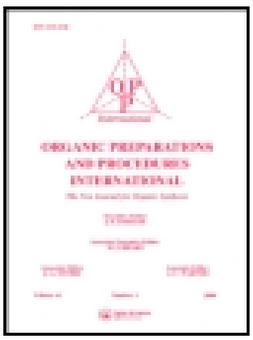

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Effect of Liquid Glass Composition on the Catalytic Preparation of Pyrano[2,3-d]pyrimidine Derivatives

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The main objective of this study was the catalytic preparation 5-aryl-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile derivatives using liquid glass as a catalyst. All reactions were performed in water under reflux conditions. As a further objective, the procedure was investigated using high-speed ball milling (HSBM) techniques. The effects of liquid glass composition and addition of metal oxide impurities were investigated.

Recently, compounds containing at least one core moiety of pyrano[2,3-d]pyrimidine have received considerable attention in synthetic organic chemistry because of their potential as drugs and bioactive compounds.[1–5] Pyrano[2,3-d]pyrimidines have attracted interest in medicine as antitumor,[2] anti-hypertensive,[3] antibacterial[4] and anti-leishmanial[5] drugs. Pyrano[2,3-d]pyrimidines have been produced by a number of methods. A complete review of the synthetic procedures and discussion about these compounds is available.[6]

Liquid glass with the formula of $Na_2(SiO_2)_nO$ is an aqueous solution of sodium silicate which can be easily prepared from the reaction of NaOH (25%) with SiO_2 or by melting sodium carbonate with silicon dioxide. Liquid glass has been used as a binding and coating agent for decades. Liquid glass is a non-toxic, heat durable, stable, low-cost and environmentally friendly material with a strong basic nature. Moreover, liquid glasses show unique chemical properties because their surface charge can be modified and their viscosity can be regulated.[7] Unfortunately their application in organic synthesis has been neglected.[8,9]

This has encouraged us to continue our investigations[10–23] on the catalytic activity of liquid glass for the synthesis of a variety of pyrano[2,3-d]pyrimidine derivatives *via*

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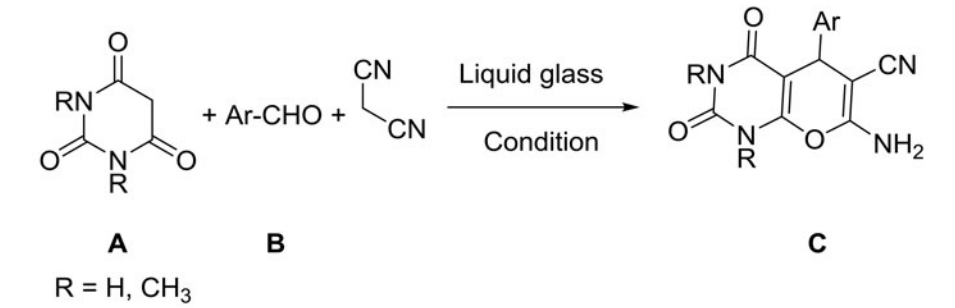
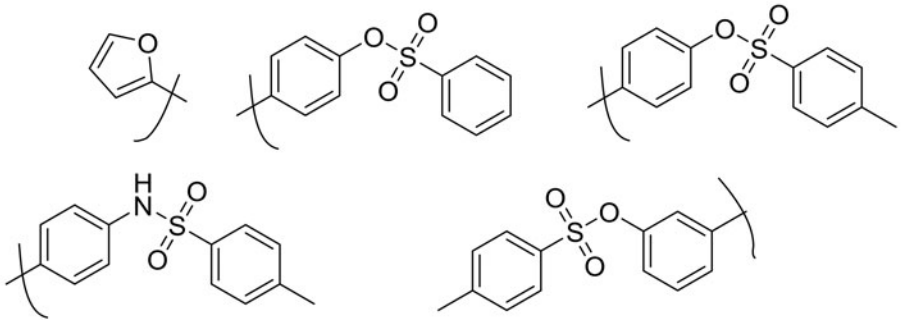
Table 1
Solvent Screening (*Scheme 1*)

Entry	Solvent (5 mL)	Temperature (°C)	Time (min)	Yield (%)[a]
1	Hexane	Reflux	120	35
2	EtOAc	Reflux	120	69
3	EtOH	Reflux	60	80
4	H_2O	Reflux	60	93
5	Et_2O	Reflux	120	–
6	CH_2Cl_2	Reflux	120	–
7	–	80	60	68

[a]Isolated yield.



Ar = Ph, 4-CH_3Ph, 4-ClPh, 4-NO_2Ph, 2-NO_2Ph, 3-NO_2Ph, 4-NCPh, 4-MeOPh, 3,4-$(MeO)_2$Ph, 3,4,5-$(MeO)_3$Ph, 2,4-Cl_2Ph, 2-ClPh, 4-BrPh, 4-FPh

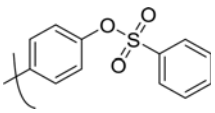
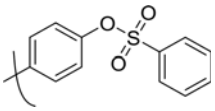
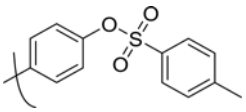
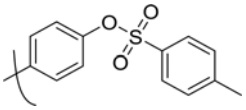
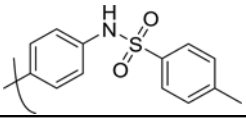


Scheme 1. Preparation of pyrano[2,3-d]pyrimidine derivatives.

a three-component reaction of malononitrile, aromatic aldehydes and barbituric acid (*Scheme 1*).

