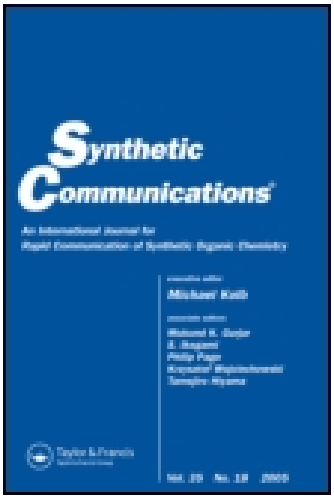

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EcoFriendly Synthesis of Tetrahydropyrimidine Derivatives in Aqueous Medium Under Ultrasonic Irradiation

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ECOFRIENDLY SYNTHESIS OF TETRAHYDROPYRIMIDINE DERIVATIVES IN AQUEOUS MEDIUM UNDER ULTRASONIC IRRADIATION

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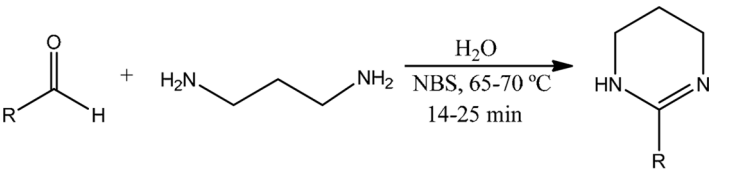
GRAPHICAL ABSTRACT



1a-s **2** **3a-s**

Abstract *A simple, efficient, and ecofriendly procedure was developed for the synthesis of 2-substituted 1,4,5,6-tetrahydropyrimidine derivatives catalyzed by N-bromosuccinimide using ultrasonic irradiation in aqueous medium. Prominent advantages of this new method are good yields, aqueous medium, short reaction times, and easy workup procedure. The compounds were characterized by infrared, NMR, liquid chromatography–mass spectrometry, and elemental analyses.*

Keywords Aqueous medium; green synthesis; NBS; tetrahydropyrimidines; ultrasound irradiation

INTRODUCTION

Pyrimidine derivatives are widely used as chemotherapeutic agents for the treatment of various diseases resulting from different microorganisms. Many useful drugs containing these skeletal structures with diverse biological activities have now emerged and are widely used against tumors and viral diseases and have been found to possess antibacterial,[1] anti-inflammatory,[2] and insecticidal activities.[3] Pyrimidine derivatives such as pyrimethamine and trimethoprim are well known to inhibit the enzyme dihydrofolate reductase, thereby blocking the reduction to tetrahydrofolic acid from its dihydro precursor, an essential coenzyme in nucleic acid synthesis.

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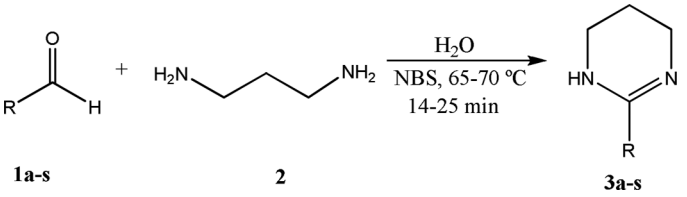


Scheme 1. Synthetic route of tetrahydropyrimidine.

In addition, the pyrimidine moiety is found in various synthetic pharmaceuticals displaying a broad spectrum of biological activity including antitumor,[4] antipyretic,[5] analgesic,[6] antihistaminic,[7] PDE4 inhibitory,[8] adenosine kinase inhibitory,[9] tyrosine kinase inhibitory,[10] and diuretic[11,12] activities.

However, many of the synthetic protocols reported so far[13,14] suffer from disadvantages such as requirement of anhydrous conditions, use of toxic organic solvents, harsh reaction conditions, prolonged reaction times, and use of metals and expensive reagents. Therefore, the development of a synthetic protocol that is cost-effective and safe and uses environmentally friendly reagents is desirable.

