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Fused Pyrimidines. Part II: Synthesis and Antimicrobial activity of Some Furo[3,2-*e*]imidazo[1,2-*c*]pyrimidines and Furo[2,3-*d*]pyrimidines

M. M. H. Bhuiyan*, Khandker M. M. Rahman, M. K. Hossain, M. A. Rahim, and M. I. Hossain

Department of Chemistry, University of Chittagong, Chittagong-4331, Bangladesh

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2-Amino-4,5-diphenylfuran-3-carbonitrile (**2**) reacted with *N*-[bis(methylthio)methylene]glycine ethyl ester (**1**) to afford a double cyclized product 5-methylthio-8,9-diphenylfuro[3,2-*e*]imidazo[1,2-*c*]pyrimidin-2(3*H*)-one (**3**). Compound **2** also reacts with benzonitrile to give 4-amino-2,5,6-triphenylfuro[2,3-*d*]pyrimidine (**4**). Treatment of **2** with $HCONH_2$, under reflux, afforded 4-amino-5,6-diphenylfuro[2,3-*d*]pyrimidine (**5**) which was then allowed to react with chloroacetaldehyde to give 8,9-diphenylfuro[3,2-*e*]imidazo[1,2-*c*]pyrimidine (**6**). Reaction of **2** with HCOOH gave 5,6-diphenylfuro[2,3-*d*]pyrimidin-4(3*H*)-one (**7**) which was then converted to its tosyl derivative (**8**). The antimicrobial activity of the synthesized compounds **2**–**8** was tested.

INTRODUCTION

Pyrimidines, being an integral part of DNA and RNA, exhibit diverse pharmacological properties as effective bactericide, fungicide, viricide, insecticide, medicide.[1–3] Certain pyrimidines and annulated pyrimidine derivatives are also known to display anticancer, antimalarial, antileishmanial and antifilarial activities.[4–7] Some furans are shown to be useful for the inhibition of thrombin formation.[8] Furans have also been extensively investigated for their pharmacological uses. Some heterocyclic systems constructed on furans, possess antihypertensive, antialergic and antidepressent activities.[9–11] In continuation of our earlier work[12] and the biodynamic properties of these ring systems prompted us to design a system, which combines these two biolabile components in a ring together to give compact structures for screening their antimicrobial activities.

EXPERIMENTAL

General

Melting points were determined on an electrothermal apparatus in an open capillary tube and are uncorrected. The ^{1}H- and ^{13}C-NMR were measured on Bruker AC 200 spectrometer using DMSO-d_6 or $CDCl_3$ as the solvent and chemical shifts were expressed as δ values in ppm against TMS as an internal standard. TLC using silica G routinely checked the purity of the compounds and the spots were exposed in iodine vapour for visualization.

*N-[Bis(methylthio)methylen]glycine ethyl ester (**1**)*

To a solution of glycine ethyl ester hydrochloride (50 mmol) and carbon disulfide (50 mmol) in chloroform (50 ml) triethylamine (105 mmol) was added dropwise. After 1 h stirring methyl iodide (55 mmol) was added and refluxed the mixture for another 1 h. The resultant mixture was

* Author to whom correspondence should be addressed. (E-mail: mosharef65@yahoo.com)

washed with water (2 × 20 ml), dried (Na_2SO_4) and evaporated the solvent. The crude oil was dissolved in acetone (30 ml), anhydrous K_2CO_3 (10 g) and methyl iodide (60.2 mmol) were added. The reaction mixture refluxed for 3 h and stirring was continued for overnight at r.t. After evaporation of the solvent, the residue was diluted with ether (20 ml), washed with water (2 × 20 ml), dried (Na_2SO_4) and the solvent was removed by evaporation. The residue was distilled under reduced pressure to furnish **1** (80 %) as colourless syrup, b.p. 96–98 °C, 0.08 mm Hg. ^{1}H-NMR ($CDCl_3$) δ/ppm: 4.29 (q, 2H, J = 7.09 Hz, OCH_2), 4.24 (s, 2H, CH_2), 2.56 (s, 3H, SCH_3), 2.45 (s, 3H, SCH_3), 1.28 (t, 3H, J = 7.09 Hz, CH_3). ^{13}C-NMR ($CDCl_3$) δ/ppm: 169.3, 162.2, 60.1, 53.7, 14.4, 14.0, 13.7.

