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Poly(*N*,*N*′-dibromo-*N*-ethyl-benzene-1,3-disulphonamide) and *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulphonamide as novel catalysts for synthesis of quinoxaline derivatives

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Abstract. Poly(*N*,*N*′-dibromo-*N*-ethyl-benzene-1,3-disulphonamide) [PBBS] and *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulphonamide [TBBDA] were used as efficient catalysts for the synthesis of quinoxaline derivatives in excellent yields from 1,2-diamines and 1,2-dicarbonyls under aqueous and solvent-free conditions.

Keywords. Quinoxaline; 1,2-diamines; 1,2-dicarbonyls; PBBS; TBBDA.

1. Introduction

Quinoxaline derivatives are the subject of considerable interest from both academic and industrial perspective. Quinoxaline and their derivatives are important in modern drug research because of their extensive biological activities.[1–4] Quinoxalines play an important role as a basic skeleton for the design of a number of antibiotic, anticancer and antiviral drugs.[5,6] In addition to medicinal applications, quinoxaline derivatives have found applications as dyes,[7] efficient electron luminescent material,[8] organic semiconductors[9] and DNA cleaving agents.[10] Based on the significant applications of quinoxaline compounds in both medicinal and industrial fields, a number of synthetic strategies have been developed for the preparation of substituted quinoxalines. The most common method is the condensation of an aryl-1,2-diamine with a 1,2-dicarbonyl compound in refluxing ethanol or acetic acid.[11] Improved methods have been reported for the synthesis of quinoxaline derivatives including the bi-catalysed oxidative coupling,[12] a solid-phase synthesis,[13] microwave,[14,15] and the use of MnO_2,[16] $POCl_3$,[17] zeolites,[18] iodine,[19] cerium ammonium nitrate,[20] $Ga(OTf)_3$,[21] $CuSO_4.5H_2O$,[22] SA/Me,[23] polyaniline-sulphate salt,[24] silica bonded s-sulphonic acid,[25] montmorillonite K-10,[26] polyethylene glycol,[27] ZrO_2/Ga_2O_3/MCM-41[28] as catalyst or promoter. However, many of these processes suffer from one or other limitations such as drastic reaction conditions, low product yields, tedious work-up procedures, the use of toxic metal salts as catalysts, and relatively expensive reagents.

2. Experimental

2.1 *General procedure for quinoxaline synthesis using TBBDA and PBBS in the presence of solvent*

To a stirred suspension of 1,2-dicarbonyl compound (1 mmol) and 1,2-diamine (1 mmol) in H_2O:EtOH (2:1) (3 mL) was added TBBDA (0.1 g, 0.2 mmol) or PBBS (0.1 g). The resulting mixture was stirred at room temperature for the specified time (table 1). The reaction was monitored by TLC (5:1, *n*-hexane/acetone). After completion of the reaction, CH_2Cl_2 (10 mL) was added and organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the crude product. Recrystallization from 96% ethanol to afford the pure product.

2.2 *General procedure for quinoxaline synthesis using TBBDA and PBBS under solvent-free conditions*

1,2-Dicarbonyl compound (1 mmol), 1,2-diamine (1 mmol), and TBBDA (0.1 g, 0.2 mmol) or PBBS (0.1 g) was placed in a test-tube. The mixture was stirred at 80°C. After completion of the reaction [table 1, monitored by TLC (5:1, *n*-hexane/acetone)],

*For correspondence

Table 1. Synthesis of different quinoxalines using symmetrical aromatic 1,2-diketone.

