Mol Divers (2013) 17:251–259
DOI 10.1007/s11030-013-9427-0

FULL-LENGTH PAPER

N, *N*, *N′*, *N′*-Tetrabromobenzene-1,3-disulfonamide and poly(*N*-bromo-*N*-ethylbenzene-1,3-disulfonamide) as new and efficient catalysts for the synthesis of highly substituted 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives

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Received: 20 October 2012 / Accepted: 15 January 2013 / Published online: 15 February 2013

Abstract Various mono and *bis*-1,6-dihydropyrazine-2,3-dicarbonitrile derivatives were efficiently synthesized by reacting 2,3-diaminomaleonitrile (DAMN), isocyanides and ketones in the presence of a catalytic amount of *N*, *N*, *N′*,*N′*-tetrabromobenzene-1,3-disulfonamide [TBBDA] and poly(*N*-bromo-*N*-ethylbenzene-1,3-disulfonamide) [PBBS] in EtOH/H_2O at ambient temperature.

Keywords Multi-component reactions (MCRs) · 1, 6-Dihydropyrazine · 2, 3-Diaminomaleonitrile (DAMN) · Isocyanides · α-Halo ketones · Aqueous conditions · TBBDA · PBBS

Introduction

The chemistry of heterocyclic compounds has attracted much attention in recent times due to its increasing importance in the field of pharmaceuticals and industrial chemicals. A number of compounds based on nitrogen-containing heterocycles show antimicrobial activity and have been developed for clinical usage such as Echinomycin, Levomycin, and Actinoleutin [1–3]. Multi-component reactions (MCRs) are significant tools for the rapid and efficient synthesis of a wide variety of organic molecules [4]. These reactions have been investigated extensively in organic and diverse-oriented synthesis, primarily due to their ability to generate complex molecular functionalities from simple starting materials via one-pot reaction [5,6]. Dihydropyrazine derivatives are an important class of heterocycles being the core fragment of different natural products and biological systems. The biological and physical roles of dihydropyrazines (DHPs) in DNA cleavage [7], growth inhibition of Escherichia coli [8], and cyclooxygenase inhibitory activity [9] are well documented.

Several methods have been developed for the synthesis of DHPs involving condensation of 1,2-diamines with α-diketones [10–12], 1,4-addition of 1,2-diamines to diazenylbutenes [13] and carbenoid N–H insertion [14]. Thus, the synthesis of dihydropyrazines is an important and useful area in organic chemistry. Whereas the derivatives of pyrazine are an excellent scaffold for drug development, they exhibit a wide variety of biological and medicinal activities. For instance, the pyrazine derivatives such as compound **A** and **B** (Fig. 1) were tested for growth inhibitory activity against human cancer cell lines, such as MCF-7 (breast cancer), NCI-H460 (non-small-cell lung cancer), and SF-268 (glioma) [15].

The great potential of isocyanides for the development of multicomponent reactions lies in the diversity of bond forming processes available, functional group tolerance, and the high levels of chemo-, regio and stereoselectivity often observed. Moreover, there is virtually no restriction on the nature of the nucleophiles and electrophiles in isocyanide multicomponent reactions (IMCRs). Multicomponent reactions involving isocyanides have emerged as valuable tools for the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds [16–23].

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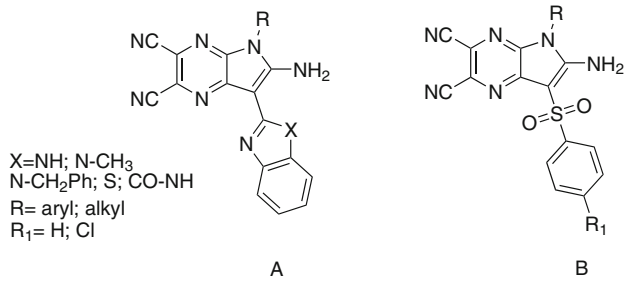
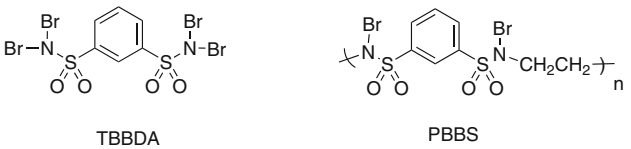
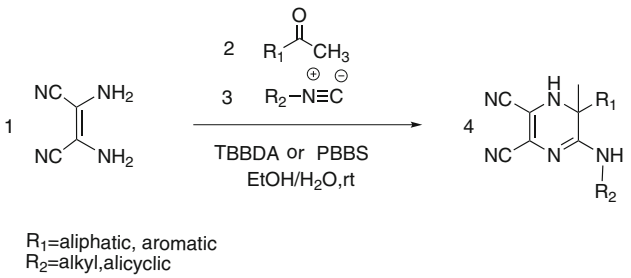


Fig. 1 Structure of biological pyrazines



Scheme 1 Catalysts structures



Scheme 2 One-pot synthesis of mono and *bis*-1,6-dihydropyrazine-2,3-dicarbonitrile derivatives

