http://dx.doi.org/10.5935/0103-5053.20150052

J. Braz. Chem. Soc., Vol. 26, No. 5, 916-923, 2015.
Printed in Brazil - ©2015 Sociedade Brasileira de Química
0103 - 5053 $6.00+0.00

Article

Cellulose Sulfuric Acid as an Eco-Friendly Catalyst for Novel Synthesis of Pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-5-ones

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A novel synthesis of a series of pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-5-ones has been developed from reactions of 1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-arylprop-2-en-1-ones and 7-amino-1,3-disubstituted[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-ones in dioxane under thermal conditions, using cellulose sulfuric acid as an eco-friendly acid catalyst. The reaction mechanism was proposed and the structures of the newly synthesized compounds were established on the basis of spectral data (mass spectrometry, infrared, ^{1}H and ^{13}C nuclear magnetic resonance) and elemental analyses.

Keywords: cellulose sulfuric acid, chalcone, annelated heterocyclic ring system

Introduction

Numerous elegant methods have been recently published to demonstrate the construction of pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidines, such as: (*i*) treatment of 2-hydrazinopyrido[2,3-*d*]pyrimidines[1-3] with various reagents, such as, triethyl orthoformate, ethyl chloroformate, chloroacetyl chloride, acetic anhydride, carbondisulfide, formic acid, and ammonium isothiocyanate; (*ii*) oxidative cyclization of hydrazino derivatives[1] in bromine-acetic acid mixture; (*iii*) reaction of 2-thioxopyrido[2,3-*d*]pyrimidines or its methylthio derivatives[4,5] with hydrazonoyl halides; (*iv*) treatment of hydrazino derivatives with aldohexose sugar followed by acetylation.[6] The curiosity for the synthetic strategy of pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidines is due to their biological activities. For example, some derivatives of the former ring system exhibit antitumor,[1] analgesic,[2] anti-inflammatory,[2] ulcerogenic,[2,6] and antimicrobial[4-6] activities.

Recently, the direction of science and technology has been shifting more towards eco-friendly, natural product resources and reusable catalysts.[7] Thus, cellulose sulfuric acid, as a promising biopolymeric solid supported acid catalyst, is an attractive candidate for acid-catalyzed reactions.[8-11] On the basis of these precedents, we attempted to report a new and efficient method for the synthesis of pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidines using cellulose sulfuric acid as an eco-friendly biopolymeric solid supported acid catalyst.

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Experimental

All melting points were determined on an electrothermal Gallenkamp apparatus and are uncorrected. Solvents were generally distilled and dried by standard literature procedures prior to use. The infrared (IR) spectra were measured on a Pye-Unicam SP300 instrument in potassium bromide discs. The ^{1}H and ^{13}C-nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury VXR-300 spectrometer (300 MHz for ^{1}H-NMR and 75 MHz for ^{13}C NMR) and the chemical shifts were related to that of the solvent deuterated dimethyl sulfoxide (DMSO-d_6). The mass spectra were recorded on a GCMS-Q1000-EX Shimadzu and GCMS 5988-A HP spectrometers, the ionizing voltage was 70 eV. Elemental analyses were carried out at the Microanalytical Centre of Cairo University, Giza, Egypt. Cellulose sulfuric acid,[10] 1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-arylprop-2-en-1-one (**1**),[12] 7-amino-1,3-disubstituted[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-ones (**2**),[13,14] 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**7**),[15] and *N*-phenyl 2-oxopropanehydrazonoyl chloride (**9**)[16] were prepared as previously reported in the respective literature.

Synthesis of pyrido[2,3-*d*][1,2,4]triazolo[4,3-a]pyrimidin-5-one derivatives **6a-s**

To a mixture of 1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-arylprop-2-en-1-one (**1**) (1 mmol) and 7-amino-1,3-disubstituted[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-ones (**2**) (1 mmol) in dioxane (15 mL) cellulose sulfuric acid (0.05 g) was added. The mixture was refluxed for 8 h then cooled to ambient temperature and cellulose sulfuric acid was filtered off. The filtrate was concentrated to dryness, and the crude solid product was crystallized from appropriate solvent to afford the pure products **6a-s**.

3-Acetyl-1,6-diphenyl-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1,5-dihydropyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-5-one (**6a**)

Yellowish-white microcrystals; IR (KBr) ν_{max}/cm^{-1} 1702, 1650 (2CO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.60 (s, 3H, CH_3), 3.31 (s, 3H, $COCH_3$), 7.43-8.05 (m, 16H, Ar-H + pyridine-H), 8.61 (s, 1H, pyrazole-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.1, 30.5, 123.9, 124.2, 124.5, 125.9, 126.4, 126.5, 128.2, 128.8, 129.1, 129.4, 129.8, 139.8, 142.2, 143.9, 147.4, 147.7, 148.8, 152.4, 153.3, 155.3, 159.1, 159.3, 168.1, 176.4; MS *m/z* (%) 537 (M$^+$, 65), 511 (100), 494 (58), 377 (52), 77 (59); anal. calcd. for $C_{32}H_{23}N_7O_2$ (537.19): C, 71.50; H, 4.31; N, 18.24; found: C, 71.31; H, 4.43; N, 18.39%.

