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Facile, capable, atom-economical one-pot multicomponent strategy for the direct regioselective synthesis of novel isoxazolo[5,4-*d*]pyrimidines

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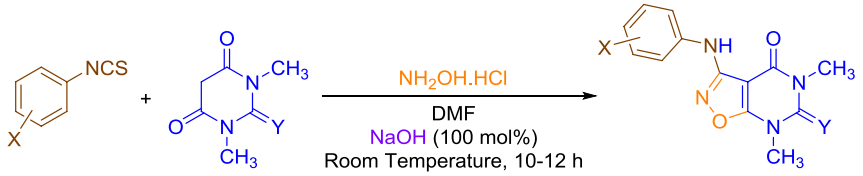
Abstract

Facile and efficient NaOH-promoted one-pot regioselective synthesis of 5,7-dimethyl-3-(arylamino)isoxazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones and 5,7-dimethyl-3-(arylamino)-6-thioxo-6,7-dihydroisoxazolo[5,4-*d*]pyrimidin-4(5*H*)-ones as pharmaceutically interesting compounds has been developed based on a three-component reaction between aryl isothiocyanates, *N*,*N*-dimethylbarbituric acid or *N*,*N*-dimethyl-2-thiobarbituric acid, and hydroxylamine hydrochloride in *N*,*N*-dimethylformamide (DMF) at room temperature. This new protocol has advantages such as simple operation, regioselectivity, metal-free operation, high atom economy, moderate to high yield, easy work-up procedure, and applicability on the gram scale.

Graphical abstract



X = 4-H, 4-Br, 4-F, 4-CH_3, 4-OCH_3, 3-Br, 3-Cl, 3-CH_3, 3-OCH_3, 2-Br, 2-CH_3, 2-OCH_3

Y = O, S

Simple operation · One-pot strategy · Regioselectivity · High atom-economy
26 Examples · Moderate to high yields · Gram scale
Pharmaceutically-interesting compounds

Keywords Isoxazolopyrimidine · Aryl isothiocyanate · One-pot · Hydroxylamine · Gram scale

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Extended author information available on the last page of the article

Introduction

Nowadays, heterocyclic chemistry is one of the major areas of organic and medicinal chemistry [1–15]. Isoxazole and fused-isoxazole frameworks, bearing both nitrogen and oxygen atoms, are important five-membered heterocyclic compounds with a wide range of biological activities [16–42]. They are important constituents of various drugs such as paliperidone (a dopamine antagonist and 5-HT_{2A} antagonist), risperidone, ocaperidone, and iloperidone (antipsychotics), zonisamide (anticonvulsant), leflunomide (antirheumatic), isoxicam and valdecoxib (non-steroidal anti-inflammatories), parecoxib (analgesic, antipyretic, non-steroidal anti-inflammatory, and selective COX-2 inhibitor), oxacillin, cloxacillin, dicloxacillin, and sulfamethoxazole (antibiotics), tivozanib (VEGF receptor tyrosine kinase inhibitor), and micafungin (antifungal) (Fig. 1) [43–55]. Among the fused isoxazole systems, isoxazolopyrimidines show potential biological activities including anti-inflammatory [56], antitumor [57, 58], adenosine antagonist [59], inhibition of receptor tyrosine kinases (RTKs) [60], and anxiolytic activity [61]. Recently, some 3-(piperidine-4-yl) isoxazolo[4,5-*d*]pyrimidine derivatives have been reported as novel PI3Kδ inhibitors [62]. Also, Kurth and co-workers reported isoxazolo[5,4-*d*]pyrimidines as novel small-molecule correctors of cystic fibrosis mutant protein ΔF508-CFTR [63]. Furthermore, in 2018, Phillips and co-workers discovered inhibitors of *Plasmodium falciparum* dihydroorotate dehydrogenase (DHODH) with antimalarial activity based on some isoxazolopyrimidine frameworks [64].

One-pot multicomponent reactions (MCRs) are an important and valuable strategy in organic synthesis [65–83]. MCRs offer pivotal advantages over classical multi-step protocols by minimizing waste production, decreasing energy consumption, being more cost-effective and time-efficient, having very simple operation, and avoiding protection and deprotection of functional groups. On the other hand, the formation of carbon–nitrogen and carbon–oxygen bonds through one-pot MCRs has received attention in organic synthesis due to their utility in the preparation of diverse bioactive molecules [84–90].

As part of our ongoing research in the field of synthesis of heterocyclic compounds via MCRs [91–101], we report herein a convenient and practical method for the regioselective synthesis of new 5,7-dimethyl-3-(arylamino)isoxazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones and 5,7-dimethyl-3-(arylamino)-6-thioxo-6,7-dihydroisoxazolo[5,4-*d*]pyrimidin-4(5*H*)-ones by NaOH-promoted one-pot three-component reaction between aryl isothiocyanates, *N*,*N*-dimethylbarbituric acid (DMBA) or *N*,*N*-dimethyl-2-thiobarbituric acid (DMTBA), and hydroxylamine hydrochloride ($NH_2OH{\cdot}HCl$) in *N*,*N*-dimethylformamide (DMF) as an organic solvent at room temperature (Scheme 1). The key advantages of this newly developed protocol are the use of sodium hydroxide (NaOH) as a very cheap base promoter, use of commercially available starting materials, regioselectivity, high atom economy, and moderate to high yield. Furthermore, this new protocol is also applicable on the gram scale. To the best of our knowledge, use of this or similar protocols for construction of isoxazolo[5,4-*d*]pyrimidine derivatives has not been reported in the literature.

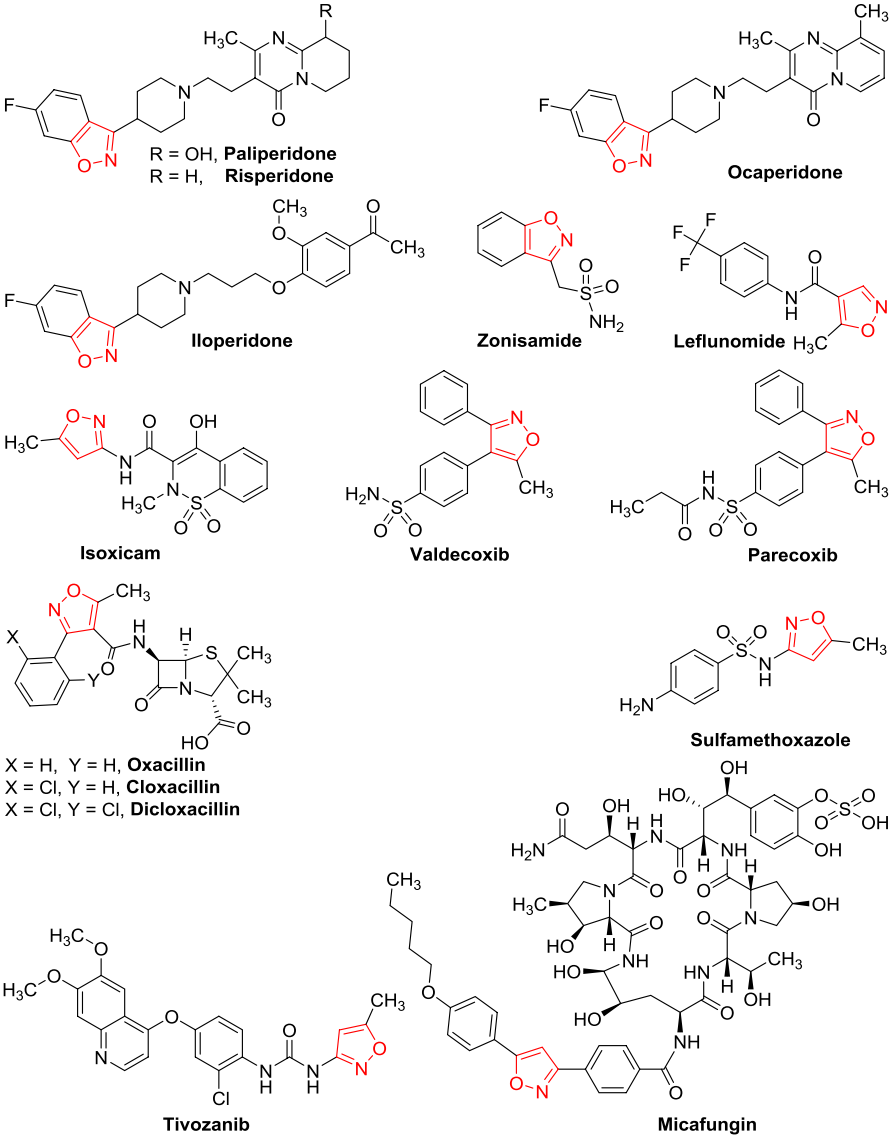
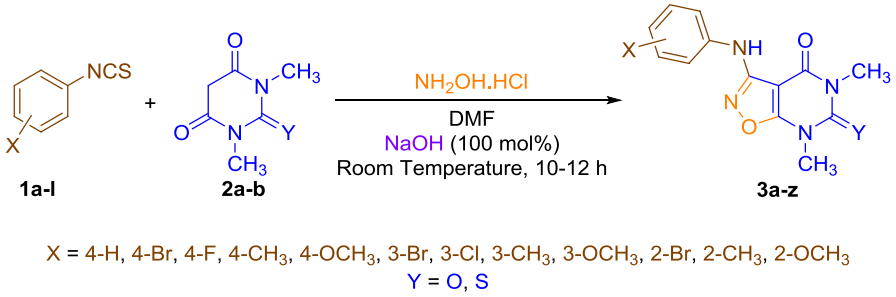