In view of this, there is a need to develop techniques that promote green chemistry concepts when compared with conventional methods. Energy conservation and waste minimization are considered processing aids for ultrasounic applications.[15] Many synthetically useful reactions utilize the energy provided by ultrasound. The influence of ultrasound on organic reactions is due to cavitation, a physical process that creates, enlarges, and implodes gaseous and vaporous cavities in an irradiated liquid, thus enhancing the mass transfer.[15a,16,17]

Use of water as solvent in organic reactions is a green method, as it is readily available, inexpensive, and nontoxic.[18] It is also nonflammable and environmentally benign, providing opportunities for clean processing and pollution prevention. Performing organic reactions in an aqueous medium has attracted great attention in recent decades, as organic reactions often display unique reactivity and selectivity because of their hydrophobic effects.[18]

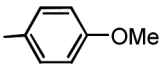
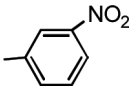
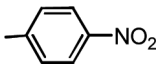
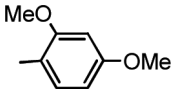
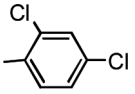
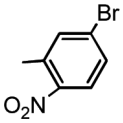
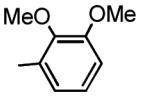
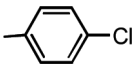
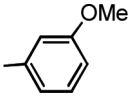
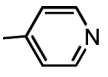
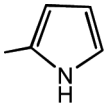
The method for forming 2-substituted-1,4,5,6-tetrahydropyrimidines under ultrasonic irradiation offers several advantages including faster reaction rates, better conversion, easy workup, and excellent yields. The primary objective of ultrasounic application is to decrease reaction times compared with conventional methods. The products were obtained in 14–25 min compared to conventional methods, which require long agitation at high temperature for completion of the reaction.

RESULTS AND DISCUSSION

In continuation of our work to develop new and ecofriendly synthetic methodologies, we herein report a green, facile, and efficient method for the synthesis of 2-substituted-1,4,5,6-tetrahydropyrimidines (**3a–s**) catalyzed by N-bromosuccinimide (NBS) under ultrasonic irradiation at 65–70 °C in 14–25 min (Scheme 1).

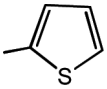
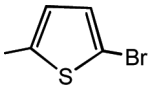
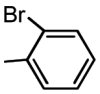
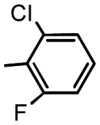
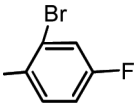
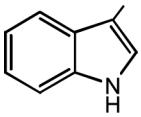
In the present work, our intention was to avoid toxic organic solvents or inert atmospheres by taking a 1:1.2 mol ratio mixture of aldehyde and 1,3-diamino

Table 1. Synthesis of tetrahydropyrimidine

Entry	R	Product	Method A		Method B		Mp (°C)[b]	
			Time (min)	Yield (%)[a]	Time (h)	Yield (%)[a]	Found	Reported
1		**3a**	17	95	4	82	133–134	132–134[14]
2		**3b**	15	92	3.2	78	128–130	—
3		**3c**	16	82	2.3	70	169–171	169–171[14]
4		**3d**	20	90	2.5	76	141–143	—
5		**3e**	18	87	6	72	115–117	—
6		**3f**	20	89	6	70	139–140	139–141[19]
7		**3g**	25	90	6	68	160–162	—
8		**3h**	18	85	4	80	143–144	144–145[19]
9		**3i**	16	86	2	77	128–129	127–130[19]
10		**3j**	16	85	5	72	142–143	—
11		**3k**	17	92	10	80	148–151	—
12		**3l**	22	94	10	81	151–153	—
13		**3m**	19	91	10	76	139–141	139–141[20]

(*Continued*)

Table 1. Continued

Entry	R	Product	Method A		Method B		Mp (°C)[b]	
			Time (min)	Yield (%)[a]	Time (h)	Yield (%)[a]	Found	Reported
14		**3n**	14	92	8	78	184–186	184–186[20]
15		**3o**	14	94	6	80	161–163	—
16		**3p**	20	86	10	75	135–136	136–137[13]
17		**3q**	21	90	11	78	138–140	—
18		**3r**	14	89	6	75	130–131	130[13]
19		**3s**	18	85	7	73	142–143	—

Notes. Method A, ultrasonic irradiation; method B, conventional.
[a]Isolated yields.
[b]All the melting points were matched with the reported data.

propane. The reaction was carried out at 65–70 °C for 14–25 min, in the presence of 1.2 mol of NBS as a catalyst using water as solvent at 50 kHz under sonication.

