Synthesis of new furo[2,3-*d*]pyrimidines and furo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines

Raafat M. Shaker

Chemistry Department, Faculty of Science, El-Minia University, El-Minia, Egypt
E-mail: rmshaker@yahoo.com

Abstract

2-Aminofuran-3-carbonitriles **(1)** reacted with triethylorthoformate **(2a)** or triethylorthoacetate **(2b)** to afford the corresponding imidates **3a,b**. Reaction of **3a,b** with semicarbazide hydrochloride gives the (4-imino-furo[2,3-*d*]pyrimidine-3-yl)ureas **5a,b**, which are in turn cyclized with dichlorotriphenylphosphorane to give the iminophosphoranes **6**. Hydrolysis of **6** leads to the 2-amino-furo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **7a,b**. Compound **7a** can also be prepared by the reaction of 4-imino-furo[2,3-*d*]pyrimidine **8,** which prepared by hydrazinolysis of **3a**, with cyanogen bromide or isothiuronium sulfate in alkaline medium. 2-Aryl-furo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **12a,b** were synthesized by the reaction of the substituted benzoic acid hydrazides **9a,b** with **3a** or **1**.

Keywords: 2-Aminofuran-3-carbonitrile, furo[2,3-*d*]pyrimidines, furo[3,2-*e*][1,2,4]triazolo [1,5*c*]-pyrimidines

Introduction

Substituted 2-Aminofuran-3-carbonitriles are well established as versatile starting materials for the synthesis of a wide variety of fused heterocyclic compounds[1-10]. Among these heterocycles, the furo[2,3-*d*]pyrimidine derivatives are an important class of heterocyclic compounds in pharmaceutical discovery research. Antifungal[2], antifolate[11-13], antibacterial[14], antitumor[12,15], antiviral[16,17], and anti-HCMV (human cytomegalovirus)[18] activities have been described for these compounds. Recently, some furopyrimidines were shown to be potent VEGFR2 (vascular endothelial growth factor receptor2) and EGFR (epidermal growth factor receptor) inhibitors[19]. Furthermore, 1,2,4-triazolo[1,5-*c*]pyrimidines exhibited antimicrobial activities ranging from antiviral[20] and antibacterial[21], to antifungal[22]. In view of the above-mentioned findings and following our work on the synthesis of polyheterocyclic systems[23-31], we here are aimed at reporting the preparation of a new furo[2,3-*d*]pyrimidines and furo[3,2-*e*][1,2,4]triazolo[1,5-

c]pyrimidines involving a 2-amino-4,5-bis(4-methoxyphenyl)furan-3-carbonitrile (**1**)[9] as starting material.

Results and Discussion

Treatment of **1** with triethylorthoformate **2a** or triethylorthoacetate **2b** in acetic anhydride at reflux afforded the corresponding imidates **3a** and **3b** respectively (Scheme 1). The IR spectra of compounds **3a,b** showed a strong absorption band of the nitrile group at 2220 cm^{-1} but no absorption frequency in the NH region. The ^1H NMR spectra of product **3a,b** were compatible with the proposed structure. For example, the CH proton of the imidate group in **3a** appeared downfield at δ 8.9, where as a triplet (3H) at δ 1.25 and quartet (2H) at δ 4.30 were assigned to the methyl and methylene protons of the ethoxy group in the same functionality. The reaction of compounds **3a,b** with semicarbazide hydrochloride in equimolar proportions in ethanol and in the presence of triethylamine gave the corresponding (4-imino-furo[2,3-*d*]pyrimidine-3-yl)urea derivatives **5a,b** (Scheme 1). The formation of **5** was rationalized in terms of the initial formation of the intermediate **4**, the nucleophilic attack of the semicarbazide *N*-2 on the neighboring nitrile group forming the furo[2,3-*d*]pyrimidine **5**. The structures of **5a,b** were established by their correct analyses and compatible spectroscopic data.