*N*3,1,6-Triphenyl-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-oxo-1,5-dihydropyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine-3-carboxamide (**6b**)

Yellowish-white microcrystals; IR (KBr) ν_{max}/cm^{-1} 3310 (NH), 1691, 1653 (2CO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.61 (s, 3H, CH_3), 7.43-8.13 (m, 21H, Ar-H + pyridine-H), 8.59 (s, 1H, pyrazole-H), 11.12 (s, 1H, NH); MS *m/z* (%) 614 (M$^+$, 77), 494 (58), 377 (52), 119 (100), 77 (53); anal. calcd. for $C_{37}H_{26}N_8O_2$ (614.22): C, 72.30; H, 4.26; N, 18.23; found: C, 72.41; H, 4.33; N, 18.33%.

3-Acetyl-6-(4-chlorophenyl)-1-phenyl-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1,5-dihydropyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-5-one (**6c**)

Yellow microcrystals; IR (KBr) ν_{max}/cm^{-1} 1703, 1652 (2CO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.60 (s, 3H, CH_3), 3.31 (s, 3H, $COCH_3$), 7.52-7.93 (m, 15H, Ar-H + pyridine-H), 8.63 (s, 1H, pyrazole-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.5, 31.1, 123.8, 124.7, 125.2, 125.9, 126.4, 126.8, 128.2, 128.8, 129.1, 129.4, 130.7, 138.9, 142.1, 143.9, 147.4, 147.7, 148.8, 152.4, 153.3, 155.3, 159.7, 160.2, 168.1, 176.7; MS *m/z* (%) 573 (M$^+$ + 2) (17), 571 (M$^+$, 56), 528 (50), 160 (96), 77 (100); anal. calcd. for $C_{32}H_{22}ClN_7O_2$ (571.15): C, 67.19; H, 3.88; N, 17.14; found: C, 67.31; H, 4.03; N, 17.39%.

3-Acetyl-1,6-bis-(4-chlorophenyl)-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1,5-dihydropyrido[2,3-*d*] [1,2,4]triazolo[4,3-*a*] pyrimidin-5-one (**6d**)

Yellowish-white microcrystals; IR (KBr) ν_{max}/cm^{-1} 1698, 1653 (2CO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.63 (s, 3H, CH_3), 3.29 (s, 3H, $COCH_3$), 7.52-8.03 (m, 14H, Ar-H + pyridine-H), 8.64 (s, 1H, pyrazole-H); MS *m/z* (%) 607 (M$^+$ + 2) (14), 605 (M$^+$, 55), 494 (100), 111 (71), 77 (65); anal. calcd. for $C_{32}H_{21}Cl_2N_7O_2$ (605.11): C, 63.37; H, 3.49; N, 16.17; found: C, 63.51; H, 3.33; N, 16.29%.

3-Acetyl-6-(4-chlorophenyl)-1-(4-methylphenyl)-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1,5-dihydropyrido[2,3-*d*] [1,2,4]triazolo[4,3-*a*]pyrimidin-5-one (**6e**)

Yellow microcrystals; IR (KBr) ν_{max}/cm^{-1} 1702, 1653 (2CO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.38 (s, 3H, Ar-CH_3), 2.60 (s, 3H, CH_3), 3.32 (s, 3H, $COCH_3$), 7.52-7.89 (m, 14H, Ar-H + pyridine-H), 8.60 (s, 1H, pyrazole-H); MS *m/z* (%) 587 (M$^+$ +2) (5), 585 (M$^+$, 12), 322 (21), 91 (8), 77 (100); anal. calcd. for $C_{33}H_{24}ClN_7O_2$ (585.17): C, 67.63; H, 4.13; N, 16.73; found: C, 67.51; H, 4.03; N, 16.59%.

3-Acetyl-6-(4-chlorophenyl)-1-(4-methoxyphenyl)-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1,5-dihydropyrido[2,3-*d*] [1,2,4]triazolo[4,3-*a*]pyrimidin-5-one (**6f**)

Yellow microcrystals; IR (KBr) ν_{max}/cm^{-1} 1703, 1652 (2CO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.59 (s, 3H, CH_3), 3.30 (s, 3H, $COCH_3$), 3.64 (s, 3H, OCH_3), 7.52-7.92 (m, 14H, Ar-H + pyridine-H), 8.63 (s, 1H, pyrazole-H); MS *m/z* (%) 603 (M$^+$ + 2) (5), 601 (M$^+$, 17), 547 (87), 189 (100), 87 (82); anal. calcd. for $C_{33}H_{24}ClN_7O_3$ (601.16): C, 65.83; H, 4.02; N, 16.29; found: C, 65.61; H, 4.09; N, 16.39%.

