Short communication

A Rapid One-pot Synthesis of Pyrido[2,3-*d*]pyrimidine Derivatives Using Brønsted-acidic Ionic Liquid as Catalyst

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Abstract

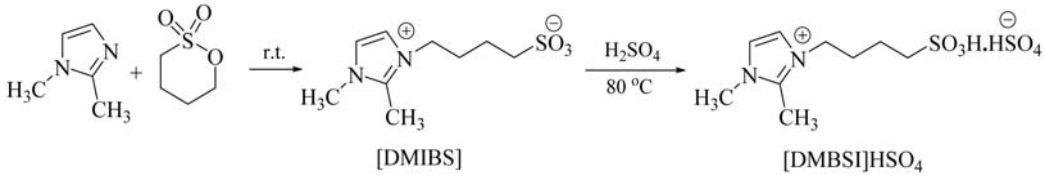
Pyrido[2,3-*d*]pyrimidine derivatives were synthesized regioselectivly in good to high yields by one-pot three-component condensation of 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one, aromatic aldehydes and ethylcyanoacetate or meldrum's acid using 1,2–dimethyl-*N*-butanesulfonic acid imidazolium hydrogen sulfate ([DMBSI]HSO_4) Brønsted-acidic ionic liquid as catalyst. Solvent-free mild reaction conditions, short reaction times, easy work-up, and reusability of the catalyst are the main advantages of this protocol.

Keywords: 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one, ethylcyanoacetate, meldrum's acid, pyrido[2,3-*d*]pyrimidine, ionic liquid, one-pot three-component reaction.

1. Introduction

The medicinal value of pyrimidine derivatives is significant among various heterocycles and they are found to possess various biological activities.[1–10] In particular, many pyrido[2,3-*d*]pyrimidine derivatives possess wide range of physiological properties, which include antibacterial,[11] antiviral,[12] diuretic, analgesic,[13] anti-inflammatory,[14] anticonvulsive,[15,16] antipyretic,[17] cardiotonic,[18,19] antitumoral,[7] bactericidal,[20] antihistaminic,[21] bronchiodilator[22] and also act as a cyclin-dependent kinase 4 inhibitors.[23] As a result, this class of compounds present considerable interest for research. The reactions of 6-amino thiouracil with precursors of α,β-unsaturated carbonyl compounds are one of the most widely employed methods, as they allow synthesis of both pyrido[2,3-*d*]pyrimidines and their dihydro derivatives with different substituents in positions 5 and 7 of the heterocyclic system.[24] The reaction between 6-aminouracils with cyano olefins,[25] intramolecular hetero Diels–Alder reactions involving 1-oxa-1,3-butadienes[26] and several others, have already been reported in the literature.[27]

On the other hand, ionic liquids have attracted an extensive interest as excellent alternatives to organic solvents, due to their favorable properties. The use of ionic liquids as reaction media may offer a convenient solution to both, the solvent emission, and catalytic recycling problems.[28,29] Recently, ionic liquids have been successfully



Scheme 1. Synthesis of [DMBSI]HSO_4

employed as solvents with catalytic activity for a variety of reactions.[30]

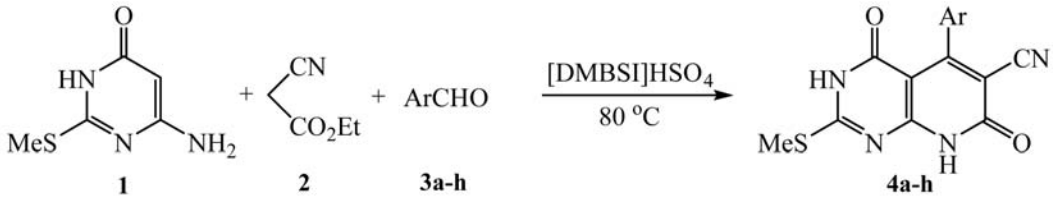
These observations led us to attempt the synthesis of some pyrido[2,3-*d*]pyrimidine derivatives using 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one in the presence of SO_3H-functional Brønsted-acidic halogen-free ionic liquid [DMBSI]HSO_4 which bears a butanesulfonic acid group in 1,2-dimethyl-imidazolium cation as catalyst (Scheme 1).

