$H_3PW_{12}O_{40}$: An Efficient and Recyclable Heterogeneous Catalyst for the Selective Synthesis of 2-Aryl-5,6-dihydro-4*H*-1,3-oxazines and 2-Aryl-1,4,5,6-tetrahydropyrimidines

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An environmentally friendly and highly efficient procedure has been developed for the selective synthesis of 2-aryl-5,6-dihydro-4*H*-1,3-oxazines and 2-aryl-1,4,5,6-tetrahydropyrimidines by cyclocondensation of arylnitriles with 3-amino-1-propanol and 1,3-diaminopropane in the presence of catalytic amounts of $H_3PW_{12}O_{40}$ under thermal conditions and MW irradiation. Under the same reaction conditions, dicyanobenzenes are transformed to their corresponding mono-oxazines and mono-tetrahydropyrimidines with excellent chemoselectivity. These reactions are simple and clean, giving the products in high yields and high purity. The catalyst can be easily recovered after the reaction and reused efficiently in subsequent runs.

Key words: Oxazines, Tetrahydropyrimidines, Microwave Irradiation, Solid Acid Catalyst, Tungstophosphoric Acid

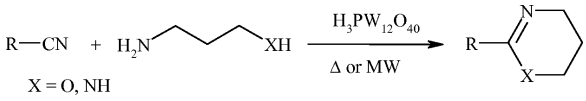
Introduction

The development of efficient and selective synthetic transformations in one operation is a major challenge in modern organic synthesis. 5,6-Dihydro-4*H*-1,3-oxazine and 1,4,5,6 tetrahydropyrimidine derivatives are of importance because of the broad spectrum of their biological and physiological properties such as choline acetyl transfer inhibitory [1], muscarinic agonist [2], antihypertensive [3], antidepressant [4], antiviral [5], and antibacterial [6] activities. These heterocyclic compounds have also been used as protecting groups [7], as monomers for polymer synthesis [8], and as precursors for the synthesis of a variety of functional groups in organic chemistry [9, 10]. Thus, the synthesis of 1,3-oxazine and tetrahydropyrimidine derivatives is in considerable demand.

Several methods for the preparation of 2-substituted 5,6-dihydro-4*H*-1,3-oxazines and 1,4,5,6-tetrahydropyrimidines have previously been reported [11 – 24]. However, some of these methods are associated with certain drawbacks such as harsh reaction conditions, the use of complex or toxic reagents, low yields of the products and long reaction times. Therefore, there is still a need to develop convenient and chemoselective synthetic methods for 1,3-oxazines and tetrahydropyrimidines (without using organic solvents) in terms of economic benefit, environmental impact and safety.

Microwave-assisted organic synthesis (MAOS) is a powerful technique that is being used more and more to accelerate thermal organic reactions. This is a consequence of the selective absorption of microwave energy by polar molecules or polar transition state intermediates formed in the course of the reaction. The notable features of the microwave approach are enhanced reaction rates, formation of purer products in high yields and easier manipulation [25, 26]. The use of solid acid catalysts with microwave irradiation provides even more benign processes.

In recent years, the use of Keggin-type heteropoly acids (HPAs) as heterogeneous and homogeneous catalysts has received considerable attention in synthetic organic chemistry [27 – 30]. Heteropoly acid catalysts have many advantages such as reusability, non-corrosive properties, easy handling, non-toxicity, easy work-up, and high stability toward air and moisture, which make them economically and environmentally attractive. Among heteropoly acids, tungstophosphoric acid ($H_3PW_{12}O_{40}$) is the most widely used catalyst



Scheme 1.

because of its high acid strength, low reducibility and selective action [31 – 33].

Recently, we have reported the synthesis of oxazolines, imidazolines and thiazolines in the presence of bulk and supported $H_3PW_{12}O_{40}$ under solvent free conditions [34, 35]. In continuation of our efforts to develop new synthetic methods for important organic compounds [36, 37], we now report a novel, efficient and environmentally benign method for the selective synthesis of 2-aryl-5,6-dihydro-4*H*-1,3-oxazines and 2-aryl-1,4,5,6-tetrahydropyrimidines using $H_3PW_{12}O_{40}$ as a reusable heterogeneous catalyst under thermal conditions and under microwave under irradiation (Scheme 1).

Results and Discussion

Initially, the reaction of 4-cyanopyridine with 3-amino-1-propanol in the presence of $H_3PW_{12}O_{40}$ was chosen as a model to optimize the reaction conditions. Different reaction temperatures and molar ratios of reagents and catalyst were examined (Table 1, entries 1 – 7). The best result was obtained by carrying out the reaction with 1 : 4 : 0.012 molar ratios of 4-cyanopyridine, 3-amino-1-propanol and $H_3PW_{12}O_{40}$ at 125 °C (Table 1, entry 5). We then screened other heteropoly acids such as $H_3PMo_{12}O_{40}$ and $H_4SiW_{12}O_{40}$ for their ability to catalyze this reaction (Table 1, entries 8 and 9). $H_3PW_{12}O_{40}$ was found to be the most efficient catalyst for this purpose. It is noteworthy that in the absence of the catalyst, the corresponding oxazine was produced in only 15 % yield

Table 1. Reaction of 4-cyanopyridine (1 mmol) with 3-amino-1-propanol in the presence of $H_3PW_{12}O_{40}$ under different conditions.