Ethyl 6-(4-chlorophenyl)-1-phenyl-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1,5-dihydro-5-oxo-pyrido[2,3-*d*][1,2,4] triazolo[4,3-*a*]pyrimidine-3-carboxylate (**6g**)

Pale yellow microcrystals; IR (KBr) ν_{max}/cm^{-1} 1723, 1653 (2CO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.44 (t, 3H, *J* 7.0 Hz, CH_3), 2.59 (s, 3H, CH_3), 4.57 (q, 2H, *J* 7.0 Hz, CH_2), 7.51-7.92 (m, 15H, Ar-H + pyridine-H), 8.63 (s, 1H, pyrazole-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 30.6, 35.6, 122.9, 124.1, 124.8, 125.7, 126.6, 126.9, 127.9, 128.4, 128.9, 129.3, 129.8, 129.9, 139.5, 142.7, 143.9, 147.7, 147.9, 148.8, 152.9, 153.8, 155.4, 159.6, 160.2, 168.1, 176.7; MS *m/z* (%) 603 (M$^+$ + 2) (8), 601 (M$^+$, 22), 322 (57), 229 (100), 120 (90); anal. calcd. for $C_{33}H_{24}ClN_7O_3$

(601.16): C, 65.83; H, 4.02; N, 16.29; found: C, 65.71; H, 4.11; N, 16.41%.

Ethyl 1,6-bis-(4-chlorophenyl)-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1,5-dihydro-5-oxo-pyrido[2,3-*d*][1,2,4] triazolo[4,3-*a*]pyrimidine-3-carboxylate (**6h**)

Pale yellow microcrystals; IR (KBr) ν_{max}/cm^{-1} 1720, 1651 (2CO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.43 (t, 3H, *J* 7.0 Hz, CH_3), 2.61 (s, 3H, CH_3), 4.53 (q, 2H, *J* 7.0 Hz, CH_2), 7.51-7.97 (m, 14H, Ar-H + pyridine-H), 8.61 (s, 1H, pyrazole-H); MS *m/z* (%) 637 (M^+ + 2) (15), 635 (M^+, 43), 250 (58), 120 (30), 77 (100); anal. calcd. for $C_{33}H_{23}Cl_2N_7O_3$ (635.12): C, 62.27; H, 3.64; N, 15.40; found: C, 62.31; H, 3.71; N, 15.49%.

Ethyl 6-(4-chlorophenyl)-1-(4-methylphenyl)-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1,5-dihydro-5-oxo-pyrido[2,3-*d*] [1,2,4]triazolo[4,3-*a*]pyrimidine-3-carboxylate (**6i**)

Yellow microcrystals; IR (KBr) ν_{max}/cm^{-1} 1722, 1655 (2CO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.42 (t, 3H, *J* 7.0 Hz, CH_3), 2.38 (s, 3H, Ar-CH_3), 2.59 (s, 3H, CH_3), 4.53 (q, 2H, *J* 7.0 Hz, CH_2), 7.53-7.90 (m, 14H, Ar-H + pyridine-H), 8.62 (s, 1H, pyrazole-H); MS *m/z* (%) 617 (M^+ + 2) (8), 615 (M^+, 22), 558 (40), 185 (55), 77 (100); anal. calcd. for $C_{34}H_{26}ClN_7O_3$ (615.18): C, 66.29; H, 4.25; N, 15.91; found: C, 66.31; H, 4.11; N, 15.81%.

*N*3,1-Diphenyl-6-(4-chlorophenyl)-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-oxo-1,5-dihydropyrido[2,3-*d*][1,2,4] triazolo[4,3-*a*]pyrimidine-3-carboxamide (**6j**)

Yellow microcrystals; IR (KBr) ν_{max}/cm^{-1} 3318 (NH), 1689, 1650 (2CO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.59 (s, 3H, CH_3), 7.38-7.92 (m, 20H, Ar-H + pyridine-H), 8.63 (s, 1H, pyrazole-H), 11.14 (s, 1H, NH); MS *m/z* (%) 650 (M^+ + 2) (20), 648 (M^+, 60), 410 (95), 119 (100), 77 (51); anal. calcd. for $C_{37}H_{25}ClN_8O_2$ (648.18): C, 68.46; H, 3.88; N, 17.26; found: C, 68.41; H, 4.73; N, 17.33%.

*N*3-Phenyl-1-(4-methylphenyl)-6-(4-chlorophenyl)-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-oxo-1,5-dihydro pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine-3-carboxamide (**6k**)

Yellow microcrystals; IR (KBr) ν_{max}/cm^{-1} 3314 (NH), 1689, 1654 (2CO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.39 (s, 3H, Ar-CH_3), 2.61 (s, 3H, CH_3), 7.38-7.98 (m, 19H, Ar-H + pyridine-H), 8.60 (s, 1H, pyrazole-H), 11.18 (s, 1H, NH); MS *m/z* (%) 664 (M^+ + 2) (20), 662 (M^+, 60), 351 (100), 119 (92), 77 (51); anal. calcd. for $C_{38}H_{27}ClN_8O_2$ (662.19): C, 68.83; H, 4.10; N, 16.90; found: C, 68.61; H, 4.01; N, 17.03%.