Table 1 Optimization of reaction conditions at room temperature

Entry	Solvent	TBBDA/PBBS (g)	Time (*min*)	Yield (%)[a]
1	EtOH–H_2O	No reagent	120	0/0
2	CH_3CN	0.05/0.1	60	35/30
3	CH_2Cl_2	0.05/0.1	60	35/25
4	THF	0.05/0.1	60	10/5
5	DMSO	0.05/0.1	60	20/15
6	DMF	0.05/0.1	60	35/10
7	CH_3OH	0.05/0.1	60	60/45
8	CH_3CO_2E	0.05/0.1	60	45/45
9	EtOH	0.05/0.1	60	70/65
10	Neat	0.05/0.1	60	55/40
11	H_2O	0.05/0.1	60	25/10
12	EtOH/H_2O	0.06/0.12	60	98/90
13	EtOH/H_2O	0.07/0.14	60	95/85
14	EtOH/H_2O	0.10/0.20	60	95/90

[a] Standardization of reaction conditions: benzyl acetone (1 mmol), 2,3-diaminomaleonitrile (1 mmol), cyclohexyl isocyanide (1 mmol)

Results and discussion

In a continuation of our interest in the application of *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide [TBBDA] and poly(*N*-bromo-*N*-ethylbenzene-1,3-disulfonamide) [PBBS] [24] (Scheme 1) in organic synthesis [25–37], we report here a facile and improved protocol for preparation of 1,6-dihydropyrazine-2,3-dicarbonitrile, from isocyanide, 2,3-diaminomaleonitrile and various aliphatic, alicyclic, and aromatic ketones in the presence of TBBDA and PBBS as catalysts in EtOH/H_2O at ambient conditions (Scheme 2).

The advantages of TBBDA and PBBS are as follows:

1. The preparation of TBBDA and PBBS is easy.
2. TBBDA and PBBS are stable under atmospheric conditions (room temperature and oxygen) for two months.
3. After completion of the reaction, the catalysts are recovered and can be reused several times without decreasing the yield.

Synthesis of organic molecules via green, mild, and simple procedures is currently receiving considerable attention. Also, reducing or eliminating the use and generation of hazardous substances is a goal of green chemistry. In this context, EtOH-H_2O is the preferred choice as a solvent. Reactions in aqueous media are generally environmentally safe, devoid of any carcinogenic effects, simple to handle, cheaper to operate, and especially important in industry [38,39]. Initially, we decided to explore the role of our catalysts in various solvents for the preparation of 5-(cyclohexylamino)-6-benzyl-6-methyl-1,6-dihydropyrazine-2,3-dicarbonitrile as a model compound (Table 2, entry 6). In the absence of catalysts, no product was observed, even after prolonged reaction times. Since the synthesis of 5-(cyclohexylamino)-6-benzyl-6-methyl-1,6-dihydropyrazine-2,3-dicarbonitrile failed in the absence of catalyst, the effect of catalysts was also investigated in various conditions, and the results are presented in Table 1. We found that the reaction was rapid and gave excellent yields when catalyzed by *N*, *N*, *N*′, *N*′-tetrabromobenzene-1,3-disulfonamide [TBBDA] (60 min, 98 %, Table 1, entry 12) and poly(*N*-bromo-*N*-ethylbenzene-1,3-disulfonamide) [PBBS] (65 min, 90 %, Table 1, entry 12).

Our preliminary examination shows that TBBDA and PBBS are reusable catalytic reagents. Thus, after the produce of 5-(cyclohexylamino)-6-benzyl-6-methyl-1,6-dihydropyrazine-2,3-dicarbonitrile in first run with TBBDA, which gave the corresponding product in 98 % isolated yield (Table 1, entry 12), the *N*, *N*, *N*′, *N*′-tetrabromobenzene-1,3-disulfonamide (TBBDA) catalyst was subjected to a second reaction from which it gave product in 90 % yield; the average chemical yield for five consecutive runs was 50 %. In this curve (Scheme3), we show that repetition has reduced

Table 2 Synthesis of 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives in the presence of TBBDA and PBBS

