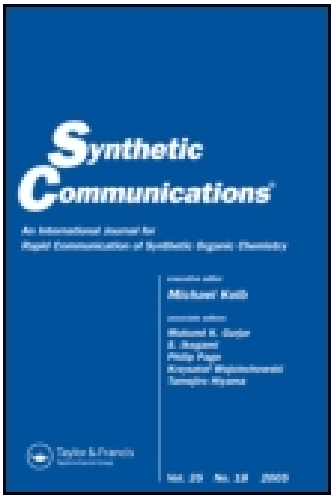

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SYNTHESIS OF BISINDOLYLINDENO[1,2-b]-QUINOXALINE AND BISINDOLYLINDENO[3,4-b]-PYRAZINE WITH POLY(*N,N′*-DIBROMO-*N*-ETHYLNAPHTHYL-2,7-DISULFONAMIDE)

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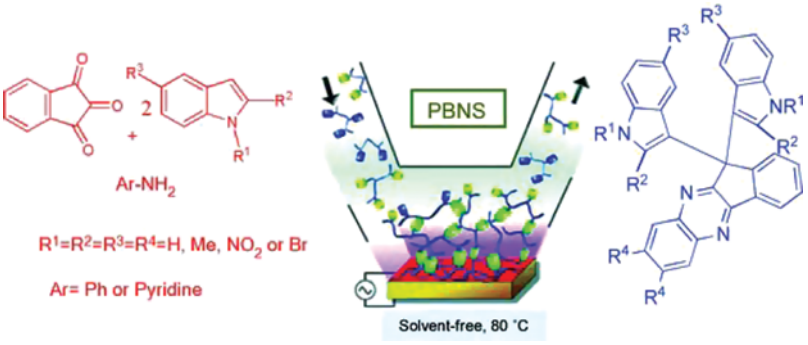
GRAPHICAL ABSTRACT



Abstract *Poly(*N,N′*-dibromo-*N*-ethylnaphthyl-2,7-disulfonamide) (PBNS) as novel reagent was synthesized. Bisindolylindeno[1,2-b]quinoxaline and bisindolylindeno[3,4-b]pyrazine derivatives were synthesized in a simple and efficient method from the three-component condensation reaction of indole, indane-1,2,3-trione, and diamine aromatic compounds by PBNS under solvent-free conditions at 80 °C in good to excellent yields, short reaction times, and a simple procedure for new derivatives.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Diamine aromatic; indane-1,2,3-trione; PBNS; pyrazine derivatives; quinoxaline derivatives

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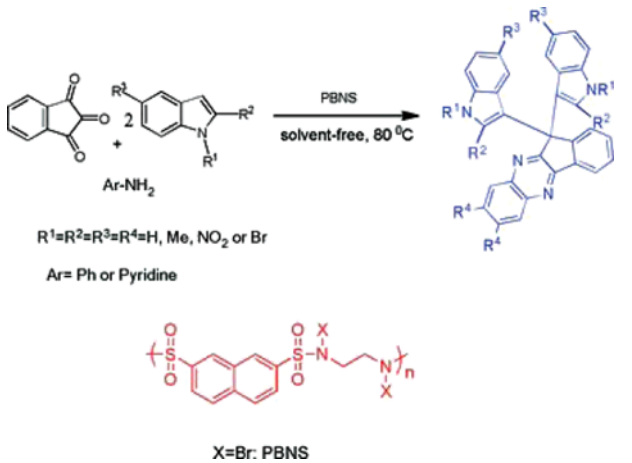
INTRODUCTION