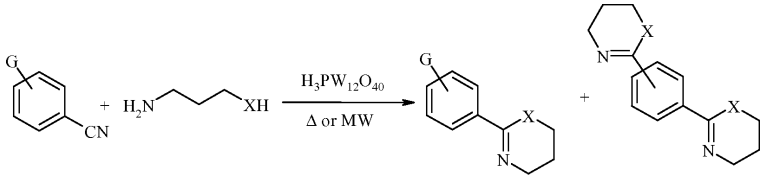
Entry	3-Amino-1-propanol (mmol)	$H_3PW_{12}O_{40}$ (mmol)	T (°C)	Yield (%)[a]
1	2	0.012	125	40
2	3	0.012	125	60
3	4	0.005	125	55
4	4	0.009	125	80
5	4	0.012	125	98
6	4	0.012	70	45
7	4	0.012	100	65
8[b]	4	0.012	125	60
9[c]	4	0.012	125	52
10	4	–	125	15

[a] Isolated yields; [b] reaction was performed in the presence of $H_3PMo_{12}O_{40}$; [c] reaction was performed in the presence of $H_4SiW_{12}O_{40}$.

(Table 1, entry 10). In the reaction of 4-cyanopyridine with 1,3-diaminopropane, the best yield of the corresponding tetrahydropyrimidine was also obtained under the same reaction conditions.

Under the optimized conditions, the $H_3PW_{12}O_{40}$-catalyzed cyclocondensations of various aromatic and heteroaromatic nitriles with 3-amino-1-propanol and 1,3-diaminopropane were investigated. All the reactions proceeded smoothly to give the corresponding 2-aryl-5,6-dihydro-4*H*-1,3-oxazines (Table 2, entries 1 – 9) and 2-aryl-1,4,5,6-tetrahydropyrimidines (Table 3, entries 1 – 8) in high yields.

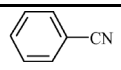
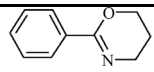
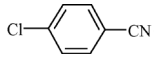
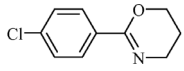
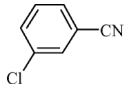
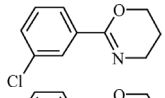
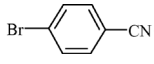
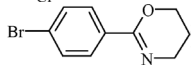
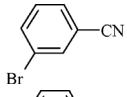
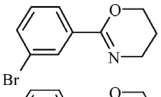
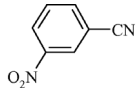
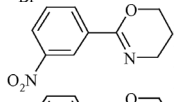
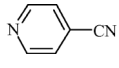
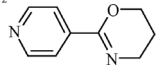
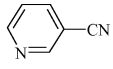
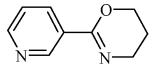
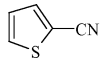
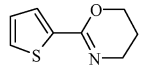
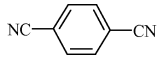
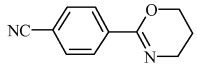
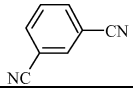
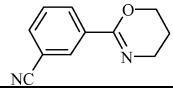
In order to expand the scope of this method further, the reactions of dinitriles with 3-amino-1-propanol and 1,3-diaminopropane were also examined. The experimental results show that dinitriles were converted to their mono-oxazines (Table 2, entries 10 and 11) and mono-tetrahydropyrimidines (Table 3, entries 9 and 10) with excellent selectivity even in the presence of a large excess of 3-amino-1-propanol and 1,3-diaminopropane or upon elongation of reaction times



1 mmol 8 mmol Following results 0%

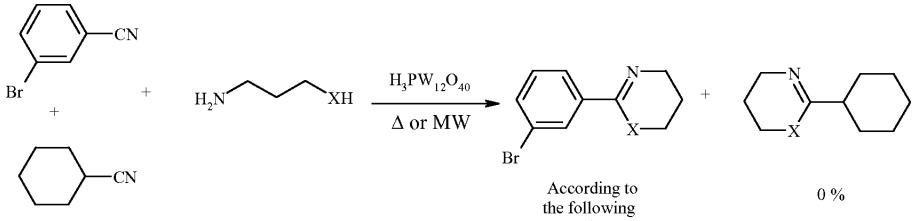
Conditions	G	X = O		X = NH	
		Yield (%)	Time	Yield (%)	Time
125 °C	3-CN	95	1 h	90	2 h
MW	3-CN	98	2 min	96	7 min
125 °C	4-CN	94	1.5 h	86	1.5 h
MW	4-CN	95	3.5 min	85	8 min

Scheme 2.

Entry	Nitrile	Product	Thermal Yield (%)[a] (Time, h)	MW Yield (%)[a] (Time, min)
1			88 (2)	97 (3)
2			90 (1.5)	93 (5)
3			90 (1)	90 (7.3)
4			96 (2.08)	88 (7)
5			92 (1.1)	95 (8)
6			80 (1.2)	70 (4)
7			98 (1.08)	97 (3)
8			90 (2)	90 (4)
9			92 (1.8)	85 (8)
10			94 (1.5)	95 (3.5)
11			95 (1)	98 (2)

[a] Isolated yields.