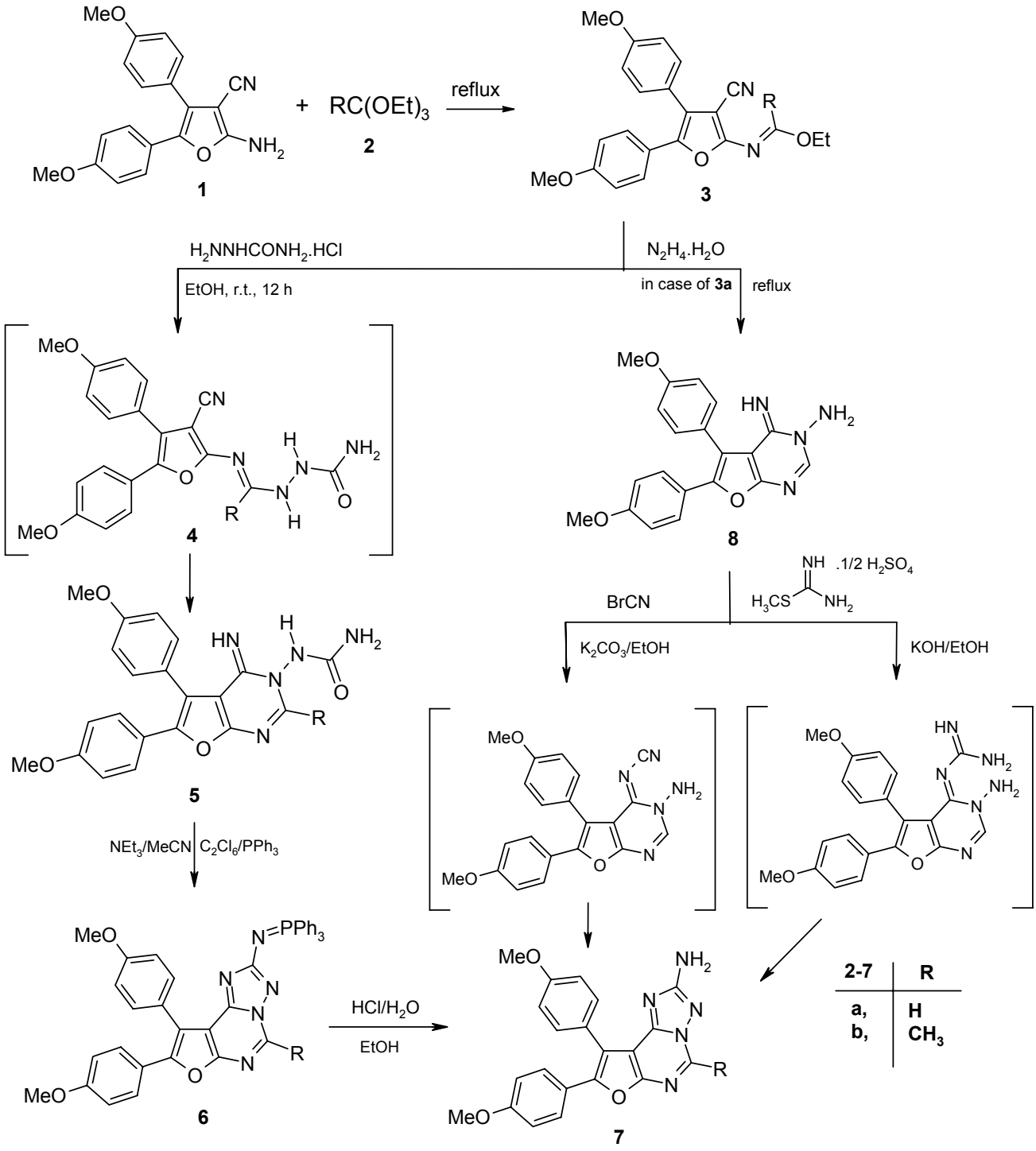
Compounds **5a,b** were readily cyclized to the corresponding iminophosphoranes **6** upon treatment with in *situ* prepared dichlorotriphenylphosphorane using a hexachloroethane-triphenylphosphine-triethylamine reagent[32,33] (Scheme 1). The molecular structures of the iminophosphoranes **6a,b** were supported on the basis of elemental and spectral analyses which were found to be in good agreement with the assigned structures.

