol), or di-*n*-butylamine (0.26 g, 2 mmol), or di-*iso*-butylamine (0.26 g, 2 mmol), or di-*n*-pentylamine (0.31 g, 2 mmol), or di-*n*-hexylamine (0.37 g, 2 mmol), or piperidine (0.17 g, 2 mmol), or morpholine (0.17 g, 2 mmol), or methol (0.04 g, 2 mmol), or *n*-propanol (0.12 g, 2 mmol), or *iso*-propanol (0.12 g, 2 mmol), or *n*-butanol (0.15 g, 2 mmol), or prop-2-en-1-ol (0.12 g, 2 mmol), or prop-2-yn-1-ol (0.11 g, 2 mmol). After the reaction mixture was stood for 1—2 h, anhydrous alcohol (10 mL) with several drops of RONa in ROH was added. The mixture was stirred for 2—5 h at room temperature (r.t.). The solution was condensed and the residual was recrystallized from ethanol to give

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7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-ones **4a** — **4m** separately.

3-(4-Chlorophenyl)-5-di(*n*-propyl)amino-6-phenyl-3,6-dihydro-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (4a) White solid, m.p. 212—214 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.20—7.27 (m, 9H, ArH), 3.07 (t, J=7.6 Hz, 4H, $2NCH_2$), 1.37—1.28 (m, 4H, $2CH_2$), 0.76 (t, J=7.2 Hz, 6H, $2CH_3$); IR (KBr) ν: 1720, 1595, 1526, 1360 cm^{-1}; MS *m*/*z* (%): 423 (M^+, 20), 323 (13), 137 (59), 111 (45), 77 (100). Anal. calcd for $C_{22}H_{23}ClN_6O$: C 62.48, H 5.48, N 19.87; found C 62.23, H 5.54, N 19.96.

3-(4-Chlorophenyl)-5-di(*n*-butyl)amino-6-phenyl-3,6-dihydro-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (4b) White solid, m.p. 118—120 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.19—7.30 (m, 9H, ArH), 3.11 (t, J=7.6 Hz, 4H, $2NCH_2$), 1.29—1.12 (m, 8H, $4CH_2$), 0.85 (t, J=7.2 Hz, 6H, $2CH_3$); IR (KBr) ν: 2961, 1727, 1533, 1361 cm^{-1}; MS *m*/*z* (%): 450 (M^+, 10), 422 (8), 366 (4), 323 (25), 287 (16), 137 (65), 77 (100). Anal. calcd for $C_{24}H_{27}ClN_6O$: C 63.92, H 6.03, N 18.64; found C 63.81, H 6.24, N 18.80.

3-(4-Chlorophenyl)-5-di(*iso*-butyl)amino-6-phenyl-3,6-dihydro-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (4c) White solid, m.p. 192—194 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.19—7.32 (m, 9H, ArH), 2.92 (d, J=7.2 Hz, 4H, $2NCH_2$), 1.93—1.85 (m, 2H, 2CH), 0.82 (d, J=6.4 Hz, 6H, $2CH_3$); IR (KBr) ν: 2962, 1720, 1526, 1386 cm^{-1}; MS *m*/*z* (%): 450 (M^+, 10), 422 (5), 323 (50), 137 (40), 41 (100). Anal. calcd for $C_{24}H_{27}ClN_6O$: C 63.92, H 6.03, N 18.64; found C 63.98, H 6.18, N 18.46.

3-(4-Chlorophenyl)-5-di(*iso*-pentyl)amino-6-phenyl-3,6-dihydro-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (4d) White solid, m.p. 115—117 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.19—7.31 (m, 9H, ArH), 3.09 (t, J=7.6 Hz, 4H, $2NCH_2$), 1.30—1.09 (m, 12H, $6CH_2$), 0.86 (t, J=7.2 Hz, 6H, $2CH_3$); IR (KBr) ν: 2954, 1720, 1596, 1536 cm^{-1}; MS *m*/*z* (%): 478 (M^+, 10), 450 (16), 323 (19), 287 (17), 77 (78), 43 (100). Anal. calcd for $C_{26}H_{31}ClN_6O$: C 65.19, H 6.52, N 17.54; found C 65.02, H 6.74, N 17.67.

3-(4-Chlorophenyl)-5-di(*iso*-hexyl)amino-6-phenyl-3,6-dihydro-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (4e) White solid, m.p. 113—114 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.19—7.27 (m, 9H, ArH), 3.09 (t, J=7.6 Hz, 4H, $2NCH_2$), 1.32—1.10 (m, 16H, $8CH_2$), 0.87 (t, J=7.2 Hz, 6H, $2CH_3$); IR (KBr) ν: 2956, 1720, 1600, 1526 cm^{-1}; MS *m*/*z* (%): 506 (M^+, 6), 478 (9), 323 (22), 287 (16), 137 (37), 43 (100). Anal. calcd for $C_{28}H_{35}ClN_6O$: C 66.32, H 6.96, N 16.57; found C 66.17, H 6.84, N 16.78.