Table 2. Synthesis of 1,3-oxazines from nitriles catalyzed by $H_3PW_{12}O_{40}$ under thermal conditions and microwave irradiation.



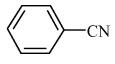
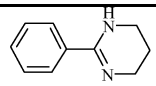
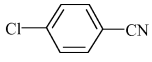
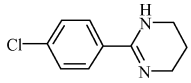
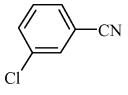
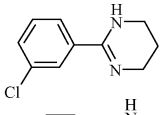
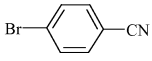
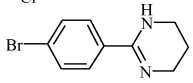
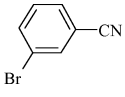
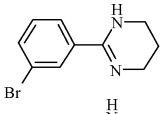
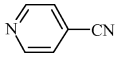
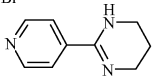
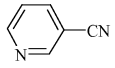
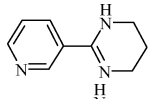
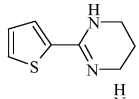
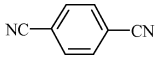
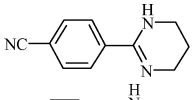
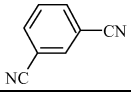
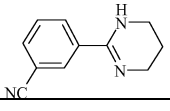
Conditions	X = O		X = NH	
	Yield (%)	Time	Yield (%)	Time
Thermal	92	1.1 h	98	2.3 h
MW	95	8 min	92	5 min

Scheme 3.

(Scheme 2). Chemoselective transformation of dinitriles to mono-oxazines and mono-tetrahydropyrimidines is of practical importance because the remaining nitrile group can be converted into other important functional groups.

It is also noteworthy that alkylnitriles did not afford the corresponding 2-substituted oxazines and tetrahydropyrimidines under the same reaction conditions. These results indicate that the present protocol is potentially applicable for the chemoselective conversion of arylnitriles to their 1,3-oxazines and tetrahydropyrimidines in the presence of alkylnitriles. To explore the selectivity of this method further, we have also investigated the competitive reac-

Table 3. Synthesis of tetrahydropyrimidines from nitriles catalyzed by $H_3PW_{12}O_{40}$ under thermal conditions and microwave irradiation.

Entry	Nitrile	Product	Thermal Yield (%)[a] (Time, h)	MW Yield (%)[a] (Time, min)
1			94 (4.25)	90 (4)
2			90 (3.5)	93 (4)
3			94 (4)	95 (4)
4			95 (6)	85 (10)
5			98 (2.3)	92 (5)
6			98 (2.3)	92 (4)
7			90 (10)	93 (5)
8			90 (3.3)	88 (4.5)
9			86 (1.5)	85 (8)
10			90 (2)	96 (7)

[a] Isolated yields.

tion of 3-bromobenzonitrile and cyclohexanecarbonitrile with 3-amino-1-propanol and 1,3-diaminopropane in the presence of the catalyst. The results showed that only 3-bromobenzonitrile reacted, whereas cyclohexanecarbonitrile remained intact in the reaction mixture (Scheme 3). Such a selectivity can be considered as a useful practical achievement in the synthesis of 1,3-oxazines and tetrahydropyrimidines.

In order to decrease the reaction time, microwave irradiation was used in these reactions. The reaction of 4-cyanopyridine with 3-amino-1-propanol was selected as a model optimize the reaction conditions. First, we performed this reaction in the absence of the catalyst, and 4-cyanopyridine (1 mmol) was reacted with 3-amino-1-propanol (4 mmol) directly under microwave irradiation with the power set at 800 W. Only 17 % of the product was obtained after 4 min at 85 °C. The reaction in the presence of 0.012 mmol of $H_3PW_{12}O_{40}$ was complete after 3 min, giving the corresponding 1,3-oxazine in 97 % yield. When the amount of the catalyst was decreased (0.005 and 0.009 mmol), the reaction proceeded more slowly, and the yields of the 1,3-oxazine were reduced to 56 and 79 %, respectively, even when the reaction was carried out for 4 min at 85 °C. Reaction temperature played a crucial role in this microwave-assisted reaction. We found that the increase of the temperature from 40 to 85 °C increased the yield from 32 to 97 %. The effect of the reaction time was also examined. It was found that as the reaction time was extended from 1 to 3 min, the yield of the desired product improved from 45 to 97 %. However, the yield was not affected when the reaction time exceeded 3 min. We also examined the molar ratio of 4-cyanopyridine to 3-amino-1-propanol. It was found that increasing the molar ratio from 1 : 2 to 1 : 4 increased the yield of the expected 1,3-oxazine from 50 to 97 %. Finally, we investigated the effect of

Table 4. Recovery and reuse of $H_3PW_{12}O_{40}$ in the reaction of 4-cyanopyridine with 3-amino-1-propanol[a].