2. Results and Discussion

As part of our program devoted to developing highly expedient, selective and environmentally friendly methodologies for the preparation of heterocyclic compounds,[31] we describe here an efficient and rapid method for the regioselective synthesis of novel pyrido[2,3-*d*]pyrimidines, using ionic liquid as catalyst. Due to the formation of different condensation products, depending on the specific conditions, reactions of 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one, aldehydes and CH-acid compounds have recently attracted the interest of many chemists.[32] Although most of these processes offer distinct advantages, they suffer from certain drawbacks such as high costs, longer reaction times, harsh reaction conditions, and the use of volatile organic solvents. Therefore, the possibility of performing reactions under solvent-free conditions with ionic liquids could enhance their efficiency from an economic as well as a green point of view.

In this report we have devised a rapid and convenient one-pot three-component reaction for the synthesis of annulated derivatives of pyrimidines (**4a-h, 7a-e**) (Schemes 2 and 3) .

In the initial experiments, the starting compound **1** was prepared by condensation of thiourea with ethylcyanoacetate in sodium ethoxide, and followed by alkylation with methyl iodide.[33] Compound **1** was then used in a three-component reaction for the synthesis of 5-(4-chlorophenyl)-3,4,7,8-tetrahydro-2-(methylthio)-4,7-dioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (**4d**) as a model compound (Scheme 2). To optimize the reaction conditions, different solvents and catalysts were screened for the preparation of **4d,** and the results are summarized in Table 1. It was found that reaction with [DMBSI]HSO_4 as catalyst at solvent-free conditions is the most effective one with the hig-



Ar = C_6H_5, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-CNC_6H_4, 2,4-$Cl_2C_6H_3$, 3-$NO_2C_6H_4$, 4-$CHOC_6H_4$

Scheme 2. Synthesis of pyrido[2,3-*d*]pyrimidine derivatives **4a-h**.

Table 1. Screening of various catalysts and solvents in the synthesis of **4d.**

Entry	catalyst	solvent	Temperature (°C)	Time	Yield (%)[a]
1	Fe^{+3}@ Mont.	EtOH	80	5 h	30
2	KSF	EtOH	80	5 h	25
3	AcOH	d	100	6.5 h	65
4	$ZnCl_2$	EtOH	80	24 h	10
5	*P*-TSA	EtOH	80	12 h	60
6	–	EtOH	80	24 h	trace
7	[TEBSA]HSO_4[b]	EtOH	80	4 h	43
8	[MBSI]HSO_4[c]	EtOH	80	7.5 h	68
9	[DMBSI]HSO_4	EtOH	80	4 min	82
10	[DMBSI]HSO_4	H_2O	80	6 min	40
11	[DMBSI]HSO_4	CH_2Cl_2	25	30 min	25
12	[DMBSI]HSO_4	d	25	30 min	30
13	[DMBSI]HSO_4	d	80	< 1 min	87[e]

[a] Isolated yield. [b] *N,N,N*-triethyl-*N*-butanesulfonic acid ammonium hydrogen sulfate. [c] 1-methyl-*N*-butanesulfonic acid imidazolium hydrogen sulfate. [d] Solvent-free reaction. [e] Short reaction time (< 1 min) and almost the same yield (85%) also remains after three reaction cycles.

hest yield (87%) and the shortest reaction time (< 1 min) among selected solvents and catalysts (Table 1, entry 13).

The results of the reaction after 3 successive runs showed no significant loss of activity (Table 1, entry 13). After completion of the reaction, ionic liquid is easily separated from the reaction medium by washing with water (ionic liquid is soluble in water). The washed ionic liquid is distilled under vacuum to recover the ionic liquid for reuse in subsequent reactions.

We also verified the amount of catalyst needed for the preparation of **4d,** and the best result was obtained by using 0.06 g [DMBSI]HSO_4 per 1 mmol of substrate (Table 2).

Table 2. Optimization of the amount of catalyst in the synthesis of **4d.**

Catalyst (g)	Time (min)	Yield (%)[a]
0.01	30	trace
0.03	10	56
0.06	< 1	87
0.08	< 1	87

[a]Isolated yield.

