Indian Journal of Chemistry
Vol. 60B, October 2021, pp. 1368-1372

An efficient solvent-free synthesis of pyrido[2,3-d]pyrimidine derivatives utilizing lactic acid as green and eco-friendly catalyst

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Received 28 February 2020; accepted (revised) 26 August 2021

An efficient, solvent-free and one-pot procedure for the synthesis of pyrido[2,3-d]pyrimidine derivatives by condensation of aromatic aldehydes, malononitrile and 6-amino-1,3-dimethyl uracil at 90°C catalyzed by lactic acid as an inexpensive, biological and eco-friendly compound is described. The remarkable benefits of this procedure are green and environmentally friendly reaction conditions, high yields, short reaction time, simple methodology and easy workup.

Keywords: Lactic acid, 6-amino-1,3-dimethyluracil, aryl aldehyde, malononitrile, solvent-free conditions

Multicomponent reactions (MCRs) have growing importance for several reasons including atom economy, reduced steps of work up, time saving, simple reaction design and minimized waste generation[1]. The first MCR was reported by Strecker for the synthesis of amino acids[2]. Pyrido[2,3-d]pyrimidines with uracil core have received considerable attention because of their biological and pharmacological activities for example, antitumor[3], antihypertension[4], antibacterial[5], antifungal[6] and antimicrobial properties[7]. Uracil derivatives are the building blocks for the synthesis of N-containing species of biological and pharmacological significance[8]. All compounds of pyrazolopyrimidines[9], xanthine derivatives[10]. Pyrazolopyridines[11] and pyramid-dopyrimidines[12] have been synthesized by the functionalization of uracil derivatives (Figure 1). Several synthetic methodologies have been reported for the preparation of them such as TEBAC[13], nano-MgO[14], microwave irradiation[15], electrolysis[16], L-proline[17] and ionic liquid[18]. However, many of these methods have limitations such as low yields, long time and specific conditions.

In continuation of our researches on MCRs[19-26], herein, we describe the efficient and simple synthesis of highly functionalized pyrido[2,3 d]pyrimidines by three component reactions of 6-aminouracil with malononitrile and aldehydes at 90°C to synthesize pyrido[2,3 d]pyrimidines in good yields (Scheme I).

Results and Discussion

At first, we optimized the reaction conditions in the preparation of pyrido[2,3-*d*]pyrimidines by performing the condensation of malononitrile, 4-chlorobenzaldehyde and 6-amino-1,3-dimethyluracil utilizing the lactic acid under various conditions (Table I). The best results were obtained at 90°C under solvent-free conditions (Table I, entries 12).

After optimization of the reaction conditions, we employed several aromatic aldehydes containing electron-withdrawing or electron-releasing groups for the synthesis of the other derivatives under optimized condition. Table II show that all products were obtained successfully in short reaction time and good

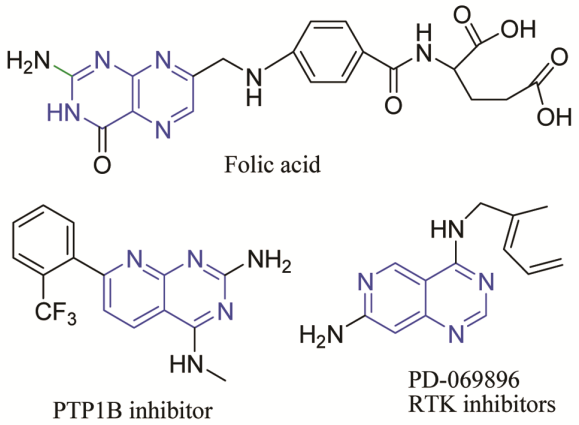
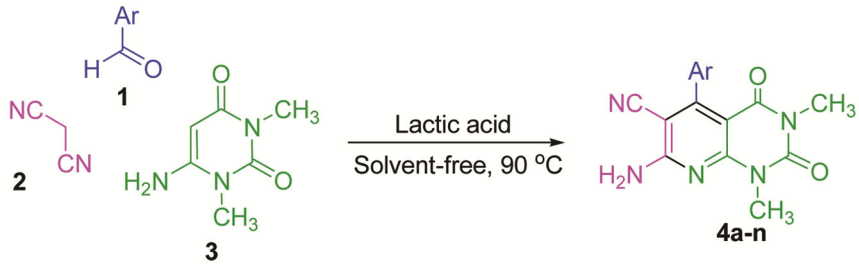