Run	Time (h)	Yield (%)[b]	Run	Time (h)	Yield (%)[b]
1	1.08	98	2	1.08	98
3	1.08	98	4	1.08	98
5	1.08	98	6	1.08	98
7	1.08	98	8	1.08	98
9	1.08	98	10	1.08	95

[a] Reaction conditions: 4-cyanopyridine (1 mmol), 3-amino-1-propanol (4 mmol), $H_3PW_{12}O_{40}$ (0.012 mmol) at 125 °C; [b] isolated yields.

the microwave irradiation power in this reaction. It was found that the yield of the desired product increased from 60 to 97 % when the microwave power was increased from 600 to 800 W. Therefore, 1 : 4 : 0.012 molar ratios of 4-cyanopyridine, 3-amino-1-propanol and $H_3PW_{12}O_{40}$ and a power of 800 W at 85 °C were found to be the optimal conditions. In the reaction of 4-cyanopyridine with 1,3-diaminopropane, the best yield of the corresponding tetrahydropyrimidine was obtained with an irradiation power of 1000 W at 100 °C.

Similarly, various aromatic and heteroaromatic nitriles reacted with 3-amino-1-propanol and 1,3-diaminopropane in the presence of catalytic amounts of $H_3PW_{12}O_{40}$, and the corresponding 1,3-oxazines (Table 2, entries 1 – 9) and tetrahydropyrimidines (Table 3, entries 1 – 8) were obtained in high yields. Inspection of the data in Tables 2 and 3 shows that the yields of the reactions under thermal conditions and microwave irradiation are comparable, but under microwave irradiation, the reaction times are considerably shorter. Chemoselective transformation of dicyanobenzenes to their mono-oxazines (Table 2, entries 10 and 11) and mono-tetrahydropyrimidines (Table 3, entries 9 and 10) (Scheme 2) and selective conversion of arylnitriles to their 1,3-oxazines and tetrahydropyrimidines in the presence of aliphatic nitriles (Scheme 3) were also achieved under microwave irradiation.

Finally, the possibility of recovering and reusing of the catalysts, which is very important from practical and economical points of view, was examined for the reaction of 4-cyanopyridine with 3- amino-1-propanol. After completion of the reaction, cold EtOH (15 mL) was added, and the catalyst was separated by filtration. The recovered catalyst could be reused nine times without any loss of catalytic activity (Table 4).

In conclusion, we have developed a novel and highly efficient method for the synthesis of 1,3-oxazines and tetrahydropyrimidines using $H_3PW_{12}O_{40}$ as a heterogeneous catalyst under thermal conditions and under microwave irradiation. The commercial availablity, non-toxicity and reusability of the catalyst, a simple experimental procedure, excellent chemoselectivity, short reaction times and high yields are the main advantages of the present method.

Experimental Section

Melting points were obtained with a Stuart Scientific apparatus and are uncorrected. Yields refer to isolated products. ^{1}H- and ^{13}C-NMR (500 and 125 MHz) spectra were recorded on a Bruker-Avance AQS 500 spectrometer in $CDCl_3$ using TMS as internal standard. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer. Mass spectra were obtained on a platform II spectrometer from Micromass; EI mode at 70 eV. The microwave system used in the experiments includes the following items: Micro-SYNTH labstation, complete with glass door, dual magnetron system with pyramid-shaped diffuser, 1000 W delivered power, exhaust system, magnetic stirrer, "quality pressure" sensor for flammable organic solvents, ATCFO fiber optic system for automatic temperature control.

General experimental procedure for the synthesis of 1,3-oxazines and tetrahydropyrimidines under thermal conditions

A mixture of arylnitrile (1 mmol), 3-amino-1-propanol or 1,3-diaminopropane (4 mmol) and $H_3PW_{12}O_{40}$ (0.012 mmol) was stirred at 125 °C for the appropriate time according to Tables 2 and 3. The progress of the reaction was monitored by TLC (eluent: ethyl acetate/*n*-hexane, 4 : 1). After completion of the reaction, the mixture was cooled to room temperature, and cold EtOH (15 mL) was added. The catalyst was separated by filtration. The filtrate was evaporated, and the crude product was purified by column chromatography on neutral alumina to afford pure products.

General experimental procedure for the synthesis of 1,3-oxazines and tetrahydropyrimidines under microwave irradiation

A mixture of arylnitrile (1 mmol), 3-amino-1-propanol or 1,3-diaminopropane (4 mmol) and $H_3PW_{12}O_{40}$ (0.012 mmol) was subjected to microwave irradiation at the required power level according to the optimized conditions for the appropriate time (Tables 2 and 3). After completion of the reaction (TLC), the mixture was cooled to r. t., and cold EtOH (15 mL) was added. The catalyst was separated by filtration. The solvent was evaporated, and the residue was purified by column chromatography on neutral alumina to give pure product.

5,6-Dihydro-2-phenyl-4H-1,3-oxazine (Table 2, entry 1)

Pale-yellow oil [21]. – IR (neat): ν = 3040, 2852, 1646 (C=N), 1600, 1344, 1262, 1125, 810, 750 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.99 (quin, J = 5.6 Hz, 2 H, $CH_2CH_2CH_2$), 3.62 (t, J = 5.9 Hz, 2 H, CH_2N), 4.37 (t, J = 5.5 Hz, 2 H, CH_2O), 7.34 – 7.43 (m, 3 H, ArH), 7.88 – 7.90 (m, 2 H, ArH).