3-Acetyl-6-(4-methylphenyl)-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1-phenyl-1,5-dihydropyrido[2,3-*d*][1,2,4] triazolo[4,3-*a*]pyrimidin-5-one (**6l**)

Yellow microcrystals; IR (KBr) ν_{max}/cm^{-1} 1705, 1651 (2CO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.39 (s, 3H, Ar-CH_3), 2.62 (s, 3H, CH_3), 3.34 (s, 3H, $COCH_3$), 7.41-8.15 (m, 15H, Ar-H + pyridine-H), 8.57 (s, 1H, pyrazole-H); MS *m/z* (%) 551 (M^+, 95), 525 (60), 262 (100), 91 (66), 77 (93); anal. calcd. for $C_{33}H_{25}N_7O_2$ (551.21): C, 71.86; H, 4.57; N, 17.78; found: C, 71.61; H, 4.43; N, 17.69%.

Ethyl 6-(4-methylphenyl)-1-phenyl-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1,5-dihydro-5-oxo-pyrido[2,3-*d*][1,2,4] triazolo[4,3-*a*]pyrimidine-3-carboxylate (**6m**)

Pale yellow microcrystals; IR (KBr) ν_{max}/cm^{-1} 1727, 1651 (2CO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.34 (t, 3H, *J* 7.0 Hz, CH_3), 2.35 (s, 3H, Ar-CH_3), 2.60 (s, 3H, CH_3), 4.51 (q, 2H, *J* 7.0 Hz, CH_2), 7.51-7.92 (m, 15H, Ar-H + pyridine-H), 8.60 (s, 1H, pyrazole-H); MS *m/z* (%) 581 (M^+, 22), 389 (100), 91 (50), 77 (58); anal. calcd. for $C_{34}H_{27}N_7O_3$ (581.22): C, 70.21; H, 4.68; N, 16.86; found: C, 70.11; H, 4.51; N, 16.71%.

*N*3,1–Diphenyl-6-(4-methylphenyl)-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-oxo-1,5-dihydropyrido[2,3-*d*][1,2,4] triazolo[4,3-*a*]pyrimidine-3-carboxamide (**6n**)

Yellow microcrystals; IR (KBr) ν_{max}/cm^{-1} 3310 (NH), 1689, 1649 (2CO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.39 (s, 3H, Ar-CH_3), 2.60 (s, 3H, CH_3), 7.38-7.98 (m, 20H, Ar-H + pyridine-H), 8.58 (s, 1H, pyrazole-H), 11.18 (s, 1H, NH); MS *m/z* (%) 628 (M^+, 50), 488 (90), 343 (100), 91 (40), 77 (70); anal. calcd. for $C_{38}H_{28}N_8O_2$ (628.23): C, 72.60; H, 4.49; N, 17.82; found: C, 72.41; H, 4.73; N, 17.63%.

3-Acetyl-6-[4-(*N*,*N*-dimethylamino)phenyl]-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1-phenyl-1,5-dihydropyrido[2,3-*d*] [1,2,4] triazolo[4,3-*a*]pyrimidin-5-one (**6o**)

Yellow microcrystals; IR (KBr) ν_{max}/cm^{-1} 1707, 1655 (2CO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.60 (s, 3H, CH_3), 3.11 (s, 6H, $N(CH_3)_2$), 3.36 (s, 3H, $COCH_3$), 7.41-8.15 (m, 15H, Ar-H + pyridine-H), 8.58 (s, 1H, pyrazole-H); MS *m/z* (%) 580 (M^+, 90), 262 (60), 118 (100), 77 (75); anal. calcd. for $C_{34}H_{28}N_8O_2$ (580.23): C, 70.33; H, 4.86; N, 19.30; found: C, 70.18; H, 4.73; N, 19.59%.

Ethyl 6-[4-(*N*,*N*-dimethylamino)phenyl]-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1-phenyl-1,5-dihydro-5-oxo-pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine-3-carboxylate (**6p**)

Yellowish-white microcrystals; IR (KBr) ν_{max}/cm^{-1} 1723, 1650 (2CO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.29

(t, 3H, *J* 7.0 Hz, CH_3), 2.60 (s, 3H, CH_3), 3.11 (s, 6H, $N(CH_3)_2$), 4.31 (q, 2H, *J* 7.0 Hz, CH_2), 7.51-7.97 (m, 15H, Ar-H + pyridine-H), 8.62 (s, 1H, pyrazole-H); MS *m/z* (%) 610 (M^+, 22), 118 (100), 77 (75); anal. calcd. for $C_{35}H_{30}N_8O_3$ (610.24): C, 68.84; H, 4.95; N, 18.35; found: C, 68.75; H, 4.81; N, 18.41%.

3-Acetyl-6-(2-thienyl)-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1-phenyl-1,5-dihydropyrido[2,3-*d*][1,2,4]triazolo[4,3-a]pyrimidin-5-one (**6q**)

Yellow microcrystals; IR (KBr) ν_{max}/cm^{-1} 1705, 1651 (2CO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.62 (s, 3H, CH_3), 3.34 (s, 3H, $COCH_3$), 7.41-8.15 (m, 14H, Ar-H + pyridine-H), 8.61 (s, 1H, pyrazole-H); MS *m/z* (%) 543 (M^+, 61), 384 (90), 77 (100); anal. calcd. for $C_{30}H_{21}N_7O_2S$ (543.15): C, 66.28; H, 3.89; N, 18.04; S, 5.90; found: C, 66.39; H, 4.03; N, 18.14; S, 5.83%.