Figure 1 — Some examples of biologically relevant compounds having pyrido[2,3-*d*]pyrimidine skeleton



Scheme I — Synthesis of pyrido[2,3-*d*]pyrimidine derivatives

Table I — Effect of the solvent, temperature and amount of the catalyst in the synthesis of compound **4f**

Entry	Solvent	Temperature (°C)	Catalyst (mol %)	Time (min)	Isolated Yield (%)[a]
1	H_2O	70	10	60	58
2	EtOH	70	10	60	63
3	$CHCl_3$	70	10	70	54
4	THF	70	10	70	48
5	–	70	10	45	68
6	–	RT	10	120	Trace
7	–	50	10	65	60
8	–	80	10	35	88
9	–	90	10	25	91
10	–	100	10	20	89
11	–	90	5	30	90
12	–	90	15	20	94
13	–	90	20	20	92

Table II — Synthesis of pyrido[2,3-*d*]pyrimidines utilizing the lactic acid in solvent-free conditions

Entry	Product	Time (min)	Isolated Yield (%)[a]	m.p. (°C) Found	m.p. (°C) Reported [Ref]
1	**4a**, Ar = Ph	30	90	>300	>300[18]
2	**4b**, Ar = 4-MeC_6H_4	40	88	>300	>300[13]
3	**4c**, Ar = 4-$MeOC_6H_4$	35	89	>300	>300[13]
4	**4d**, Ar = 2-ClC_6H_4	25	93	>300	>300[14]
5	**4e**, Ar = 3-ClC_6H_4	30	91	>300	>300[14]
6	**4f**, Ar = 4-ClC_6H_4	20	94	>300	>300[14]
7	**4g**, Ar = 3-BrC_6H_4	30	92	>300	>300[18]
8	**4h**, Ar = 4-BrC_6H_4	20	93	>300	>300[13]
9	**4i**, Ar = 4-FC_6H_4	20	94	>300	>300[18]
12	**4j**, Ar = 3-FC_6H_4	30	92	>300	This work
13	**4k**, Ar = 2-MeC_6H_4	30	91	>300	This work
14	**4l**, Ar = 3-Pyridyl	25	92	290-292	This work
15	**4m**, Ar = 4-Pyridyl	25	93	>300	This work
16	**4n**, Ar = 2-Thienyl	30	91	>300	This work

Table III — Comparison of lactic acid with previously reported catalysts for the synthesis of compound **4f**

Entry	Catalyst	Time (min)	Conditions	Yield (%)	Ref.
1	TEBAC	720	H_2O, 90°C	96	13
2	Electrolysis	20	EtOH, KBr	71	16
3	Nano-MgO	15	H_2O, 80°C	90	14
5	Lactic acid	20	Solvent free, 90°C	94	Present work

yields. It was shown that the aldehydes with electron-withdrawing groups gave shorter times and good yields than aldehydes with electron-releasing groups.

To demonstrate the merit of our work, we compared the results of this work with the literature as shown in Table III. The data in Table III show that lactic acid can act as an efficient catalyst with respect

to reaction yields and the obtained products. The products **4l-p** are new compounds which were characterized by IR, ^{1}H and ^{13}C NMR and MS.

Experimental Section

All the chemicals were purchased from chemical producers Merck or Fluka and used without further purification. Melting points and IR spectra of all compounds were determined using an FT-IR-JASCO-460 plus spectrometer and Electrothermal 9100 apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra of compounds were recorded on a Bruker DRX-300 Avance instrument in DMSO-d_6 at 300 MHz. Vincinal aromatic hydrogen coupling constants were in the range of 6-8 Hz. Mass spectra were obtained on the Sciex-3200 Technology spectrometer operating at an ionization potential of 70 eV.

General procedure for the synthesis of 2-aminopyrimidinomethylnaphthols

To a mixture of aromatic aldehyde (1.0 mmol), malononitrile (1.0 mmol) and 6-amino-1,3-dimethyluracil (1.0 mmol), lactic acid (15 mol %) were added. The mixture was stirred at 90°C and reaction progress was monitored through TLC. After completion of the reaction, the mixture was cooled and washed with water. Lactic acid was removed from the mixture. The filter cake obtained was recrystallized from ethanol to obtain the pure product.