Hydrolysis of compound **6** leads to the 2-amino-furo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **7a,b** (Scheme 1). The structure of **7a,b** was deduced on the basis of analytical and spectral data. Thus, the appearance of intense absorption bands at 3480-3300 cm^{-1} and a broad signal for 2H at 5.65-5.85 ppm for NH_2 in the IR and ^1H NMR spectra respectively. Furthermore, the fragmentation patterns of the mass spectra of **7a** and **7b** showing the molecular ion peak at m/z 387 (M^+, 45%) and m/z 401 (M^+, 55%), respectively, which were found to be in good agreement with the assigned structure.

Hydrazinolysis of compound **3a** in ethanol at 40°C for one hour yielded the 3-amino-5,6-di-(4-methoxyphenyl)-4-imino-3*H*,4*H*-furo[2,3-*d*]pyrimidine **(8)** (Scheme 1). The structure of compound **8** was determined on the basis of elemental analysis, spectral data and the chemical transformations outlined below. In addition, the structure of **7a** was confirmed further by an alternative synthesis by the reaction of compound **8** with cyanogen bromide or isothiuronium sulfate in ethanol and in the presence of K_2CO_3 or KOH, respectively (Scheme 1).

Scheme 2 outlines the synthesis of 2-aryl-furotriazolopyrimidine **(12a,b)** from the reaction of the imidoesters **3a** with the corresponding substituted benzoic acid hydrazides **9a,b** in refluxing

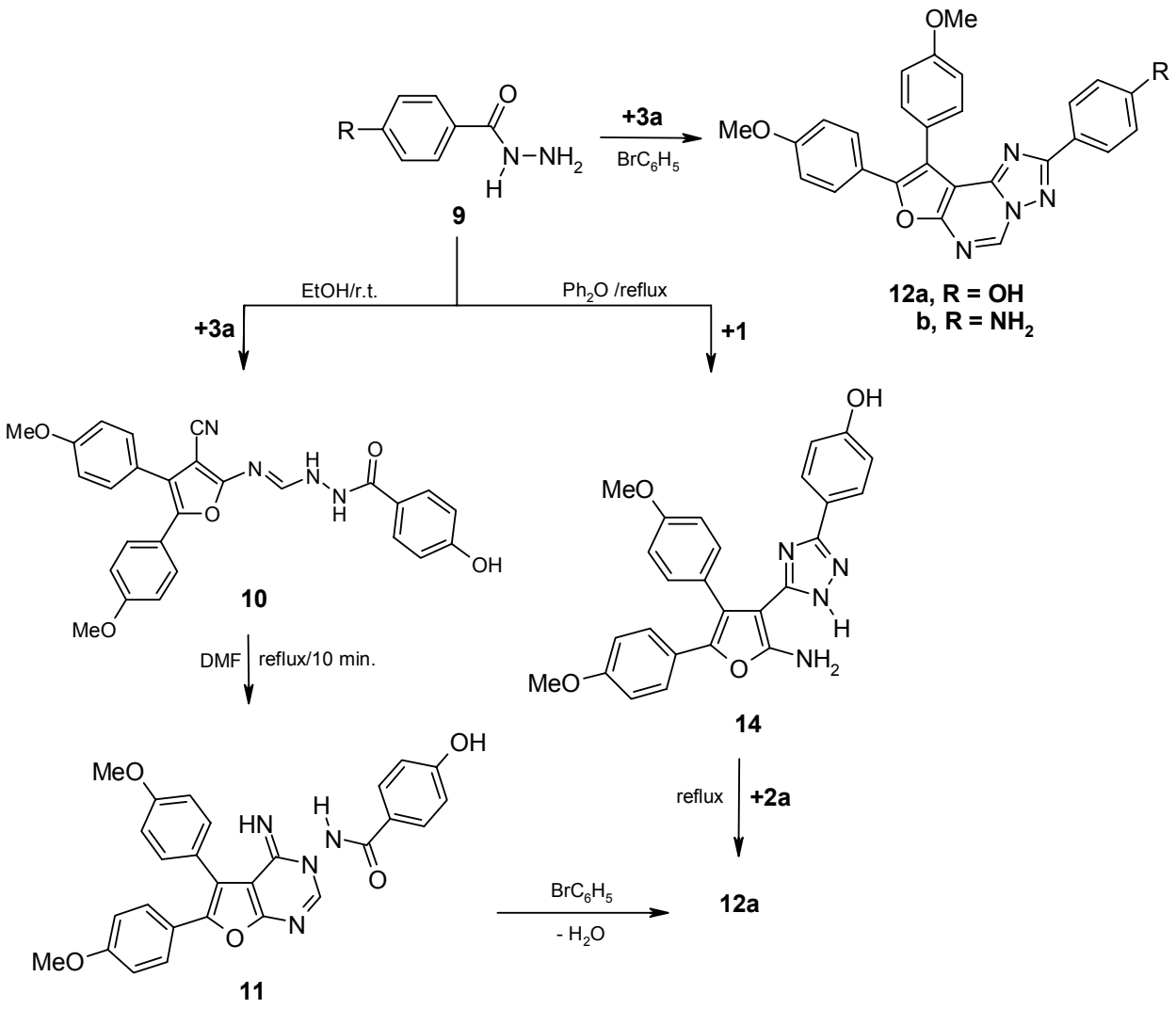
bromobenzene. Structures of **12a,b** were based on the correct elemental analyses and spectral data.