*5-Methylthio-8,9-diphenylfuro[3,2-e]imidazo[1,2-c]-pyrimidin-2(3H)-one (**3**)*

Equimolar amounts of **1** and **2** in acetic acid were refluxed for 8 h. The reaction mixture was cooled and poured into water. The solid so formed was collected by filtration and crystallized from EtOH to furnish **3** as yellowish crystals (82 %), m.p. > 270 °C. *Analysis Calcd*. for $C_{21}H_{15}N_3O_2S$ (373.44): C 67.54, H 4.05, N 11.25; Found: C 67.49, H 4.11, N 11.21. ^{1}H-NMR ($CDCl_3$) δ/ppm: 7.69 (m, 5H, Ar-H), 7.47 (m, 5H, Ar-H), 4.20 (s, 2H, CH_2), 2.70 (s, 3H, SCH_3). ^{13}C-NMR ($CDCl_3$) δ/ppm: 170.14, 166.32, 162.07, 139.63, 137.52, 132.76, 131.14, 130.18, 129.53, 129.11, 128.45, 127.51, 125.41, 121.78, 113.31, 50.43, 13.25.

*4-Amino-2,5,6-triphenylfuro[2,3-d]pyrimidine (**4**)*

A mixture of **2** (1.92 mmol), NaOMe (3.84 mmol) and benzonitrile (1.92 mmol) in 2-propanol (10 ml) was refluxed for 20 h. On cooling the precipitate was filtered off and recrystallized from EtOH to afford **4** (68 %) as brown crystals, m.p. 250–252 °C. *Analysis Calcd*. for $C_{24}H_{17}N_3O$ (363.42): C 79.32, H 4.72, N 11.56; Found: C 79.28, H 4.74, N 11.52. ^{1}H-NMR (DMSO-d_6) δ/ppm: 7.89 (m, 5H, Ar-H), 7.62 (m, 5H, Ar-H), 7.40 (m, 5H, Ar-H), 4.95(s, 2H, NH_2). ^{13}C-NMR (DMSO-d_6) δ/ppm: 170.14, 140.26, 131.19, 129.00, 128.60, 128.18, 127.45, 127.26, 127.05, 126.66.

*4-Amino-5,6-diphenylfuro[2,3-d]pyrimidine (**5**)*

A solution of **2** (3.85 mmol) in formamide (5 ml) was refluxed for 2 h. The precipitate that formed on cooling was filtered off and recrystallized from EtOH to give **5** (63 %) as brown crystals, m.p. 252–254 °C. ^{1}H-NMR ($CDCl_3$) δ/ppm: 7.16 (s, 1H, CH), 7.02 (m, 10H, 2 × Ph), 6.12 (s, 2H, NH_2). ^{13}C-NMR ($CDCl_3$) δ/ppm: 163.27, 156.25, 151.57, 144.57, 129.93, 127.86, 127.41, 126.83, 124.36, 113.65.

*8,9-Diphenylfuro[3,2-e]imidazo[1,2-c]pyrimidine (**6**)*

A mixture of **5** (0.52 mmol), NaOAc (0.1 g) and 40 % chloroacetaldehyde (0.45 ml) in water (1.5 ml) was heated on steam bath for 2 h with stirring. Extraction by chloroform and evaporation of solvent to give **6** (66 %), m.p. > 270 °C. *Analysis Calcd*. for $C_{20}H_{13}N_3O$ (311.35): C 77.16, H 4.21, N 13.50; Found: C 77.13, H 4.24, N 13.48. ^{1}H-NMR ($CDCl_3$) δ/ppm: 8.31 (s, 1H, H-5), 7.60 (d, 1H, J = 2.4 Hz, H-2), 7.50 (d, 1H, J = 2.4 Hz, H-3), 7.41 (m, 10H, 2 × Ph). ^{13}C-NMR ($CDCl_3$) δ/ppm: 165.34, 157.41, 153.15, 147.67, 134.51, 131.21, 130.21, 129.72, 128.80, 127.13, 126.50, 114.41.

*5,6-Diphenylfuro[2,3-d]pyrimidin-4(3H)-one (**7**)*

A suspension of **2** (1.92 mmol) in formic acid (10 ml, 85 %) was refluxed for 4 h. The solid that precipitated was collected and recrystallized from EtOH to give **7** (75.2 %), m.p. 210–212 °C. ^{1}H-NMR ($CDCl_3$) δ/ppm: 8.00 (s, 1H, NH), 7.84 (s, 1H, H-2), 7.57 (m, 5H, Ar-H), 7.52 (m, 5H, Ar-H). ^{13}C-NMR ($CDCl_3$) δ/ppm: 187.96, 164.02, 144.82, 139.89, 130.56, 130.18, 129.27, 128.74, 128.30, 126.77.

