A facile synthesis of polysubstituted furo[2,3-d]pyrimidinones and 1,2,4-triazole-fused derivatives

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Abstract
In this paper, a series of polysubstituted furo[2,3-d]pyrimidinones, including 1,2,4-triazole-fused derivatives, are synthesized via aza-Wittig reactions of iminophosphoranes, under mild conditions.

Keywords
carbodiimide, iminophosphorane, aza-Wittig reaction, furo[2,3-d]pyrimidin-4(3H)-ones, 1,2,4-triazole

Introduction
Heterocycles containing the furopyrimidinone system are considered templates for drug design and discovery because of their remarkable biological activities. Thus, some of them have shown anti-inflammatory,¹ antiviral,² analgesic,³ anti-proliferative,⁴ and antimicrobial⁵ activities. Heterocycles containing the 1,2,4-triazole nucleus also possess diverse biological activities such as fungicidal, bactericidal, insecticidal, antitumor and as anti-inflammatory agents.⁶–¹⁰ We expected therefore, that the combination of a 1,2,4-triazole and a furo[3,2-d]pyrimidin-4(3H)-one would produce compounds that might have significant biological activity.

The aza-Wittig reactions of iminophosphoranes have received considerable attention in view of their utility in the synthesis of N-heterocyclic compounds. Annelation of rings with N-heterocycles by means of an aza-Wittig reaction has been widely utilized.¹¹,¹² In the course of our work aimed at drug discovery, we recently became interested in the synthesis of a series of new heterocyclic compounds via aza-Wittig reactions.¹³,¹⁴

Based on our background in poly-substituted furo[2,3-d]pyrimidin-4(3H)-ones, we decided to add a fused 1,2,4-triazole ring, hoping for biologically active compounds. Herein, we report the results of that investigation.

Results and discussion
Diethyl 2-amino-5-methylfuran-3,4-dicarboxylate (1), obtained by combination of ethyl 2-chloro-3-oxobutanoate and ethyl 2-cyanoacetate under basic conditions,¹⁵ was converted into diethyl 2-methyl-5-[(triphenyl phosphoranylidene)amino]-furan-3,4-dicarboxylate (2) (an iminophosphorane) via reaction with triphenylphosphine, hexachloroethane and triethylamine (Scheme 1).

Iminophosphorane 2 was reacted successively with aromatic isocyanates and then with hydrazine hydrate, at room temperature, to give 3-amino-5-ethoxycarbonyl-6-methyl-2-arylamino)-furo[2,3-d]pyrimidin-4(3H)-ones 3 in 85%–88% yields. Compounds 3 were further converted via non-isolated iminophosphorane intermediates 4, produced by reaction with triphenylphosphine, hexachloroethane and triethylamine. To these, without isolation, phenylisocyanate or alkyl isocyanates were added. The synthetic sequence proceeded well at room temperature producing polysubstituted tricycles 5 as crystalline solids in excellent yields (80%–86%, Scheme 2, Table 1). It is noteworthy that the separation of products 5 from the reaction mixture can be easily carried out by simple filtration.

The structures of 5a-5e were confirmed based on ¹H NMR, ¹³C NMR, mass spectrometry, infrared and elemental analyses. For example, the ¹H NMR spectrum of 5e
showed the signals of -OCH$_2$ at 4.38 ppm as quartets, signals of CH$_3$ at 1.28, 1.45 and 2.60 ppm as doublet, triplet or singlet. The signal attributable to the NCH was found at 4.19–4.25 ppm as a multiplet. The aromatic signals are found at 7.29–7.52 ppm as a multiplet. The IR spectra of 5e revealed N-H and C=O absorption bands at 3240 and 1698 cm$^{-1}$ respectively. The mass spectrum of 5e shows a strong molecular ion peak at m/z 413 with 52% abundance.