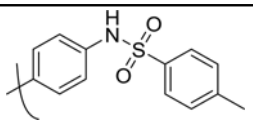
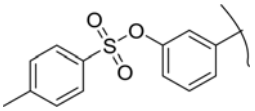
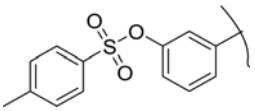
Initially, the liquid glass catalytic potential was investigated for the preparation of 7-amino-2,4-dioxo-5-phenyl-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (**1C**) through the cyclocondensation reaction of benzaldehyde (1 mmol), malononitrile, (1 mmol) and barbituric acid (1 mmol) in different solvents. The results are summarized in *Table 1*. In solvents with boiling points less than 50 °C, *e. g.*, Et_2O and CH_2Cl_2, no product was formed. Solvent screening with non-protic solvents such as CH_3CN and

Table 2
Preparation of Compounds **1C-38C** using Liquid Glass as Catalyst (Scheme 1)

Entry	Ar	R	Compound	Method A: Time (min)/ Yield (%)[a]	Method B: Time (min)/ Yield (%)[a]
1	Ph	H	**1C**	60/93	20/89
2	Ph	CH_3	**2C**	60/90	20/93
3	4-CH_3Ph	H	**3C**	80/86	30/89
4	4-CH_3Ph	CH_3	**4C**	80/88	30/94
5		H	**5C**	70/79	30/83
6		CH_3	**6C**	70/75	30/80
7	4-ClPh	H	**7C**	45/91	15/94
8	4-ClPh	CH_3	**8C**	45/95	15/93
9	4-NO_2Ph	H	**9C**	45/88	15/94
10	4-NO_2Ph	CH_3	**10C**	45/90	15/97
11	2-NO_2Ph	H	**11C**	60/71	25/79
12	2-NO_2Ph	CH_3	**12C**	60/68	25/83
13	3-NO_2Ph	H	**13C**	45/86	15/86
14	3-NO_2Ph	CH_3	**14C**	45/82	15/90
15	4-NCPh	H	**15C**	45/94	15/92
16	4-NCPh	CH_3	**16C**	45/96	15/89
17		H	**17C**	45/87	15/93
18		CH_3	**18C**	45/86	15/91
19		H	**19C**	45/81	15/92
20		CH_3	**20C**	45/87	15/98
21		H	**21C**	45/86	15/86

(*Continued*)

Table 2
(*Continued*)

22		CH_3	**22C**	45/90	15/89
23		H	**23C**	45/91	15/87
24		CH_3	**24C**	45/83	15/82
25	4-MeOPh	H	**25C**	80/80	30/91
26	4-MeOPh	CH_3	**26C**	80/85	30/89
27	3,4-$(MeO)_2$Ph	H	**27C**	90/87	35/89
28	3,4-$(MeO)_2$Ph	CH_3	**28C**	90/83	35/84
29	3,4,5-$(MeO)_3$Ph	H	**29C**	90/80	30/88
30	3,4,5-$(MeO)_3$Ph	CH_3	**30C**	90/79	30/87
31	2,4-Cl_2Ph	H	**31C**	60/89	30/79
32	2,4-Cl_2Ph	CH_3	**32C**	60/87	30/82
33	2-ClPh	H	**33C**	60/79	20/87
34	2-ClPh	CH_3	**34C**	60/78	20/84
35	4-BrPh	H	**35C**	45/96	15/93
36	4-BrPh	CH_3	**36C**	45/97	15/95
37	4-FPh	H	**37C**	60/81	25/84
38	4-FPh	CH_3	**38C**	60/82	25/80

[a]Isolated yield; All products were characterized on the basis of NMR analysis. Method A: Water, Reflux; Method B: Solvent-free, 50°C, HSBM technique.

EtOAc showed lower product yields. It was demonstrated that water as solvent gave a higher yield (*Table 1*, entry 4). The stabilization of ionic intermediates in water is higher than other solvents which makes water a suitable medium for the reaction of organic substances catalyzed by liquid glass.

After solvent screening, the substrate scope was investigated (*Table 2*, Method A). Aromatic aldehydes containing electron-withdrawing groups as well as electron-donating groups were well tolerated in the reaction, producing the desired pyrano[2,3-d]pyrimidines in high yields (*Table 2*). In general, the electronic nature of the substituents had little influence on the product yields, but it did have considerable influence on the reaction times. Aromatic aldehydes substituted at *para* and *meta* positions with electron-withdrawing groups (*e. g.*, NO_2, CN, Cl, Br) showed more reactivity compared to those of electron-donating groups (*e. g.*, CH_3, OCH_3). *ortho*-Substituted aldehydes showed longer reaction times than their *para*-counterparts. Furfural could also achieve a high yield in a reasonably short time. Aldehydes substituted with benzenesulfonate, 4-methyl benzenesulfonate and tosylamide gave the desired product in high yields in