Fig. 1 Selected examples of isoxazole-based drugs

Results and discussion

Considering the broad range of remarkable properties and applications of isoxazole skeletons in medicinal chemistry, development of novel, simple, and efficient strategies for the construction of new isoxazole derivatives is always desirable in the synthetic community. In our initial trials, phenyl isothiocyanate (**1a**), *N*,*N*-dimethylbarbituric acid (**2a**), and hydroxylamine hydrochloride (**7**) were reacted in the presence



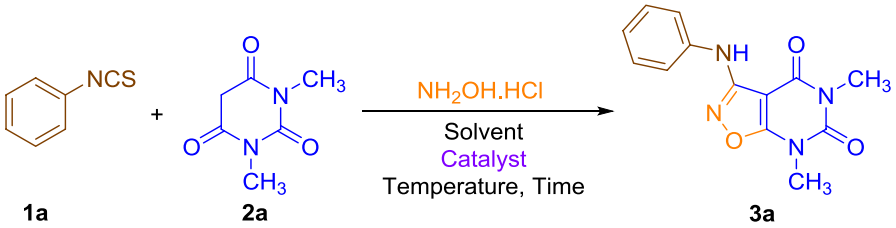
Scheme 1 One-pot regioselective synthesis of new isoxazolo[5,4-*d*]pyrimidine derivatives

of potassium hydroxide (KOH) in DMF as a polar aprotic solvent at room temperature for 10 h. The desired product, 5,7-dimethyl-3-(phenylamino)isoxazolo[5,4-*d*] pyrimidine-4,6(5*H*,7*H*)-dione (**3a**) was successfully obtained in 81 % yield (Table 1, entry 1). No improved yield was observed upon using dimethyl sulfoxide (DMSO), CH_2Cl_2, dioxane, ethanol, or water as solvent (Table 1, entries 2–6). Next, a series of bases, namely 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), NaOH, and K_2CO_3, were screened (Table 1, entries 7–11). Interestingly, sodium hydroxide was found to be the most suitable base for this valuable one-pot transformation (Table 1, entry 10). Notably, decreasing or increasing the molar ratio of NaOH (100 mol%), resulted in a diminished yield of the desired isoxazolo[5,4-*d*]pyrimidine (**3a**) (Table 1, entries 12–14). Furthermore, increasing the reaction temperature led to the reduction of the yield (Table 1, entry 15). Also, when the reaction was carried out in the catalyst-free condition, a trace amount of **3a** was obtained (Table 1, entry 16). Note that, when the above-mentioned one-pot reaction was carried out in DMF or DMSO, water was needed to extract the desired product **3a** from the reaction medium. In this regard, after reaction completion in DMF or DMSO (in the presence of all mentioned catalysts except K_2CO_3), **3a** was obtained as yellow sediment after adding water (10–15 mL). However, when the reaction was carried out in the presence of K_2CO_3 as a base promoter, no sediment was observed after adding water (10–100 mL). Therefore, to obtain the desired product **3a**, 2 M HCl solution (10 mL) was added to the reaction pot (Table 1, entry 11).

After establishing the optimized reaction conditions, we explored the substrate scope and limitations of the methodology. In this regard, we employed a wide range of aryl isothiocyanates (**1a**–**m**) with both *N*,*N*-dimethylbarbituric acid (**2a**) and *N*,*N*-dimethyl-2-thiobarbituric acid (**2b**). In general, aryl isothiocyanates bearing electron-withdrawing or electron-donating functional groups at different positions reacted smoothly to generate the corresponding products (**3a**–**z**) in moderate to high yield.

The structural elucidation and attribution of all the newly obtained isoxazolo[5,4-*d*]pyrimidine derivatives (**3a**–**z**) were unambiguously determined by their Fourier-transform infrared (FT-IR), ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopic data, CHN analysis, and melting point; For example, in the ^{1}H NMR

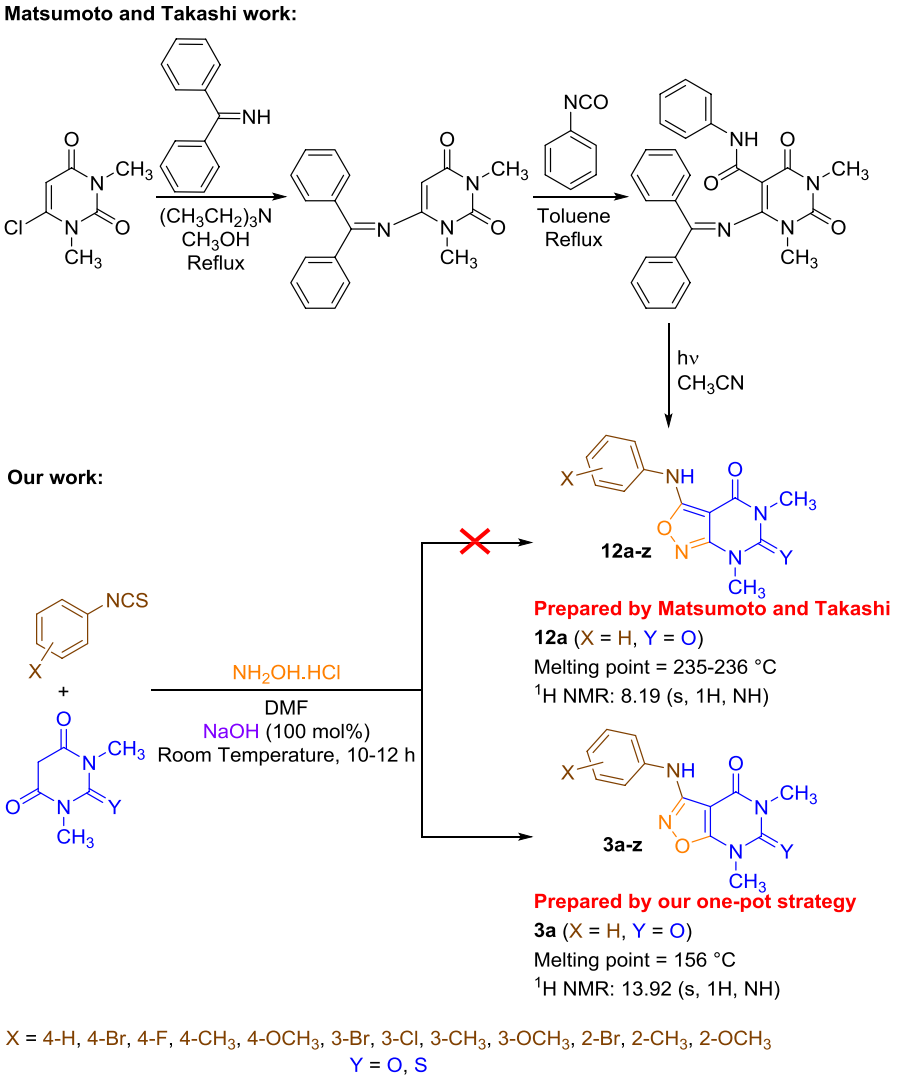
Table 1 Optimization of the reaction conditions