2-(4-Chlorophenyl)-5,6-dihydro-4H-1,3-oxazine (Table 2, entry 2)

Colorless oil [38]. – IR (neat): ν = 3060, 2855, 1648 (C=N), 1562, 1453, 1350, 1220, 1085, 840 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.97 (quin, J = 5.6 Hz, 2 H, $CH_2CH_2CH_2$), 3.60 (t, J = 5.9 Hz, 2 H, CH_2N), 4.35 (t, J = 5.5 Hz, 2 H, CH_2O), 7.30 – 7.35 (m, 2 H, ArH), 7.80 – 7.84 (m, 2 H, ArH). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.8 ($CH_2CH_2CH_2$), 42.6 (CH_2N), 65.2 (CH_2O), 128.2 (2 CH), 128.3 (2 CH), 132.6 (C), 136.3 (C), 154.7 (OCN).

2-(3-Chlorophenyl)-5,6-dihydro-4H-1,3-oxazine (Table 2, entry 3)

Colorless oil. – IR (neat): ν = 3052, 2950, 1660 (C=N), 1602, 1560, 1348, 1230, 1085, 808, 720 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.98 (quin, J = 5.6 Hz, 2 H, $CH_2CH_2CH_2$), 3.60 (t, J = 5.9 Hz, 2 H, CH_2N), 4.36 (t, J = 5.4 Hz, 2 H, CH_2O), 7.26 – 7.30 (m, 1 H, ArH), 7.30 (d, J = 8 Hz, 1 H, ArH), 7.77 (d, J = 7.8 Hz, 1 H, ArH), 7.89 (s, 1 H, ArH). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.9 ($CH_2CH_2CH_2$), 42.7 (CH_2N), 65.3 (CH_2O), 125.1 (CH), 127.2 (CH), 129.2 (CH), 130.3 (CH), 134.2 (C), 135.9 (C), 154.4 (OCN). – MS (EI, 70 eV): *m/z* (%) = 197.09 (3.59) $[M+2]^+$, 195.10 (10.68) $[M]^+$, 149.08 (83.31), 139.04 (100), 111.05 (73.13), 75.05 (43.10), 61.06 (29.48). – $C_{10}H_{10}ClNO$: calcd. C 61.39, H 5.15, N 7.16; found C 61.28, H 5.12, N 7.20.

2-(4-Bromophenyl)-5,6-dihydro-4H-1,3-oxazine (Table 2, entry 4)

M. p. 73 – 75 °C [24]. – IR (KBr): ν = 3050, 2900, 1665 (C=N), 1605, 1480, 1340, 1265, 1115, 830 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.99 (quin, J = 5.6 Hz, 2 H, $CH_2CH_2CH_2$), 3.60 (t, J = 5.9 Hz, 2 H, CH_2N), 4.36 (t, J = 5.5 Hz, 2H, CH_2O), 7.49 (d, J = 10.9 Hz, 2 H, ArH), 7.78 (d, J = 10.9 Hz, 2 H, ArH).

2-(3-Bromophenyl)-5,6-dihydro-4H-1,3-oxazine (Table 2, entry 5)

Yellow oil. – IR (neat): ν = 3072, 2905, 1651 (C=N), 1570, 1460, 1353, 1250, 1120, 860, 795, 710 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.98 (quin, J = 5.6 Hz, 2 H, $CH_2CH_2CH_2$), 3.61 (t, J = 5.9 Hz, 2 H, CH_2N), 4.36 (t, J = 5.4 Hz, 2 H, CH_2O), 7.21 – 7.26 (m, 1 H, ArH), 7.53 (d, J = 9.9 Hz, 1 H, ArH), 7.83 (d, J = 8.9 Hz, 1 H, ArH), 8.05 (s, 1 H, ArH). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.8 ($CH_2CH_2CH_2$), 42.7 (CH_2N), 65.3 (CH_2O), 122.2 (C), 125.5 (CH), 129.5 (CH), 130.1 (CH), 133.2 (CH), 134.9 (C), 153.5 (OCN). – MS (EI, 70 eV): *m/z* (%) = 241.06 (5.99) $[M+2]^+$, 239.08 (7.63) $[M]^+$, 238.09 (8.74), 183.05 (48.09), 155.03 (31.14), 102.08 (29.66), 76.11 (92.37), 57.17 (50.21). – $C_{10}H_{10}BrNO$: calcd. C 50.03, H 4.20, N 5.83; found C 50.10, H 4.12, N 5.76.

5,6-Dihydro-2-(3-nitrophenyl)-4H-1,3-oxazine (Table 2, entry 6)

M. p. 94 – 95 °C [39]. – IR (KBr): ν = 3085, 2920, 1652 (C=N), 1612, 1521, 1465, 1350, 1259, 1130, 1105, 840, 800, 692 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 2.02 (quin, J = 5.6 Hz, 2 H, $CH_2CH_2CH_2$), 3.65 (t, J = 5.9 Hz, 2 H, CH_2N), 4.44 (t, J = 5.5 Hz, 2 H, CH_2O), 7.54 (t, J = 8 Hz, 1 H, ArH), 8.24 – 8.28 (m, 2 H, ArH), 8.74 (s, 1 H, ArH).

5,6-Dihydro-2-(pyridin-4-yl)-4H-1,3-oxazine (Table 2, entry 7)

M. p. 53 – 55 °C [40]. – IR (KBr): ν = 3052, 2905, 2850, 1640 (C=N), 1600, 1541, 1453, 1340, 1220, 1152, 1060, 844 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 2.00 (quin, J = 5.6 Hz, 2 H, $CH_2CH_2CH_2$), 3.63 (t, J = 5.9 Hz, 2 H, CH_2N), 4.38 (t, J = 5.4 Hz, 2 H, CH_2O), 7.73 (d, J = 6 Hz, 2 H, ArH), 8.65 (d, J = 6 Hz, 2 H, ArH).