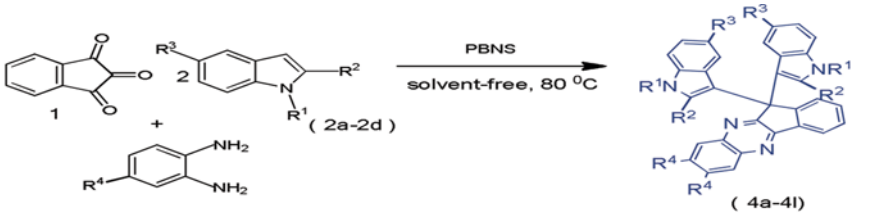
The exploitation of reagents for developing new synthetic methods is an art and a challenging process in organic chemistry. *N*-Halo compounds are versatile reagents that have been employed as potentially reactive intermediates and are widely used in organic synthesis. *N*-Halo reagents are easy to handle with all of the halogen being consumed, not half, as in the case of elemental halogens. Depending on the conditions, a number of highly reactive intermediates can be formed: halogen radicals, halogen cations, halogen anions, *N*-radicals, *N*-cations, *N*-anions, etc. Derivatives pyrazines are well known for their antitumor, antibiotic, and diuretic activities.[1] Quinoxaline derivatives are a very important class of nitrogen-containing compounds and have been widely used in dyes, pharmaceuticals,[2,3] and electrical/photochemical materials.[4–9] Quinoxaline ring moiety constitutes part of the chemical structures of various antibiotics such as echinomycin, levomycin, and actinoleutin[10,11] that are known to inhibit growth of Gram-positive bacteria and are active against various transplantable tumors. A number of synthetic strategies have been developed for the preparation of substituted quinoxalines.[12–14] There is only one report on the synthesis of bisindolylindeno[1,2-b]quinoxaline, that is, using montmorillonite K-10 under microwave irradiation.[15] Herein we disclose our results for the synthesis of quinoxalines and pyrazines derivatives using by poly(*N,N*′-dibromo-*N*-ethylnaphthyl-2,7-disulfonamide) (PBNS) under solvent-free conditions at 80 °C (Scheme 1).

RESULTS AND DISCUSSION

As part of our current studies on the design of new routes for the preparation of biologically active heterocyclic compounds, Herein, we describe a simple and convenient method for the efficient synthesis of new bisindolylindeno[1,2-b]quinoxaline and bisindolylindeno[3,4-b]pyrazine derivatives by the synthesized PBNS (see supplementary data) with short time and good yields (Schemes 2 and 3). A series



Scheme 1. Synthesis of bisindolylindeno[1,2-b]quinoxaline and bisindolylindeno[3,4-b]pyrazine with PBNS. (Figure is provided in color online.)



4a: 1+ 2a (R^1=R^2=R^3=H) + 3a(R^4=H)
4b: 1+ 2a + 3b(R^4=NO_2)
4c: 1+ 2a + 3c(R^4=Me)
4d: 1+ 2b (R^1= R^3=H, R^2=Me) + 3c
4e: 1+ 2c(R^1=Me, R^2=R^3=H) + 3c
4f: 1+ 2d (R^1=R^2=H, R^3=Br) + 3c
4g: 1+ 2d + 3b
4h: 1+3a
4i: 1+3b
4j: 1+3c

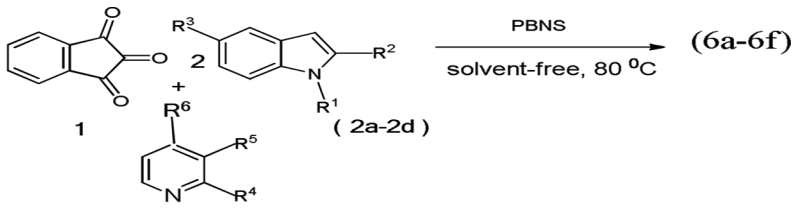
Scheme 2. Synthesis of bisindolylindeno[1,2-b]quinoxaline derivatives. (Figure is provided in color online.)

of substituted indole and diamine aromatics compounds with electron-donating or electron-withdrawing groups attaching indane-1,2,3-trione were investigated. Quinoxaline and pyrazine derivatives with both electron-donating or electron-withdrawing groups gave good yields of the desired products (Table 1).

The advantages to use PBNS as reagent are as follows:

1. The preparation of PBNS is easy and not expensive.
2. It is a versatile reagent and can be separated by a simple method.
3. PBNS is stable for 4 months.
4. The present methodology offers a simple procedure rather than microwave irradiation.[15]

The results of the synthesis **(4a)** using a variety of *N*-halo compounds and acid catalyst as reagents are shown (Table 2). We employed N-bromosuccinimide (NBS), trichloroisocyanuric acid (TCCA), *N*-bromosaccharin (NBSa), silica sulfuric acid (SSA), and $Al(HSO_4)_3$. Comparison of these compounds showed that greater activity and yields could be achieved using PBNS. None of these compunds were



6a: 1+ 2a + 5a(R^4=R^5=NH_2, R^6=H)
6b: 1+ 2a + 5b(R^4=H, R^5=R^6=NH_2)
6c: 1+ 2b + 5a
6d: 1+ 2d + 5b
6e: 1+5b
6f: 1+5a

Scheme 3. Synthesis of bisindolylindeno[1,2-b]pyrazine derivatives.