A wide range of substituted and structurally diverse aldehydes was used to synthesize the title compounds in good yields. For an obvious examination of the influence of ultrasound irradiation in this transformation, comparison of the reaction under two methods, ultrasound irradiation at ambient temperature (method A) and reflux conditions (method B), was performed. As illustrated in Table 1, method A is comparatively better than method B in both yield and especially reaction times.

Using these optimized conditions, we initiated our investigation into the aromatic aldehydes with 1,3-diamino propane in presence of the NBS, and the results are summarized in Table 1. Various aromatic/heterocyclic aldehydes reacted with 1,3-diaminopropane to give the corresponding 2-substituted-1,4,5,6-tetrahydropyrimidines. In the presence of both electron-releasing groups such as methoxy and electron-withdrawing groups such as nitro, the corresponding 2-substituted-1,4,5,6-tetrahydropyrimidines were obtained in moderate to very good yields. The presence

of an electron-releasing group at the *para* position such as methoxy resulted in the greatest yield of pyrimidine (entry 1) in both method A and method B, whereas the presence of an electron-withdrawing group such as nitro at the *para* position reduced the yield of the corresponding pyrimidine to 82% (entry 3).

The presence of an electron-releasing methoxy group at the *meta* position decreased the yield of the reaction (entries 10), whereas the nitro group at the *meta* position increased the yield of the reaction (entry 2).

We were pleased to note that under our optimized reaction conditions, heterocyclic aldehydes also reacted with 1,3-diamino propane to afford the corresponding pyrimidine derivatives.

The present method does not require toxic or anhydrous organic solvents to prepare **3a–s** compared with conventional methods. The transformations were carried out with good yields without any significant amounts of undesirable side products. All the products were characterized by NMR, infrared (IR), and mass spectrometry (MS) and also by comparison with authentic samples. A wide range of aromatic/heterocyclic aldehydes were employed, and all the title compounds (**3a–s**) were obtained in good yields. (Table 1, method A, entries 1–19), and both electron-withdrawing and electron-releasing substituents reacted with the same ease.

To evaluate the applicability of this method, we also concentrated our study by using different aldehydes (Table 1). The results reveal that the high ability of this method is proved undoubtedly for the synthesis of tetrahydropyrimidine derivatives with different substituents at the 2-position.

CONCLUSION

In conclusion, we have reported the preparation of 2-substituted-1,4,5,6-tetrahydropyrimidines using an efficient and environmentally benign synthetic protocol. The simplicity, use of water instead of organic solvents as reaction medium, good yields (82–95%), short reaction times (14–25 min), and ultrasonic irradiation make this synthetic protocol highly attractive and ecofriendly in nature.

EXPERIMENTAL

Chemicals were procured from Sigma-Aldrich, Merck, and Lancaster and used as such without further purification. Melting points (mp) were determined using a calibrated thermometer on a Buchi melting-point apparatus B-545. They are expressed in degrees centigrade (°C) and are uncorrected. Thin-layer chromatography (TLC) was performed using Merck silica-gel 60 F254 precoated plates (0.25 mm) and visualized by ultraviolet (UV) fluorescence lamp. Silica gel (particle size 100–200 mesh) was used for chromatography. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400-MHz instrument. ^{1}H NMR spectra were reported using Me_4Si (δ 0.0 ppm) as internal standard. ^{13}C NMR were reported relative to $CDCl_3$ (δ 77.16 ppm) and dimethylsulfoxide (DMSO-d_6), δ 48.5 ppm. Fourier transform (FT–IR spectra were recorded on a Nicolet 6700 spectrometer and are reported in wave numbers (cm^{-1}). Optical rotations (in degrees, °) were recorded in methanol on a Perkin-Elmer model 241 polarimeter at the sodium D line. Liquid chromatography (LC) mass spectra were recorded on a Jeol S × 102 DA/600 mass spectrometer.