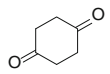
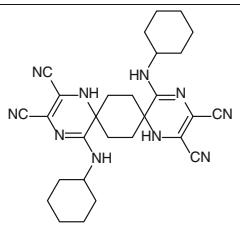
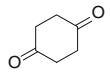
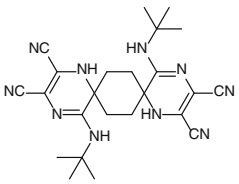
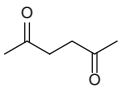
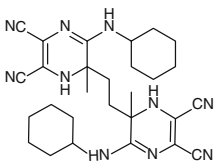
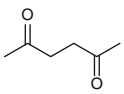
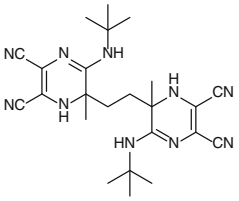
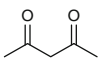
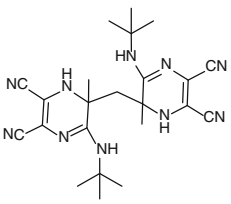
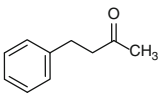
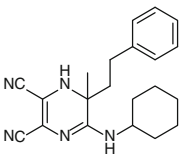
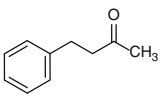
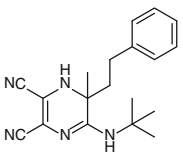
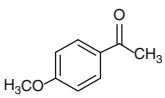
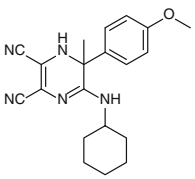
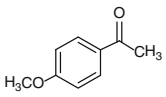
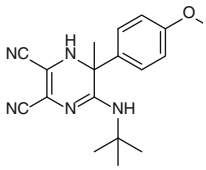
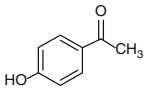
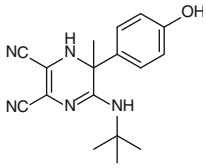
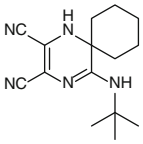
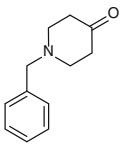
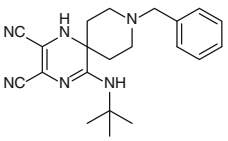
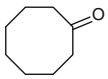
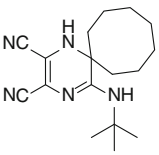
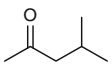
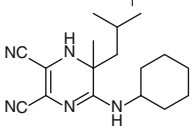
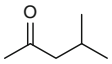
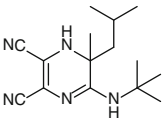
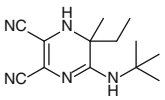
Entry	Ketone	Isocyanide	Product[a]	TBBDA		PBBS	
				Time (min)	Yield (%)	Time (min)	Yield (%)
1		cyclohexyl		90	95	120	90
2		*tert*-butyl		80	98	80	90
3		Cyclohexyl		60	85	65	80
4		*tert*-butyl		40	94	60	85
5		*tert*-butyl		80	85	120	80
6		cyclohexyl		60	98	65	90
7		*tert*-butyl		30	98	35	80
8		cyclohexyl		40	94	50	45

Table 2 continued

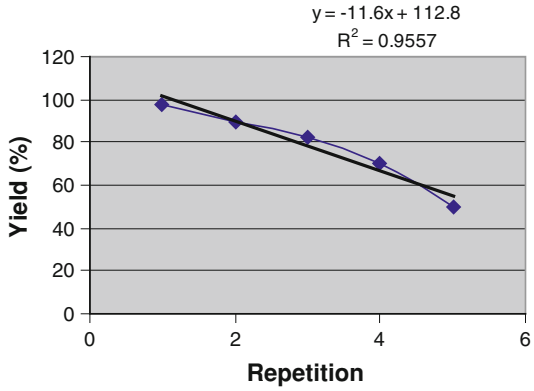
Entry	Ketone	Isocyanide	Product[a]	PBBS		PBBS	
				Time (min)	Yield (%)	Time (min)	Yield (%)
9		*tert*-butyl		60	90	75	60
10		*tert*-butyl		80	96	40	80
11		*tert*-butyl		20	98	30	85
12		*tert*-butyl		100	60	120	40
13		*tert*-butyl		20	95	30	80
14		cyclohexyl		10	94	25	90
15		*tert*-butyl		20	90	20	70
16		*tert*-butyl		15	94	20	80

[a] Isolated yield

gradually. The data shows a good agreement with the function of $y = -11.6x + 112.8$ with a regression coefficient of $R^2 = 0.955$.

To test the generality and versatility of this new procedure in the synthesis of pyrazines, we examined a number of aliphatic and aromatic ketones and cyclohexyl and *tert*-butyl isocyanide under optimized conditions (Table 2).

Mechanistically, it is likely that TBBDA or PBBS releases Br^+ in situ, which acts as an electrophilic species and the mechanism shown in Scheme 4 is proposed for the synthesis of the 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives. In summary, we have developed a new and facile protocol for the synthesis of new aliphatic and aromatic 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives, from the reaction of ketones, 2,3-diaminomaleonitrile (DAMN) and isocyanide compounds using TBBDA and PBBS at room temperature. Initially, the reaction involves a Br^+ transfer from the catalysts to an amino group to form (*Z*)-2-amino-



Scheme 3 Reusable catalytic reagents

N-bromo-1,2-dicyanoethenaminium (**A**). Then, reaction of **A** with ketone followed by elimination of H_2O produced imine intermediate (**D**). After a nucleophilic attack by isocyanide, intramolecular cyclization (**E**) and imine-enamine tautomerization of intermediate (**F**) 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives (**G**) are obtained.