Scheme 1

The reaction mechanism illustrated in Scheme 2 has been confirmed by the synthesis of the intermediate **10** and **11** in the reaction of the imidoester **3a** with **9a** under milder conditions. Thus, the amidrazone **10** was obtained by short-term reflux of an ethanolic solution of the imidoester **3a** and 4-hydroxybenzoylhydrazine (**9a**) applied in equimolar amounts. The IR as well as the mass spectrum agreed with the proposed structure **10**. Heating a dimethylformamide solution of the amidrazone **10** gives rise to 4-imino-furopyrimidine **11**, the IR spectrum of which revealed the absence of CN and the presence of absorption bands at 1675, 3150 and 3306-3175 cm^{-1} corresponding to the CO, NH and OH, respectively. Also, the ^1H NMR spectrum of compound **11** revealed the presence of two signals at δ = 10.33, and 10.53 ppm due to two NH groups, in addition to the signals at δ = 8.85 and 10.87 ppm due to pyrimidine-CH and OH protons. The cyclization of **11** to **12a**, *via* elimination of a molecule of water, proceeds upon reflux in bromobenzene for 8 hours. The structure of 2-aryl-furotriazolopyrimidine **12a** was confirmed from its elemental and spectral analyses, which showed the molecular ion peak at m/z 464 (M^+, 35%). Also, the IR spectrum of **12a** revealed the absence of the characteristic stretching vibrations due to the NH and amidic carbonyl groups, which appear in the IR spectrum of compound **11**. In addition, the ^1H NMR spectrum of **12a** demonstrated characteristic singlet at δ 3.75 and 3.90 for the two-methoxy protons, a multiplet at δ 6.97-7.28 for phenyl protons, a sharp signal at δ 8.48 for the H-5 proton in the pyrimidine ring and broad signal at δ 11.08 for the hydroxyl proton.

Further confirmation of structure **12a** was made via the synthesis of compound **14**, prepared from the reaction of compound **1** with **9a**. Subsequent refluxing of **14** in orthoester **2a** smoothly converts it to the final product **12a** (Scheme 2). The identity of the products of the cyclization of **14** with those obtained by the cyclization of **11** was confirmed by comparison of their IR and ^1H NMR spectra.