General Procedure for the Synthesis of Pyrimidine Derivatives

A mixture of 4-methoxy benaldehyde **1** (1.0 mmol) and 1,3-diamino propane **2** (1.2 mmol) in water (12 mL) was added to reaction flask with the aid of an adapter attached to the reaction glass container, and the mixture was sonicated for 2 min. Later, NBS (1.2 mmol) was added to the mixture and the reaction temperature was raised to 65–70 °C and sonicated for 17 min (Scheme 1). Then the reaction mixture was cooled to room temperature, and aqueous NaOH (20%) was added to the reaction mixture. Finally, the solution was extracted with ethyl acetate (3×15 mL), and the combined organic layers were washed with water (2×10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the 2-(4-methoxyphenyl)-1,4,5,6-tetrahydropyrimidine (**3a**) with excellent purity. The same experimental procedure was adopted for the preparation of the remaining title compounds (**3b–s**).

Selected Data

2-(4-Nitrophenyl)-1,4,5,6-tetrahydropyrimidine (3b). Yield 86%, mp 128–130 °C; IR (KBr) cm^{-1}: 3352 (N-H), 1624 (C=N); ^1H NMR (400 MHz, DMSO-d_6) δ 1.81–1.86 (m, 2H, CH_2), 3.50 (t, $J = 5.7$ Hz, 4H, $2 \times CH_2$), 5.51 (br s, 1H, NH), 7.90–8.02 (m, 3H, Ar). ^{13}C NMR (125 MHz, DMSO-d_6) δ 20.2, 39.5, 40.2, 124.5 (2C), 132.6 (2C), 140.1, 151.2, 155.8. APCI: m/z 206 [M + 1], Anal. calcd for $C_{11}H_{14}N_2O$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.47; H, 5.35; N, 20.42.

2-(2,4-Dimethoxyphenyl)-1,4,5,6-tetrahydropyrimidine (3d). Yield 90%, mp 141–143 °C; IR (KBr) cm^{-1}: 3328 (N-H), 1626 (C=N); ^1H NMR (400 MHz, DMSO-d_6) δ 1.81–1.85 (m, 2H, CH_2), 3.48 (t, $J = 8.0$ Hz, 4H, $2 \times CH_2$), 4.42 (br s, 1H, NH), 7.01 (d, $J = 8.6$ Hz, 1H, Ar), 7.27–7.33 (m, 2H, Ar). ^{13}C NMR (125 MHz, DMSO-d_6) δ 20.5, 40.2, 55.8, 101.2, 102.9, 106.7, 131.2, 156.7, 161.4, 163.9. APCI: m/z 206 [M + 1], Anal. calcd. for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.37; H, 7.27; N, 12.68.

2-(2,4-Dichlorophenyl)-1,4,5,6-tetrahydropyrimidine (3e). Yield 87%, mp 115–117 °C; IR (KBr) cm^{-1}: 3298 (N-H), 1622 (C=N); ^1H NMR (400 MHz, DMSO-d_6) δ1.85–1.91 (m, 2H, CH_2), 3.48 (t, $J = 8.0$ Hz, 4H, $2 \times CH_2$), 4.42 (br s, 1H, NH), 7.05–7.08 (m, 1H, Ar), 7.31–7.36 (m, 2H, Ar). APCI: m/z 228 [M+], 229 [M + 1], 230 [M + 2], 232 [M + 4], 196, 161, 127, 99. Anal. calcd. for $C_{10}H_{10}Cl_2N_2$: C, 52.42; H, 4.40; N, 12.23. Found: C, 52.36; H, 4.37; N, 12.19.

2-(2,3-Dimethoxyphenyl)-1,4,5,6-tetrahydropyrimidine (3g). Yield 90%: mp 160–162 °C; IR (KBr) cm^{-1}: 3355 (N-H), 1628 (C=N); ^1H NMR (300 MHz, DMSO-d_6) δ 1.78–1.86 (m, 2H, CH_2), 3.52 (t, $J = 5.7$ Hz, 4H, $2 \times CH_2$), 3.78 (s, 6H, OCH_3), 5.02 (br s, 1H, NH), 7.22–7.42 (m, 3H, Ar). APCI: m/z 220 [M + 1]. Anal. calcd. for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.37; H, 7.28; N, 12.67.