Ethyl 6-(2-thienyl)-1-phenyl-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1,5-dihydro-5-oxo-pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine-3-carboxylate (**6r**)

Pale yellow microcrystals; IR (KBr) ν_{max}/cm^{-1} 1728, 1647 (2CO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.32 (t, 3H, *J* 7.0 Hz, CH_3), 2.61 (s, 3H, CH_3), 4.53 (q, 2H, *J* 7.0 Hz, CH_2), 7.51-7.95 (m, 14H, Ar-H + pyridine-H), 8.61 (s, 1H, pyrazole-H); MS *m/z* (%) 573 (M^+, 58), 168 (88), 148 (92), 80 (100), 77 (89); anal. calcd. for $C_{31}H_{23}N_7O_3S$ (573.16): C, 64.91; H, 4.04; N, 17.09; S, 5.59; found: C, 65.11; H, 4.15; N, 16.91; S, 5.36%.

*N*3,1-Diphenyl-6-(2-thienyl)-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-oxo-1,5-dihydropyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine-3-carboxamide (**6s**)

Yellow microcrystals; IR (KBr) ν_{max}/cm^{-1} 3310 (NH), 1689, 1649 (2CO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.60 (s, 3H, CH_3), 7.38-7.98 (m, 19H, Ar-H + pyridine-H), 8.60 (s, 1H, pyrazole-H), 11.21 (s, 1H, NH); MS *m/z* (%) 620 (M^+, 77), 440 (100), 168 (88), 80 (94), 77 (50); anal. calcd. for $C_{35}H_{24}N_8O_2S$ (620.17): C, 67.73; H, 3.90; N, 18.05; S, 5.17; found: C, 67.51; H, 4.03; N, 18.16; S, 5.11%.

Synthesis of 5-phenyl-7-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-thioxo-2,3-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-4-one (**8**)

To a mixture of 1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-phenylprop-2-en-1-one (**1**) (1 mmol) and 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**7**) (0.143 g, 1 mmol) in dioxane (15 mL) was added cellulose sulfuric acid (0.05 g). The mixture was refluxed for 8 h, then cooled to ambient temperature and cellulose sulfuric acid was filtered off. The filtrate was concentrated to dryness, and the crude solid product was crystallized from dioxane to afford the pure product 8.

Yield 75%, (0.31 g); pale yellow microcrystals; mp 247-249 °C (DMF/EtOH); IR (KBr) ν_{max}/cm^{-1} 3414, 3252 (2 NH), 1665 (CO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.61 (s, 3H, CH_3), 6.91-8.02 (m, 11H, Ar-H + pyridine-H), 8.63 (s, 1H, pyrazole-H), 11.82 (s, 1H, br, NH), 12.36 (s, 1H, br, NH); MS *m/z* (%) 411 (M^+, 100), 380 (92), 325 (81), 77 (50); anal. calcd. for $C_{23}H_{17}N_5OS$ (411.12): C, 67.13; H, 4.16; N, 17.02; S, 7.79; found: C, 67.26; H, 4.27; N, 16.88; S, 7.83%.