7-Amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-phenylpyrido[2,3-d]pyrimidine-6-carbonitrile, 4a

IR (KBr): 3452, 3317, 3223, 2212, 1716, 1667, 1624, 1557, 1508, 1439, 1369, 1309 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.09 (s, CH_3, 3H), 3.52 (s, CH_3, 3H), 7.10-7.46 (5H, $H_{aromatic}$), 7.95 (s, NH_2, 2H,).

7-Amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-p-tolylpyrido[2,3-d]pyrimidine-6-carbonitrile, 4b

IR (KBr): 3457, 3310, 3219, 2212, 1716, 1667, 1624, 1563, 1509, 1440, 1367 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.39 (s, CH_3, 3H), 3.09 (s, CH_3, 3H), 3.51 (s, CH_3, 3H), 7.11 (d, $H_{aromatic}$, 2H,), 7.23 (d, $H_{aromatic}$, 2H), 7.85 (s, NH_2, 2H).

7-Amino-1,2,3,4-tetrahydro-5-(4-methoxyphenyl)-1,3-dimethyl-2,4-dioxopyrido[2,3-d]pyrimidine-6-carbonitrile, 4c

IR (KBr): 3458, 3316, 3218, 2213, 1714, 1664, 1622, 1550, 1506, 1435, 1367, 1291 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.09 (s, CH_3, 3H), 3.51 (s, CH_3, 3H), 3.83 (s, CH_3, 3H), 6.97 (d, $H_{aromatic}$, 2H), 7.16 (d, $H_{aromatic}$, 2H), 7.82 (s, NH_2, 2H).

7-Amino-5-(2-chlorophenyl)-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrido[2,3-d]pyrimidine-6-carbonitrile, 4d

IR (KBr): 3455, 3367, 3273, 2254, 1689, 1667, 1645, 1583, 1496, 1445, 1380, 1352, 1298, 1271 cm^{-1}.

7-Amino-5-(3-chlorophenyl)-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrido[2,3-d]pyrimidine-6-carbonitrile, 4e

IR (KBr): 3397, 3328, 3224, 2224, 1712, 1662, 1630, 1557, 1507, 1435, 1366, 1308, 1288 cm^{-1}.

7-Amino-5-(4-chlorophenyl)-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrido[2,3-d]pyrimidine-6-carbonitrile, 4f

IR (KBr): 3461, 3320, 3220, 2214, 1715, 1662, 1622, 1568, 1548, 1509, 1494, 1369, 1301 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.09 (s, CH_3, 3H), 3.51 (s, CH_3, 3H), 7.26 (d, $H_{aromatic}$, 2H), 7.49 (d, $H_{aromatic}$, 2H), 7.95 (s, NH_2, 2H).

7-Amino-5-(3-bromophenyl)-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrido[2,3-d]pyrimidine-6-carbonitrile, 4g

IR (KBr): 3460, 3317, 3222, 2215, 1717, 1660, 1623, 1565, 1515, 1479, 1443, 1371, 1279 cm^{-1}.

7-Amino-5-(4-bromophenyl)-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrido[2,3-d]pyrimidine-6-carbonitrile, 4h

IR (KBr): 3460, 3313, 3220, 2960, 2214, 1715, 1663, 1623, 1569, 1546, 1509, 1493, 1438, 1369, 1277 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.09 (s, CH_3, 3H), 3.51 (s, CH_3, 3H), 7.21 (d, $H_{aromatic}$, 2H), 7.63 (d, $H_{aromatic}$, 2H), 7.93 (s, NH_2, 2H).

7-Amino-5-(4-fluorophenyl)-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrido[2,3-d]pyrimidine-6-carbonitrile, 4i

IR (KBr): 3401, 3329, 3224, 2228, 1715, 1671, 1634, 1598, 1557, 1510, 1440, 1368, 1311 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.10 (s, CH_3, 3H), 3.52 (s, CH_3, 3H), 7.27-7.32 (m, $H_{aromatic}$, 4H), 7.90 (s, NH_2, 2H).

7-Amino-5-(3-fluorophenyl)-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrido[2,3-d]pyrimidine-6-carbonitrile, 4j

IR (KBr): 3487, 3400, 3324, 3222, 3075, 2219, 1715, 1670, 1631, 1563, 1492, 1430, 1391, 1367 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.10 (s,

CH_3, 3H), 3.52 (s, CH_3, 3H), 7.08-7.31 (m, $H_{aromatic}$, 3H), 7.46-7.53 (m, $H_{aromatic}$, 1H), 7.95 (s, NH_2, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.1, 30.0, 88.8, 99.1, 114.8, 115.1, 115.3, 115.5, 123.9, 130.3, 130.5, 139.8, 140.0, 151.3, 154.0, 158.1, 158.8, 160.4, 160.6, 163.7; MS: *m/z* (%) 185.1 (4), 256.2 (6), 274.2 (15), 282.2 (20), 290.2 (12), 302.2 (25), 304.2 (100), 326.1 (25), 327.1 (M^+, 3).