Scheme 2

Experimental Section

General Procedures. All mp's. were recorded on a Gallen Kamp apparatus and are uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer 880 spectrophotometer. The ^{1}H NMR spectra were measured in DMSO-d_6 with a JEOL Lambda 400 (400 MHz) spectrometer using TMS as an internal standard. The chemical shifts are expressed as δ values (ppm). Mass spectra were determined on a Shimadzu QP 5050 A mass spectrometer operating at 70 eV. Reaction monitoring and purity controls of the synthesized compounds were performed by TLC (silica gel, aluminum sheets 60 Pf_{254}, Merck). The Microanalytical Unit at Chemistry Department,

University of Hull, UK, performed elemental analyses. Compound **1** was prepared according to the method reported in the literature [9].

Synthesis of imidates 3a,b. A mixture of compound **1** (10 mmol) and triethylorthoformate **2a** or triethylorthoacetate **2b** (3 ml) in redistilled acetic anhydride (25 ml) was refluxed for 1 h. After cooling, the precipitated pale yellow crystalline product was filtered off and washed thoroughly with ethanol and recrystallized from ethanol to yield **3a,b** as yellow crystals.

4,5-Di-(4-methoxyphenyl)-2-(ethoxymethylene)aminofuran-3-carbonitrile (3a). Yield: 74%, mp 148-150 °C. IR (υ, cm^{-1}): 3050 (CH-aromatic), 2980, 2920 (CH-aliphatic), 2220 (CN), 1620 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ ppm 1.25 (t, 3H, *J* = 7 Hz, CH_3), 3.73 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.30 (q, 2H, *J* = 7 Hz, OCH_2), 7.22-7.40 (m, 8H, Ar-H), 8.9 (s, 1H, N=CH). Anal. Calcd. for $C_{22}H_{20}N_2O_4$ (376.42): C, 70.20; H, 5.36; N, 7.44; Found: C, 70.18; H, 5.42; N, 7.37.

4,5-Di-(4-methoxyphenyl)-2-(ethoxyethylene)amino-furan-3-carbonitrile (3b). Yield: 70%, mp 155-157 °C. IR (υ, cm^{-1}): 3053 (CH-aromatic), 2983, 2925 (CH-aliphatic), 2220 (CN), 1615 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ ppm 1.20 (t, 3H, *J* = 7 Hz, CH_3), 2.65 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.35 (q, 2H, *J* = 7 Hz, OCH_2), 7.20-7.45 (m, 8H, Ar-H). Anal. Calcd. for $C_{23}H_{22}N_2O_4$ (390.44): C, 70.75; H, 5.68; N, 7.17; Found: C, 70.69; H, 5.62; N, 7.26.

Synthesis of (4-imino-furo[2,3-*d*]pyrimidine-3-yl)ureas 5a,b. A suspension of **3** (5 mmol) and semicarbazide hydrochloride (560 mg, 5 mmol) in ethanol (20 ml) and triethylamine (1 ml) was stirred at room temperature over night. The resulting precipitate was filtered and washed with water and ethanol, dried and crystallized from EtOH.

(5,6-Di-(4-methoxyphenyl)-4-imino-furo[2,3-*d*]pyrimidine-3-yl)urea (5a). Orange crystals (yield: 79 %), mp 225-227 °C. IR (υ, cm^{-1}): 3400-3170 (NH, NH_2), 3050 (CH-aromatic), 1660 (CO), 1635 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ ppm 3.73 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.35 (br s, 2H, NH_2), 6.90 (brs, 1H, NH), 7.00-7.35 (m, 8H, Ar-H), 7.87 (br s, 1H, NH), 8.50 (s, 1H, CH-pyrimidine). MS [m/z (% rel. int.)]: 405 [M^+, 24%]. Anal. Calcd. for $C_{21}H_{19}N_5O_4$ (405.42): C, 62.22; H, 4.72; N, 17.27; Found: C, 62.31; H, 4.66; N, 17.34.