Therfore, all reactions described in this report were performed under optimized conditions to afford pyrido[2,3-*d*]pyrimidines **4a-h** (Scheme 2) in high yields (79–95%) and short reaction times (< 1–3 min) (Table 3).

In order to extend the scope of this protocol for the synthesis of other derivatives of pyridopyrimidines, we investigated the reaction of 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one (**1**), heteroaromatic aldehydes (**6**) and Meldrum's acid (**5**), in the presence of [DMBSI] HSO_4 and obtained pyrido[2,3-*d*]pyrimidines **7a-e** (Scheme 3) in high yields (80–90%) (Table 4).

Heteroaromatic aldehydes **(6a-e)** were prepared according to the known procedure.[34] The mechanism of this multi-component reaction (MCR) involves the reaction between Meldrum's acid (**5**) and heteroaromatic aldehydes (**6a-e**), resulting in arylidene intermediate, followed by Michael addition of enaminone **1**, cyclization and removal of CO_2 and acetone to form the reaction products (**7a-e)** (Scheme 4).

Electron-withdrawing substituents improved the efficiency of this cyclocondensation reaction (Table 3 and 4). The reaction is very clean and no side-products are formed. All of the synthesized pyrido[2,3-*d*]pyrimidines were characterized with elemental analyses, ^1H and ^{13}C NMR, and IR spectroscopy.

Table 3: Synthesis of pyrido[2,3-*d*]pyrimidine derivatives **4a-h**.

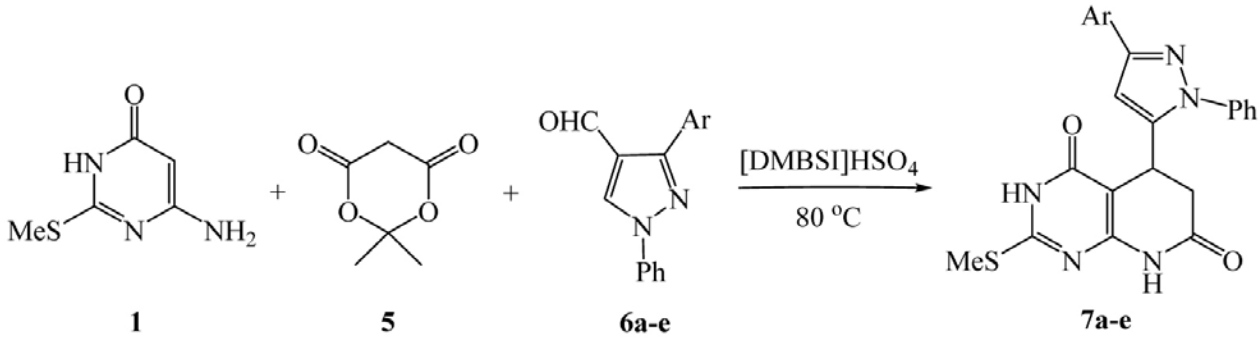
Entry	Product	Ar	Time (min)	Yield (%)[a]
1	**4a**	C_6H_5	3	80
2	**4b**	4-MeC_6H_4	2	79
3	**4c**	4-FC_6H_4	< 1	95
4	**4d**	4-ClC_6H_4	< 1	90
5	**4e**	4-CNC_6H_4	< 1	93
6	**4f**	2,4-$Cl_2C_6H_3$	< 1	95
7	**4g**	3-$NO_2C_6H_4$	2	87
8	**4h**	4-$CHOC_6H_4$	3	84

[a] Isolated yield.

Table 4. Synthesis of pyrido[2,3-d]pyrimidine-4,7(3H,8H)-diones 7a-e.

Entry	Product	Ar	Time (min)	Yield (%)[a]
1	**7a**	C_6H_5	6	81
2	**7b**	4-$OMeC_6H_4$	6	80
3	**7c**	4-ClC_6H_4	5	84
4	**7d**	3-$NO_2C_6H_4$	4	90
5	**7e**	4-$NO_2C_6H_4$	4	86