3-(4-Chlorophenyl)-6-phenyl-5-(1-piperidinyl)-3,6-dihydro-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (4f) White solid, m.p.: 208—210 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.19—7.36 (m, 9H, ArH), 3.22 (t, J=5.2 Hz, 4H, $2NCH_2$), 1.51—1.28 (m, 6H, $3CH_2$); IR (KBr) ν: 1720, 1596, 1532, 1358 cm^{-1}; MS *m*/*z* (%): 406 (M^+, 100), 378 (45), 349 (12), 212 (26), 77 (93). Anal. calcd for $C_{21}H_{19}ClN_6O$: C 61.99, H 4.71, N 20.66; found C 61.74, H 4.90, N, 20.46.

3-(4-Chlorophenyl)-5-(4-morpholinyl)-6-phenyl-3,6-dihydro-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (4g) White solid, m.p. 259—261 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.13—7.38 (m, 9H, ArH), 3.47 (t, J=3.2 Hz, 4H, $2OCH_2$), 3.24 (t, J=3.2 Hz, 4H, $2NCH_2$); IR (KBr) ν: 1717, 1596, 1533, 1118 cm^{-1}; MS *m*/*z* (%): 408 (M^+, 100), 379 (28), 323 (15), 214 (11), 137 (34), 77 (98). Anal. calcd for $C_{20}H_{17}ClN_6O$: C 58.75, H 4.19, N 20.56; found C 58.54, H 4.11, N 20.80.

3-(4-Chlorophenyl)-5-methoxy-6-phenyl-3,6-dihydro-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (4h) White solid, m.p.>300 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.13—7.23 (m, 9H, ArH), 4.04 (s, 3H, OCH_3); IR (KBr) ν: 1737, 1598, 1558, 1257 cm^{-1}; MS *m*/*z* (%): 353 (M^+, 50), 325 (26), 303 (64), 137 (75), 91(100). Anal. calcd for $C_{17}H_{12}ClN_5O_2$: C 57.72, H 3.42, N 19.80; found C 57.58, H 3.45, N 19.69.

3-(4-Chlorophenyl)-6-phenyl-5-(*n*-propoxy)-3,6-dihydro-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (4i) White solid, m.p. 198—200 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.12—7.23 (m, 9H, ArH), 4.40 (t, J=6.4 Hz, 2H, OCH_2), 1.69—1.63 (m, 2H, CH_2), 0.81 (t, J=7.2 Hz, 3H,CH_3); IR (KBr) ν: 1733, 1598, 1558, 1258 cm^{-1}; MS *m*/*z* (%): 383 (20), 381 (M^+, 76), 311 (50), 248 (33), 111 (57), 43 (100). Anal. calcd for $C_{19}H_{16}ClN_5O_2$: C 59.77, H 4.22, N 18.34; found C 59.57, H 4.36, N 18.12.

3-(4-Chlorophenyl)-6-phenyl-5-(*iso*-propoxy)-3,6-dihydro-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (4j) White solid, m.p. 192—194 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.12—7.20 (m, 9H, ArH), 5.41—5.35 (m, 1H, OCH), 1.29 (d, J=6.4 Hz, 6H, 2 CH_3); IR (KBr) ν: 1727, 1596, 1541, 1250 cm^{-1}; MS *m*/*z* (%): 383 (17), 381 (M^+, 67), 367 (12), 339 (30), 77 (30), 43 (100); Anal. calcd for $C_{19}H_{16}ClN_5O_2$: C 59.77, H 4.22, N 18.34; found C 59.90, H 4.12, N 18.18.

5-(*n*-Butoxy)-3-(4-chlorophenyl)-6-phenyl-3,6-dihydro-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (4k) White solid, m. p. 188—190 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.13—7.22 (m, 9H, ArH), 4.44 (t, J=6.4 Hz, 2H, OCH_2), 1.64—1.60 (m, 2H, CH_2), 1.26—1.20 (m, 2H, CH_2), 0.84 (t, J=7.2 Hz, 3H, CH_3); IR (KBr) ν: 1731, 1597, 1559, 1258 cm^{-1}; MS *m*/*z* (%): 395 (M^+, 100), 367 (6), 311 (33), 282 (20), 248 (22), 77 (22). Anal. calcd for $C_{20}H_{18}ClN_5O_2$: C 60.68, H 4.58, N 17.69; found C 60.53, H 4.71, N 17.45.

5-Allyloxy-3-(4-chlorophenyl)-6-phenyl-3,6-dihydro-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (4l) White solid, m.p. 210—212 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.12—7.24 (m, 9H, ArH), 5.91—5.84 (m, 1H, =CH), 5.24—5.13 (m, 2H, $=CH_2$), 4.93 (t, J=5.2 Hz, 2H, OCH_2); IR (KBr) ν: 3095, 1730, 1550, 1249 cm^{-1}; MS *m*/*z* (%): 379 (M^+, 8), 334 (12), 306 (8), 276 (6), 146 (23), 41 (100). Anal. calcd for $C_{19}H_{14}ClN_5O_2$: C 60.09, H 3.72, N 18.44; found C 60.33, H 3.56, N 18.57.