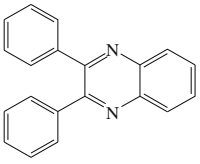
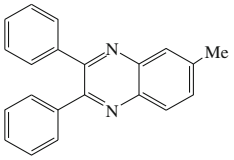
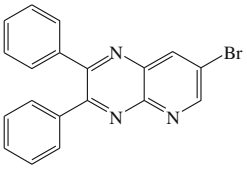
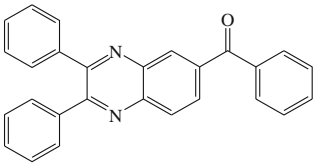
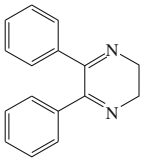
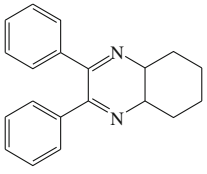
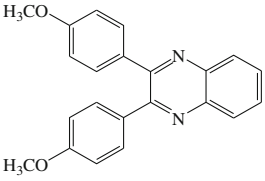
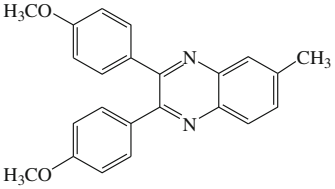
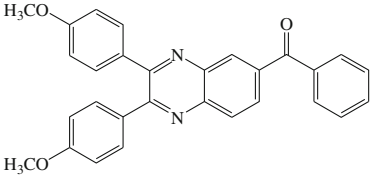
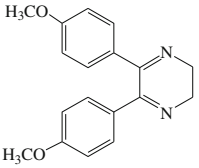
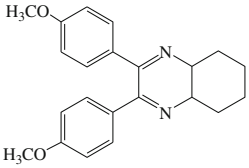
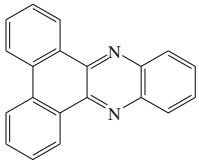
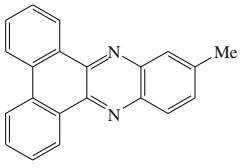
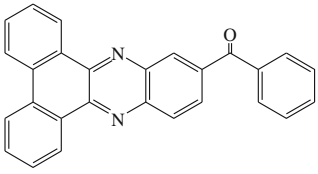
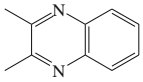
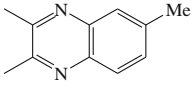
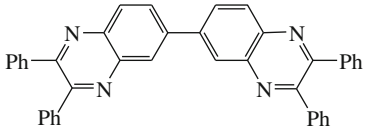
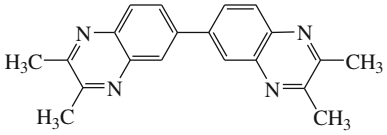
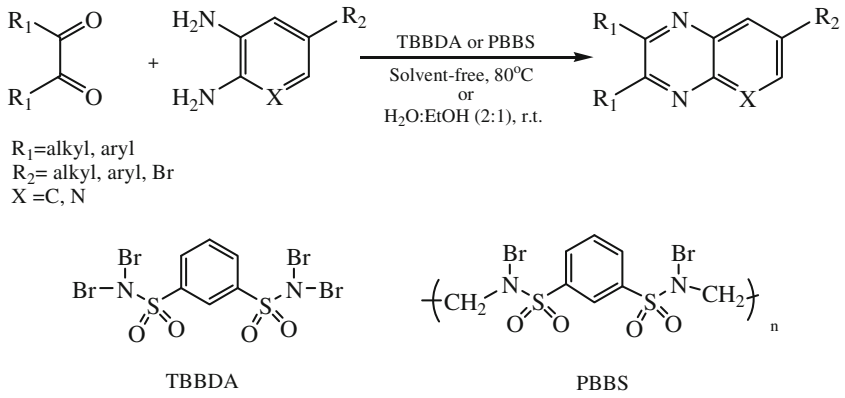
Entry	Product[a]	TBBDA (solvent-free) Yield/time (%/min)	PBBS (solvent-free) Yield/time (%/min)	TBBDA (H2O:EtOH) Yield/time (%/min)	PBBS (H2O:EtOH) Yield/time (%/min)
1		98/3	90/15	95/10	85/30
2		95/5	90/20	95/10	90/35
3		90/25	85/60	80/70	75/120
4		90/25	85/45	85/120	80/180
5		95/5	90/15	95/10	95/20
6		94/8	90/25	95/10	87/30
7		95/5	90/15	95/15	90/35
8		92/8	85/20	90/15	80/35
9		90/20	80/50	70/120	75/180

Table 1. (continued).