5,6-Dihydro-2-(pyridin-3-yl)-4H-1,3-oxazine (Table 2, entry 8)

Yellow oil. – IR (neat): ν = 3047, 2995, 1655 (C=N), 1593, 1470, 1342, 1280, 1130, 1115, 1023, 810, 705 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.98 (quin, J = 5.6 Hz, 2 H, $CH_2CH_2CH_2$), 3.59 (t, J = 6.6 Hz, 2 H, CH_2N), 4.36 (t, J = 5.4 Hz, 2 H, CH_2O), 7.25 – 7.28 (m, 1 H, ArH), 8.14 (d, J = 9.6 Hz, 1 H, ArH), 8.61 (d, J = 5.6 Hz, 1 H, ArH), 9.07 (s, 1 H, ArH). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.9 ($CH_2CH_2CH_2$), 42.7 (CH_2N), 65.3 (CH_2O), 122.8 (CH), 129.8 (C), 134.4 (CH), 148.6 (CH), 151.1 (CH), 153.9 (OCN). – MS (EI, 70 eV): *m/z* (%) = 162.15 (48.05) $[M]^+$, 161.14 (28.08) $[M-1]^+$, 122 (17.69), 106.12 (100), 78 (53.25). – $C_9H_{10}N_2O$: calcd. C 66.65, H 6.22, N 17.27; found C 66.54, H 6.25, N 17.17.

5,6-Dihydro-2-(thiophen-2-yl)-4H-1,3-oxazine (Table 2, entry 9)

M. p. 51 – 53 °C [41]. – IR (KBr): ν = 3090, 2884, 1644 (C=N), 1522, 1425, 1350, 1120, 1088, 850, 830, 718 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.98 (quin, J = 5.6 Hz, 2 H,

$CH_2CH_2CH_2$), 3.57 (t, J = 5.9 Hz, 2 H, CH_2N), 4.34 (t, J = 5.4 Hz, 2 H, CH_2O), 7.00 – 7.02 (m, 1 H, ArH), 7.33 (d, J = 5 Hz, 1 H, ArH), 7.46 (d, J = 3.6 Hz, 1 H, ArH).

4-(5,6-Dihydro-4H-1,3-oxazine-2-yl)benzonitrile (Table 2, entry 10)

M. p. 162 – 163 °C. – IR (KBr): ν = 3045, 2920, 2210 (CN), 1644 (C=N), 1503, 1420, 1343, 1260, 1133, 1090, 842 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 2.00 (quin, J = 5.6 Hz, 2 H, $CH_2CH_2CH_2$), 3.63 (t, J = 5.8 Hz, 2 H, CH_2N), 4.38 (t, J = 5.4 Hz, 2 H, CH_2O), 7.65 (d, J = 8.4 Hz, 2 H, ArH), 8.00 (d, J = 8.4 Hz, 2 H, ArH). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.8 ($CH_2CH_2CH_2$), 42.8 (CH_2N), 65.4 (CH_2O), 113.7 (C), 118.6 (C), 127.5 (2 CH), 131.8 (2 CH), 138.3 (C), 154.1 (OCN). – MS (EI, 70 eV): *m/z* (%) = 186.33 (38.30) $[M]^+$, 160.13 (3.19), 130.23 (47.87), 102.07 (9.57), 76.28 (31.91), 52.18 (100). – $C_{11}H_{10}N_2O$: calcd. C 70.96, H 5.41, N 15.04; found C 70.83, H 5.37, N 15.15.

3-(5,6-Dihydro-4H-1,3-oxazine-2-yl)benzonitrile (Table 2, entry 11)

M. p. 153 – 155 °C. – IR (KBr): ν = 3062, 2920, 2222 (CN), 1660 (C=N), 1580, 1478, 1375, 1170, 1090, 800, 740 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.99 (quin, J = 5.6 Hz, 2 H, $CH_2CH_2CH_2$), 3.61 (t, J = 5.8 Hz, 2 H, CH_2N), 4.37 (t, J = 5.3 Hz, 2 H, CH_2O), 7.46 (t, J = 7.9 Hz, 1 H, ArH), 7.67 (d, J = 8.6 Hz, 1 H, ArH), 8.13 (d, J = 9 Hz, 1 H, ArH), 8.19 (s, 1 H, ArH). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.8 ($CH_2CH_2CH_2$), 42.7 (CH_2N), 65.5 (CH_2O), 112.4 (C), 118.5 (C), 128.9 (CH), 130.8 (CH), 131.1 (CH), 133.4 (CH), 135.4 (C), 153.6 (OCN). – MS (EI, 70 eV): *m/z* (%) = 186.09 (5.06) $[M]^+$, 185.08 (6.47) $[M–1]^+$, 149.03 (100), 130.04 (30.65), 102.04 (34.85), 76.03 (55.11). – $C_{11}H_{10}N_2O$: calcd. C 70.96, H 5.41, N 15.04; found C 70.85, H 5.35, N 15.13.