Entry	Solvent	Catalyst (mol%)	Temperature (°C)	Time (h)	Yield (%)
1	DMF	KOH (100)	rt	10	81
2	DMSO	KOH (100)	rt	10	76
3	Dioxane	KOH (100)	rt	24	38
4	CH_2Cl_2	KOH (100)	rt	24	NR
5	CH_3CH_2OH	KOH (100)	rt	24	NR
6	H_2O	KOH (100)	rt	24	NR
7	DMF	DABCO (100)	rt	24	66
8	DMF	DBU (100)	rt	24	69
9	DMF	DBN (100)	rt	24	74
10	DMF	NaOH (100)	rt	10	85
11	DMF	K_2CO_3 (100)	rt	10	84
12	DMF	NaOH (20)	rt	24	39
13	DMF	NaOH (50)	rt	12	58
14	DMF	NaOH (150)	rt	24	30
15	DMF	NaOH (100)	70	12	44
16	DMF	–	rt	24	Trace

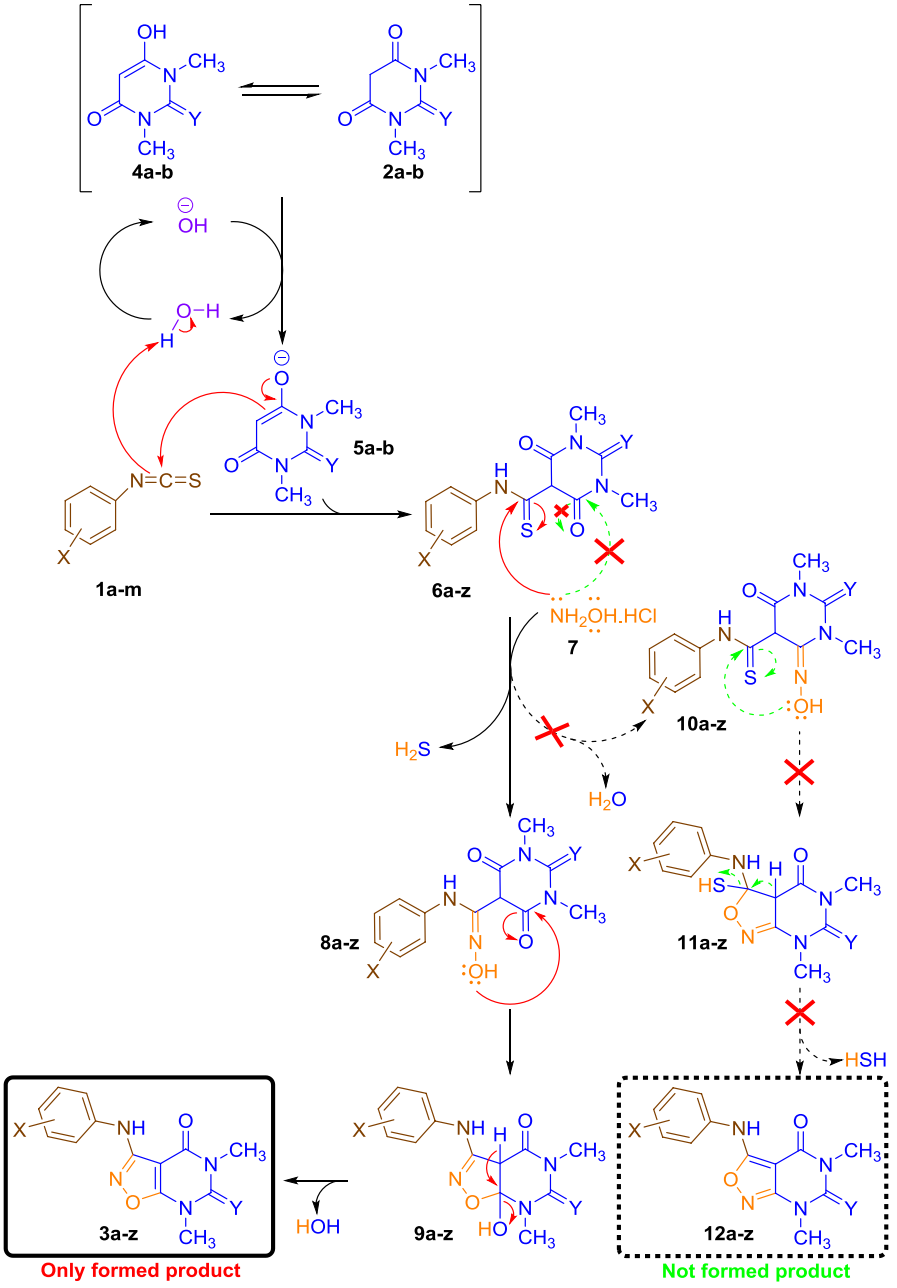
spectrum of compound **3a**, the presence of a singlet peak in the downfield region at $\delta = 13.92$ ppm is ascribed to the NH proton. Furthermore, the ^{1}H NMR spectrum of **3a** showed multiplet peaks between $\delta = 7.44$–7.34 ppm for the aromatic protons and also two peaks at $\delta = 3.48$ ppm and $\delta = 3.42$ ppm belonging to the two N–CH_3 groups. On the other hand, the observation of 11 distinct signals in the ^{13}C NMR spectrum of compound **3a** is in agreement with the proposed structure. It is noteworthy that Matsumoto and Takashi [102] reported synthesis of a 5,7-dimethyl-3-(phenylamino)isoxazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione derivative (**12a**) by a classical step-by-step synthetic operation. Differences in melting point and ^{1}H NMR spectroscopic data (especially NH proton) confirm our structural assignment (Scheme 2). The ^{1}H NMR spectra of **12a** showed a singlet peak at $\delta = 8.19$ ppm for NH proton, whereas **3a** showed a corresponding singlet peak at $\delta = 13.92$ ppm.

A plausible reaction mechanism for the synthesis of the new isoxazolo[5,4-*d*]pyrimidine derivatives is outlined in Scheme 3. First, in the presence of NaOH



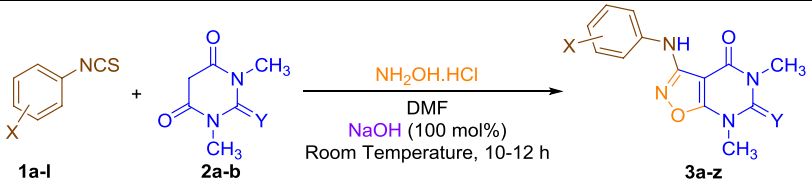
Scheme 2 Reported synthesis of 5,7-dimethyl-3-(phenylamino)isoxazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**12a**) for comparison with **3a** in this present work

as an inorganic base promoter, **2a**, **b** converts to the anionic form (intermediate **5a**–**b**). Subsequently, attack of **5a**–**b** on the aromatic isothiocyanate (**1a**–**m**) affords β-oxo thioamide (intermediate **6a**–**z**). Next, **6a**–**z** readily undergoes regioselective nucleophilic attack by the NH_2 group of hydroxylamine hydrochloride (**7**) preferentially at the soft electrophilic center of the intermediate β-oxo thioamide (**8a**–**z**), in agreement with the hard and soft Lewis acid and base (HSAB) principle [54, 103–107], which subsequently gives the final product (**3a**–**z**) through cyclization with the oxo functionality and elimination of water. Note that, in $NH_2OH{\cdot}HCl$ as a