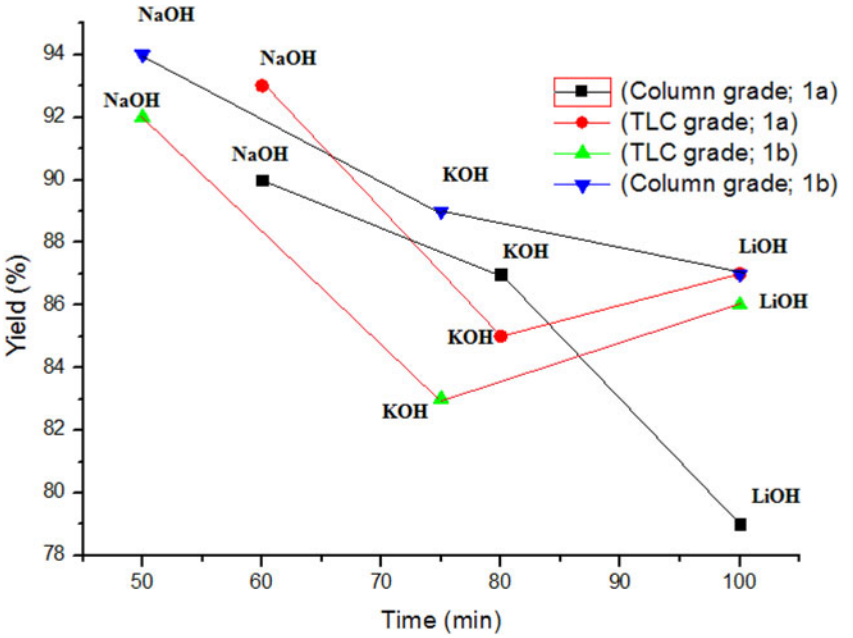


Figure 1. Preparation of 7-Amino-2,4-dioxo-5-phenyl-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile: Effect of liquid glass composition (37% solution in water, MOH bases; silica (TLC and column grade)). **1a:** Si/M ratio: 1.5; **1b**: Si/M ratio: 1.

shorter reaction times compared with benzaldehyde. In summary, all of the reactions took place in good to excellent yields.

Next, we were interested to explore the substrate scope of the liquid glass catalyzed methodology using high speed ball milling (HSBM) techniques (Method B). Implementing HSBM can be useful because it can promote the reaction under milder conditions. The results are summarized in *Table 2*. In all cases, aldehydes with electron-withdrawing substituents had slower reaction times than those with electron-donating substituents. Compared with solvent media (Method A), the solvent-free conditions (Method B) have shorter reaction times, but no considerable effect was observed on the product yields.

Additionally, we investigated the large-scale synthesis of 7-amino-2,4-dioxo-5-phenyl-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (**1C**) through cyclocondensation of benzaldehyde (50 mmol), malononitrile, (50 mmol) and barbituric acid (50 mmol) under solvent-free conditions using HSBM. Our result (86% yield, see Experimental Section) shows that the synthetic methodology can be applied for the large-scale synthesis of pyrano[2,3-d]pyrimidines.

The key parameters that determine the properties of liquid glasses are the weight ratio of Si to Na, the kind of bases used and the amount and kind of impurities. Thus we continued our investigations using liquid glasses with different weight ratios of Si/Na. Two different kinds of silica were used, including TLC grade and column grade. All experiments were done in aqueous media at reflux. The results show that silica sources have no significant effect on the product yield and reaction time. However, the kind of base can influence the reaction rate significantly (*Figure 1*). Three different bases, including NaOH, KOH and LiOH, were used (*Figure 1*). Under the same

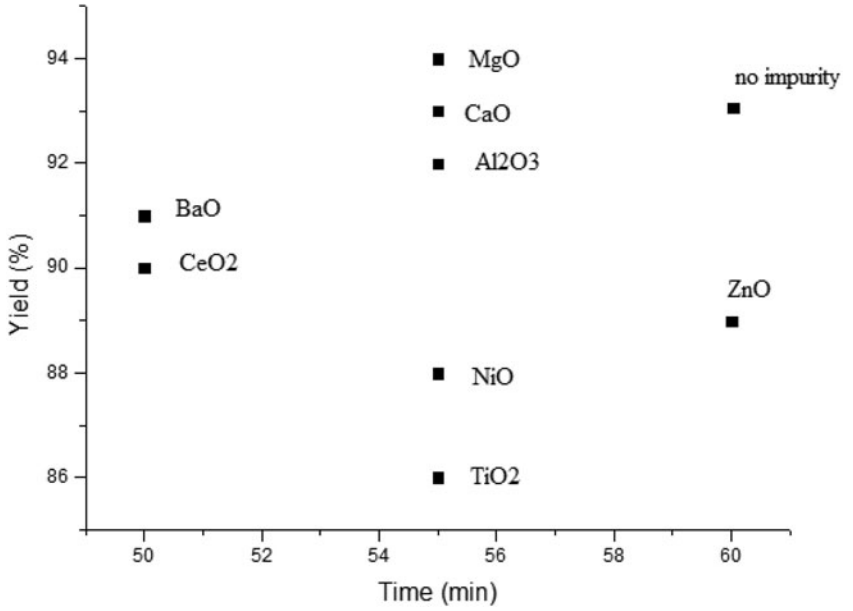


Figure 2. Effect of different metal oxide impurities on the liquid glasses (NaOH; silica TLC grade; 37% solution in water, Si/Na ratio: 1.5) catalyzed preparation of 7-amino-2,4-dioxo-5-phenyl-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile.