(5,6-Di-(4-methoxyphenyl)-4-imino-2-methyl-furo[2,3-*d*]pyrimidine-3-yl)urea (5b). Orange crystals (yield: 69 %), mp 228-230 °C. IR (υ, cm^{-1}): 3430-3100 (NH, NH_2), 3050 (CH-aromatic), 1680 (CO), 1630 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ ppm 2.95 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.45 (br s, 2H, NH_2), 6.95 (br s, 1H, NH), 6.90-7.30 (m, 8H, Ar-H), 8.00 (s, 1H, NH). MS [m/z (% rel. int.)]: 419 [M^+, 35%]. Anal. Calcd. for $C_{22}H_{21}N_5O_4$ (419.44): C, 63.00; H, 5.05; N, 16.70; Found: C, 63.12; H, 5.13; N, 16.59.

Synthesis of iminophosphoranes 6a,b. A suspension of **5** (2.6 mmol), hexachloroethane (1.48 g, 6.2 mmol) and triphenylphosphane (1.63 g, 6.2 mmol) was stirred under nitrogen in absolute acetonitrile (25 ml). Triethylamine (2 ml, 14 mmol) was added dropwise and refluxed for 8 hours. The resulting precipitate was filtered and washed with ethanol, dried and crystallized from dioxane.

8,9-Di-(4-methoxyphenyl)-2-triphenylphosphoranylideneamino-furo[3,2-*e*][1,2,4]triazolo [1,5-*c*]pyrimidine (6a). Orange crystals (yield: 67 %), mp 260-262 °C. IR (υ, cm^{-1}): 3050 (CH-aromatic), 1630 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ ppm 3.73 (s, 3H, OCH_3), 3.83 (s, 3H,

OCH_3), 7.15-7.32 (m, 8H, Ar-H), 8.53 (s, 1H, CH-pyrimidine). Anal. Calcd. for $C_{39}H_{30}N_5O_3P$ (647.68): C, 72.33; H, 4.67; N, 10.81; Found: C, 72.26; H, 4.59; N, 10.73.

8,9-Di-(4-methoxyphenyl)-5-methyl-2-triphenylphosphoranylideneamino-furo[3,2-*e*][1,2,4]-triazolo[1,5-*c*]pyrimidine (6b). Orange crystals (yield: 64 %), mp 264-265 °C. IR (υ, cm^{-1}): 3053 (CH-aromatic), 1635 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6) δ ppm 2.95 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 7.33-7.44 (m, 8H, Ar-H). Anal. Calcd. for $C_{40}H_{32}N_5O_3P$ (661.71): C, 72.61; H, 4.87; N, 10.58; Found: C, 72.54; H, 4.94; N, 10.49.

Synthesis of furo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines 7 from iminophosphoranes 6. The iminophosphorane **6** (1 mmol) in ethanol (25 ml) and water (2 ml) with 5 drops of conc. HCl was refluxed for 12 hours. After cooling, the resulting precipitate was filtered and washed with ethanol, dried and crystallized from EtOH.

2-Amino-8,9-di-(4-methoxyphenyl)furo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (7a). Orange crystals (yield: 92 %), mp 243-244 °C. IR (υ, cm^{-1}): 3480, 3300 (NH_2), 3050 (CH-aromatic), 1620 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6) δ ppm 3.70 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.65 (br s, 2H, NH_2, exchangeable with D_2O), 7.22-7.37 (m, 8H, Ar-H), 8.48 (s, 1H, CH-pyrimidine). MS [m/z (% rel. int.)]: 387 [M^+, 45%]. Anal. Calcd. for $C_{21}H_{17}N_5O_3$ (387.40): C, 65.11; H, 4.42; N, 18.08; Found: C, 65.20; H, 4.50; N, 18.20.

2-Amino-8,9-di-(4-methoxyphenyl)-5-methyl-furo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (7b). Orange crystals (yield: 89 %), mp 248-250°C. IR (υ, cm^{-1}): 3480, 3380 (NH_2), 3040 (CH-aromatic), 1615 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6) δ ppm 2.65 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 5.85 (br s, 2H, NH_2, exchangeable with D_2O), 7.13-7.33 (m, 8H, Ar-H). MS [m/z (% rel. int.)]: 401 [M^+, 55%]. Anal. Calcd. for $C_{22}H_{19}N_5O_3$ (401.43): C, 65.83; H, 4.77; N, 17.45; Found: C, 65.70; H, 4.60; N, 17.50.