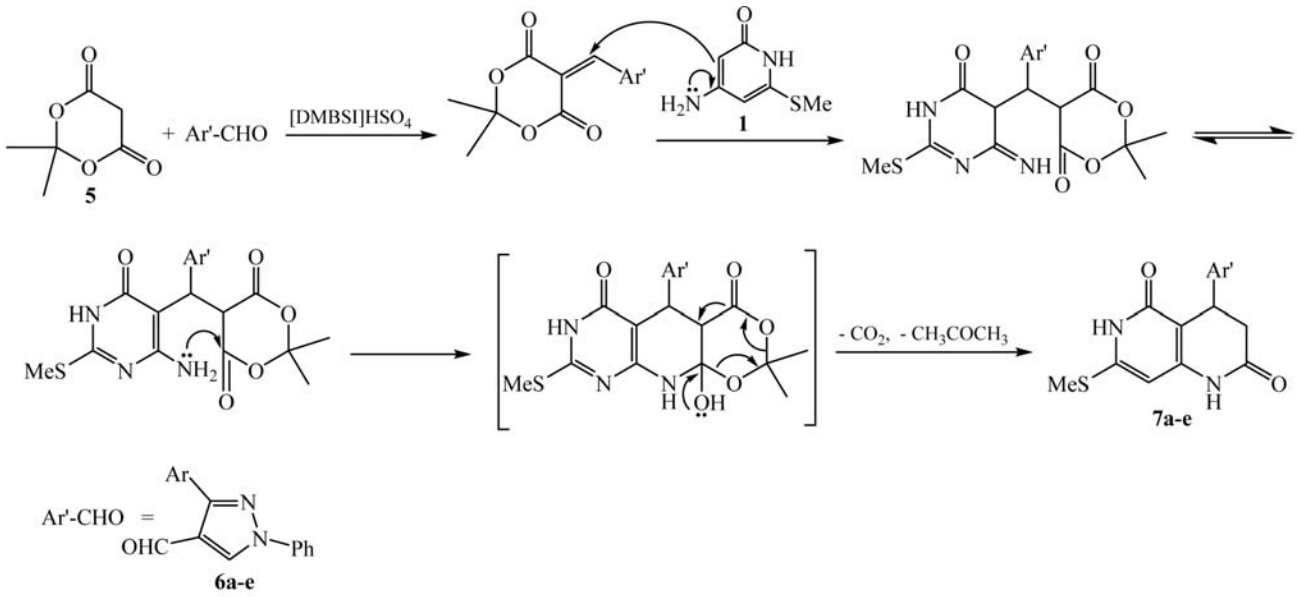
[a] Isolated yield.



1 5 6a-e 7a-e

Ar = C_6H_5, *p*-ClC_6H_4, *p*-$OCH_3C_6H_4$, *p*-$NO_2C_6H_4$, *m*-$NO_2C_6H_4$

Scheme 3. Synthesis of pyrido[2,3-d]pyrimidine-4,7(3H,8H)-diones **7a-e**.



Scheme 4. Plausible mechanism for the synthesis of pyrido[2,3-d]pyrimidine-4,7(3H,8H)-diones 7a-e.

3. Experimental

Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. IR spectra were determined on a Shimadzo IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker DRX-400, using DMSO-d_6 as solvent and TMS as an internal standard. Mass spectra were documented on an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were done on a Carlo-Erba EA1110CNNO-S analyzer and agreed with the calculated values. Chemicals were purchased from Merck and Fluka. All solvents used were dried and distilled according to standard procedures.

SO_3H-functionalized ionic liquid [DMBSI]HSO_4 was synthesized by adapting the reported procedure.[35]

3. 1. Synthesis 1,2-dimethyl-imidazoliumbutane Sulfonate (DMIBS)

To a solution of 1,2-dimethyl-1*H*-imidazole (0.10 mol) in ethanol (25 mL) 0.1 mol 1,4-butanesultone was added in portions within 30 min, and the mixture was stirred for 48 h at room temperature (25 °C). The white precipitate thus formed was filtered and washed with petroleum ether. The product was recrystallized with EtOH, which gave DMIBS in 95 % yield as white solid with m.p. 268–270 °C.

3. 2. Synthesis of 1,2–dimethyl-N-butanesulfonic Acid Imidazolium Hydrogen Sulfate [DMBSI]HSO_4 Ionic Liquid

Equimolar amounts of 1,2-dimethylimidazoliumbutane sulfonate (DMIBS) and sulfuric acid solutions (96%) were mixed and stirred for 6 h at 80 °C. The combined solution was then dried in a vacuum at 100 °C. The residue was washed repeatedly with diethyl ether to remove unreacted material and dried under vacuum again. The ionic liquid was obtained quantitatively in high purity as colorless viscose oil.