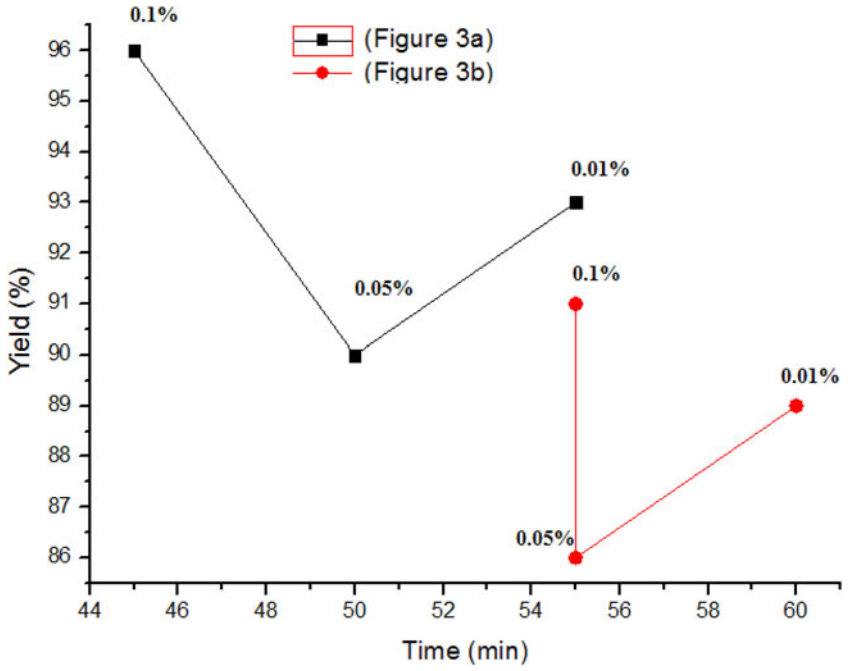


Figure 3. Effect of MgO (**3a**) ZnO (**3b**) and impurity on the liquid glasses (NaOH; silica TLC grade; 37% solution in water, Si/Na ratio: 1.5) catalyzed preparation of 7-amino-2,4-dioxo-5-phenyl-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile.

Table 3
Comparison Results

Entry	Catalyst	Condition [Ref.]	Time (min)/ Yield (%)[a]
1	Iron ore pellet	EtOH: H_2O (1:1), reflux [24]	8/73
2	Dibutylamine (20 mol%)	EtOH: H_2O (1:1), reflux [25]	58/94
3	L-proline (25 mol)	EtOH: H_2O (1:1), r.t. [26]*	130/76
4	$(NH_4)_2HPO_4$ (10 mol%)	EtOH: H_2O (1:1), reflux [27]*	120/74
5	$FeCl_3{\cdot}6H_2O$ (25 mol%)	H_2O, reflux [-]	90/35
6	Dibutylamine (25 mol%)	H_2O, reflux [-]	90/58
7	Pyridine (25 mol%)	H_2O, reflux [-]	90/45
8	Triethyl amine (25 mol%)	H_2O, reflux [-]	90/-
9	Morpholine (25 mol%)	H_2O, reflux [-]	90/35
10	Diethyl amine (25 mol%)	H_2O, reflux [-]	90/-
11	L-proline (25 mol%)	H_2O, reflux [-]	90/69
12	$(NH_4)_2HPO_4$ (25 mol%)	H_2O, reflux [-]	90/51
13	$Ca(OH)_2$ (25 mol%)	H_2O, reflux [-]	90/35
14	$Mg(OH)_2$ (25 mol%)	H_2O, reflux [-]	90/48
15	SiO_2-SO_3H (25 mol%)	H_2O, reflux [-]	90/64
16	Al_2O_3 (25 mol%)	H_2O, reflux [-]	90/-
17	SiO_2/NaOH (1g/0.25 g) (25 mol%)	H_2O, reflux [-]	90/55
18	SiO_2 (25 mol%)	H_2O, reflux [-]	90/-
19	Liquid glass (25 mol%)	H_2O, reflux [-]	60/93

[a]Isolated yield; based on the synthesis of **1C**.
*This reference does not report product **1C** *per se*, so we prepared it using the reported conditions.

conditions, the liquid glasses prepared from NaOH have higher activity than those of KOH and LiOH sources. This may be due to the stronger basicity of NaOH than KOH and LiOH.

The variation of the silica composition with the addition of impurities can strongly affect the reaction rate. Such impurities as Lewis acids or Lewis bases increase the reaction rate. Different metal oxides including MgO, ZnO, CaO, NiO, TiO_2, Al_2O_3, BaO and CeO_2 were investigated. The results are summarized in *Figure 2*. From *Figure 2*, the reaction rate can be categorized as follows: Pure silica $\approx$ ZnO $<$ MgO $\approx$ CaO $\approx$ NiO $\approx$ TiO_2 $\approx$ Al_2O_3 $<$ BaO $\approx$ CeO_2.