Scheme 3 Plausible mechanism for the NaOH-promoted one-pot regioselective synthesis of isoxazolo[5,4-*d*]pyrimidines

Table 2 One-pot regioselective synthesis of novel isoxazolo[5,4-*d*]pyrimidines



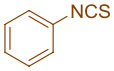
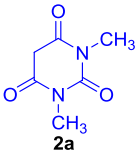
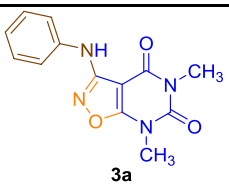
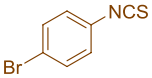
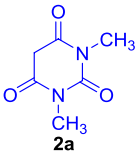
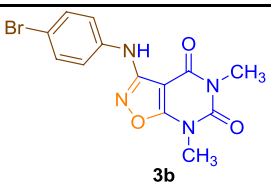
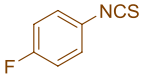
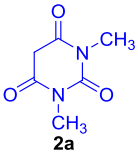
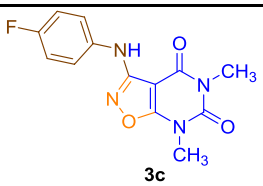
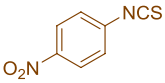
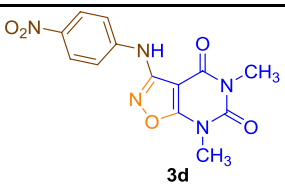
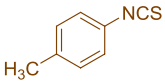
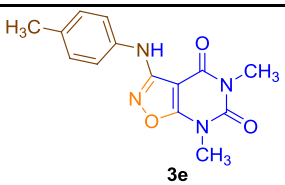
Entry	Aryl isothiocyanate	DMBA or DMTBA	Isoxazolo[5,4-*d*]pyrimidine	Time (h)	Yield (%)
1	 **1a**	 **2a**	 **3a**	10	85
2	 **1b**	 **2a**	 **3b**	10	89
3	 **1c**	 **2a**	 **3c**	10	83
4	 **1d**	 **2a**	 **3d**	11	81
5	 **1e**	 **2a**	 **3e**	10	83

Table 2 (continued)

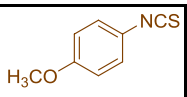
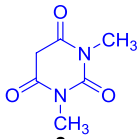
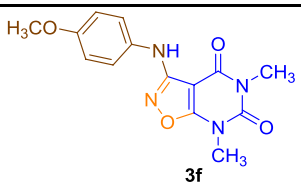
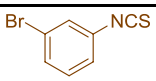
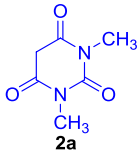
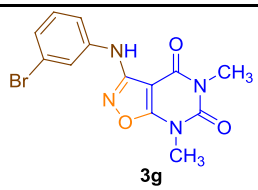
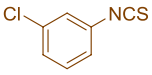
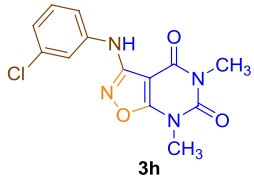
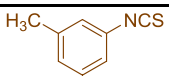
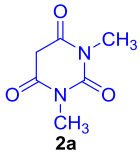
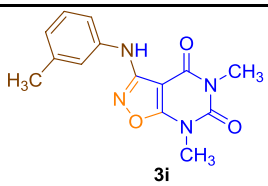
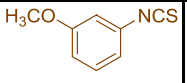
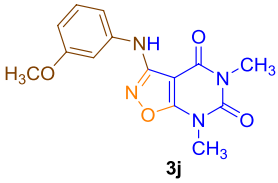
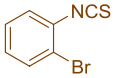
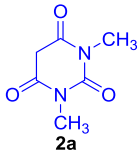
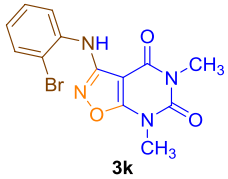
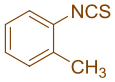
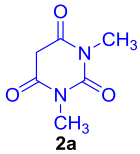
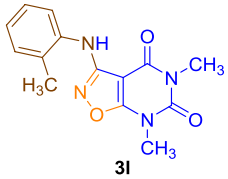
6	 **1f**	 **2a**	 **3f**	10	87
7	 **1g**	 **2a**	 **3g**	12	72
8	 **1h**	 **2a**	 **3h**	12	71
9	 **1i**	 **2a**	 **3i**	11	78
10	 **1j**	 **2a**	 **3j**	11	75
11	 **1k**	 **2a**	 **3k**	10	90
12	 **1l**	 **2a**	 **3l**	11	78

Table 2 (continued)

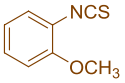
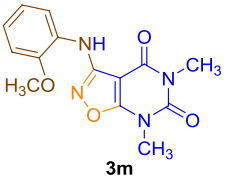
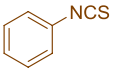
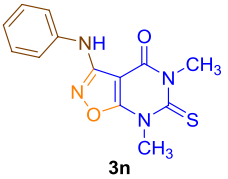
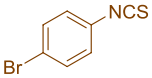
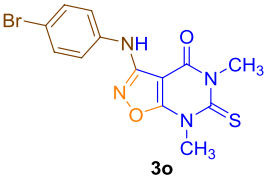
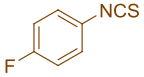
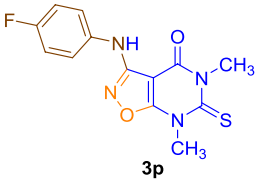
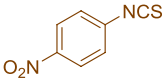
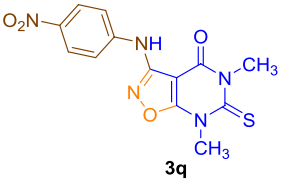
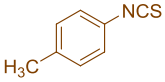
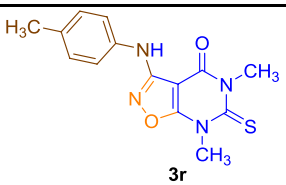
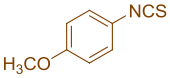
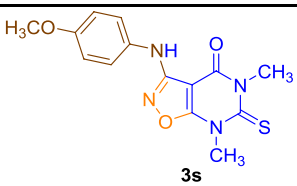
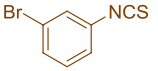
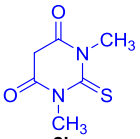
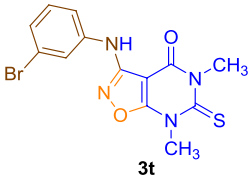
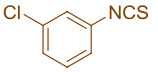
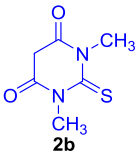
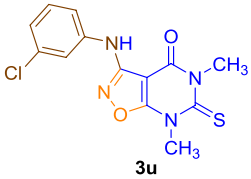
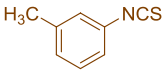
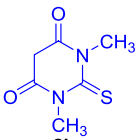
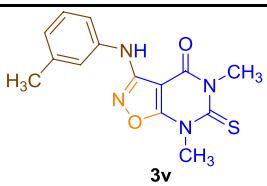
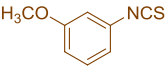
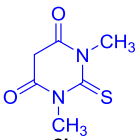
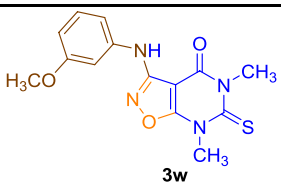
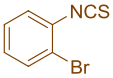
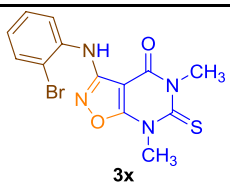
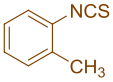
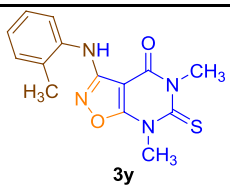
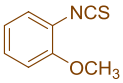
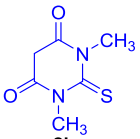
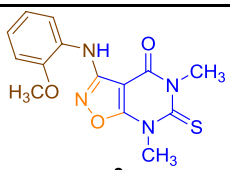
13	 **1m**	 **2a**	 **3m**	10	86
14	 **1a**	 **2b**	 **3n**	12	70
15	 **1b**	 **2b**	 **3o**	10	88
16	 **1c**	 **2b**	 **3p**	11	81
17	 **1d**	 **2b**	 **3q**	11	79
18	 **1e**	 **2b**	 **3r**	11	82
19	 **1f**	 **2b**	 **3s**	10	86