The spectral data for 1,2–dimethyl-*N*-butanesulfonic acid imidazolium hydrogen sulfate [DMBSI]HSO_4: ^{1}H NMR (400 MHz, D_2O): δ 1.45 (m, 2H, CH_2), 1.68 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.66 (t, J = 7.6, CH_2-S), 3.49 (s, 3H, CH_3), 3.88 (t, J = 7.2, 2H, CH_2–N), 7.05 (d, J = 2.0, 1H, CH=), 7.10 (d, J = 2.0, 1H, = CH); ^{13}C NMR (100 MHz, D_2O): δ 8.6, 20.9, 27.6, 34.4, 47.3, 50.0, 120.7, 122.0, 144.1.

3. 3. General Procedure for Preparation of Compounds 4a-h and 7a-e

A mixture of equimolar amounts of 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one (**1**) (1 mmol), ethylcyanoacetate or meldrum's acid (**2** or **5**) (1 mmol) and aldehyde (**3** or **6**) (1 mmol) was added to a vial containing a magnetic stirring bar and [DMBSI]HSO_4 (0.18 mmol, 0.06g) and heated at 80 °C in an oil bath. Stirring at 80 °C was continued until disappearance of the starting materials. At this stage, due to the poor solubility in the ionic liquid, the product appears as a precipitate. The reaction mixture was cooled and washed with water to extract the ionic liquid. The solid obtained was recrystallized from ethanol to furnish the desired pure product.

The ionic liquid was recovered from the aqueous extracts by evaporation under reduced pressure, and reused in the next run.

Tetrahydro-2-(methylthio)-4,7-dioxo-5-phenylpyrido[2,3-*d*]pyrimidine-6-carbonitrile (4a)

White solid, mp > 400 °C, IR (KBr): υ 3150, 3050, 2960, 2880, 2220, 1630, 1530, 1500, 1490, 1340, 760, 700 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.59 (s, 3H, CH_3), 7.21–7.43 (m, 5H, Ar-H), 12.90 (bs. s, 1H, NH), 12.98 (br. s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSOd_6): δ 13.4, 99.4, 102.7, 115.8, 127.7, 128.2, 129.0, 136.7, 155.9, 158.3, 160.5, 161.6, 167.3 ppm. Anal. Calcd. for $C_{15}H_{10}N_4O_2S$ (310.33): C, 58.05; H, 3.25; N, 18.05; Found: C, 57.91; H, 3.11; N, 17.93.

3,4,7,8-Tetrahydro-2-(methylthio)-4,7-dioxo-5-*p*-tolyl pyrido[2,3-*d*]pyrimidine-6-carbonitrile (4b)

White solid, mp = 342–344 °C, IR (KBr): υ 3030, 2900, 2750, 2220, 1630, 1540, 1460, 1350, 795 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.41 (s, 3H, CH_3), 2.59 (s, 3H, SCH_3), 7.19 (d, J = 8.0 Hz, 2H, Ar-H), 7.24 (d, J = 8.0 Hz, 2H, Ar-H), 12.87 (bs. s, 1H, NH), 12.98 (br. s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.4, 21.5, 99.4, 102.8, 116.0, 127.7, 128.7, 133.7, 138.4, 155.9, 158.3, 160.5, 161.7, 167.2 ppm. Anal. Calcd. for $C_{16}H_{12}N_4O_2S$ (324.36): C, 59.25; H, 3.73; N, 17.27; Found: C, 59.18; H, 3.75; N, 17.15.