However, the role of impurities is not clear. While some of them increased the yield, most impurities actually decreased the yield of the reaction (*Figure 2*). *Figure 3* shows the effect of different concentration of MgO and ZnO impurities respectively. When the impurity percentage increased, the rate of the reaction increased (*Figure 3*).

Comparing the results of the catalytic activity of liquid glass in the synthesis of **1C** with literature reports (such as iron ore pellets [ref.24], dibutylamine [ref. 25], L-proline [ref. 26], $(NH_4)_2HPO_4$ [ref. 27]) has shown that the liquid glass exhibits a significant catalytic potential compared to the other catalysts with regard to reaction time and yield of desired product. The comparison results are shown in *Table 3*. In order to perform a

reasonable and realistic comparison, we performed the reactions using the specified catalytic systems (both reported and unreported) under our optimized conditions. Non-volatile secondary and tertiary amines such as dibutyl amine, pyridine and morpholine gave low to moderate yields, while such volatile amines as triethylamine and diethylamine do not form any product. This is likely due to the simple evaporative removal of the volatile amines from the reaction media. Compared to Lewis and Bronsted acids—such as $FeCl_3{\cdot}6H_2O$, L-proline, $(NH_4)_2HPO_4$ and SiO_2-SO_3H—liquid glass shows better reaction time and yield. Some basic catalytic systems—such as $Ca(OH)_2$, $Mg(OH)_2$ and mechanically mixed SiO_2/NaOH (1g/0.25 g)—have shown moderate yields, while Al_2O_3 and SiO_2 do not give product. Generally, liquid glass showed better results.

In summary, we developed practical methods for the facile liquid glass catalyzed synthesis of 7-amino-2,4-dioxo-5-aryl-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitriles *via* a solvent-free one-pot reaction of aromatic aldehydes, malononitrile and barbituric acids. In our investigations, we explored the bases, sources of silica and impurities. The compounds may be obtained in high yields. The products could be isolated from the reaction mixture with exceptional ease. No by-product was formed during the reaction. This methodology is applicable to both laboratory scale and large scale. Compared to other methods for the preparation of these compounds, ours offers simplicity of operation, convenience and the avoidance of reaction solvents. Our results indicate that liquid glass is a promising catalyst for applications in synthetic organic chemistry.

Experimental Section

All reagents were purchased from Merck and Aldrich and used without further purification. The NMR spectra were recorded on a Bruker Avance DPX 400 MHz instrument. The spectra were measured in DMSO-d_6 relative to TMS (0.00 ppm). Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus. TLC was performed on silica gel Polygram SIL G/UV 254 plates. Elemental analysis was performed on a Heraeus CHNS-O-Rapid analyzer. All compounds gave ^{1}H and ^{13}C-NMR data compatible with the proposed structures and with literature values. Representative characterization data, including satisfactory elemental analyses, are shown below for compounds **1C-23C**.

General Procedure (Method A)

To a mixture of barbituric acid or 1,3-dimethylbarbituric acid (1 mmol), malononitrile (1 mmol) and aryl aldehyde (1 mmol) in 5 mL water, liquid glass (three drops, 25 mol%) was added and the mixture was refluxed until TLC showed complete disappearance of starting material (*Table 2*). After completion of the reaction, the mixture was cooled to 25 °C and the solid product was filtered off and purified by recrystallization from ethanol.

General Procedure (Method B)

A mixture of barbituric acid or 1,3-dimethylbarbituric acid (1 mmol), malononitrile (1 mmol), aryl aldehyde (1 mmol) and liquid glass (three drops, 25 mol%) was milled in a stainless steel grinding vial (10 mL volume) equipped with a stainless steel ball (diameter: 6 mm; mass: 1.04 g) for 20-30 min at 25 Hz and 60 °C. After completion of the reaction, which was confirmed by TLC (eluent: n-hexane/ethyl acetate, 4/1), the

resulting crude product mixture was mixed with $CHCl_3$, and the catalyst was filtered. The solvent was evaporated. Then the solid product was purified by recrystallization from aqueous EtOH.

Large-scale Procedure

A mixture of barbituric acid (50 mmol), malononitrile (50 mmol), benzaldehyde (50 mmol) and liquid glass (25 mol%) was milled in a stainless steel grinding vial (65 mL volume) equipped with four stainless steel balls (diameter 6.35 mm) for 30 min at 25 Hz and 60 °C. The remainder of the procedure was similar to Method B (86%).

7-Amino-2,4-dioxo-5-phenyl-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (1C)

mp 219-221 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 4.28 (s, 1H, CH), 7.04 (s, 2H, NH_2), 7.15 (t, J = 7.8 Hz, 1H), 7.24 (d, J = 7.8 Hz, 2H), 7.32 (t, J = 7.8 Hz, 2H), 11.34 (s, 1H, NH), 12.03 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 38.6, 61.9, 118.8, 127.1, 128.4, 128.3, 129.3, 145.0, 152.4, 159.0, 161.7, 162.8.

Anal. Calcd for $C_{14}H_{10}N_4O_3$: C, 59.57; H, 3.57; N, 19.85. Found: C, 59.48; H, 3.46; N, 19.80.