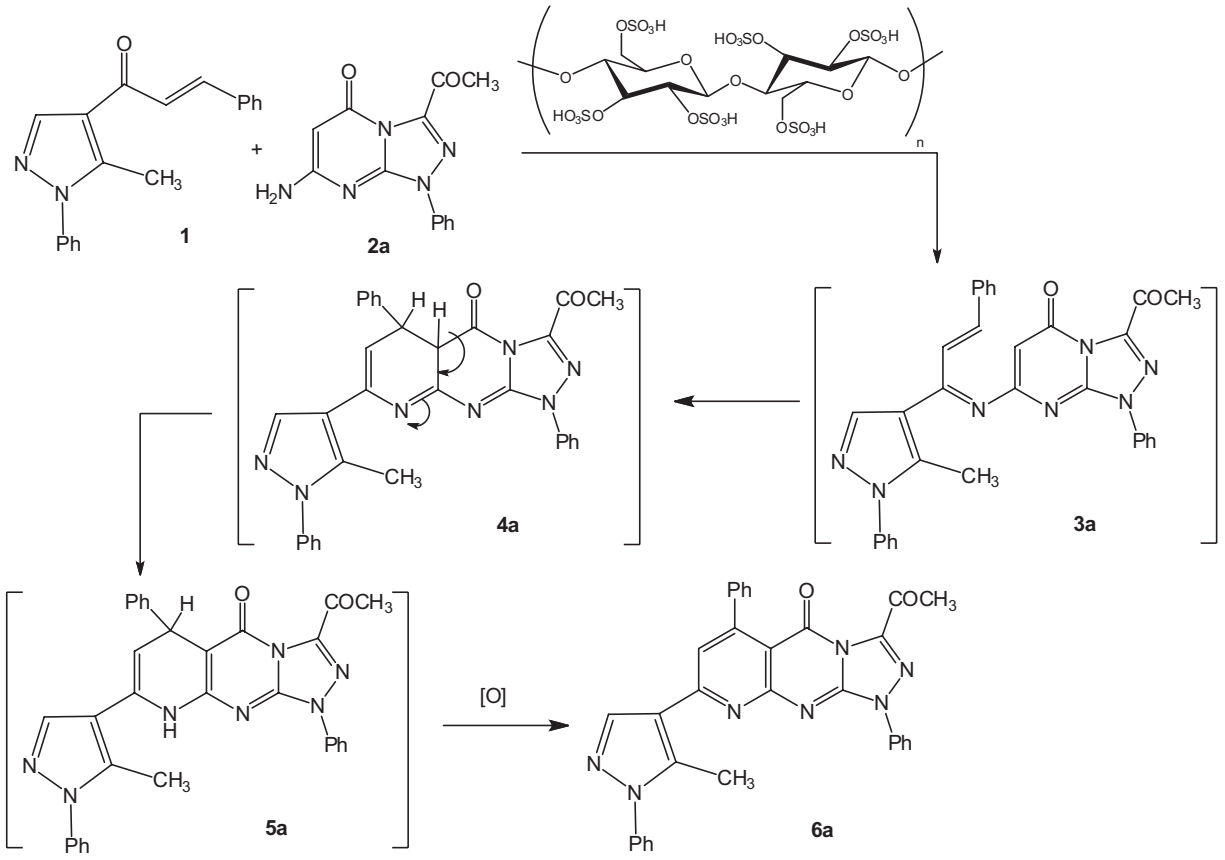
Alternative synthesis of 3-acetyl-1,6-diphenyl-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1,5-dihydropyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-5-one (**6a**)

To a mixture of equimolar amounts of **8** (0.411 g, 1 mmol) and *N*-phenyl 2-oxopropanehydrazonoyl chloride (**9**) (0.196 g, 1 mmol) in dioxane (15 mL) was added triethylamine (0.14 mL, 1 mmol). The reaction mixture was refluxed till all of the starting materials had disappeared and hydrogen sulfide gas ceased to evolve (8 h, monitored by thin layer chromatography). The solvent was evaporated and the residue was treated with methanol. The solid formed was filtered and recrystallized from dimethylformamide (DMF) to give compound **6a** as authentic sample.

Results and Discussion

We initiated our study with the investigation of the nature of solvent and amount of acid catalyst on the optimization of the product yields. Thus, treatment of 1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-phenylprop-2-en-1-one (**1**) with 3-acetyl-7-amino-1-phenyl[1,2,4]triazolo[4,3-*a*] pyrimidin-5(1*H*)-one (**2**) in different solvents under thermal condition, in presence of catalytic amount of cellulose sulfuric acid, led to formation of novel annelated heterocyclic ring system, namely, pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-5-one **6a** (Scheme 1, Table 1).

We have found that, in non-polar aprotic solvents (benzene, toluene, and xylene) the product yields are low (runs 1-3). On the other hand, by using polar aprotic solvent (acetonitrile, DMF, and dioxane) the product yields improve (runs 4-6). Thus, dioxane was found to be the most suitable solvent for the formation of product **6a**. The relationship between the yields of annelated product **6a** and the amount of acid-catalyst was investigated. As shown in Table 1, the yield of **6a** increased with an increase of the amount of catalyst (0.01 g up to 0.05 g) (runs 7-11) and then the yield decreased (run 12).



Scheme 1. Proposed mechanism for the synthesis of pyridotriazolopyrimidinone **6a**.

Table 1. Effect of solvent and amount of acid-catalyst on the product yields

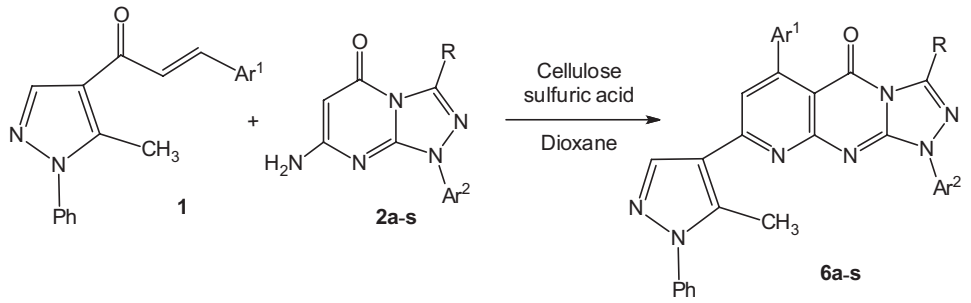
Run	Solvent	Amount of catalyst / g	Yield / %	Run	Solvent	Amount of catalyst	Yield / %
1	Benzene	0.05	43	7	Dioxane	0.01	40
2	Toluene	0.05	48	8	Dioxane	0.02	51
3	Xylene	0.05	47	9	Dioxane	0.03	65
4	Acetonitrile	0.05	62	10	Dioxane	0.04	71
5	DMF	0.05	70	11	Dioxane	0.05	75
6	Dioxane	0.05	75	12	Dioxane	0.06	66

The efficiency of the cellulose sulfuric acid reagent compared to various acidic catalysts was also examined (Table 2). In this study, it was found that cellulose sulfuric acid is more efficient and superior catalyst (run 1) over other acidic catalysts (runs 2-4) with respect to the percent yield of the desired product. It was also observed that the yield of the product was only 10% in the absence of the cellulose sulfuric acid reagent (run 5).