5-(4-Fluorophenyl)-3,4,7,8-tetrahydro-2-(methylthio)-4,7-dioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (4c)

Yellow solid, mp = 389–392 °C, IR (KBr): υ 3050, 2910, 2850, 2215, 1675, 1630, 1600, 1530, 1480, 1450, 1340, 1140, 825 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.60 (s, 3H, CH_3), 7.28 (t, J = 9.1 Hz, 2H, Ar-H), 7.36–7.40 (m, 2H, Ar-H), 12.99 (bs. s, 1H, NH), 13.02 (bs, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.4, 99.5, 103.0, 115.1, 115.3, 115.8, 130.2 (d, $^3J_{CF}$ = 9 Hz), 132.9 (d, $^4J_{CF}$ = 3.0 Hz), 157.1 (d, $^1J_{CF}$ = 242.0 Hz), 160.5 (d, $^2J_{CF}$ = 15.0 Hz), 161.5, 164.0, 167.4 ppm. Anal. Calcd. for $C_{15}H_9FN_4O_2S$ (328.32): C, 54.87; H, 2.76; N, 17.06; Found: C, 54.64; H, 2.70; N, 16.88.

5-(4-Chlorophenyl)-3,4,7,8-tetrahydro-2-(methylthio)-4,7-dioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (4d)

White solid, mp = 324–326 °C, IR (KBr): υ 3040, 2900, 2700, 2210, 1630, 1540, 1460, 1355, 800 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.54 (s, 3H, CH_3), 7.35 (br. s, 2H, Ar-H), 7.50 (bs, 2H, Ar-H), 13.0 (bs. s, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.4, 99.4, 102.7, 115.8, 128.3, 129.7, 133.8, 135.6, 156.0, 158.5, 160.3, 160.4, 167.6 ppm. Anal. Calcd. for $C_{15}H_9ClN_4O_2S$ (344.78): C, 52.25; H, 2.63; N, 16.25; Found: C, 52.11; H, 2.48 N, 16.10.

5-(4-Cyanophenyl)-3,4,7,8-tetrahydro-2-(methylthio)-4,7-dioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (4e)

White solid, mp = 370–372 °C. IR (KBr): υ 3100, 3000, 2800, 2200, 1650, 1570, 1535, 1440, 1400, 820 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 2.40 (s, 3H, CH_3), 7.45 (d, J = 8.0 Hz, 2H, Ar-H), 7.87 (d, J = 8.0 Hz, 2H, Ar-H), 11.60 (bs. s, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.6, 98.3, 99.6, 110.8, 116.6, 119.4, 128.7, 132.0, 143.8, 157.4, 160.4, 160.8, 164.0, 172.6 ppm. Anal. Calcd. for $C_{16}H_9N_5O_2S$ (335.34); C, 57.31; H, 2.71; N, 20.88; Found: C, 57.38; H, 2.60; N, 20.89.

5-(2,4-Dichlorophenyl)-3,4,7,8-tetrahydro-2-(methylthio)-4,7-dioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (4f)

Yellow solid, mp = 324–326, IR (KBr): υ 3100, 2995, 2900, 2800, 2205, 1640, 1570, 1538, 1440, 1390, 818, 850 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.61 (s, 3H, CH_3), 7.40 (d, J = 8.4 Hz, 1H, Ar-H), 7.55 (m, 1H, Ar-H), 7.77 (d, J = 1.2 Hz, 1H, Ar-H), 13.15 (bs. s, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.5, 99.5, 102.8, 115.1, 127.9, 129.0, 130.5, 132.0, 134.5, 135.0, 156.0, 157.3, 158.1, 160.3, 168.0 ppm. Anal. Calcd. for $C_{15}H_8Cl_2N_4O_2S$ (379.22): C, 47.51; H, 2.31; N, 14.77; Found: C, 47.35; H, 2.20; N, 14.72.

3,4,7,8-Tetrahydro-2-(methylthio)-5-(3-nitrophenyl)-4,7-dioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (4g)

Pale yellow solid, mp = 360–363 °C, IR (KBr): υ 3030, 2920, 2700, 2205, 1640, 1530, 1460, 1345, 800, 720, 695 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.61 (s, 3H, CH_3), 7.67–7.84 (m, 2H, Ar-H), 8.26 (s, 1H, Ar-H), 8.33 (d, J = 7.2 Hz, 1H, Ar-H), 13.03 (bs. s, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.5, 99.5, 102.8, 115.6, 123.1, 124.0, 130.1, 134.6, 138.3, 147.6, 156.0, 158.7, 158.8, 160.4, 167.8 ppm. Anal. Calcd. for $C_{15}H_9N_5O_4S$ (355.33); C, 50.70; H, 2.55; N, 19.71; Found: C, 50.60; H, 2.43; N, 19.58.