Conclusions

In summary, we have developed a new and facile protocol for the synthesis of mono and *bis*-1,6-dihydropyrazine-2,3-dicarbonitrile derivatives starting from simple and readily available substrates (mono and *bis*-aliphatic, alicyclic and aromatic ketones, 2,3-diaminomaleonitrile, cyclohexyl isocyanide and *tert*-butyl isocyanide), using stable and inexpensive *N*-halo catalysts (TBBDA and PBBS) at room temperature. This reaction can be regarded as a new approach for the preparation of potential pharmaceutically relevant, highly substituted 1,6-dihydropyrazine-2,3 dicarbonitrile derivatives.

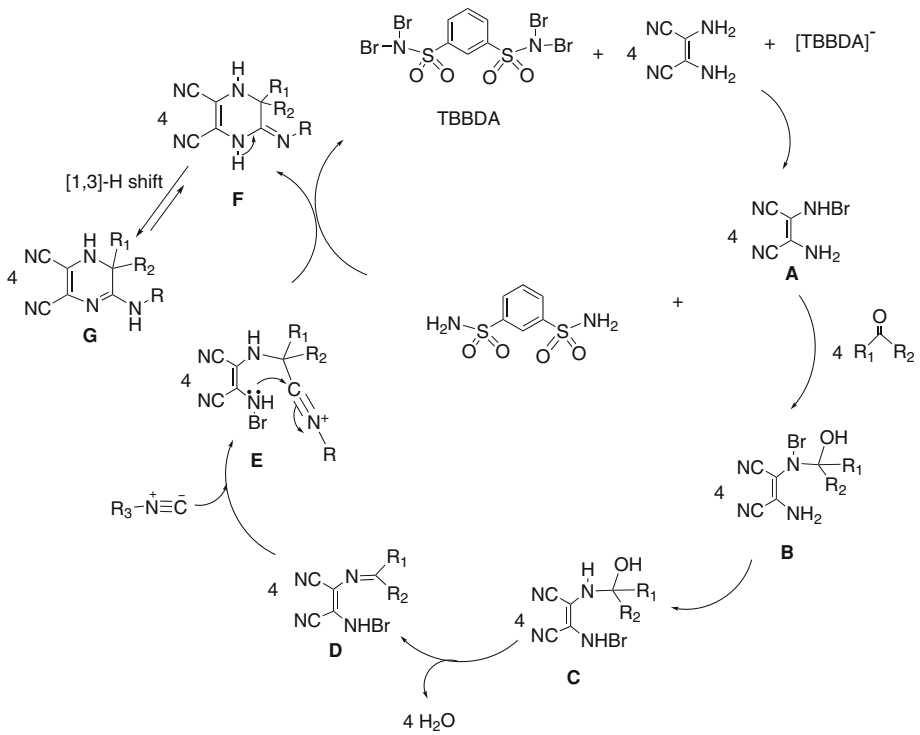
Experimental

All commercially available chemicals were obtained from Merck and Fluka companies, and used without further purification unless otherwise stated. Nuclear magnetic resonance, ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 FT NMR spectrometer. Infrared (IR) spectroscopy was conducted on a Perkin Elmer GX FT-IR spectrometer. Mass spectra were recorded on a Shimadzu QP 1100 BX Mass spectrometer. Elemental analyses (CHN) were performed with a Heraeus CHN-Rapid analyzer.

Typical procedure for the synthesis of 5-(cyclohexylamino)-6-benzyle-6-methyl-1,6-dihydropyrazine-2,3-dicarbonitrile

To a solution of DAMN (1 mmol, 0.108 g), benzylacetone (1 mmol, 0.148, g), and cyclohexyl isocyanide (1 mmol, 0.109 g) in 5 mL of EtOH/H_2O (4:1) TBBDA (0.109 mmol, 0.06 g) or PBBS (0.12 g) was added. The resulting mixture was stirred for 60 min at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 3:2), the solid products were precipitated

Scheme 4 Proposed mechanism for the formation of products



by addition of crushed ice (10 g), filtered off and washed with water. Then, the filtered solid was added to cold dichloromethane (30 mL) and stirred for 10 min at ambient temperature. The catalyst was removed by simple filtration. Removal of the solvent under reduced pressure gave the desired crude product. The crude product was recrystallized from ethyl acetate/*n*-hexane (1:5) to give the pure product (98 %) as a yellow powder.

Typical procedure for the synthesis of bis-5-(cyclohexylamino)-6,6′-cyclohexyl-1,6-dihydropyrazine-2,3-dicarbonitrile

To a solution of DAMN (0.216 g, 2 mmol), cyclohexane-1,4-dione (0.112 g, 1 mmol), cyclohexyl isocyanide (0.218 g, 2 mmol) in 5 mL of EtOH/H_2O (4:1), was added TBBDA (0.12 g, 0.218 mmol) or PBBS (0.24 g). The resulting mixture was stirred for 90 min at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 3:2), the solid product was precipitated by addition of crushed ice (10 g), filtered off and washed with water. Then, the filtered solid was added to cold dichloromethane (30 mL) and stirred for 10 min at ambient temperature. The catalyst was removed by simple filtration. Removal of the solvent under reduced pressure gave the desired crude product. The crude product was recrystallized from ethyl acetate/*n*-hexane (1:5) to give the pure product (95 %) as a white powder.