To account for the formation of product **6a**, we proposed the mechanism shown in Scheme 1. Condensation of 1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-phenylprop-2-en-1-one (**1**) with 3-acetyl-7-amino-1-phenyl[1,2,4] triazolo[4,3-*a*]pyrimidin-5(1*H*)-one (**2a**) afforded non-isolable intermediate **3a**. Intramolecular cyclization with concurrent auto-oxidation[17,18] of intermediate **3a** gave the

Table 2. Effect of acid-catalysts on the product yields

Run	Catalyst	Amount of catalyst / mmol	Yield / %
1	Cellulose sulfuric acid	0.05	75
2	*p*-Toluenesulfonic acid	0.1	52
3	Acetic acid	0.1	60
4	Sulfuric acid in acetic acid	0.1	62
5	No catalyst	None	10



Scheme 2. Synthesis of pyridotriazolopyrimidinone derivatives **6a**-**s**.

Table 3. Synthesis of pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-5-ones **6a**-**s**

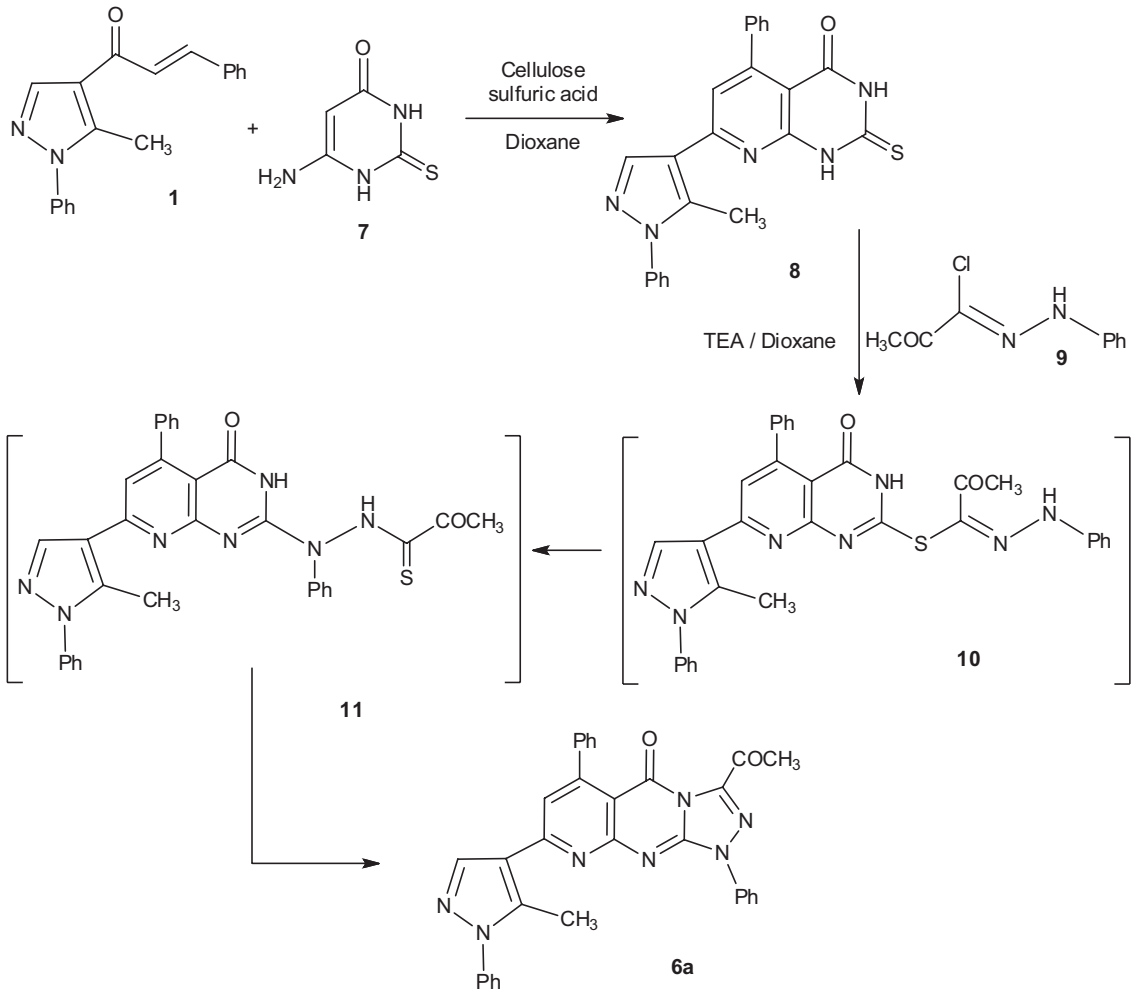
Compound No.	Ar^1	R	Ar^2	Solvent of crystalization	Melting point / °C	Yield / %
6a	C_6H_5	$COCH_3$	C_6H_5	DMF	236-238	75
6b	C_6H_5	CONHPh	C_6H_5	DMF	252-254	75
6c	4-ClC_6H_4	$COCH_3$	C_6H_5	DMF	216-218	80
6d	4-ClC_6H_4	$COCH_3$	4-ClC_6H_4	DMF	226-228	70
6e	4-ClC_6H_4	$COCH_3$	4-$CH_3C_6H_4$	DMF/EtOH	243-245	75
6f	4-ClC_6H_4	$COCH_3$	4-$CH_3OC_6H_4$	DMF/EtOH	254-256	66
6g	4-ClC_6H_4	$COOC_2H_5$	C_6H_5	EtOH	206-208	75
6h	4-ClC_6H_4	$COOC_2H_5$	4-ClC_6H_4	EtOH	213-215	70
6i	4-ClC_6H_4	$COOC_2H_5$	4-$CH_3C_6H_4$	EtOH	218-220	70
6j	4-ClC_6H_4	CONHPh	C_6H_5	DMF	262-264	70
6k	4-ClC_6H_4	CONHPh	4-$CH_3C_6H_4$	DMF/EtOH	231-233	65
6l	4-$CH_3C_6H_4$	$COCH_3$	C_6H_5	DMF/EtOH	244-246	80
6m	4-$CH_3C_6H_4$	$COOC_2H_5$	C_6H_5	EtOH	189-191	75
6n	4-$CH_3C_6H_4$	CONHPh	C_6H_5	DMF	263-265	65
6o	4-$N(CH_3)_2C_6H_4$	$COCH_3$	C_6H_5	DMF	244-246	65
6p	4-$N(CH_3)_2C_6H_4$	$COOC_2H_5$	C_6H_5	EtOH	203-205	60
6q	2-thienyl	$COCH_3$	C_6H_5	DMF/EtOH	238-240	70
6r	2-thienyl	$COOC_2H_5$	C_6H_5	EtOH	213-214	70
6s	2-thienyl	CONHPh	C_6H_5	DMF	267-269	70