*4-Oxo-5,6-diphenylfuro[2,3-d]pyrimidin-3-p-toluene sulfonate ester (**8**)*

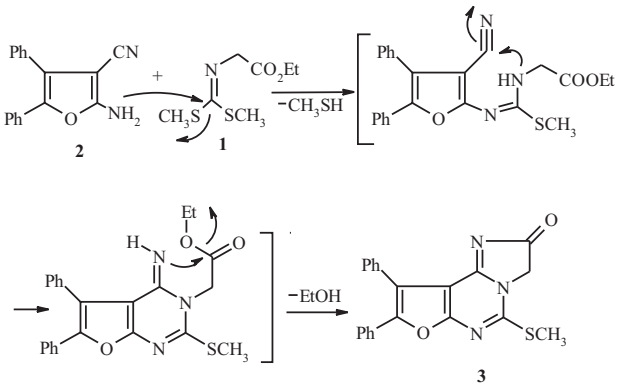
A solution of **7** (0.86 mmol), *p*-TsCl (0.86 mmol) in ether (5 ml) was heated at 30 °C for 5 h. After evaporation of ether, the resulting solid was recrystallized from EtOH to give **8** (66 %) as yellowish crystals, m.p. > 270 °C. *Analysis Calcd*. for $C_{25}H_{18}N_2O_4S$ (442.50): C 67.86, H 4.10, N 6.33; Found: C 67.81, H 4.15, N 6.36. ^{1}H-NMR ($CDCl_3$) δ/ppm: 7.62 (s, 1H, H-2), 7.51 (d, 2H, J = 8.0 Hz, Ar-H), 7.45 (m, 5H, Ph), 7.32(m, 5H, Ph), 7.15 (d, 2H, J = 8.0 Hz, Ar-H), 2.24 (s, CH_3). ^{13}C-NMR ($CDCl_3$) δ/ppm: 188.14, 183.43, 182.74, 179.50, 160.10, 153.91, 148.48, 144.83, 131.50, 130.55, 129.08, 128.55, 127.60, 118.39, 28.92.

RESULTS AND DISCUSSION

The annelating reagent, *N*-[bis(methylthio)methylene]glycine ethyl ester (**1**) was prepared by reacting glycine ethyl ester hydrochloride with CS_2/Et_3N/MeI and subsequently accomplishing the alkylation of the intermediate thus obtained with MeI/K_2CO_3 as described in the literature.[13]

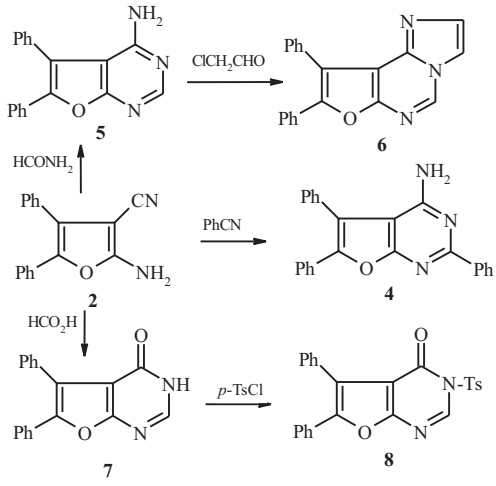
The starting material, 2-amino-4,5-diphenylfuran-3--carbonitrile (**2**) was prepared according to a modified Gewald method.[14]

Refluxing an equimolar mixture of **1** and **2** in dry acetic acid allows one-pot annelation yielded in a remarkably easy way and efficient double cyclized product 5-methylthio-8,9-diphenylfuro[3,2-*e*]imidazo[1,2-*c*]pyrimidin-2(3*H*)-one (**3**) in 82 % yield (Scheme 1). The ^{1}H-NMR spectrum of **3** exhibited a two-proton singlet for CH_2 at δ 4.20 ppm, a three-proton singlet for one SCH_3 at δ 2.70 ppm, two multiplets at δ 7.69 and 7.47 ppm for ten protons of two phenyl groups. No peaks were found for NH_2 (δ 5.10 ppm) and a carboethoxy group (δ 4.29 and 1.28 ppm). The ^{13}C-NMR spectrum displayed signals at δ 170.14 ppm for C=O carbon and at δ 50.43 ppm for methylene carbon at position C-3 of the molecule. The rest of the spectrum was in good agreement with the structure **3**.



Scheme 1.