5-(4-Formylphenyl)-3,4,7,8-tetrahydro-7-methylene-2-(methylthio)-4-oxopyrido [2,3-*d*]pyrimidine-6-carbonitrile (4h)

Pale yellow solid, mp = 347–349 °C, IR (KBr): υ 3100, 3050, 2900, 2205, 2700, 2800, 1700, 1640, 1600, 1540, 1520, 1460, 1350, 818 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.60 (s, 3H, CH_3), 7.55 (d, J = 8.4 Hz, 2H, Ar-H), 8.14 (d, J = 8.4 Hz, 2H, Ar-H), 8.50 (s, 1H, CHO); 12.98 (br s, 1H, NH), 13.06 (bs. s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.5, 99.4, 103.3, 115.7, 116.2, 128.7, 130.8, 131.8, 141.8, 155.0, 156.0, 160.1, 160.4, 162.3 ppm. Anal. Calcd. for $C_{16}H_{10}N_4O_3S$ (338.34): C, 56.80; H, 2.98; N, 16.56; Found: C, 56.68; H, 2.90; N, 16.44.

5,6-Dihydro-2-(methylthio)-5-(1,3-diphenyl-1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7a)

White solid, mp = 214–216 °C: IR (KBr): υ 3490, 3380, 3050, 2960, 2700, 1705, 1640, 1575, 1540, 750, 695, 690 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.40 (s, 3H, CH_3), (dd, J = 15.2, 6.8 Hz, 1H, CH), 3.10 (dd, J = 15.2, 7.6 Hz, 1H, CH), 4.66 (t, J = 7.6 Hz, 1H, CH), 6.01

(s, 1H, =CH), 7.28–7.42 (m, 3H, Ar-H), 7.51 (t, *J* = 8.4 Hz, 2H, Ar-H), 7.73 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.84 (d, *J* = 7.6 Hz, 2H, Ar-H), 8.38 (s, 1H, NH), 11.71 (bs. s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.8, 28.1, 37.0, 93.8, 118.4, 122.5, 126.4, 128.1, 128.2, 128.3, 128.6, 130.0, 134.0, 140.0, 150.8, 159.7, 162.6, 172.2 ppm. Anal. Calcd. for $C_{23}H_{19}N_5O_2S$ (429.49): C, 64.32; H, 4.46; N, 16.31; Found: C, 64.20; H, 4.33; N, 16.43.

5,6-Dihydro-5-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-5-yl)-2-(methylthio)pyrido[2,3-*d*] pyrimidine-4,7(3*H*,8*H*)-dione (7b)

White solid, mp = 200–202 °C, IR (KBr): υ 3490, 3390, 3050, 2920, 2700, 1718, 1620, 1610, 1570, 1540, 1500, 1240, 1020, 830, 770, 690 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.40 (s, 3H, CH_3), 3.03 (m, 2H, CH_2), 3.98 (s, 3H, OMe), 4.63 (bs. s, 1H, CH), 6.02 (s, 1H, =CH), 6.95 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.29 (m, 1H, Ar-H), 7.49 (m, 2H, Ar-H), 7.66 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.83 (d, *J* = 7.6 Hz, 2H, Ar-H), 8.35 (s, 1H, NH), 11.74 (bs, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.9, 28.2, 37.0, 55.6, 93.8, 114.0, 118.3, 122.1, 126.2, 126.4, 128.1, 129.6, 130.0, 140.1, 150.6, 159.3, 159.7, 162.6, 172.2 ppm. Anal. Calcd. for $C_{24}H_{21}N_5O_3S$ (459.52): C, 62.73; H, 4.61; N, 15.24; Found: C, 62.82; H, 4.50; N, 15.31.