Synthesis of 3-Amino-5,6-di-(4-methoxyphenyl)-4-imino-3H,4H-furo[2,3-*d*]pyrimidine (8). A mixture of compound 3a (10 mmol), hydrazine hydrate (5 ml, 80%) in ethanol (20 ml) was heated with stirring at 40°C for 1 h. The yellow precipitate formed after cooling was filtered off, dried and recrystallized from EtOH to give 8 as a yellow crystals (yield: 81 %), mp 217-219 °C. IR (υ, cm^{-1}): 3375-3170 (NH, NH_2), 3053 (CH-aromatic), 1624 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6) δ ppm 3.65 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 5.45 (br s, 2H, NH_2), 6.97-7.25 (m, 8H, Ar-H), 8.45 (s, 1H, CH-pyrimidine), 9.41 (s, 1H, NH). MS [m/z (% rel. int.)]: 362 [M^+, 25%]. Anal. Calcd. for $C_{20}H_{18}N_4O_3$ (362.39): C, 66.29; H, 5.01; N, 15.46; Found: C, 66.40; H, 4.90; N, 15.50.

Alternative synthesis of 7a from 8

Method A. A mixture of **8** (10 mmol), K_2CO_3 (0.69 g, 10 mmol) and cyanogen bromide (0.53 g, 10 mmol) in ethanol (30 ml) was refluxed for 10 hours. The reaction mixture was cooled, neutralized with dil. HCl. The solid was collected by filtration, washed with water, ethanol, dried and crystallized from EtOH to give **7a** in 64% yield.

Method B. A solution of **8** (2.5 mmol) and isothiuronium sulfate (0.28 g, 1 mmol) in alcoholic potassium hydroxide (0.5 *N*) was heated under reflux for 8 hours. After cooling, the mixture was poured on water to give an orange precipitate, which was collected, washed with water and recrystallized from EtOH to yield **7a** in 67% yield.

Synthesis of 4,5-di-(4-methoxyphenyl)-2-[2-(4-hydroxybenzoyl)-1-hydrazinomethyliden-amino]-3-furancarbonitrile (10). A solution of equimolar amounts of imidoester **3a** and 4-hydroxybenzoic acid hydrazide **(9)** in 5 ml of ethanol (5 mmol) was refluxed for 1 h. The precipitate was filtered off, washed with ethanol and water, dried and crystallized from dioxane to give **10** as a crystalline yellow (yield: 45 %), mp 288-290 °C. IR (υ, cm^{-1}): 3310-3173 (OH), 3350, 3250 (NH), 3060 (CH-aromatic), 2200 (CN), 1670 (CO), 1640 (C=N) cm^{-1} MS [m/z (% rel. int.)]: 482 [M^+, 55%]. Anal. Calcd. for $C_{27}H_{22}N_4O_5$ (482.50): C, 67.21; H, 4.60; N, 11.61; Found: C, 67.30; H, 4.50; N, 11.50.

Synthesis of *N*-(5,6-di-(4-methoxyphenyl)-4-imino-furo[2,3-*d*]pyrimidin-5-yl)-4-hydroxy-benzamide (11). A suspension of carbonitrile **10** (5 mmol) in 5 ml of DMF was heated to reflux for 10 min. The precipitate was filtered off, washed with hexane, dried, and crystallized from DMF/EtOH to give **11** as yellow crystals (yield: 76 %), mp 283-285 °C. IR (υ, cm^{-1}): 3306-3175 (OH), 3150 (NH), 3050 (CH-aromatic), 1675 (CO), 1620 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ ppm 3.73 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 7.27-7.62 (m, 12H, Ar-H), 8.50 (s, 1H, CH-pyrimidine), 10.33 (s, 1H, NH), 10.53 (br s, 1H, NHCO), 10.87 (s, 1H, OH), MS [m/z (% rel. int.)]: 482 [M^+, 45%]. Anal. Calcd. for $C_{27}H_{22}N_4O_5$ (482.50): C, 67.21; H, 4.60; N, 11.61; Found: C, 67.10; H, 4.70; N, 11.70.