Compound **2** was readily cyclized to the corresponding 4-amino-2,5,6-triphenylfuro[2,3-*d*]pyrimidine (**4**) upon treatment with benzonitrile and NaOMe in refluxing 2-propanol (Scheme 2). Reaction of compound **2** with formamide gave the corresponding 4-amino-5,6-diphenylfuro[2,3-*d*]pyrimidine (**5**) which was then allowed to react with chloroacetaldehyde to yield 8,9-diphenylfuro[3,2-*e*]-imidazo[1,2-*c*]pyrimidine (**6**). The ^{1}H-NMR and ^{13}C-NMR spectra supported the assigned products **4**, **5** and **6** respectively (see Experimental).



Scheme 2.

Compound **2** also underwent cyclization with formic acid to afford 5,6-diphenylfuro[2,3-*d*]pyrimidin-4(3*H*)-one (**7**) which was then converted to its tosyl derivative (**8**) with *p*-TsCl. The proposed structures for the products **7** and **8** were supported by their spectral data (see Experimental).

ANTIMICROBIAL SCREENING

Antibacterial activity

Newly synthesized compounds **3**–**8** were screened *in vitro* for their antimicrobial activities against bacteria *B. cereus, S. dysenteriae* and *S. typhi* using disc diffusion method.[15] *N,N*-Dimethyl formamide (DMF) was used, as a solvent to prepare desired solution (1 %) of the compounds initially. Proper control was maintained with DMF. The inhibition zones of microbial growth (100 μg/disc) produced by different compounds were measured in millimeters at the end of an incubation period of 48 h at (35±2) °C (Table I). DMF alone showed no inhibiton zone. Ampicillin (25 μg/disc) was used as a standard antibiotic for the evaluation of the antimicrobial activity. The screening results indicate that not all compounds exhibited antibacterial activity. Some compounds showed weak to moderate activity against all the organisms tested. Compound **3** showed better activity compared with other synthesized products.

TABLE I. Antibacterial activity of compounds **3–8**.

Comp.	*B. cereus*	*S. dysenteriae*	*S. typhi*
3	14	9	17
4	7	–	–
5	–	–	–
6	6	–	8
7	8	6	–
8	6	–	7
Ampicillin	21	30	24

Antifungal activity

Newly synthesized compounds **3–8** were screened for their antifungal against *M. phaseolina, F. equiseti, A. alternata* and *C. corchori* using poisoned-food technique.[16] DMF (1 %) was used as solvent and the inhibition zones were measured in millimeters at the end of an incubation period of 48 h at (35±2) °C (Table II). Nystatin was used as a reference to evaluate the potency of the tested chemicals.

TABLE II. Antifungal activity of compounds **3–8**.

Comp.	*M. phaseolina*	*F. equiseti*	*A. alternata*	*C. corchori*
3	65.52	68.75	42.31	22.72
4	29.4	55.0	27.1	35.5
5	42.0	28.35	61.30	33.0
6	25.7	55.0	48.2	20.45
7	31.9	29.0	22.9	22.10
8	50.0	19.2	52.4	26.68
Nystatin	71.78	44.7	51.55	40.51

Amongst the synthesized compounds screened for the antifungal activity, compounds **3**, **4** and **6** showed excellent results against *F. equiseti*, which were also greater than that of the standard antibiotic, Nystatin. Compound **3** also showed better inhibition for other fungi. The other compounds also exhibited moderate to good activity against the tested organisms.

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SAŽETAK

Kondenzirani pirimidini. II dio: Sinteza i antimikrobna aktivnost nekih furo[3,2-*e*]imidazo[1,2-*c*]pirimidina i furo[2,3-*d*]pirimidina

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2-Amino-4,5-difenilfuran-3-karbonitril (**2**) u reakciji s etilnim esterom *N*-[bis(metiltio)metilen]glicina (**1**) daje produkt dvostruke ciklizacije – 5-metiltio-8,9-difenilfuro[3,2-*e*]imidazol[1,2-*c*]pirimidin-2(3*H*)-on (**3**). Također, u reakciji s benzonitrilom spoj **2** daje 4-amino-2,5,6-trifenilfuro[2,3-*d*]pirimidin (**4**). Grijanjem spoja **2** s $HCONH_2$ dobiven je 4-amino-5,6-difenilfuro[2,3-*d*]pirimidin (**5**), koji reakcijom s kloracetaldehidom daje 8,9-difenilfuro[2,3-*d*]imidazo[1,2-*c*]pirimidin (**6**). Reakcijom **2** s HCOOH dobiven je 5,6-difenilfuro[2,3-*d*]pirimidin-4(3*H*)-on (**7**), koji je preveden u tozilat (**8**). Spojevima **2-8** ispitana je antimikrobna aktivnost.