The spectral (IR,[1] H NMR, [13] C NMR, Ms, CHN) data for the selected compounds are presented below

Table 2, entry 1: $bis-5-(cyclohexylamino)-6,6'-cyclohexyl-1,6-dihydropyrazine-2,3-dicarbonitrile$. (95 %); mp 290–292 °C; IR (KBr) (ν_{max}, cm^{-1}) 3450, 3344 (N–H), 2932, 2855 (C–H), 2214 (C≡N), 1564, 1456; δ_H (300 MHz, DMSO-d_6) 1.06–1.52 (28H, m, cyclohexyl), 3.71 (2H, m, *CH*–NH), 6.49 (2H, br s, CH–*NH*), 7.02 (2H, br s, NH); δc (75 MHz, DMSO-d_6); 25.21, 25.64, 26.36, 50.54, 50.68, 108.05, 112.84, 114.99, 117.89, 152.64; MS, m/z (%): 510 (M^+, 4), 296 (14), 215 (16), 159 (16), 83 (23), 55 (49), 41 (55), 29 (9), 18 (4); [found C, 66.18; H, 6.72; N, 27.50. $C_{28}H_{34}N_{10}$ requires C, 65.86; H, 6.71; N, 27.43 %].

Table 2, entry 2: $bis-5-(tert-butylamino)-6,6'-cyclohexyl-1,6-dihydropyrazine-2,3-dicarbonitrile$. (98 %); mp 296–298 °C; IR (KBr) (ν_{max}, cm^{-1}) 3460, 3384, 3355 (N–H), 2943, 2934 (C–H), 2221 (C≡N), 1541, 1536; δ_H (300 MHz, DMSO-d_6) 1.33 (18H, s, *tert*-butyl), 1.54-1.64 (8H, m, cyclohexyl), 5.68 (2H, br s,*CH*–NH), 7.09 (2H, br s, CH–*NH*); δc (75 MHz, DMSO-d_6); 26.49, 28.63, 50.42, 53.17, 108.36, 111.86, 114.87, 117.83, 151.47; MS, m/z (%): 458 (M^+, 3), 148 (14), 57 (43), 41 (78), 39 (100), 27 (53), 15 (42); [found C, 62.97; H, 6.60; N, 30.50. $C_{24}H_{30}N_{10}$ requires C, 62.86; H, 6.59; N, 30.54 %].

Table 2, entry 3: $bis(5-(cyclohexylamino)-6-methyl-6,6'-(ethane-1,2-diyl)1,6-dihydropyrazine-2,3-dicarbonitrile)$. (85 %); mp 180–182 °C; IR (KBr) (ν_{max}, cm^{-1}) 3451, 3340 (N–H), 2933, 2855 (C–H), 2214 (C≡N), 1564, 1566; δ_H (300 MHz, DMSO-d_6) 0.95 (6H, s, $2CH_3$), 1.16–1.65 (20H, m, cyclohexyl), 1.8–2.1 (4H, m, $–CH_2CH_2–$), 3.40, 3.64 (2H, m, *CH*–NH), 7.03, 7.3 (2H, br s, CH–*NH*); δc (75. MHz, DMSO-d_6); 25.12, 25.59, 25.69, 31.67, 32.46, 36.46, 40.77, 48.83, 50.24, 50.34, 60.85, 71.34, 108.78, 114.33, 115.71, 118.64, 154.62, 171.49; MS, m/z (%): 512 (M^+, 4), 296 (100), 215 (14), 55 (49), 41 (55), 18 (3); [found C, 65.90; H, 7.18; N, 27.38. $C_{28}H_{36}N_{10}$ requires C, 65.60; H, 7.08; N, 27.32 %].

Table 2, entry 4: $bis(5-(tert-butylamino)-6-methyl-6,6'-(ethane-1,2-diyl)1,6-dihydropyrazine-2,3-dicarbonitrile)$. (95 %); mp 251–253 °C; IR (KBr) (ν_{max}, cm^{-1}) 3363, 3305 (N–H), 2932, 2854 (C–H), 2211(C≡N), 1658, 1626; δ_H (300 MHz, DMSO-d_6) 0.87, 1.66 (6H, ss, $2CH_3$), 1.18, 1.29 (18H, ss, 2 *tert*-butyl), 1.8-2.1 (4H, m, $–CH_2CH_2–$), 6.51 (2H, br s, NH), 6.76 (2H, br s, NH); δc (75 MHz, DMSO-d_6); 22.37, 24.78, 28.61, 28.65, 32.66, 36.51, 51.14, 52.62, 60.69, 71.95 108.76, 113.56, 115.75, 118.75, 153.61, 171.99; MS, m/z (%): 460 (M^+, 5), 296 (85), 214 (55), 54 (35), 41 (100), 18 (15); [found C, 62.81; H, 7.04; N, 30.29. $C_{24}H_{32}N_{10}$: C, 62.59; H, 7.00; N, 30.41 %].