Table 2 (continued)

20	 **1g**	 **2b**	 **3t**	12	71
21	 **1h**	 **2b**	 **3u**	12	70
22	 **1i**	 **2b**	 **3v**	12	76
23	 **1j**	 **2b**	 **3w**	12	74
24	 **1k**	 **2b**	 **3x**	10	89
25	 **1l**	 **2b**	 **3y**	11	77
26	 **1m**	 **2b**	 **3z**	10	85

hetero-binucleophile molecule, nitrogen center is softer as well as more nucleophilic in nature than the oxygen center (Table 2).

To demonstrate the practical utility of the present one-pot three-component protocol, a gram-scale reaction was performed successfully with **1a** (1.08 g, 8 mmol), **2a** (1.25 g, 8 mmol), and hydroxylamine hydrochloride (0.56 g, 8 mmol) using 100 mol% (0.32 g) of NaOH at room temperature in DMF, achieving synthesis of **3a** in 70 % yield (Scheme 4).

Experimental

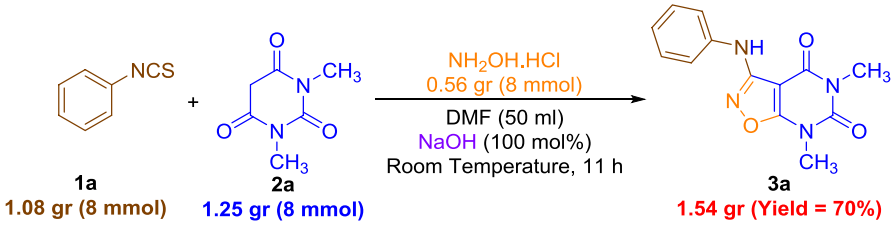
Melting points were determined on an Electrothermal 9200 apparatus. Infrared spectra were recorded on a Perkin Elmer Spectrum Two FT-infrared spectrophotometer, measured as KBr disks. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer at 300 and 75 MHz, respectively. Chemical shifts were measured in DMSO-d_6 as solvent relative to tetramethylsilane (TMS) as the internal standard. Elemental analyses were performed by using a Leco Analyzer 932.

General procedure for the one-pot synthesis of isoxazolo[5,4-*d*]pyrimidines (3a–z)

In a round-bottomed flask (25 mL) equipped with a magnetic stirrer, in the presence of sodium hydroxide (100 mol%), a mixture of aryl isothiocyanate (1 mmol), *N*,*N*-dimethylbarbituric acid or *N*,*N*-dimethyl-2-thiobarbituric acid (1 mmol), and hydroxylamine hydrochloride (1 mmol) in DMF (5 mL) was stirred at 25 °C (room temperature). After reaction completion, water (10–15 mL) was added to the reaction mixture. Then, the precipitate was filtered and washed with hot methanol (3 × 5 mL) to afford the pure products.

5,7-Dimethyl-3-(phenylamino)isoxazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3a)

Yellow powder; 85 %; m.p. 156 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): 13.92 (s, 1H, NH), 7.44–7.34 (m, 5H, Ar), 3.48 (s, 3H, N–CH_3), 3.42 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 185.6, 168.0, 163.9, 137.3, 130.1, 128.1, 126.8, 126.5,



Scheme 4 Gram-scale synthesis of **3a**

124.7, 28.2, 27.4; FT-IR (KBr) *v*: 3400, 2922, 2865, 1716, 1597, 1545, 1452, 1384, 1295, 1237, 1102, 1002, 815, 759, 688, 619, 503 cm^{-1}. Anal. calcd. for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.48; H, 4.49; N, 20.38.

5,7-Dimethyl-3-((4-bromophenyl)amino)isoxazolo[5,4-*d*] pyrimidine-4,6(5*H*,7*H*)-dione (**3b**)

Yellow powder; 89 %; m.p. 147 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): 13.91 (s, 1H, NH), 7.55 (d, $J=6.9$ Hz, 2H, Ar), 7.34 (d, $J=7.2$ Hz, 2H, Ar), 3.47 (s, 3H, N–CH_3), 3.40 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 186.3, 168.1, 163.8, 136.4, 133.3, 133.2, 131.2, 128.4, 126.2, 28.3, 26.4; FT-IR (KBr) *v*: 3392, 3084, 2925, 1710, 1635, 1578, 1535, 1488, 1447, 1396, 1378, 1073, 1013, 869, 830, 791, 752, 619, 505 cm^{-1}. Anal. calcd. for $C_{13}H_{11}BrN_4O_3$: C, 44.46; H, 3.16; N, 15.96. Found: C, 44.56; H, 3.10; N, 16.26.

5,7-Dimethyl-3-((4-fluorophenyl)amino)isoxazolo[5,4-*d*] pyrimidine-4,6(5*H*,7*H*)-dione (**3c**)

White powder; 83 %; m.p. 139 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): 13.83 (s, 1H, NH), 7.45–7.35 (m, 2H, Ar), 7.13 (t, $J=8.7$ Hz, 2H, Ar), 3.48 (s, 3H, N–CH_3), 3.41 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 186.5, 168.0, 163.9, 152.6, 132.2, 128.8, 126.6, 117.3, 117.0, 114.8, 28.3, 27.2; FT-IR (KBr) *v*: 3420, 3076, 2962, 2863, 1703, 1625, 1604, 1448, 1397, 1213, 1198, 1092, 1000, 836, 814, 789, 754, 657, 489 cm^{-1}. Anal. calcd. for $C_{13}H_{11}FN_4O_3$: C, 53.80; H, 3.82; N, 19.30. Found: C, 53.92; H, 3.85; N, 19.59.

5,7-Dimethyl-3-((4-nitrophenyl)amino)isoxazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**3d**)

Yellow powder; 81 %; m.p. 139 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): 14.38 (s, 1H, NH), 8.00 (d, $J=7.5$ Hz, 1H, Ar), 7.76 (d, $J=7.5$ Hz, 2H, Ar), 7.10 (d, $J=7.5$ Hz, 1H, Ar), 3.50 (s, 3H, N–CH_3), 3.42 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 187.3, 168.4, 163.8, 125.9, 125.6, 124.4, 124.3, 123.7, 123.4, 29.4, 28.5; FT-IR (KBr) *v*: 3420, 3387, 3101, 3068, 2974, 2900, 1718, 1637, 1579, 1536, 1450, 1434, 1394, 1381, 1201, 1000, 819, 790, 781, 752, 604, 504 cm^{-1}. Anal. calcd. for $C_{13}H_{11}N_5O_5$: C, 49.22; H, 3.49; N, 22.07. Found: C, 49.33; H, 3.55; N, 22.34.

5,7-Dimethyl-3-(*p*-tolylamino)isoxazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**3e**)

Yellow powder; 83 %; m.p. 159 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): 13.82 (s, 1H, NH), 7.34–7.21 (m, 4H, Ar), 3.41 (s, 3H, N–CH_3), 3.34 (s, 3H, N–CH_3), 2.39 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 185.3, 167.8, 163.9, 137.7, 134.7, 130.7, 128.7, 126.6, 124.5, 28.1, 27.3, 22.0; FT-IR (KBr) *v*: 3402, 3068, 2966, 2925, 1706, 1630, 1581, 1515, 1500, 1448, 1399, 1379, 1300, 1200, 1107, 1002, 799, 752, 636,

487 cm^{-1}. Anal. calcd. for $C_{14}H_{14}N_4O_3$: C, 58.74; H, 4.93; N, 19.57. Found: C, 58.90; H, 4.95; N, 19.88.