2-(3-Methoxyphenyl)-1,4,5,6-tetrahydropyrimidine (3j). Yield 85%, mp 142–143 °C; IR (KBr) cm^{-1}: 3323 (N-H), 1630 (C=N); ^1H NMR (400 MHz, DMSO-d_6) δ 1.91–1.94 (m, 2H, CH_2), 3.50 (t, $J = 5.7$ Hz, 4H, $2 \times CH_2$), 3.79 (s,

3H, OCH_3), 5.09 (br s, 1H, NH), 7.24 (d, $J = 8.2$ Hz, 1H, Ar), 7.26–7.30 (m, 2H, Ar), 7.36 (d, $J = 7.7$ Hz, 1H, Ar).^{13}C NMR (125 MHz, DMSO-d_6) δ 20.2, 40.2 (2C), 55.8, 110.6, 111.4, 121.1, 128.2, 132.0, 156.7, 160.4. APCI: m/z 191[M + 1]. Anal. calcd. for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.40; H, 7.34; N, 14.69.

2-(Pyridin-4-yl)-1,4,5,6-tetrahydropyrimidine (3l). Yield 94%, mp 151–153 °C; IR (KBr) cm^{-1}: 3322 (N-H), 1626 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83–1.88 (m, 2H, CH2), 3.51 (t, $J = 5.6$ Hz, 4H, $2 \times CH_2$), 4.83 (br s, 1H, NH), 7.18 (m, 4H, Ar). APCI: m/z 162 [M + 1], Anal. calcd. for $C_9H_{11}N_3$: C, 67.06; H, 6.88; N, 26.07. Found: C, 67.0; H, 6.84; N, 26.02.

2-(1H-Pyrrol-2-yl)-1,4,5,6-tetrahydropyrimidine (3m). Yield 91%, mp 124–126 °C; IR (KBr) cm^{-1}: 3325 (N-H), 1631 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6) δ1.87–1.91 (m, 2H, CH_2), 3.48 (t, $J = 8.0$ Hz, 4H, $2 \times CH_2$), 5.02 (br s, 1H, NH), 7.08–7.16 (m, 2H, Ar), 7.28–7.32 (m, 1H, Ar), 7.51 (s, NH). APCI: m/z 150 [M + 1], Anal. calcd. for $C_8H_{11}N_3$: C, 64.40; H, 7.43; N, 28.16. Found: C, 64.35; H, 7.39; N, 28.12.

2-(5-Bromothiophen-2-yl)-1,4,5,6-tetrahydropyrimidine (3o). Yield 95%, mp 161–163 °C; IR (KBr) cm^{-1}: 3324 (N-H), 1621 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6) 1.82–1.88 (m, 2H, CH_2), 3.48 (t, $J = 5.7$ Hz, 4H, $2 \times CH_2$), 7.06–7.10 (m, 1H, Ar), 7.20–7.24 (m, 1H, Ar). APCI: m/z 245 [M + 1].

2-(2-Bromophenyl)-1,4,5,6-tetrahydropyrimidine (3p). Yield 86%, mp 144–146 °C; IR (KBr) cm^{-1}: 3338 (N-H), 1622 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83–1.88 (m, 2H, CH_2), 3.48 (t, $J = 5.8$ Hz, 4H, $2 \times CH_2$), 4.83 (br s, 1H, NH), 7.20 (d, $J = 8.0$ Hz, 1H, Ar), 7.27–7.31 (m, 2H, Ar), 7.41 (d, $J = 7.7$ Hz, 1H, Ar). ^{13}C NMR (125 MHz, DMSO-d_6) δ 20.5, 42.2 (2C), 120.7, 127.3, 129.9, 130.2, 132.7, 139.3, 155.3. APCI: m/z calcd. for $C_{10}H_{12}BrN_2$ $[M + H]^+$ 239.