Table 2, entry 5: $bis(5-(tert-butylamino)-6-methyl-6,6'-methylene-1,6-dihydropyrazine-2,3-dicarbonitrile)$. (85 %), mp 282–284 °C; IR (KBr) (ν_{max}, cm^{-1}) 3413, 3324 (N–H), 2976, 2933 (C–H), 2212 (C≡N), 1565, 1542; δ_H (300 MHz, DMSO-d_6) 0.88, 1.65 (6H, ss, $2CH_3$), 1.14, 1.22 (18H, ss, 2*tert*-butyl), 1.81 (2H, s, $–CH_2–$), 6.50 (2H, br s, NH), 6.70 (2H, br s, NH); δc (75 MHz, DMSO-d_6); 22.37, 24.78, 28.61, 32.66, 36.51, 51.14, 52.62, 60.69, 71.95 108.76, 113.56, 115.75, 118.75, 153.61, 171.99; MS, m/z (%): 446 (M^+), [found C, 62.11; H, 6.74; N, 31.39. $C_{23}H_{30}N_{10}$ requires C, 61.86; H, 6.77; N, 31.37 %].

Table 2, entry 6: *5-(cyclohexylamino)-6-benzyl-6-methyl-1,6-dihydropyrazine-2,3-dicarbonitrile*. (98 %); mp 186–188 °C; IR (KBr) (ν_{max}, cm^{-1}) 3354, 3300 (N–H), 2926, 2854 (C–H), 2212 (C≡N), 1564, 1541; δ_H (300 MHz, DMSO-d_6) 1.30 (3H, s, CH_3), 1.58–1.90 (12H, m, CH_2, cyclohexyl), 2.45 (2H, t, CH_2-Ph), 3.70 (1H, m, *CH*–NH), 6.90 (1H, br s, NH), 7.01 (1H, br s, NH), 7.14–7.23 (5H, m, Ph); δc (75 MHz, DMSO-d_6); 23.70, 25.22, 25.71, 29.53, 31.99, 32.08, 49.94, 53.12, 53.20, 109.53, 110.66, 114.83, 118.54, 126.30, 128.60, 128.83, 141.79, 154.76; MS, m/z (%): 347 (M^+, 3), 243 (5), 103 (54), 91 (100), 77 (57), 41 (63), 39 (62) 15 (3); [found C, 72.77; H, 7.16; N, 19.92. $C_{21}H_{25}N_5$ requires C, 72.59; H, 7.25; N, 20.16 %].

Table 2, entry 7: *5-(tert-butylamino)-6-benzyl-6-methyl-1, 6-dihydropyrazine-2,3-dicarbonitrile*). (98 %); mp 150–152 °C; IR (KBr) (ν_{max}, cm^{-1}) 3414, 3349 (N–H), 2960, 2954 (C–H), 2210 (C≡N), 1544, 1495 (C=N); δ_H (300 MHz, DMSO-d_6) 1.26 (3H, s, CH_3), 1.28 (9H, s, *tert*-butyl), 1.84 (2H, t, -$CH_2$$CH_2$-Ph), 2.17 (2H, t-$CH_2$$CH_2$-Ph), 6.30 (1H, s, NH), 6.81 (1H, s, NH) 7.26 (5H, m, Ph); δc (75 MHz, DMSO-d_6); 1.32 (1H, s), 1.34(9H, s), 1.59 (2H, t), 1.66 (2H, t), 6.33 (1H, br s), 7.13 (1H, br s) 7.16-7.27 (5H, s); 23.3, 28.6, 29.4, 52.6, 52.8, 108.9, 110.6, 114.7, 118.5, 126.3, 128.8, 141.9, 154.04; MS, m/z (%): 321 (M^+, 1), 160 (12), 91 (22), 57 (36), 41 (100), 39 (72), 15 (38); [found: C, 71.47; H, 7.24; N, 21.62. $C_{19}H_{23}N_5$ requires C, 71.00; H, 7.21; N, 21.79 %].

Table 2, entry 8:*5-(cyclohexylamino)-6-(4-methoxyphenyl) -6-methyl-1,6-dihydropyrazine-2,3-dicarbonitrile*) (94 %); mp 166–168 °C; IR (KBr) (ν_{max}, cm^{-1}) 3450, 3380 (N–H), 2938, 2848 (C–H), 2210 (C≡N), 1554, 1546 (C=N); δ_H (300 MHz, DMSO-d_6) 1.01-1.89 (10H, m, cyclohexyl), 1.60 (3H, s, CH_3), 3.45 (1H, m, *CH*–NH), 3.75 (3H, s, –OCH_3), 6.58 (1H, br s), 6.9–7.25 (4H, m, ph), 7.31 (1H, br s); δc (75 MHz, DMSO-*d*6); 21.70, 25.22, 28.71, 29.53, 35.99, 49.94, 53.12, 53.20, 55.34, 109.53, 110.66, 114.83, 118.54, 126.30, 128.60, 128.83, 141.79, 164.76; MS, m/z (%): 349 (M^+ 5), 296 (50), 252 (2), 91 (50), 57 (60), 41 (85), 39 (49), 15 (15); [found C, 69.05; H, 6.54; N, 20.13. $C_{20}H_{23}N_5O$ requires C, 68.74; H, 6.63; N, 20.04 %].