5,7-Dimethyl-3-((4-methoxyphenyl)amino)isoxazolo[5,4-*d*] pyrimidine-4,6(5*H*,7*H*)-dione (3f)

Yellow powder; 87 %; m.p. 159 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): 13.74 (s, 1H, NH), 7.31 (d, $J = 8.7$ Hz, 2H, Ar), 6.95 (d, $J = 8.4$ Hz, 2H, Ar), 3.84 (s, 3H, OCH_3), 3.46 (s, 3H, N–CH_3), 3.40 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 185.4, 167.8, 163.9, 130.0, 128.1, 126.0, 126.0, 115.3, 113.3, 54.4, 27.1, 26.2; FT-IR (KBr) *v*: 3412, 3318, 3105, 3072, 2945, 2847, 1714, 1582, 1556, 1545, 1508, 1444, 1397, 1374, 1257, 1175, 1035, 829, 750, 505 cm^{-1}. Anal. calcd. for $C_{14}H_{14}N_4O_4$: C, 55.63; H, 4.67; N, 18.53. Found: C, 55.77; H, 4.61; N, 18.73.

5,7-Dimethyl-3-((3-bromophenyl)amino)isoxazolo[5,4-*d*] pyrimidine-4,6(5*H*,7*H*)-dione (3g)

White powder; 72 %; m.p. 146 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): 13.97 (s, 1H, NH), 7.65 (s, 1H, Ar), 7.48–7.25 (m, 3H, Ar), 3.48 (s, 3H, N–CH_3), 3.40 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 186.6, 168.1, 163.8, 131.3, 129.8, 129.4, 129.2, 127.7, 125.5, 123.3, 122.4, 28.3, 26.4; FT-IR (KBr) *v*: 3457, 3383, 3093, 3072, 2966, 2884, 1716, 1637, 1576, 1535, 1449, 1428, 1395, 1381, 1295, 1193, 1070, 998, 815, 779, 752, 691, 615, 503 cm^{-1}. Anal. calcd. for $C_{13}H_{11}BrN_4O_3$: C, 44.46; H, 3.16; N, 15.96. Found: C, 44.57; H, 3.20; N, 16.26.

5,7-Dimethyl-3-((3-chlorophenyl)amino)isoxazolo[5,4-*d*] pyrimidine-4,6(5*H*,7*H*)-dione (3h)

White powder; 71 %; m.p. 159 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): 13.97 (s, 1H, NH), 7.51 (s, 1H, Ar), 7.39–7.28 (m, 3H, Ar), 3.48 (s, 3H, N–CH_3), 3.41 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 186.6, 168.1, 163.8, 138.5, 131.1, 128.9, 127.0, 126.5, 126.5, 125.0, 122.8, 28.3, 27.4; FT-IR (KBr) *v*: 3457, 3117, 3084, 2958, 1710, 1636, 1607, 1592, 1511, 1450, 1398, 1379, 1347, 1110, 1004, 858, 785, 753, 700, 615, 505 cm^{-1}. Anal. calcd. for $C_{13}H_{11}ClN_4O_3$: C, 50.91; H, 3.62; N, 18.27. Found: C, 50.99; H, 3.57; N, 18.48.

5,7-Dimethyl-3-(*m*-tolylamino)isoxazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3i)

Yellow powder; 78 %; m.p. 162 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): 13.88 (s, 1H, NH), 7.38–7.12 (m, 4H, Ar), 3.47 (s, 3H, N–CH_3), 3.41 (s, 3H, N–CH_3), 2.40 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 185.2, 167.9, 163.9, 137.2, 129.9, 129.4, 127.8, 127.2, 125.2, 123.9, 121.6, 28.2, 27.2, 22.2; FT-IR (KBr) *v*: 3387,

3322, 3019, 2929, 2798, 1705, 1662, 1590, 1554, 1494, 1447, 1398, 1382, 1320, 1293, 1109, 887, 791, 772, 681, 499 cm^{-1}. Anal. calcd. for $C_{14}H_{14}N_4O_3$: C, 58.74; H, 4.93; N, 19.57. Found: C, 58.86; H, 5.00; N, 19.89.

5,7-Dimethyl-3-((3-methoxyphenyl)amino)isoxazolo[5,4-*d*] pyrimidine-4,6(5*H*,7*H*)-dione (3j)

Yellow powder; 75 %; m.p. 153 °C (dec.). ^1H NMR (300 MHz, $CDCl_3$): 13.92 (s, 1H, NH), 7.38–7.25 (m, 1H, Ar), 7.01 (d, $J = 8.7$ Hz, 2H, Ar), 6.87 (d, $J = 8.1$ Hz, 1H, Ar), 3.82 (s, 3H, OCH_3), 3.46 (s, 3H, N–CH_3), 3.39 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 185.3, 167.9, 163.9, 138.4, 130.8, 128.7, 116.8. 114.3, 114.3, 112.4, 110.2, 54.4, 28.2, 27.3; FT-IR (KBr) *v*: 3441, 3301, 3105, 3011, 2966, 2839, 1717, 1639, 1614, 1588, 1547, 1450, 1397, 1295, 1223, 1158, 1050, 855, 776, 752, 689, 505 cm^{-1}. Anal. calcd. for $C_{14}H_{14}N_4O_4$: C, 55.63; H, 4.67; N, 18.53. Found: C, 55.74; H, 4.73; N, 18.80.

5,7-Dimethyl-3-((2-bromophenyl)amino)isoxazolo[5,4-*d*] pyrimidine-4,6(5*H*,7*H*)-dione (3k)

White powder; 90 %; m.p. 148 °C (dec.). ^1H NMR (300 MHz, $CDCl_3$): 13.79 (s, 1H, NH), 7.70 (d, $J = 7.8$ Hz, 1H, Ar), 7.55 (d, $J = 8.1$ Hz, 1H, Ar), 7.39 (t, $J = 7.5$ Hz, 1H, Ar), 7.25 (d, $J = 8.4$ Hz, 1H, Ar), 3.48 (s, 3H, N–CH_3), 3.42 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 187.4, 168.1, 163.8, 130.4, 130.3, 130.1, 128.9, 128.2, 128.1, 126.7, 126.6, 28.3, 27.5; FT-IR (KBr) *v*: 3400, 3232, 3142, 3064, 2966, 1707, 1627, 1572, 1505, 1449, 1399, 1377, 1303, 1205, 1001, 791, 770, 762, 755, 729, 660, 497 cm^{-1}. Anal. calcd. for $C_{13}H_{11}BrN_4O_3$: C, 44.46; H, 3.16; N, 15.96. Found: C, 44.58; H, 3.20; N, 16.21.

5,7-Dimethyl-3-(*o*-tolylamino)isoxazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3l)

White powder; 78 %; m.p. 161 °C (dec.). ^1H NMR (300 MHz, $CDCl_3$): 13.63 (s, 1H, NH), 7.36–7.24 (m, 4H, Ar), 3.48 (s, 3H, N–CH_3), 3.42 (s, 3H, N–CH_3), 2.28 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 186.1, 167.8, 164.0, 130.0, 129.4, 128.2, 127.6, 127.3, 127.2, 126.1, 125.6, 28.1, 27.4, 17.1; FT-IR (KBr) *v*: 3408, 3109, 2956, 1719, 1631, 1571, 1453, 1302, 1115, 1005, 808, 753, 644, 506 cm^{-1}. Anal. calcd. for $C_{14}H_{14}N_4O_3$: C, 58.74; H, 4.93; N, 19.57. Found: C, 58.87; H, 4.96; N, 19.83.