2-(2-Chloro-6-fluorophenyl)-1,4,5,6-tetrahydropyrimidine (3q). Yield 89%, mp 138–140 °C; IR (KBr) cm^{-1}: 3358 (N-H), 1624 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.81–1.86 (m, 2H, CH_2), 3.48 (t, $J = 5.7$ Hz, 4H, $2 \times CH_2$), 5.02 (br s, 1H, NH), 7.72–8.01 (m, 3H, Ar). APCI: m/z 214 [M + 2], 213 [M + 1], 212 [M+], 195, 179, 161, 145, 99. Anal. calcd. for $C_{10}H_{10}ClFN_2$: C, 56.48; H, 4.74; N, 13.17. Found: C, 56.41; H, 4.70; N, 13.14.

3-(1,4,5,6-Tetrahydropyrimidin-2-yl)-1h-indole (3s). Yield 85%, mp 142–143 °C; IR (KBr) cm^{-1}: 3352 (N-H), 1625 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.82–1.87 (m, 2H, CH_2), 3.61 (t, $J = 6.3$ Hz, 4H, $2 \times CH_2$), 5.15 (br s, 1H, NH), 7.01 (d, $J = 8.2$ Hz, 1H, Ar), 7.27–7.35 (m, 4H, Ar). ^{13}C NMR (125 MHz, DMSO-d_6) δ 20.3, 40.4 (2C), 110.4, 111.1, 120.3, 121.5, 121.7, 126.3, 130.5, 137.1, 154.7. APCI: m/z 200 [M + 1]. Anal. calcd. for $C_{12}H_{13}N_3$: C, 72.33; H, 6.58; N, 21.09. Found: C, 72.27; H, 6.54; N, 21.04.

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REFERENCES

1. Matsumoto, J.; Minami, S. Quinuclidine chemistry, 3: β-*cis*-2-(4′-Chloro-benzhydryl)-3-quinuclidinol, a new central nervous system stimulant: Importance of the benzhydryl configuration. *J. Med. Chem.* **1975**, *18*, 74–79.
2. Suzuki, N. Synthesis of antimicrobial agents, V: Synthesis and antimicrobial activities of some heterocyclic condensed 1,8-naphthyridine derivatives. *Chem. Pharm. Bull.* **1980**, *28*, 761–768
3. Rita, B.; Shrivastava, S. P. Synthesis and in vitro antimicrobial, anthelmintic, and insecticidal activities study of 4(4′-bromophenyl)-6-substituted-aryl-1-acetyl pyrimidine-2--thiols. *E-J. Chem.* **2010**, *7* (3), 935–941.
4. Corde, L.; Cubedo Bandres Rebollo, A. E.; Saenz, X.; Font, M. Biological profile of new apoptotic agents based on 2,4-pyrido[2,3-d]pyrimidine derivatives. *Bioorg. Med. Chem.* **2007**, *15*, 1659–1669.
5. Piper, J. R.; McCaleb, G. S.; Montgomery, J. A.; Kisliuk, R. L.; Gaumont, Y.; Sirotnaks, F. M. Syntheses and antifolate activity of 5-methyl-5-deaza analogs of aminopterin, methotrexate, folic acid, and N10-methylfolic acid. *J. Med. Chem.* **1986**, *29*, 1080–1087.
6. Robins, B. R.; Hitciings, G. Studies on condensed pyrimidine systems. XIX: A new synthesis of pyrido [2, 3-d]pyrimidines: The condensation of 1,3-diketones and 3-ketoaldehydes with 4-aminopyrimidines. *J. Am. Chem. Soc.* **1958**, *80*, 3449–3457.
7. Quintela, J. M.; Peinador, C.; Botana, L.; Estevez, M.; Riguera, R. Synthesis and antihistaminic activity of 2-guanadino-3-cyanopyridines and pyrido[2,3-d]-pyrimidines. *Bioorg. Med. Chem.* **1997**, *5*, 1543–1553.
8. Nam, G.; Min Yoon, C.; Kim, E.; Rhee, C. K.; Hyup Kim, J.; Hyu Shin, J.; Hoon Kim, S. Syntheses and evaluation of pyrido[2,3-d]pyrimidine-2,4-diones as PDE 4 inhibitors. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 611–614.
9. Zhu Zheng, G.; Mao, Y.; Hung Lee, C.; Patt, J. K., Koenig, J. P.; Perner, R. J. Adenosine kinase inhibitors: Polar 7-substitutent of pyridopyrimidine derivatives improving their locomotor selectivity. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3041–3044.
10. Connolly, C. J.; Hamby, J. M.; Schroeder, M. C.; Barvian, M.; Lu, G. H.; Panek, R. L. Discovery and structure–activity studies of a novel series of pyrido[2,3-d]pyrimidine tyrosine kinase inhibitors. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2415–2420.
11. Monge, A.; Martinez-Merino, V.; Sanmartin, C.; Fernandez, F. J.; Ochoa, M. C.; Bellver, C. 2-Arylamino-4-oxo-3,4-dihydropyrido[2,3-d]pyrimidines: Synthesis and diuretic activity. *Eur. J. Med. Chem.* **1989**, *24*, 209
12. Parish, H. A.; Gilliom, R. D. Syntheses and diuretic activity of 1,2-dihydro-2-(3-pyridyl)-3H-pyrido[2,3-d]pyrimidin-4-one and related compounds. *J. Med. Chem.* **1982**, *25*, 98–102.
13. Tsukasa, M.; Shinya, O.; Nobutaka, F.; Hiroaki, O. Efficient synthesis of pyrimido [1,2-c][1,3]benzothiazin-6-imines and related tricyclic heterocycles by SNAr-Type C-S, C-N, or C-O bond formation with heterocumulenes. *J. Org. Chem.* **2010**, *75*, 265–268.
14. Tsukasa, M.; Shinsuke, I.; Shinya, O.; Nobutaka, F.; Hiroaki, O. Cu(II)-mediated oxidative intermolecular ortho C–H functionalisation using tetrahydropyrimidine as the directing group. *Chem. Commun.* **2009**, 3413.
15. (a) Manson, T. J. Ultrasound in synthetic organic chemistry. *Chem. Soc. Rev.* **1997**, *26*, 443–451; (b) Cella, R.; Stefani, H. A. Ultrasound-assisted synthesis of Z and E stilbenes by Suzuki cross-coupling reactions of organotellurides with potassium organotrifluoroborate salts. *Tetrahedron* **2006**, *62*, 5656–5662; (c) Guzen, K. P.; Guarezemini, A. S.; Orfao, A. T. G.; Cella, R.; Pereira, C. M. P.; Stefani, H. A. Eco-friendly synthesis of imines by ultrasound irradiation. *Tetrahedron Lett.* **2007**, *48*, 1845–1848.