5-(3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-5-yl)-5,6-dihydro-2-(methylthio)pyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7c)

White solid, mp = 195–197 °C, IR (KBr): υ 3480, 3390, 1720, 1610, 1520, 1500, 1025, 840, 755, 690 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39 (s, 3H, CH_3S), 3.0 (dd, *J* = 14.8, 6.8 Hz, 1H, CH_2, diastereotopic), 3.09 (dd, *J* = 14.8, 6.8 Hz, 1H, CH_2, diastereotopic), 4.65 (t, *J* = 6.8 Hz, 1H, CH), 6.09 (s, 1H, = CH), 7.31 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.43 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.51 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.73 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.84 (d, *J* = 8.0 Hz, 2H, Ar-H), 8.40 (s, 1H, NH), 11.69 (bs. s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.8, 28.0, 37.0, 93.6, 118.4, 122.7, 126.5, 128.5, 128.6, 130.0, 132.7, 132.8, 139.4, 149.7, 159.7, 162.5, 172.1 ppm. Anal. Calcd. for $C_{23}H_{18}ClN_5O_2S$ (463.94): C, 59.54; H, 3.91; N, 15.10; Found: C, 59.41; H, 3.85; N, 15.16.

5,6-Dihydro-2-(methylthio)-5-(3-(3-nitrophenyl)-1-phenyl-1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione (7d)

Pale yellow solid, mp = 208–210 °C, IR (KBr): υ 3490, 3390, 2920, 2800, 1700, 1620, 1565, 1525, 1340, 815, 760, 690 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.37 (s, 3H, CH_3S), 3.08 (m, 2H, CH_2, diastereotopic), 4.69 (t, *J* = 7.2 Hz , 1H, CH), 6.10 (s, 1H, =CH), 7.34 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.53 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.66 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.88 (d, *J* = 7.6 Hz, 2H, Ar-H), 8.08 (d, *J* = 7.6, Hz 1H, Ar-H), 8.21 (dd, *J* = 8.4, 1.2 Hz, 1H, Ar-H), 8.41 (s, 1H, Ar-H), 8.51 (s, 1H, NH), 11.66 (bs. s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.8, 27.8, 37.0, 93.6, 118.6, 122.8, 123.2, 126.7, 128.6, 130.0, 130.1, 134.9, 135.6, 139.8, 148.1, 149.0, 159.7, 162.5, 172.1 ppm. Anal. Calcd. for $C_{23}H_{18}N_6O_4S$ (474.49): C, 58.22; H, 3.82; N, 17.71; Found: C, 58.30; H, 3.70; N, 17.55.

5,6-Dihydro-2-(methylthio)-5-(3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidine-4,7 (3*H*,8*H*)-dione (7e)

White solid, mp(dec.) = 360–362 °C, IR (KBr): υ 3400, 3200, 1700, 1650 1520, 1350, 875, 790, 690 cm^{-1}. Due to very low solubility the NMR data for this product cannot be reported. MS (m/z, %): 474 (M^+, 0.9), 397 (2.8), 369 (24.5), 368 (52.6), 352 (1.8), 264 (23.5), 210 (2.3), 187 (6.5), 122 (4.9), 105 (15.5), 77 (37.4), 73 (16.5), 57 (100); Anal. Calcd. for $C_{23}H_{18}N_6O_4S$ (474.49); C, 63.15; H, 5.30; N, 14.73; Found: C, 63.00; H, 5.22; N, 14.68.

4. Conclusion

In summary, we have developed a simple and efficient protocol for the synthesis of pyrido[2,3-*d*]pyrimidine derivatives in the presence of ionic liquid [DMBSI]HSO_4 as a readily available catalyst. Mild reaction conditions, short reaction times, the easy work-up of the products, high yields, and reusability of the catalyst are the notable features of this protocol.

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6. References

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Povzetek

Avtorji v prispevku poročajo o regoselektivni pripravi pirido[2,3-*d*]pirimidinskih derivatov z dobrimi izkoristki s pomočjo uporabe enostopenjske trikomponentne kondenzacijske reakcije med 6-amino-2-(metiltio)pirimidin-4(3*H*)-ononom, aromatskimi aldehidi in etilcianoacetatom oziroma meldrumovo kislino. Pri reakciji so kot katalizator uporabili ionsko tekočino (Brønstedovo kislino); 1,2–dimetil-*N*-butansulfonsko kislino-imidazolijev hidrogensulfat ([DMBSI]HSO_4. Reakcije potekajo hitro, pri milih pogojih, brez uporabe topila in z enostavno izolacijo produktov ter z enostavno reciklažo katalizatorja.