In conclusion, we have developed an efficient synthesis of ethyl 6-methyl-8-oxo-3-phenyl-2-(phenylamino/alkylamino)-3,8-dihydrofuro[2,3-d]-1,2,4-triazolo-[1,5-a]pyrimidine-7-carboxylates 5, having a furo[2,3-d] pyrimidinone fused to a 1,2,4-triazole, via aza-Wittig reactions. The method utilizes easily accessible starting materials, needs only mild reaction conditions, and features straightforward product isolation and good yields. Further optimization and bioassay and structure–activity relationship studies of the title compounds are underway.

**Experimental section**

**General**

Analytical grade reagents were purchased from standard suppliers and used without further purification. Solvents were dried and purified using standard techniques. Reactions were monitored by thin layer chromatography on silica gel GF254 pre-coated plates. Melting points were determined with an uncorrected X-4 digital melting point apparatus. Mass spectra were measured on a Finnigan Trace MS spectrometer. NMR spectra were recorded on a Bruker UltrashieldTM 400 MHz Plus spectrometer. IR were recorded on a PE-983 infrared spectrometer as KBr pellets with absorptions in cm$^{-1}$. Elementary analysis was carried out on a PerkinElmer CHN 2400 instrument.

**General procedure for the preparation of ethyl 3-amino-6-methyl-4-oxo-2-(aryl)-3,4-dihydrofuro[2,3-d]pyrimidine-5-carboxylates 3a-3b**

A general synthetic approach to 2 had been reported previously. To a solution of iminophosphorane 2 (2 mmol) in anhydrous dichloromethane (25 mL) was added an aromatic isocyanate under N$_2$ at rt. After the mixture was kept for 24–30 h at 0–5 °C, the solvent was removed under reduced pressure and diethyl ether/petroleum ether (1:2, 20 mL) was added to precipitate the Ph$_3$PO. After filtration, the solvent was removed to give the key intermediate, which was used directly without further purification by adding to a stirring solution of hydrazine hydrate (15 mmol) in EtOH (50 mL). After 5–6 h, the solution was concentrated under reduced pressure and the residue was recrystallized from methylene chloride/petroleum ether to give ethyl 3-amino-6-methyl-4-oxo-2-(aryl)-3,4-dihydrofuro[2,3-d]pyrimidine-5-carboxylate 3a-3b.

**Scheme 1.** Synthesis of diethyl 2-methyl-5-[(triphenylphosphoranylidene)amino]-furan- 3,4-dicarboxylate.

**Scheme 2.** Synthesis of ethyl 3-amino-6-methyl-4-oxo-2-(aryl)-3,4-dihydrofuro[2,3-d] pyrimidin-5-carboxylate (3b).
General method for the preparation of ethyl 6-methyl-8-oxo-2-(phenylamino)-3-phenyl-3,8-dihydrofuro[2,3-d]-1,2,4-triazolo[1,5-a]pyrimidine-7-carboxylates 5a-5e

To a mixture of 3 (3 mmol), triphenylphosphine (1.57 g, 6 mmol) and hexachloroethane (1.42 g, 6 mmol) in dry acetonitrile (15 mL), was added dropwise triethylamine (66 μL, 0.6 mmol) at room temperature. After the reaction mixture was stirred for 6–8 h, completion of the reaction was verified by TLC, and then an isocyanate (2 mmol) was added under nitrogen at room temperature. After stirring for 2–3 h, the solution was concentrated under reduced pressure and the residue was recrystallized from methylene chloride/petroleum ether to produce the product, 5a-5e.

Ethyl 6-methyl-8-oxo-2-(phenylamino)-3-phenyl-3,8-dihydrofuro[2,3-d]-1,2,4-triazolo[1,5-a]pyrimidine-7-carboxylate (5a).