Entry	Product[a]	TBBDA (solvent-free) Yield/time (%/min)	PBBS (solvent-free) Yield/time (%/min)	TBBDA (H2O:EtOH) Yield/time (%/min)	PBBS (H2O:EtOH) Yield/time (%/min)
10		95/5	90/10	80/30	80/55
11		96/10	90/20	85/30	75/65
12		95/5	90/15	90/10	85/25
13		97/8	90/20	85/15	85/25
14		90/35	75/90	85/120	70/250
15		95/8	90/25	90/10	85/40
16		97/5	94/20	90/15	80/25
17		85/20	85/45	95/30	90/70
18		95/15	87/60	90/40	80/60

[a]Products were characterized from their physical properties, by comparison with authentic samples, and by spectroscopic methods.

CH_2Cl_2 (10 mL) was added, and catalyst was removed by filteration. The organic phase was washed with H_2O (10 mL) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the crude product. Recrystallization from 96% ethanol to afford the pure product.



Scheme 1. Synthesis of quinoxaline derivatives.

2.2a *Analytical data for* $C_{19}H_{12}BrN_3$ *(entry 3)*: Solid; mp 157–158°C. IR (KBr): 3062, 1658, 1593, 1450 cm^{-1}. ^1H NMR (FT-90 MHz, $CDCl_3$) $\delta = 9.1$ (d, J 2.6 Hz, 1H), 8.6 (d, J 2.4 Hz, 1H), 7.25–7.7 (m, 10H); ^{13}c NMR (FT-90 MHz, $CDCl_3$) δ = 156.17, 155.14, 154.8, 139.4, 137,77, 137.45, 129.50, 129.30, 129.26, 128.12, 124.9; $m/z = 362$.

2.2b *Analytical data for* $C_{18}H_{18}N_2O_2$ *(entry10)*: Solid; mp 113–115°C. IR (KBr): 3057, 2939, 2841, 1664, 1602, 1556,1440, 850 cm^{-1}. ^1H NMR (FT-90 MHz, $CDCl_3$) $\delta = 7.29$ (d, J 8.7 Hz, 4H), 6.79 (d, J 9 Hz, 4H), 3.76 (s, 6H), 3.61 (s, 4H); ^{13}C NMR (FT-500 MHz, $CDCl_3$) $\delta = 161.06$, 159.92, 130.91, 129.93, 113.83, 55.62, 46.07; $m/z = 294$.

2.2c *Analytical data for* $C_{22}H_{24}N_2O_2$ *(entry11)*: Solid; mp 173–175°C. IR (KBr): 2933–3079, 2933, 2831, 1608, 1456–1596, 1336, 800 cm^{-1}. ^1H NMR (FT-90 MHz, $CDCl_3$): δ = 7.33 (d, J 7.8 Hz, 4H), 6.79 (d, J 8.5 Hz, 4H), 3.73 (s, 6H), 2.8 (m, 2H), 2.4 (m, 2H), 1.3–1.9 (m, 6H); ^{13}C NMR (FT-500 MHz, $CDCl_3$) δ = 161.06, 159.40, 130.57, 113.92, 59.71, 55.68, 33.97, 25.8; $m/z = 348$.