2-Phenyl-1,4,5,6-tetrahydropyrimidine (Table 3, entry 1)

M. p. 86 – 87 °C [42]. – IR (KBr): ν = 3350 (NH), 2805, 1641 (C=N), 1620, 1400, 1315, 1245, 850, 730 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.88 (quin, J = 5.8 Hz, 2 H, $CH_2CH_2CH_2$), 3.40 (t, J = 5.8 Hz, 4H, 2 CH_2N), 4.6 (br s,1 H, NH), 7.36 (t, J = 7.8 Hz, 2 H, ArH), 7.49 (t, J = 7.4 Hz, 1 H, ArH), 7.87 (d, J = 7.4 Hz, 2 H, ArH).

2-(4-Chlorophenyl)-1,4,5,6-tetrahydropyrimidine (Table 3, entry 2)

M. p. 144 – 145 °C [43]. – IR (KBr): ν = 3250 (NH), 3040, 2904, 1620 (C=N), 1540, 1410, 1360, 1282, 1180, 1060, 830 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.86 (quin, J = 5.8 Hz, 2 H, $CH_2CH_2CH_2$), 3.49 (t, J = 5.8 Hz, 4 H, 2 CH_2N), 4.9 (br s, 1 H, NH), 7.33 (d, J = 11 Hz, 2 H, ArH), 7.37 (d, J = 11 Hz, 2 H, ArH).

2-(3-Chlorophenyl)-1,4,5,6-tetrahydropyrimidine (Table 3, entry 3)

M. p. 131 – 132 °C. – IR (KBr): ν = 3300 (NH), 2922, 2800, 1620 (C=N), 1571, 1550, 1373, 1330, 1220, 1110, 840, 715 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.87 (quin, J = 5.8 Hz, 2 H, $CH_2CH_2CH_2$), 3.48 (t, J = 5.7 Hz, 4 H, 2 CH_2N), 4.9 (br s, 1 H, NH), 7.26 – 7.30 (m, 1 H, ArH), 7.37 (d, J = 10.9 Hz, 1 H, ArH), 7.56 (d, J = 10.2 Hz, 1 H, ArH), 7.66 (s, 1 H, ArH). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.6 ($CH_2CH_2CH_2$), 42.2 (2 CH_2N), 124.2 (CH), 126.6 (CH), 129.6 (CH), 129.8 (CH), 134.4 (C), 138.7 (C), 153.7 (NCN). – $C_{10}H_{11}ClN_2$: calcd. C 61.70, H 5.70, N 14.39; found C 61.54, H 5.75, N 14.32.

2-(4-Bromophenyl)-1,4,5,6-tetrahydropyrimidine (Table 3, entry 4)

155 – 156 °C [44]. – IR (KBr): ν = 3420 (NH), 2905, 1610 (C=N), 1540, 1460, 1250, 1170, 1110, 820 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.84 (quin, J = 5.8 Hz, 2 H, $CH_2CH_2CH_2$), 3.47 (t, J = 6.6 Hz, 4 H, 2 CH_2N), 4.9 (br s, 1 H, NH), 7.47 (d, J = 8.6 Hz, 2 H, ArH), 7.52 (d, J = 8.6 Hz, 2 H, ArH). – MS (EI, 70 eV): *m/z* (%) = 239.99 (32.58) $[M+2]^+$, 237.99 (34.84) $[M]^+$, 236.98 (59.28) $[M–1]^+$, 181.90 (35.75), 159.01 (10.41), 102.91 (32.13), 74.94 (64.25), 60.93 (100).

2-(3-Bromophenyl)-1,4,5,6-tetrahydropyrimidine (Table 3, entry 5)

M. p. 138 – 139 °C. – IR (KBr): ν = 3192 (NH), 3059, 2933, 1607 (C=N), 1547, 1512, 1362, 1302, 1194, 862, 798, 713 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.86 (quin, J = 5.8 Hz, 2 H, $CH_2CH_2CH_2$), 3.51 (t, J = 5.7 Hz, 4 H, 2 CH_2N), 5.2 (br s, 1 H, NH), 7.23 (t, J = 7.6 Hz, 1 H, ArH), 7.51 (d, J = 10.8 Hz, 1 H, ArH), 7.57 (d, J = 10.2 Hz, 1 H, ArH), 7.82 (s, 1 H, ArH). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.7 ($CH_2CH_2CH_2$), 42.0 (2 CH_2N), 122.5 (C), 124.8 (CH), 129.5 (CH), 129.9 (CH), 132.9 (CH), 138.5 (C), 153.8 (NCN). – MS (EI, 70 eV): *m/z* (%) = 240.03 (37.91) $[M+2]^+$, 238.04 (40.11) $[M]^+$, 237.04 (100) $[M–1]^+$, 182.02 (57.14), 159.15 (47.25), 102.10 (94.51), 76.12 (91.21). – $C_{10}H_{11}BrN_2$: calcd. C 50.23, H 4.64, N 11.72; found C 50.37, H 4.69, N 11.64.