7-Amino-1,3-dimethyl-2,4-dioxo-5-phenyl-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (2C)

mp 217-219°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.11 (s, 3H, NCH_3), 3.42 (s, 3H, NCH_3), 4.32 (s, 1H, CH), 6.99 (s, 2H, NH_2), 7.15 (t, J = 7.8 Hz, 1H), 7.23 (d, J = 7.8 Hz, 2H), 7.31 (t, J = 7.8 Hz, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 29.4, 31.1, 38.9, 62.1, 118.9, 127.1, 128.4, 128.3, 129.3, 145.0, 152.4, 159.0, 161.9, 163.0.

Anal. Calcd for $C_{16}H_{14}N_4O_3$: C, 61.93; H, 4.55; N, 18.06. Found: C, 61.87; H, 4.48; N, 18.00.

7-Amino-2,4-dioxo-5-(p-tolyl)-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (3C)

mp 214-216 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.26 (s, 3H, CH_3), 4.21 (s, 1H, CH), 6.99 (s, 2H, NH_2), 7.06 (d, J = 7.7 Hz, 2H), 7.18 (d, J = 7.8 Hz, 2H), 11.09 (s, 1H, NH), 11.98 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 21.4, 38.7, 61.8, 119.2, 126.1, 129.2, 129.5, 139.1, 149.9, 152.4, 158.9, 161.7, 162.7.

Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.67; H, 3.89; N, 18.78.

7-Amino-1,3-dimethyl-2,4-dioxo-5-(p-tolyl)-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (4C)

mp 207-209 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.27 (s, 3H, CH_3), 3.10 (s, 3H, NCH_3), 3.42 (s, 3H, NCH_3), 4.29 (s, 1H, CH), 6.91 (s, 2H, NH_2), 7.06 (d, J = 7.6 Hz,

2H), 7.17 (d, $J = 7.6$ Hz, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 21.3, 29.4, 31.2, 39.4, 62.2, 119.3, 126.8, 127.4, 129.3, 138.3, 145.1, 152.4, 159.0, 161.9, 162.9.

Anal. Calcd for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 62.87; H, 4.93; N, 17.24.

7-Amino-5-(furan-2-yl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (5C)

mp 278-28 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 4.38 (s, 1H, CH), 6.48 (d, $J = 8.4$ Hz, 1H), 6.59 (d, $J = 8.5$ Hz, 1H), 7.23 (s, 2H, NH_2), 7.26 (d, $J = 8.6$ Hz, 1H), 11.97 (s, 1H, NH), 12.19 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 37.9, 62.3, 106.9, 111.5, 120.3, 129.5, 143.8, 152.4, 155.9, 161.3, 161.7, 162.7.

Anal. Calcd for $C_{12}H_8N_4O_4$: C, 52.95; H, 2.96; N, 20.58. Found: C, 53.14; H, 3.12; N, 20.49.

7-Amino-5-(furan-2-yl)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (6C)

mp 265-267 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.12 (s, 3H, NCH_3), 3.43 (s, 3H, NCH_3), 4.41 (s, 1H, CH), 6.48 (d, $J = 8.4$ Hz, 1H), 6.58 (d, $J = 8.5$ Hz, 1H), 7.17 (s, 2H, NH_2), 7.24 (d, $J = 8.6$ Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 29.3, 31.3, 39.8, 62.3, 107.7, 111.3, 120.3, 129.2, 142.7, 152.0, 154.3, 155.8, 160.8, 162.9.

Anal. Calcd for $C_{14}H_{12}N_4O_4$: C, 56.00; H, 4.03; N, 18.66. Found: C, 56.14; H, 4.12; N, 18.55.

7-Amino-5-(4-chlorophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (7C)

mp 239-241 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 4.43 (s, 1H, CH), 7.19 (s, 2H, NH_2), 7.24 (d, $J = 7.9$ Hz, 2H), 7.36 (d, $J = 7.9$ Hz, 2H), 11.23 (s, 1H, NH), 12.56 (s, 1H, NH).

Anal. Calcd for $C_{14}H_9ClN_4O_3$: C, 53.10; H, 2.86; N, 17.69. Found: C, 53.21; H, 2.99; N, 17.77.

7-Amino-5-(4-chlorophenyl)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (8C)

mp 210-212 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.10 (s, 3H, NCH_3), 3.42 (s, 3H, NCH_3), 4.44 (s, 1H, CH), 7.22 (s, 2H, NH_2), 7.24 (d, $J = 7.8$ Hz, 2H), 7.36 (d, $J = 7.8$ Hz, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 29.5, 31.4, 39.8, 62.4, 120.1, 128.3, 128.8, 129.3, 136.1, 145.1, 152.0, 154.4, 161.6, 162.9.

Anal. Calcd for $C_{16}H_{13}ClN_4O_3$: C, 55.74; H, 3.80; N, 16.25. Found: C, 55.85; H, 3.75; N, 16.33.

7-Amino-5-(4-nitrophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (9C)

mp 242-244 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 5.07 (s, 1H, CH), 7.14 (s, 2H, NH_2), 7.47 (d, J = 7.8 Hz, 2H), 8.22 (d, J = 7.8 Hz, 2H), 11.31 (s, 1H, NH), 12.76 (s, 1H, NH).