respective pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-5-one **6a** as end product.

Having established the feasibility of the reaction of **1** with **2a**, attention was directed to extend the scope of this reaction on 1,3-disubstituted[1,2,4]triazolo[4,3-*a*] pyrimidin-5(1*H*)-ones. Thus, refluxing of **1** with **2a**-**s** in dioxane, containing 0.05 g of cellulose sulfuric acid afforded 1,3,6,8-tetrasubstituted pyrido[2,3-*d*][1,2,4] triazolo[4,3-*a*]pyrimidin-5-one **6a**-**s** (Scheme 2, Table 3).

The structures of the products **6a**-**s** were established by elemental analyses and spectral data. The IR spectra showed in each case one absorption band at ν = 1647-1655 cm^{-1}, assignable to (CO-amide). ^1H NMR revealed a singlet signal at δ = 7.56-7.62 ppm, assignable to pyridine-H on fused pyridine ring[19] and another singlet signal at δ = 8.57-8.64 ppm, corresponding to pyrazole (H-3).[20] Further, ^{13}C NMR of the products confirmed the presence of [1,2,4]triazolo[4,3-*a*]pyrimidine ring by exhibiting signal at δ = 168.1 ppm corresponding to (C=O) group attached to sp^3 nitrogen atom.[13]

The assigned structure and the proposed mechanism were further confirmed by alternate synthesis of **6a** as a typical example of the series prepared. Thus, treatment of 1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-phenylprop-2-en-1-one (**1**) with 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**7**) in dioxane in the presence of catalytic amount of cellulose sulfuric acid under reflux afforded the respective 2-thioxopyrido[2,3-*d*]pyrimidine-4-one (**8**)



Scheme 3. Alternative synthesis of **6a**.

(Scheme 3). Heating of compound **8** with *N*-phenyl 2-oxopropanehydrazonoyl chloride (**9**) in dioxane, in the presence of triethylamine, furnished 3-acetyl-1,6-diphenyl-8-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-1,5-dihydropyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-5-one (**6a**) as authentic product (Scheme 3). The conversion of **8** into product **6a** proceeded through *S*-alkylation[21] to give *S*-alkylated product (intermediate **10**) followed by Smiles rearrangement,[22] affording intermediate **11**, which eliminated hydrogen sulfide gas to give the desired product **6a**.

Conclusions

A series of novel annelated heterocyclic ring system, namely, pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-5-ones **6a**-**s** were prepared via reaction of chalcone with amino[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-ones in the presence of catalytic amount of cellulose sulfuric acid as eco-friendly acid catalyst.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br as PDF file.

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Submitted: September 18, 2014
Published online: March 6, 2015