2.2d *Analytical data for* $C_{27}H_{16}N_2O$ *(entry14)*: Solid; mp 210–213°C. IR (KBr): 3060, 29 26, 1723, 1654, 1602–1404, 1258, 756 cm^{-1}. ^1H NMR (FT-90 MHz, $CDCl_3$): $\delta = 9.32$ (m, 2H), 8.39–8.8 (m, 4H), 7.4–7.94 (m, 10H; ^{13}C NMR (FT-90 MHz, $CDCl_3$) δ = 181.33, 146.40, 143.57, 142.92, 140.21, 138.4, 136.04, 134.5, 130.47, 129.62, 128.47, 126.2, 124.03; $m/z = 384$.

2.2e *Analytical data for* $C_{20}H_{18}N_4$ *(entry18)*: Solid; mp 238–240°C. IR (KBr): 3050, 2925, 2848, 1656, 1597, 722 cm^{-1}. ^1H NMR (FT-400 MHz, $CDCl_3$): δ = 8.36 (s, 2H), 8.1 (s, 4H), 2.7 (s, 12H); ^{13}C NMR (FT-400 MHz, $CDCl_3$) δ = 154.33, 142.50, 141.07, 142.92, 140.51, 139.4, 138.04, 130.15, 130.47, 20.78; $m/z = 314$.

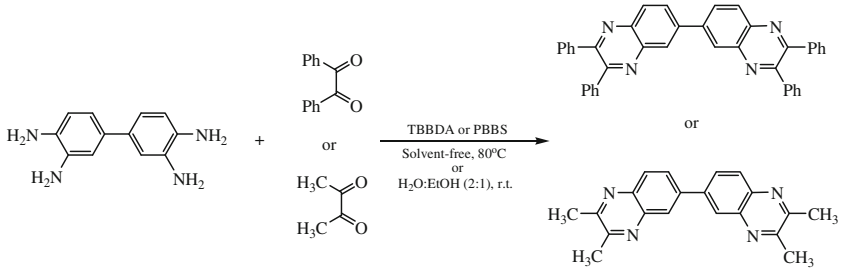
3. Results and discussion

In continuation of our interest in the application of poly(N,N'-dibromo-N-ethyl-benzene-1,3-disulphonamide) [PBBS], N,N,N',N'-tetrabromobenzene-1,3-disulphonamide [TBDDA],[29] in organic synthesis,[30–40] we report here a convenient method for the preparation of quinoxaline derivatives from various 1,2-diamines with 1,2-dicarbonyls in the presence of TBBDA and PBBS under (i) aqueous and (ii) solvent-free conditions (scheme 1).

Under solvent-free conditions, most of the reactions proceeded to afford the corresponding product in less time. In another study, the effect of different solvents upon the reaction was investigated (table 2). The results showed that the examined solvents were not suitable separately. The satisfactory results were obtained when a mixture H_2O and EtOH was used as solvent. The best ratio of H_2O/EtOH (v/v) was found to be 2/1.

Table 2. Screening for optimum reaction conditions.

Entry	Conditions	Time (min)	Yield (%)
1	EtOH	45	90
2	$CHCl_3$	100	65
3	H_2O	40	85
4	CH_3CN	70	97
5	CH_2Cl_2	120	70
6	H_2O/EtOH (2:1)	10	95
7	Solvent-free (80°C)	3	98
8	Solvent-free (r.t)	240	–



Scheme 2. Synthesis of biquinoxalinyl.

Table 3. The recycling of TBBDA in the synthesis of quinoxaline.