Anal. Calcd for $C_{14}H_9N_5O_5$: C, 51.38; H, 2.77; N, 21.40. Found: C, 51.46; H, 2.90; N, 21.33.

7-Amino-1,3-dimethyl-5-(4-nitrophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (10C)

mp 213-215 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.11 (s, 3H, NCH_3), 3.43 (s, 3H, NCH_3), 5.08 (s, 1H, CH), 7.11 (s, 2H, NH_2), 7.47 (d, J = 7.8 Hz, 2H), 8.22 (d, J = 7.8 Hz, 2H).

Anal. Calcd for $C_{16}H_{13}N_5O_5$: C, 54.09; H, 3.69; N, 19.71. Found: C, 54.15; H, 3.77; N, 19.65.

7-Amino-5-(2-nitrophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (11C)

mp 235-237 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 5.11 (s, 1H, CH), 7.44 (t, J = 7.6 Hz, 1H), 7.46 (s, 2H, NH_2), 7.53 (d, J = 7.6 Hz, 2H), 7.67 (t, J = 7.6 Hz, 1H), 7.86 (d, J = 7.6 Hz, 2H), 11.02 (s, 1H, NH), 12.22 (s, 1H, NH).

Anal. Calcd for $C_{14}H_9N_5O_5$: C, 51.38; H, 2.77; N, 21.40. Found: C, 51.46; H, 2.74; N, 21.32.

7-Amino-1,3-dimethyl-5-(2-nitrophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (12C)

mp 211-213 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.08 (s, 3H, NCH_3), 3.39 (s, 3H, NCH_3), 5.10 (s, 1H, CH), 7.44 (t, J = 7.6 Hz, 1H), 7.49 (s, 2H, NH_2), 7.53 (d, J = 7.6 Hz, 2H), 7.67 (t, J = 7.6 Hz, 1H), 7.86 (d, J = 7.6 Hz, 2H).

Anal. Calcd for $C_{16}H_{13}N_5O_5$: C, 54.09; H, 3.69; N, 19.71. Found: C, 54.22; H, 3.84; N, 19.60.

7-Amino-5-(3-nitrophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (13C)

mp 256-258 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 5.04 (s, 1H, CH), 7.39 (s, 2H, NH_2), 7.64-7.67 (m, 2H), 7.97 (s, 1H), 8.10 (d, J = 7.5 Hz, 1H), 11.18 (s, 1H, NH), 12.29 (s, 1H, NH).

Anal. Calcd for $C_{14}H_9N_5O_5$: C, 51.38; H, 2.77; N, 21.40. Found: C, 51.43; H, 2.77; N, 21.35.

7-Amino-1,3-dimethyl-5-(3-nitrophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (14C)

mp 210-212 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.09 (s, 3H, NCH_3), 3.41 (s, 3H, NCH_3), 5.03 (s, 1H, CH), 7.44 (s, 2H, NH_2), 7.64-7.67 (m, 2H), 7.98 (s, 1H), 8.12 (d, J = 7.5 Hz, 1H).

Anal. Calcd for $C_{16}H_{13}N_5O_5$: C, 54.09; H, 3.69; N, 19.71. Found: C, 54.17; H, 3.88; N, 19.64.

7-Amino-5-(4-cyanophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (15C)

mp 253-255 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 5.03 (s, 1H, CH), 7.34 (s, 2H, NH_2), 7.42 (d, J = 7.9 Hz, 2H), 7.74 (d, J = 7.9 Hz, 2H), 11.64 (s, 1H, NH), 12.87 (s, 1H, NH).

Anal. Calcd for $C_{15}H_9N_5O_3$: C, 58.63; H, 2.95; N, 22.79. Found: C, 58.56; H, 2.94; N, 22.65.

7-Amino-5-(4-cyanophenyl)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (16C)

mp 236-238 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.11 (s, 3H, NCH_3), 3.43 (s, 3H, NCH_3), 5.07 (s, 1H, CH), 7.37 (s, 2H, NH_2), 7.42 (d, J = 7.9 Hz, 2H), 7.74 (d, J = 7.9 Hz, 2H).

Anal. Calcd for $C_{17}H_{13}N_5O_3$: C, 60.89; H, 3.91; N, 20.89. Found: C, 60.97; H, 4.03; N, 20.85.

4-(7-Amino-6-cyano-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidin-5-yl)phenyl benzenesulfonate (17C)

mp 267-269 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 4.97 (s, 1H, CH), 7.18 (s, 2H, NH_2), 7.17 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.58 (t, J = 8.3 Hz, 2H), 7.70 (t, J = 8.3 Hz, 1H), 7.81 (d, J = 8.3 Hz, 2H), 11.54 (s, 1H, NH), 12.34 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 38.7, 64.7, 119.2, 121.7, 126.8, 128.1, 129.5, 129.9, 131.8, 135.3, 145.1, 149.4, 152.3, 161.1, 161.9, 163.0.

Anal. Calcd for $C_{20}H_{14}N_4O_6S$: C, 54.79; H, 3.22; N, 12.78; S, 7.31. Found: C, 54.88; H, 3.31; N, 12.69; S, 7.23.