16. Cintas, P.; Luche, J. L. Green chemistry: The sonochemical approach. *Green Chem.* **1999**, *115*, 1.
17. Martins, M. A. P.; Pereira, C. M. P.; Cunico, W.; Moura, S.; Rosa, F. A.; Peres, R. L.; Machado, P.; Zanatta, N.; Bonacorso, H. G. Ultrasound-promoted synthesis of 5-hydroxy-5-trihalomethyl-4,5-dihydroisoxazoles and β-enamino trihalomethyl ketones in water. *Ultrason. Sonochem.* **2006**, *13*, 364–370.
18. (a) Dallinger, D.; Kappe, C. O. Microwave-assisted synthesis in water as solvent. *Chem. Rev.* **2007**, *107*, 2563–2591; (b) Lindstrom, U. M. Stereoselective organic reactions in water. *Chem. Rev.* **2002**, *102*, 2751–2772.
19. Valentine, G. N.; Vasiliy, M. M.; Aleksey, V. S.; Elizabeth, S. B.; Evgeniy, V. K.; Igor, A. U.; Alexander, Y. R. Fragmentation of trifluoromethylated alkenes and acetylenes by *N,N*-binucleophiles: Synthesis of imidazolines or imidazolidines (oxazolidines) controlled by substituent. *J. Org. Chem.* **2010**, *75*, 5679–5688.
20. Eleftherios, P. P.; Babu, G. Heterocycles from *N*-ethoxycarbonylthioamides and dinucleophilic reagents, 3: Six- and seven-membered rings with two or three heteroatoms. *J. Org. Chem.* **1977**, *42* (14), 2530–2532.