5,7-Dimethyl-3-((2-methoxyphenyl)amino)isoxazolo[5,4-*d*] pyrimidine-4,6(5*H*,7*H*)-dione (3m)

White powder; 86 %; m.p. 149 °C (dec.). ^1H NMR (300 MHz, $CDCl_3$): 13.77 (s, 1H, NH), 7.32 (d, $J = 7.5$ Hz, 1H, Ar), 7.32 (d, $J = 8.1$ Hz, 1H, Ar), 7.02 (t, $J = 8.4$ Hz,

2H, Ar), 3.88 (s, 3H, OCH_3), 3.47 (s, 3H, N–CH_3), 3.42 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 185.1, 167.8, 163.8, 127.9, 127.5, 126.1, 125.7, 119.2, 119.1, 110.5, 110.4, 55.8, 28.1, 27.4; FT-IR (KBr) *v*: 3399, 3120, 3060, 2942, 2832, 2763, 1711, 1583, 1542, 1497, 1445, 1290, 1251, 1192, 1118, 1027, 920, 854, 741, 579, 503, 456 cm^{-1}. Anal. calcd. for $C_{14}H_{14}N_4O_4$: C, 55.63; H, 4.67; N, 18.53. Found: C, 55.76; H, 4.60; N, 18.79.

5,7-Dimethyl-3-(phenylamino)-6-thioxo-6,7-dihydroisoxazolo[5,4-*d*] pyrimidin-4(5*H*)-one (**3n**)

White powder; 70 %; m.p. 178 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): 13.96 (s, 1H, NH), 7.50–7.32 (m, 5H, Ar), 3.91 (s, 3H, N–CH_3), 3.84 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 185.5, 166.4, 161.8, 130.3, 130.2, 128.2, 126.8, 126.8, 124.7, 37.3, 36.6; FT-IR (KBr) *v*: 3427, 3227, 3177, 2950, 1636, 1589, 1539, 1480, 1451, 1434, 1412, 1331, 1116, 766, 689, 651, 484 cm^{-1}. Anal. calcd. for $C_{13}H_{12}N_4O_2S$: C, 54.16; H, 4.20; N, 19.43. Found: C, 54.28; H, 4.13; N, 19.70.

5,7-Dimethyl-3-((4-bromophenyl)amino)-6-thioxo-6,7-dihydroisoxazolo[5,4-*d*] pyrimidin-4(5*H*)-one (**3o**)

Yellow powder; 88 %; m.p. 208 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): 13.97 (s, 1H, NH), 7.58 (d, $J=8.7$ Hz, 2H, Ar), 7.36 (d, $J=8.4$ Hz, 2H, Ar), 3.91 (s, 3H, N–CH_3), 3.83 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 186.2, 166.5, 161.7, 133.4, 133.3, 131.3, 126.2, 126.1, 126.1, 37.4, 36.7; FT-IR (KBr) *v*: 3411, 3093, 2922, 1633, 1579, 1536, 1437, 1363, 1132, 1116, 1018, 829, 788, 647, 611, 491 cm^{-1}. Anal. calcd. for $C_{13}H_{11}BrN_4O_2S$: C, 42.52; H, 3.02; N, 15.26. Found: C, 42.67; H, 3.11; N, 15.58.

5,7-Dimethyl-3-((4-fluorophenyl)amino)-6-thioxo-6,7-dihydroisoxazolo[5,4-*d*] pyrimidin-4(5*H*)-one (**3p**)

Yellow powder; 81 %; m.p. 149 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): 13.88 (s, 1H, NH), 7.45–7.35 (m, 2H, Ar), 7.15 (t, $J=8.4$ Hz, 2H, Ar), 3.90 (s, 3H, N–CH_3), 3.83 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 186.4, 166.4, 161.7, 128.8, 128.8, 126.6, 126.5, 117.4, 117.1, 117.0, 37.3, 36.3; FT-IR (KBr) *v*: 3407, 3137, 3062, 1639, 1605, 1547, 1508, 1412, 1364, 1332, 1238, 1157, 1117, 835, 774, 517 cm^{-1}. Anal. calcd. for $C_{13}H_{11}FN_4O_2S$: C, 50.97; H, 3.62; N, 18.29. Found: C, 51.11; H, 3.70; N, 18.59.

5,7-Dimethyl-3-((4-nitrophenyl)amino)-6-thioxo-6,7-dihydroisoxazolo[5,4-*d*] pyrimidin-4(5*H*)-one (**3q**)

Yellow powder; 79 %; m.p. 176 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): 14.41 (s, 1H, NH), 8.32 (d, $J=9$ Hz, 2H, Ar), 7.78 (d, $J=8.7$ Hz, 2H, Ar), 3.93 (s, 3H, N–CH_3), 3.84 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 187.3, 166.8, 161.7,

125.7, 125.7, 125.6, 124.5, 124.4, 123.5, 37.5, 36.8; FT-IR (KBr) *v*: 3111, 3085, 2980, 2872, 1647, 1608, 1588, 1517, 1437, 1405, 1339, 1260, 1113, 855, 833, 761, 647, 615, 483 cm^{-1}. Anal. calcd. for $C_{13}H_{11}N_5O_4S$: C, 46.84; H, 3.33; N, 21.01. Found: C, 46.99; H, 3.26; N, 21.35.

5,7-Dimethyl-3-(*p*-tolylamino)-6-thioxo-6,7-dihydroisoxazolo[5,4-*d*] pyrimidin-4(5*H*)-one (3r)

Yellow powder; 82 %; m.p. 169 °C (dec.). ^1H NMR (300 MHz, $CDCl_3$): 13.88 (s, 1H, NH), 7.35–7.22 (m, 5H, Ar), 3.90 (s, 3H, N–CH_3), 3.83 (s, 3H, N–CH_3), 2.40 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 185.1, 166.2, 161.8, 130.8, 128.8, 128.8, 128.7, 124.4, 124.4, 38.5, 37.3, 36.6; FT-IR (KBr) *v*: 3460, 3101, 2917, 2864, 1662, 1509, 1468, 1393, 1255, 1112, 860, 818, 741, 517 cm^{-1}. Anal. calcd. for $C_{14}H_{14}N_4O_2S$: C, 55.62; H, 4.67; N, 18.53. Found: C, 55.72; H, 4.65; N, 18.76.

5,7-Dimethyl-3-((4-methoxyphenyl)amino)-6-thioxo-6,7-dihydroisoxazolo[5,4-*d*] pyrimidin-4(5*H*)-one (3s)

Yellow powder; 86 %; m.p. 178 °C (dec.). ^1H NMR (300 MHz, $CDCl_3$): 13.80 (s, 1H, NH), 7.33 (d, $J = 8.7$ Hz, 2H, Ar), 6.97 (d, $J = 9$ Hz, 2H, Ar), 3.89 (s, 3H, OCH_3), 3.85 (s, 3H, N–CH_3), 3.83 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 185.2, 166.1, 161.8, 129.9, 125.9, 115.4, 115.3, 113.5, 113.4, 56.4, 37.2, 36.6; FT-IR (KBr) *v*: 3401, 3202, 2999, 2962, 2832, 1609, 1590, 1542, 1511, 1480, 1332, 1246, 1116, 1030, 827, 619, 517 cm^{-1}. Anal. calcd. for $C_{14}H_{14}N_4O_3S$: C, 52.82; H, 4.43; N, 17.60. Found: C, 52.99; H, 4.49; N, 17.96.

5,7-Dimethyl-3-((3-bromophenyl)amino)-6-thioxo-6,7-dihydroisoxazolo[5,4-*d*] pyrimidin-4(5*H*)-one (3t)

Yellow powder; 71 %; m.p. 155 °C (dec.). ^1H NMR (300 MHz, $CDCl_3$): 14.00 (s, 1H, NH), 7.66 (s, 1H, Ar), 7.48 (d, $J = 7.5$ Hz, 1H, Ar), 7.42 (d, $J = 6.6$ Hz, 1H, Ar), 7.33 (d, $J = 6.3$ Hz, 1H, Ar), 3.90 (s, 3H, N–CH_3), 3.83 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 186.5, 166.6, 161.7, 138.5, 131.8, 131.4, 129.3, 127.6, 127.5, 125.4, 122.5, 37.4, 36.7; FT-IR (KBr) *v*: 3466, 3097, 3064, 1636, 1578, 1532, 1465, 1434, 1413, 1362, 1331, 1258, 1201, 1118, 877, 811, 780, 693, 615, 484 cm^{-1}. Anal. calcd. for $C_{13}H_{11}BrN_4O_2S$: C, 42.52; H, 3.02; N, 15.26. Found: C, 42.65; H, 3.11; N, 15.54.