White crystals, mp >300 °C. 1H NMR (400 MHz, CDCl3): δ = 1.40 (t, J = 7.2 Hz, 3H, CH3), 2.53 (s, 3H, CH3), 4.38 (q, J = 7.2 Hz, 2H, OCH2), 7.30–7.52 (m, 4H, Ar-H). 13C NMR (100 MHz, CDCl3): δ = 162.8, 162.4, 154.8, 150.0, 148.6, 146.8, 138.8, 131.3, 128.7, 126.6, 122.6, 119.0, 117.0, 116.7, 110.0, 97.2, 60.3, 14.0, 13.2. IR (KBr) 3238 (N-H), 1720 (C=O), 1558, 1376 cm⁻¹. MS (70 eV) m/z (%): 395 (M⁺, 100), 349 (75), 321 (74), 243 (91), 201 (36), 118 (19), 91 (14), 77 (16). Anal. Calcd for C23H23N5O4 (409.4): C, 60.75; H, 5.35; N, 17.71; Found: C, 60.71, H, 5.28, N, 16.74.

Ethyl 6-methyl-8-oxo-2-(i-propylamino)-3-(p-fluro-phenyl)-3,8-dihydrofuro[2,3-d]-1,2,4-triazolo[1,5-a]pyrimidine-7-carboxylate (5d).

White crystals; mp 234–236 °C. 1H NMR (400 MHz, CDCl3): δ = 0.92 (t, J = 7.2 Hz, 3H, CH3), 1.33–1.37 (m, 2H, CH2), 1.44 (t, J = 7.2 Hz, 3H, CH3), 1.58–1.65 (m, 2H, CH2), 2.50 (s, 3H, CH3), 3.48 (q, J = 6.0 Hz, 2H, CH2), 4.55 (s, 1H, NH), 4.38 (q, J = 7.2 Hz, 2H, OCH2), 7.30–7.53 (m, 4H, Ar-H). 13C NMR (100 MHz, CDCl3): δ = 162.4 (2), 154.4, 151.4, 150.1, 146.7, 130.4, 129.9, 128.0, 110.2, 97.1, 60.2, 41.8, 30.4, 19.5, 14.0, 13.7, 13.2. IR (KBr) 3250 (N-H), 1730 (C=O), 1555, 1372, 1211, 1082 cm⁻¹. MS (70 eV) m/z (%): 427 (M⁺, 34), 381 (69), 353 (100), 323 (27), 134 (32), 109 (32), 83 (13). Anal. Calcd for C21H19FN5O4 (427.4): C, 59.01; H, 5.19; N, 16.38; Found: C, 59.15; H, 5.32; N, 16.51.

Ethyl 6-methyl-8-oxo-2-(3-butylo/phenyl)-3-(p-fluro-phenyl)-3,8-dihydrofuro[2,3-d]-1,2,4-triazolo[1,5-a]pyrimidine-7-carboxylate (5e).

White crystals; mp 229–230 °C. 1H NMR (400 MHz, CDCl3): δ = 1.28 (d, J = 6.4 Hz, 6H, 2×CH3), 1.45 (t, J = 7.2 Hz, 3H, CH3), 2.50 (s, 3H, CH3), 1.55–1.60 (m, 2H, CH2), 4.08 (s, 1H, NH), 4.19–4.25 (m, 1H, CH), 4.38 (q, J = 7.2 Hz, 2H, OCH2), 7.29–7.52 (m, 4H, Ar-H). 13C NMR (100 MHz, CDCl3): δ = 162.4 (2), 154.5, 151.3, 150.1, 146.7, 130.4, 129.9, 128.0, 110.1, 97.0, 60.2, 44.5, 21.8, 14.0, 13.2. IR (KBr) 3250 (N-H), 1698 (C=O), 1548, 1375, 1285 cm⁻¹. MS (70 eV) m/z (%): 413 (M⁺, 52), 367 (100), 340 (44), 261 (72), 219 (45), 136 (14), 95 (10). Anal. Calcd for C22H22FN5O4 (413.4): C, 58.11; H, 4.88; N, 16.94; Found: C, 58.01; H, 4.94; N, 16.78.

Declaration of conflicting interests

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