Synthesis of 2-aryl-furotriazolopyrimidines 12a,b. Method A. An equimolar amounts of imidoester **3a** and the corresponding substituted benzoic acid hydrazide **9a,b** in bromobenzene (15 ml) was refluxed for 10-12 h, allowed to reach room temperature and the precipitate formed was filtered off, washed with ethanol, dried and crystallized from dioxane.

Alternative synthesis of 12a (Method B). A suspension of pyrimidine **11** (5 mmol) in 10 ml of bromobenzene was refluxed for 8 h, then cooled to room temperature. The formed precipitate was filtered off and purified as in method A.

2-(4-Hydroxyphenyl)-8,9-di-(4-methoxyphenyl)-furo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (12a). Yellow crystals (yield: 85 %), mp 272-274 °C. IR (υ, cm^{-1}): 3311-3170 (OH), 3045 (CH-aromatic), 1620 (C=N) cm^{-1}.^{1}H NMR (DMSO-d_6) δ ppm 3.75 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.97-7.28 (m, 12H, Ar-H), 8.48 (s, 1H, CH-pyrimidine), 11.08 (s, 1H, OH). MS [m/z (% rel. int.)]: 464 [M^+, 35%]. Anal. Calcd. for $C_{27}H_{20}N_4O_4$ (464.48): C, 69.82; H, 4.34; N, 12.06; Found: C, 69.90; H, 4.30; N, 12.10.

2-(4-Aminophenyl)-8,9-di-(4-methoxyphenyl)-furo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (12b). Yellow crystals (yield: 81 %), mp 276-278 °C. IR (υ, cm^{-1}): 3430-3320 (NH_2), 3050 (CH-aromatic), 1610 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ ppm 3.85 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 5.45 (br s, 2H, NH_2), 6.97-7.33 (m, 12H, Ar-H), 8.45 (s, 1H). MS [m/z (% rel. int.)]: 463 [M^+, 25%]. Anal. Calcd. for $C_{27}H_{21}N_5O_3$ (463.50): C, 69.97; H, 4.57; N, 15.11; Found: C, 70.10; H, 4.50; N, 15.20.

Synthesis of 2-amino-4,5-bis(4-methoxyphenyl)-3-[3-(4-hydroxyphenyl)-1,2,4-triazolo-5-yl]furan (14). A mixture of **1** (20 mmol) and **9** (24 mmol) in diphenyl ether (50 ml), was stirred at reflux temperature for 5 h. The mixture was allowed to cool to room temperature and *n*-Hexane (150 ml) was added. The precipitate was collected by filtration, washed with additional

n-Hexane then extracted with methanol. The residue, obtained after evaporation of the solvent, was crystallized from methanol/ethyl acetate to give **14** as yellow crystals (yield: 65.5 %), mp 235-237 °C. IR (υ, cm^{-1}): 3450-3150 (NH, NH_2), 3045 (CH-aromatic) cm^{-1}. ^1H NMR (DMSO-d_6) δ ppm 3.70 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.73 (s, 2H, NH_2), 7.22-7.58 (m, 12H, Ar-H), 10.87 (s, 1H, OH), 11.62 (s, 1H, NH). MS [m/z (% rel. int.)]: 454 [M^+, 55%]. Anal. Calcd. for $C_{26}H_{22}N_4O_4$ (454.49): C, 68.71; H, 4.88; N, 12.33; found: C, 68.80; H, 4.80; N, 12.40.

Alternative synthesis of 12a from 14

A suspension of 14 (10 mmol) in triethylorthoformate **2a** (30 ml) was refluxed for 12 hours. The excess of **2a** was removed in vacuum and the residue crystallized from dioxane to give **12a** in 73% yield.

Conclusions

We have presented various methods for the synthesis of new furo[2,3-*d*]pyrimidines and furo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines.

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