5,7-Dimethyl-3-((3-chlorophenyl)amino)-6-thioxo-6,7-dihydroisoxazolo[5,4-*d*] pyrimidin-4(5*H*)-one (3u)

White powder; 70 %; m.p. 164 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): 14.01 (s, 1H, NH), 7.52 (s, 1H, Ar), 7.42–7.30 (m, 3H, Ar), 3.91 (s, 3H, N–CH_3), 3.83 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 186.5, 166.6, 161.7, 131.2, 129.0, 127.0, 126.9, 126.7, 124.9, 122.9, 122.7, 37.4, 36.7; FT-IR (KBr) *v*: 3410, 3097, 3072, 2849, 1637, 1599, 1579, 1536, 1467, 1433, 1413, 1363, 1331, 1201, 1118, 1037, 881, 781, 696, 488 cm^{-1}. Anal. calcd. for $C_{13}H_{11}ClN_4O_2S$: C, 48.38; H, 3.44; N, 17.36. Found: C, 48.49; H, 3.35; N, 17.70.

5,7-Dimethyl-3-(*m*-tolylamino)-6-thioxo-6,7-dihydroisoxazolo[5,4-*d*] pyrimidin-4(5*H*)-one (3v)

White powder; 76 %; m.p. 156 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): 13.92 (s, 1H, NH), 7.35 (d, $J=7.8$ Hz, 1H, Ar), 7.23 (s, 1H, Ar), 7.17 (d, $J=7.2$ Hz, 2H, Ar), 3.90 (s, 3H, N–CH_3), 3.84 (s, 3H, N–CH_3), 2.41 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 185.1, 166.3, 161.8, 139.4, 137.1, 129.7, 129.7, 127.9, 127.2, 123.8, 121.6, 39.3, 37.3, 36.4; FT-IR (KBr) *v*: 3113, 2953, 2921, 2798, 1667, 1604, 1586, 1549, 1492, 1440, 1396, 1332, 1313, 1117, 887, 787, 742, 681, 482 cm^{-1}. Anal. calcd. for $C_{14}H_{14}N_4O_2S$: C, 55.62; H, 4.67; N, 18.53. Found: C, 55.72; H, 4.60; N, 18.83.

5,7-Dimethyl-3-((3-methoxyphenyl)amino)-6-thioxo-6,7-dihydroisoxazolo[5,4-*d*] pyrimidin-4(5*H*)-one (3w)

Yellow powder; 74 %; m.p. 161 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): 13.97 (s, 1H, NH), 7.36 (t, $J=8.1$ Hz, 1H, Ar), 7.02 (d, $J=7.8$ Hz, 2H, Ar), 6.90 (d, $J=8.7$ Hz, 1H, Ar), 3.90 (s, 3H, OCH_3), 3.84 (s, 3H, N–CH_3), 3.83 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 185.2, 166.3, 161.8, 131.0, 128.9, 118.9, 116.8, 116.7, 114.6, 112.6, 110.1, 56.4, 37.3, 36.6; FT-IR (KBr) *v*: 3418, 3097, 2980, 2872, 1647, 1608, 1588, 1517, 1437, 1405, 1339, 1261, 1113, 855, 833, 761, 647, 615, 483 cm^{-1}. Anal. calcd. for $C_{14}H_{14}N_4O_3S$: C, 52.82; H, 4.43; N, 17.60. Found: C, 52.97; H, 4.49; N, 17.92.

5,7-Dimethyl-3-((2-bromophenyl)amino)-6-thioxo-6,7-dihydroisoxazolo[5,4-*d*] pyrimidin-4(5*H*)-one (3x)

Yellow powder; 89 %; m.p. 165 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): 13.83 (s, 1H, NH), 7.71 (d, $J=8.1$ Hz, 1H, Ar), 7.56 (d, $J=8.1$ Hz, 1H, Ar), 7.41 (d, $J=7.8$ Hz, 1H, Ar), 7.25 (d, $J=8.7$ Hz, 1H, Ar), 3.91 (s, 3H, N–CH_3), 3.85 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 187.3, 166.5, 161.7, 132.3, 132.2, 130.5, 129.9, 129.0, 128.4, 126.8, 126.7, 37.4, 36.7; FT-IR (KBr) *v*: 3203, 3056, 2950, 1643, 1573, 1517, 1468, 1435, 1410, 1362, 1330, 1117, 1026, 786, 761, 720, 663, 460 cm^{-1}. Anal. calcd. for $C_{13}H_{11}BrN_4O_2S$: C, 42.52; H, 3.02; N, 15.26. Found: C, 42.69; H, 3.11; N, 15.54.

5,7-Dimethyl-3-(*o*-tolylamino)-6-thioxo-6,7-dihydroisoxazolo[5,4-*d*] pyrimidin-4(5*H*)-one (3y)

White powder; 77 %; m.p. 142 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): 13.70 (s, 1H, NH), 7.33–7.27 (m, 4H, Ar), 3.90 (s, 3H, N–CH_3), 3.84 (s, 3H, N–CH_3), 2.95 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 186.1, 167.8, 164.0, 134.6, 130.0, 129.4, 127.6, 127.3, 127.2, 126.1, 125.6, 37.4, 36.7, 30.1; FT-IR (KBr) *v*: 3445, 3184, 2962, 1638, 1582, 1522, 1434, 1332, 1208, 1118, 896, 788, 648, 467 cm^{-1}. Anal. calcd. for $C_{14}H_{14}N_4O_2S$: C, 55.62; H, 4.67; N, 18.53. Found: C, 55.72; H, 4.62; N, 18.88.

5,7-Dimethyl-3-((2-methoxyphenyl)amino)-6-thioxo-6,7-dihydroisoxazolo[5,4-*d*] pyrimidin-4(5*H*)-one (3z)

White powder; 85 %; m.p. 169 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): 13.83 (s, 1H, NH), 7.76 (d, J = 7.5 Hz, 1H, Ar), 7.38–7.28 (m, 1H, Ar), 7.03 (t, J = 8.4 Hz, 2H, Ar), 3.90 (s, 3H, OCH_3), 3.85 (s, 3H, N–CH_3), 3.81 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 181.3, 167.8, 161.7, 134.3, 129.4, 127.9, 127.7, 126.1, 121.6, 119.4, 119.2, 58.8, 38.4, 36.4; FT-IR (KBr) *v*: 3453, 3118, 2949, 1649, 1604, 1540, 1466, 1435, 1406, 1367, 1333, 1312, 1260, 1112, 1025, 764, 673, 489 cm^{-1}. Anal. calcd. for $C_{14}H_{14}N_4O_3S$: C, 52.82; H, 4.43; N, 17.60. Found: C, 52.94; H, 4.48; N, 17.89.

Conclusions

We report a new, simple, and efficient NaOH-promoted regioselective synthesis of a wide range of isoxazolo[5,4-*d*]pyrimidines as pharmaceutically interesting compounds via the one-pot three-component reaction of aryl isothiocyanates, *N*,*N*-dimethylbarbituric acid or *N*,*N*-dimethyl-2-thiobarbituric acid, and hydroxylamine hydrochloride in DMF at room temperature. The impressive features of this new one-pot protocol are high regioselectivity, simple operation, very easy work-up, high atom economy, moderate to high yield, and the purity of the products. Also, this reaction could be performed on the gram scale, and the obtained compounds have potential pharmaceutical properties.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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