3-(4-Chlorophenyl)-6-phenyl-5-(prop-2-yn-1-yl

oxy)-3,6-dihydro-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (4m) White solid, m.p. 238—240 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.16—7.25 (m, 9H, ArH), 5.01 (s, 2H, OCH_2), 2.56 (s, H, ≡CH); IR (KBr) ν: 3296, 2129, 1727, 1249 cm^{-1}; MS *m*/*z* (%): 377 (M^+, 23), 311 (7), 179 (6), 91 (20), 39 (100). Anal. calcd for $C_{19}H_{12}ClN_5O_2$: C 60.41, H 3.20, N 18.54; found C 60.56, H 3.02, N 18.75.

Results and discussion

Iminophosphorane **1** reacted with phenyl isocyanate to give carbodiimide **2**. After removing the by-product Ph_3PO by recrystallization, the solution of **2** was divided equally into several parts to which were added various amines and alcohols separately. The resulted solution was stood at room temperature for 1—2 h and catalytic amount of sodium alkoxide was added. After reaction at room temperature for further 2—5 h, the solvent was removed in reduced pressure and the residue was recrystallized to give various 5-amino or 5-alkoxy substituted 7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-ones (**4**) in satisfactory yields. The formation of **4** can be rationalized in terms of an initial nucleophilic addition to give the intermediate **3**, which cyclized to give **4** in the basic condition. When HY (Table 1) is an amine, the reaction can be carried out at r.t. even as Y is bulky di-*iso*-propylamine. The yields of products **4** are related to the *N*-substituents of the secondary amines. High yields are obtained as the *N*-substituents are cyclic alkyl group (**4f**, **4g**, Table 1), however, relatively lower yield is gotten when the *N*-substituent is long chain alkyl group (**4e**, Table 1). When HY is an alcohol, the cyclization was also achieved at room temperature and **4** can be isolated from the reaction mixture in moderate to good yields. The relatively lower yield of the compound **4m** might be due to the influence of the alkynyl group

Scheme 1

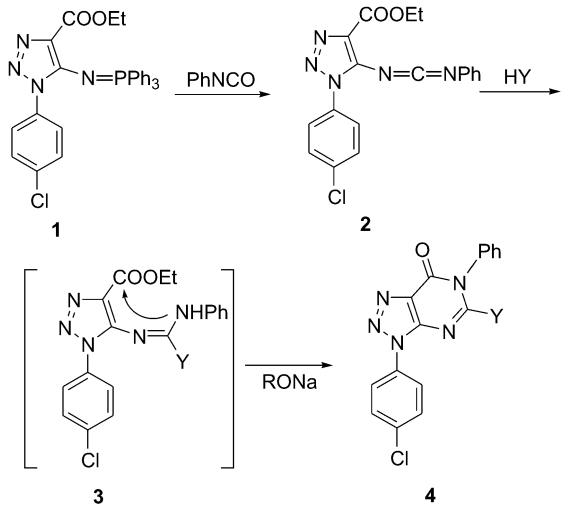

Table 1 Preparation of 7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-ones **4**

Compound	Y	Condition	Yield[a]/%
4a	N(*n*-Pr)$_2$	r.t./2 h	85
4b	N(*n*-Bu)$_2$	r.t./2 h	84
4c	N(*iso*-Bu)$_2$	r.t./3 h	89
4d	N(*n*-C_5H_{11})$_2$	r.t./3 h	88
4e	N(*n*-C_6H_{13})$_2$	r.t./3 h	83
4f	1-Piperidinyl	r.t./2 h	90
4g	4-Morpholinyl	r.t./2 h	91
4h	MeO	r.t./2 h	92
4i	*n*-PrO	r.t./2 h	78
4j	*iso*-PrO	r.t./2 h	88
4k	*n*-BuO	r.t./3 h	80
4l	CH_2=$CHCH_2O$	r.t./4 h	86
4m	HC≡CCH_2O	r.t./5 h	55

[a] Isolated yields based on iminophosphorane **1**.

of the alcohol under the basic condition. The results are listed in Table 1.

The structure of **4** has been confirmed by spectral data of ^{1}H NMR, IR and MS. For example, the ^{1}H NMR spectral data of **4a** show the signals of —NCH_2 at δ 3.07 as triplets, signals of CH_2 at δ 1.37—1.28 as multiplets, and signals of CH_3 at δ 0.76 as triplets. The phenyl signals appeared at δ 8.20—7.27 as multiplets. The IR of **4a** showed the strong stretching resonance peak of pyrimidinone C=O at 1720 cm^{-1}. The MS of **4a** showed M^+ at *m*/*z* 423 with 20% abundance.

In summary, the above solution-phase parallel synthetic method provides a high-speed synthesis of 5-substituted 7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-ones. Due to the easily accessible and versatile starting material, this method has the potential in synthesis of many biologically and pharmaceutically active 7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one derivatives.

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