2-(4-Pyridyl)-1,4,5,6-tetrahydropyrimidine (Table 3, entry 6)

M. p. 97 – 99 °C. – IR (KBr): ν = 3200 (NH), 2921, 2854, 1622 (C=N), 1596, 1533, 1362, 1305, 1280, 826 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.87 (quin, J = 5.8 Hz,

2 H, $CH_2CH_2CH_2$), 2.8 (br s, 1 H, NH), 3.53 (t, J = 5.8 Hz, 4 H, 2 CH_2N), 7.54 (d, J = 6.1 Hz, 2 H, ArH), 8.63 (d, J = 6.1 Hz, 2 H, ArH). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.4 ($CH_2CH_2CH_2$), 42.2 (2 CH_2N), 120.4 (2 CH), 144.3 (C), 150.1 (2 CH), 152.7 (NCN). – MS (EI, 70 eV): *m/z* (%) = 161.15 (61.69) $[M]^+$, 160.15 (100) $[M–1]^+$, 105.10 (94.81), 131.11 (16.54), 78.11 (44.81). – $C_9H_{11}N_3$: calcd. C 67.06, H 6.88, N 26.07; found C 66.89, H 6.93, N 25.93.

2-(3-Pyridyl)-1,4,5,6-tetrahydropyrimidine (Table 3, entry 7)

Yellow oil. – IR (neat): v = 3300 (NH), 2805, 1617 (C=N), 1593, 1421, 1394, 1200, 1019, 817, 770, 700 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.90 (quin, J = 5.8 Hz, 2 H, $CH_2CH_2CH_2$), 2.6 (br s, 1 H, NH), 3.54 (t, J = 5.7 Hz, 4 H, 2 CH_2N), 7.26 – 7.32 (m, 1 H, ArH), 8.02 (d, J = 9.5 Hz, 1 H, ArH), 8.64 (d, J = 4.8 Hz, 1 H, ArH), 8.87 (s, 1 H, ArH). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.7 ($CH_2CH_2CH_2$), 42.3 (2 CH_2N), 123.2 (CH), 132.7 (C), 134.1 (CH), 147.2 (CH), 150.8 (CH), 152.6 (NCN). – $C_9H_{11}N_3$: calcd. C 67.06, H 6.88, N 26.07; found C 67.19, H 6.81, N 26.13.

2-(2-Thienyl)-1,4,5,6-tetrahydropyrimidine (Table 3, entry 8)

M. p. 183 – 185 °C [24]. – IR (KBr): v = 3192 (NH), 3061, 2934, 2852, 1607 (C=N), 1549, 1525, 1514, 1431, 1362, 1325, 1302, 1194, 1166, 862, 798, 712 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.87 (quin, J = 5.8 Hz, 2 H, $CH_2CH_2CH_2$), 3.50 (t, J = 5.6 Hz, 4 H, 2 CH_2N), 5.1 (br s, 1 H, NH), 6.90 – 7.01 (m, 1 H, ArH), 7.20 (dd, J = 3.7, 0.9 Hz, 1 H, ArH), 7.31 (dd, J = 5.0, 0.9 Hz, 1 H, ArH).

2-(4-Cyanophenyl)-1,4,5,6-tetrahydropyrimidine (Table 3, entry 9)

M. p. 69 – 71 °C. – IR (KBr): v = 3213 (NH), 3020, 2922, 2240 (CN), 1626 (C=N), 1537, 1492, 1367, 1308, 1186, 835 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.84 (quin, J = 5.7 Hz, 2 H, $CH_2CH_2CH_2$), 3.49 (t, J = 6.3 Hz, 4 H, 2 CH_2N), 4.1 (br s, 1 H, NH), 7.63 (d, J = 8.3 Hz, 2 H, ArH), 7.75 (d, J = 8.3, Hz, 2 H, ArH). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.7 ($CH_2CH_2CH_2$), 41.4 (2 CH_2N), 112.5 (C), 117.9 (C), 126.7 (2 CH), 131.3 (2 CH), 140.1 (C), 153.1 (NCN). – $C_{11}H_{11}N_3$: calcd. C 71.33, H 5.99, N 22.69; found C 71.18, H 5.90, N 22.77.

2-(3-Cyanophenyl)-1,4,5,6-tetrahydropyrimidine (Table 3, entry 10)

M. p. 136 – 139 °C. – IR (KBr): v = 3177 (NH), 3025, 2959, 2220 (CN), 1622 (C=N), 1541, 1475, 1367, 1194, 806 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.87 (quin, J = 5.7 Hz, 2 H, $CH_2CH_2CH_2$), 3.51 (t, J = 5.8 Hz, 4 H, 2 CH_2N), 4.2 (br s, 1 H, NH), 7.47 (t, J = 7.8 Hz, 1 H, ArH), 7.66 (d, J = 5.1 Hz, 1 H, ArH), 7.90 (d, J = 5.3 Hz, 1 H, ArH), 7.96 (s, 1 H, ArH). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.6 ($CH_2CH_2CH_2$), 42.4 (2 CH_2N), 112.5 (C), 118.4 (C), 129.2 (CH), 129.9 (CH), 130.4 (CH), 132.9 (CH), 138.5 (C), 152.7 (NCN). – MS (EI, 70 eV): *m/z* (%) = 185.13 (52.98) $[M]^+$, 184.13 (100) $[M–1]^+$, 129.08 (91.39), 102.07 (47.68), 75.06 (22.02). – $C_{11}H_{11}N_3$: calcd. C 71.33, H 5.99, N 22.69; found C 71.21, H 5.94, N 22.75.

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