Table 2, entry 9: *5-(tert-butylamino)-6-(4-methoxyphenyl) -6-methyl-1,6-dihydropyrazine-2,3-dicarbonitrile*). (85 %); mp 146–148 °C; IR (KBr) (ν_{max}, cm^{-1}) 3440, 3350 (N–H), 2928, 2858 (C–H), 2215 (C≡N), 1564, 1546 (C=N); δ_H (300 MHz, DMSO-d_6) 1.38 (9H, s, *tert*-butyl), 1.63 (3H, s, CH_3), 3.7 (3H, s, –OCH_3), 6.51 (1H, br s), 6.8 (2H, d), 7.13 (2H, d), 7.90 (1H, br s); δc (75 MHz, DMSO-*d*6); 25.6, 28.5, 53.1, 54.8, 54.9, 55.5, 110.22, 111.1, 114.2, 114.6, 111, 126.6, 134.5, 152.5, 159.1; MS, m/z (%): 323 (M^+, 2), 296 (48) 57 (100), 41 (97), 39 (49), 29 (36), 15 (13); [found: C, 66.35; H, 6.56; N, 21.63. $C_{18}H_{21}N_5O$ requires C, 66.85; H, 6.55; N, 21.66 %].

Table 2, entry 10: *5-(tert-butylamino)-6-(4-hydroxyphenyl) -6-methyl-1,6-dihydropyrazine-2,3-dicarbonitrile*). (96 %); mp 187–189 °C; IR (KBr) (ν_{max}, cm^{-1}) 3364, 3351 (N–H), 2954, 2853 (C–H), 2211(C≡N), 1669, 1564 (C=N); δ_H (300 MHz, DMSO-d_6) 1.36 (9H, s, *tert*-butyl), 1.59 (3H, s, CH_3), 6.42 (1H, br s, NH), 6.68–7.01 (4H, d, Ar), 7.82 (1H, br s, NH), 9.46 (1H, s, OH); δc (75 MHz, DMSO-*d*6); 21.5, 24.9, 24.8, 34.4, 48.4, 53.3, 55.8, 104.2, 114.2, 114.4, 128.4, 132.2, 139.5, 158.6, 164.1; MS, m/z (%): 309 (M^+, 5), 296 (35), 215 (16), 56 (50), 41 (55), 39 (15), 18, (5); [found C, 66.26; H, 6.30; N, 22.60. $C_{17}H_{19}N_5O$ requires C, 66.00; H, 6.19; N, 22.64 %].

Table 2, entry 11: *5-(tert-butylamino)-6-cyclohexyl-1,6-dihydropyrazine-2,3-dicarbonitrile*).(98 %);mp 202–204 °C; IR (KBr) (ν_{max}, cm^{-1}) 3405, 3320 (N–H), 2933, 2860 (C–H), 2213 (C≡N), 1563, 1542 (C=N); δ_H (300 MHz, DMSO-d_6) 1.36 (9H, s, *tert*-butyl), 1.4–1.6 (10H, m, cyclohexyl), 6.13 (1H, br s), 6.8 (1H, br s); δc (75 MHz, DMSO-*d*6); 20.4, 24.9, 28.5, 29.6, 51.7, 52.6, 108.6, 111.3, 115.07, 118.27, 153.7; MS, m/z (%): 271 (M^+, 16), 215 (50), 172, (65), 57 (92), 41 (92), 29 (56), 14 (100); [found C, 66.88; H, 7.81; N, 25.77. $C_{15}H_{21}N_5$ requires C, 66.39; H, 7.80; N, 25.81 %].

Table 2, entry 12: *5-(tert-butylamino)-6-N-benzylpiperidin-1,6-dihydropyrazine-2,3-dicarbonitrile*). (45 %); mp 260–262 °C; IR (KBr) (ν_{max}, cm^{-1}) 3410, 3350 (N–H), 2936, 2864 (C–H), 2225, 2219 (C≡N), 1560, 1526 (C=N); δ_H (300 MHz, DMSO-d_6) 1.28 (9H, s, *tert*-butyl), 1.84 (2H, t, CH_2–C) 2.17 (2H, t, *CH_2*–C), 3.43 (2H, s, –N*CH_2*Ph), 2.54 (2H, t, CH_2–N), 3.43 (2H, t, CH_2–N), 6.30 (1H, br s), 6.81 (1H, br s) 7.26 (5H, m, Ph); δc (75 MHz, DMSO-*d*6); 28.4, 29.4, 47.7, 50.16, 52.75, 62.54, 107.9, 111.7, 115.1, 118.1, 127.3, 128.6, 129.3, 138.8, 152.4; MS, m/z (%): 362 (M^+, 1), 91 (88), 57 (67), 41 (100), 39 (60), 15 (18); [found C, 69.66; H, 7.20; N, 23.24 $C_{21}H_{26}N_6$ requires C, 69.58; H, 7.23; N, 23.19 %].