4-(7-Amino-6-cyano-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidin-5-yl)phenyl benzenesulfonate (18C)

mp 251-253 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.09 (s, 3H, NCH_3), 3.41 (s, 3H, NCH_3), 4.99 (s, 1H, CH), 7.13 (s, 2H, NH_2), 7.17 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.57 (t, J = 8.3 Hz, 2H), 7.69 (t, J = 8.3 Hz, 1H), 7.80 (d, J = 8.3 Hz, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 29.5, 31.2, 38.7, 64.7, 119.2, 121.7, 126.8, 128.1, 129.5, 129.9, 131.8, 135.3, 145.1, 149.4, 152.3, 161.1, 161.9, 163.0.

Anal. Calcd for $C_{22}H_{18}N_4O_6S$: C, 56.65; H, 3.89; N, 12.01; S, 6.87. Found: C, 56.74; H, 3.88; N, 12.12; S, 6.79.

4-(7-Amino-6-cyano-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidin-5-yl)phenyl 4-methylbenzenesulfonate (19C)

mp 274-276 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.39 (s, 3H, CH_3), 4.95 (s, 1H, CH), 7.12 (s, 2H, NH_2), 7.17 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H), 11.48 (s, 1H, NH), 12.26 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 21.0, 38.7, 64.7, 119.2, 121.7, 126.9, 128.0, 129.6, 130.2, 131.8, 144.7, 145.1, 149.9, 152.4, 161.3, 161.8, 162.8.

Anal. Calcd for $C_{21}H_{16}N_4O_6S$: C, 55.75; H, 3.56; N, 12.38; S, 7.09. Found: C, 55.82; H, 3.66; N, 12.29; S, 7.03.

4-(7-Amino-6-cyano-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidin-5-yl)phenyl 4-methylbenzenesulfonate (20C)

mp 259-261 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.39 (s, 3H, CH_3), 3.09 (s, 3H, NCH_3), 3.41 (s, 3H, NCH_3), 4.96 (s, 1H, CH), 7.07 (s, 2H, NH_2), 7.18 (d, J = 7.9 Hz, 2H), 7.24 (d, J = 7.9 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 21.0, 29.4, 31.2, 38.9, 64.8, 119.4, 121.6, 127.0, 128.1, 129.5, 130.1, 131.8, 144.6, 145.1, 149.9, 152.3, 161.4, 161.7, 162.9.

Anal. Calcd for $C_{23}H_{20}N_4O_6S$: C, 57.49; H, 4.20; N, 11.66; S, 6.67. Found: C, 57.61; H, 4.32; N, 11.58; S, 6.59.

N-(4-(7-Amino-6-cyano-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidin-5-yl)phenyl)-4-methylbenzenesulfonamide (21C)

mp >300 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.36 (s, 3H, CH_3), 4.81 (s, 1H, CH), 7.06 (s, 2H, NH_2), 7.12 (d, J = 7.8 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 7.73 (d, J = 8.6 Hz, 2H), 9.51 (s, 1H, NH), 11.19 (s, 1H, NH), 12.03 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 20.8, 38.6, 64.5, 114.6, 119.4, 127.8, 128.9, 129.5, 129.9, 136.3, 136.8, 144.6, 145.1, 152.3, 161.2, 161.8, 162.9.

Anal. Calcd for $C_{21}H_{17}N_5O_5S$: C, 55.87; H, 3.80; N, 15.51; S, 7.10. Found: C, 56.01; H, 3.93; N, 15.44; S, 7.06.

N-(4-(7-Amino-6-cyano-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidin-5-yl)phenyl)-4-methylbenzenesulfonamide (22C)

mp 291-293 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.38 (s, 3H, CH_3), 3.10 (s, 3H, NCH_3), 3.42 (s, 3H, NCH_3), 4.82 (s, 1H, CH), 7.06 (s, 2H, NH_2), 7.12 (d, J = 7.9 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 8.5 Hz, 2H), 9.49 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 20.9, 29.3, 31.2, 38.8, 64.3, 114.6, 120.7, 127.1, 128.3, 129.1, 129.7, 136.3, 136.7, 144.1, 145.2, 151.4, 153.8, 160.6, 162.5.

Anal. Calcd for $C_{23}H_{21}N_5O_5S$: C, 57.61; H, 4.41; N, 14.61; S, 6.69. Found: C, 57.52; H, 4.35; N, 14.49; S, 6.58.

3-(7-Amino-6-cyano-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidin-5-yl)phenyl benzenesulfonate (23C)

mp 266-268 °C;^{1}H-NMR (400 MHz, DMSO-d_6): δ = 4.77 (s, 1H, CH), 6.99-7.34 (m, 6H), 7.56 (t, J = 8.4 Hz, 2H), 7.68 (t, J = 8.4 Hz, 1H), 7.80 (d, J = 8.6 Hz, 2H), 11.11 (s, 1H, NH), 12.02 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 38.6, 64.6, 111.2, 119.9, 120.4, 121.5, 127.8, 128.6, 129.1, 129.2, 131.4, 134.4, 142.6, 151.4, 152.6, 160.7, 161.3, 162.9.

Anal. Calcd for $C_{20}H_{14}N_4O_6S$: C, 54.79; H, 3.22; N, 12.78; S, 7.31. Found: C, 54.70; H, 3.16; N, 12.70; S, 7.26.

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