7-Amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-o-tolylpyrido[2,3-d]pyrimidine-6-carbonitrile, 4k

IR (KBr): 3455, 3311, 3217, 2953, 2213, 1715, 1655, 1622, 1564, 1546, 1494, 1435, 1370, 1278 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.02 (s, CH_3, 3H), 3.09 (s, CH_3, 3H), 3.53 (s, CH_3, 3H), 7.01 (d, $H_{aromatic}$, 1H), 7.21-7.34 (m, $H_{aromatic}$, 3H), 7.90 (s, NH_2, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 19.5, 28.1, 30.0, 88.6, 99.3, 115.4, 125.9, 127.0, 128.4, 129.8, 134.3, 137.7, 151.3, 154.1, 158.8, 159.6, 160.9; MS: *m/z* (%) 59.0 (4), 62.0 (100), 88.9 (3), 97.0 (7), 255.2 (2), 320.4 ($[M-H]^+$, 20).

7-Amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-(pyridin-3-yl)pyrido[2,3-d]pyrimidine-6-carbonitrile, 4l

IR (KBr): 3350, 3198, 2214, 1709, 1642, 1575, 1480, 1444, 1418, 1370 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.10 (s, CH_3, 3H), 3.52 (s, CH_3, 3H), 7.47 (t, $H_{aromatic}$, 1H), 7.72-7.76 (m, $H_{aromatic}$, 1H), 7.99 (s, NH_2, 2H), 8.46 (d, $H_{aromatic}$, 1H), 8.63 (dd, $H_{aromatic}$, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.2, 30.1, 89.0, 99.2, 115.6, 123.2, 133.7, 135.6, 147.9, 149.6, 151.2, 154.0.

7-Amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-(pyridin-4-yl)pyrido[2,3-d]pyrimidine-6-carbonitrile, 4m

IR (KBr): 3382, 3040, 2220, 1708, 1666, 1602, 1571, 1539, 1519, 1440, 1367 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.10 (s, 3H, CH_3), 3.52 (s, 3H, CH_3), 7.29 7.31 (dd, $H_{aromatic}$, 2H), 8.03 (s, NH_2, 2H), 8.66-8.68 (dd, $H_{aromatic}$, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.1, 30.0, 88.0, 98.7, 115.3, 122.6, 145.9, 149.6, 151.3, 154.0, 156.8, 158.9, 160.7; MS: *m/z* (%) 59.0 (5), 62.0 (100), 89.0 (3), 255.2 (5), 307.2 ($[M-H]^+$, 12).

7-Amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-(thiophen-2-yl)pyrido[2,3-d]pyrimidine-6-carbonitrile, 4n

IR (KBr): 3446, 3315, 3222, 2957, 2212, 1715, 1667, 1623, 1557, 1510, 1450, 1427, 1367, 1277 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.12 (s, CH_3, 3H), 3.50 (s, CH_3, 3H), 7.07-7.15 (m, $H_{aromatic}$, 2H), 7.72-7.74 (dd, $H_{aromatic}$, 1H), 7.91 (s, NH_2, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.2, 30.1, 90.1, 100.0, 115.5, 127.1, 127.9, 128.1, 136.7, 151.2, 152.6, 154.1, 158.5, 160.5; MS: *m/z* (%) 102.2 (12), 230.3 (15), 274.2 (100), 282.3 (35), 304.3 (90), 314.1 ([M+H]+, 15).

Conclusion

In summary, we have demonstrated a highly efficient one-pot procedure for the three-component synthesis of pyrido[2,3-*d*]pyrimidines *via* condensation of an aldehyde, malononitrile and 6-amino-1,3-dimethyluracil in the presence of the lactic acid as an environmentally benign catalyst in solvent-free conditions. Lactic acid is green, inexpensive and readily commercially available catalyst. Easy and clean preparation, operationally simple, good yields, reasonable time, product purity, non-toxic and mild conditions are advantages of this method.

Acknowledgment

The authors gratefully acknowledge financial support from the Research Council of the University of Sistan and Baluchestan.

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