Table 2, entry 13: *5-tert-butylamino)-6-cyclooctyl-1,6-dihydropyrazine-2,3-dicarbonitrile*. (95 %); mp 250–252 °C; IR (KBr) (ν_{max}, cm^{-1}) 3415, 3398 (N–H), 2922, 2854(C–H), 2225, 2210 (C≡N), 1564, 1526 (C=N); δ_H (300 MHz, DMSO-d_6) 1.3 (9H, s, *tert*-butyl), 1.40-1.51 (10H, m, cyclooctyl), 1.82 (4H, t, cyclooctyl), 5.81 (1H, br s, NH), 6.95 (1H, br s, NH); δc (75 MHz, DMSO-*d*6); 21.1, 24.2, 27.8, 28.5, 29.4, 52.8, 54.7, 109.05, 110.9, 114.9, 118.2, 153.8; MS, m/z (%): 299 (M^+ 10), 215 (60), 172 (50), 57 (58), 41 (100), 29 (25), 14 (15); [found C, 68.20; H, 8.38; N, 23.35. $C_{17}H_{25}N_5$ requires C, 68.19; H, 8.42; N, 23.39 %].

Table 2, entry 14: *5-(cyclohexylamino)-6-isobutyl-6-methyl-1,6-dihydropyrazine-2,3-dicarbonitrile*. (94 %); mp 180–182 °C; IR (KBr) (ν_{max}, cm^{-1}) 3351 (N–H), 2933, 2856 (C–H), 2213 (C≡N) 1584, 1544 (C=N); δ_H (300 MHz, DMSO-d_6) 0.83–0.84 (6H, d, $2CH_3$), 1.07–1.21 (3H, m, CH_2–*CH*), 1.32 (3H, s, CH_3), 1.38–1.76 (10H, m, cyclohexyl), 3.67 (1H, m, *CH*–NH), 6.89 (1H, br s, NH), 7.10 (1H, br s, NH); δc (75 MHz, DMSO-*d*6); 24.9, 25.2, 25.24, 25.7, 31.8, 32.1, 49.9, 53.05, 53.12, 109.53, 110.28, 110.38, 114.83, 118.59, 155.1, 155.2; MS, m/z (%): 299 (M^+), [found C, 68.63; H, 8.69; N, 23.25. $C_{17}H_{25}N_5$ requires C, 68.19; H, 8.42; N, 23.39 %].

Table 2, entry 15: *5-(tert-butylamino)-6-isobutyl-6-methyl-1,6-dihydropyrazine-2,3-dicarbonitrile*. (90 %); mp 210–212 °C; IR (KBr) (ν_{max}, cm^{-1}) 3412, 3320 (N–H), 2930, 2844 (C–H), 2225, 2216 (C≡N), 1543, 1551 (C=N); δ_H (300 MHz, DMSO-d_6) 0.84–0.86 (6H, d, $2CH_3$), 1.13–1.17 (2H, d, –CH_2–), 1.3 (9H, s, *tert*-butyl), 1.33 (3H, s, –CH_3), 1.64 (1H, m, –*CH*(CH_3)$_2$), 6.19 (1H, br s, NH), 7.12 (1H, br s, NH); δc (75 MHz, DMSO-*d*6); 23.4, 23.5, 24.4, 25.01, 28.5, 43.8, 52.56, 52.8, 108.9, 110.3, 114.7, 118.5, 154.3;

MS, m/z (%): 273 (M^+, 2), 160 (12), 57 (12), 41 (100), 39 (68), 27 (16), 15 (48); [found C, 65.66; H, 8.42; N, 25.67. $C_{15}H_{23}N_5$requires C, 65.90; H, 8.48; N, 25.62 %].

Table 2, entry 16: *5-(tert-butylamino)-6-ethyl-6-methyl-1,6-dihydropyrazine-2,3-dicarbonitrile*. (98 %); mp 175–177 °C; IR (KBr) (ν_{max}, cm^{-1}) 3394, 3334 (N–H), 2969, 2924
(C–H), 2225 (C≡N), 1549, 1541 (C=N); δ_H (300 MHz, DMSO-d_6) 0.75 (3H, t, CH_3–CH_2), 1.26 (3H, s, CH_3), 1.31 (9H, s, *tert*-butyl), 1.55 (2H, q, CH_2–), 6.17 (1H, br s), 7.1 (1H, br s); δc (75 MHz, DMSO-*d*6); 22.6, 28.6, 28.9, 52.6, 53.02, 53.1, 109.14, 110.52, 114.81, 118.53, 154.07, 154.14; MS, m/z (%): 246 (M^+, 2), 159 (17), 56 (15), 42 (27), 41 (85), 29 (84), 27 (100), 15 (85); [found C, 63.76; H, 7.85; N, 28.70. $C_{13}H_{19}N_5$requires C, 63.65; H, 7.81; N, 28.55 %].

Acknowledgments We are thankful to Bu-Ali Sina University, Center of Excellence in development of environmentally friendly methods for chemical synthesis (CEDEFMCS) for financial support.

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