Entry	Time (min)	Yield (%)
1	3	98
2	3	95
3	3	92
4	3	88

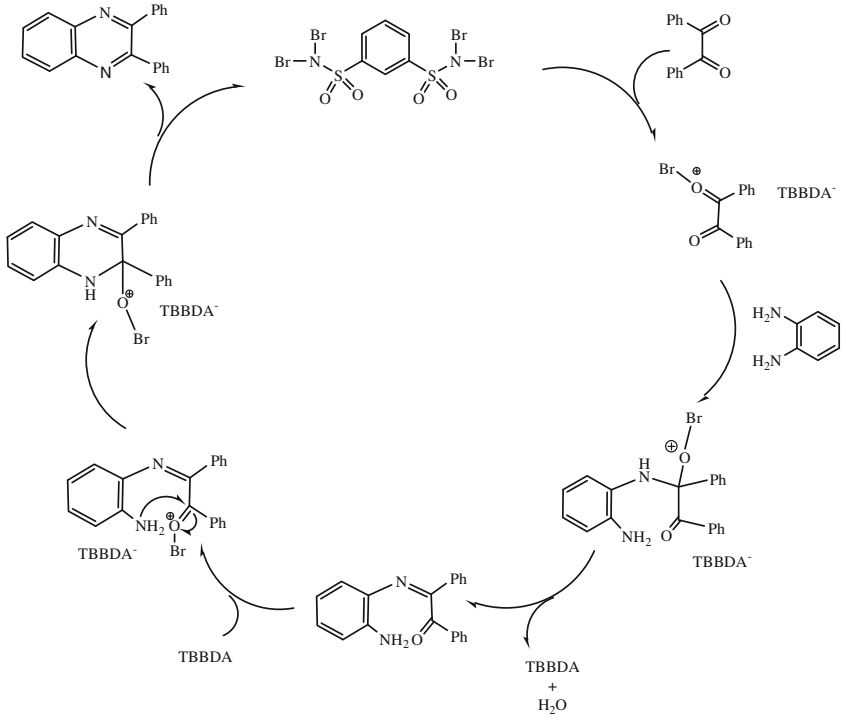
So we chose this solvent system for environmental acceptability.

Substituted quinolines were prepared from various 1,2-diamines with 1,2-dicarbonyls compounds. The results are presented in table 1. In the absence of TBBDA or PBBS, the reaction did not proceed even for period of 10 h.

Poly(*N*, *N*′-dibromo-*N*-ethyl-benzene-1, 3-disulphonamide) [PBBS], *N*, *N*, *N*′, *N*′-tetrabromobenzene-1,3-disulphonamide [TBDDA] are inexpensive and non-hazardous catalyst. They react under heterogeneous conditions, are conveniently handled, and can be removed from the reaction mixture by simple filtration. We also found that TBBDA and PBBS were reusable catalyst runs, the catalytic activities of the reagent were almost the same as those of fresh catalysts.

In conclusion, we have described an efficient method for the synthesis of quinoxaline derivatives utilizing TBBDA and PBBS. This method provides an excellent complement quinoxaline derivatives synthesis and also avoids the use of hazardous acids or bases.

Also, we have synthesized biquinoxalinyl (scheme 2) by the condensation of 3,3′,4,4′-tetramino-1,1′-biphenyl with two equivalents of 1,2-dicarbonyl compounds



Scheme 3. Possible mechanism for the synthesis of quinoxaline derivatives.

under (i) solvent-free at 80°C, and (ii) solvent conditions (H_2O:EtOH at room temperature).

Our experiments also determined that TBBDA is a reusable catalyst and after four runs its catalytic activity is almost the same as that of a fresh catalyst. The summary of this part of the experiment is shown in table 3. The first run, in the presence of TBBDA and under solvent-free conditions, gave 98% yield of quinoxaline. The second run, with TBBDA recovered from the first run, gave 95% of the products. The average chemical yield for four consecutive runs was 93%. The result of all four runs are shown in table 3.

Since TBBDA contains bromine atoms which are bonded to nitrogen atoms, it is possible that this catalyst releases Br^+ *in situ*, which can act as an electrophilic species.[30–40] Therefore, the following mechanism can be suggested for the synthesis of quinoxaline derivatives (scheme 3).

4. Conclusion

In conclusion, we have described an efficient method for the synthesis of quinoxaline derivatives utilizing TBBDA and PBBS. This method provides an excellent complement quinoxaline derivatives synthesis and also avoids the use of hazardous acids or bases.

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