Table 1. Formation of bisindolylindeno[1,2-b]quinoxaline and bisindolylindeno[3,4-b]pyrazine with PBNS under solvent-free conditions at 80 °C

Entry	Product	Time (min)	Yield (%)
1	4a	6	97
2	4b	5	93
3	4c	6	94
4	4d	8	95
5	4e	6	94
6	4f	7	94
7	4g	6	94
8	4h	6	94
9	4i	6	94
10	4j	7	93
11	6a	5	95
12	6b	6	90
13	6c	8	89
14	6d	8	90
15	6e	6	95
16	6f	7	93

carried out under room temperature. PBNS can be separated by a simple method and gave the best yield of the desired product (Table 2).

When the same reaction was carried out using different amounts of reagent the greatest yield was obtained in the presence of 0.1 mmol%. Lower and higher amounts of the reagent did not improved the yield of the product even after longer reaction time (Table 2).

We carried out the reaction in various solvents to compare the outcome of the reaction in terms of the yield and the rate of the reaction. None of them were carried out under room temperature. Better yields were obtained with using solvent-free conditions at 80 °C (Table 3).

The reagent releases Br^+ in situ, which can act as an electrophilic species. A plausible mechanism for the synthesis of bisindolylindeno[1,2-b]quinoxaline and bisindolylindeno[3,4-b]pyrazine derivatives with PBNS is shown (Scheme 4).[15]

Table 2. Comparison of different compounds employed for preparation of **4a** under solvent-free conditions at 80 °C after 6 min

Entry	*N*-Halo compounds	Catalyst amount (mmol %)	Yield (%)
1	NBS	0.20	50
2	NBSa	0.20	50
3	TCCA	0.10	65
4	SSA	0.10	65
5	$Al(HSO_4)_3$	0.1	55
6	Montmorillonite K-10(μW)	0.5	94[15]
7	PBNS	0.05	82
8	PBNS	0.10	97
9	PBNS	0.15	92
10	PBNS	0.2	88

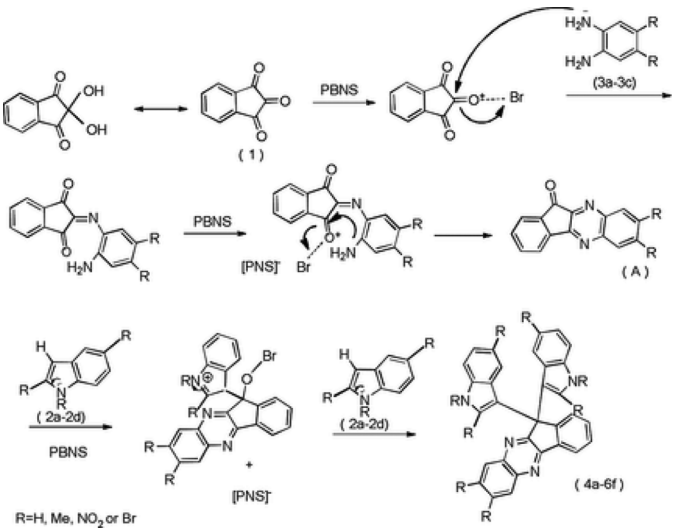
Table 3. Evaluation of solvents and temperature for **4a**

Entry	Conditions	Time (min)	Temperature °C	Yield (%)
1	CH_2Cl_2	60	80	30
2	$CHCl_3$	60	80	25
3	CH_3OH	60	80	15
4	CH_3CN	60	80	10
5	n-Hexane	60	80	25
6	solvent-free	6	50	85
7	solvent-free	6	80	97
8	solvent-free	6	100	93

Ninhydrin is in equilibrium with indane-1,2,3-trione **(1)**. Initially the condensation of ninhydrin **(1)** and 1,2-phenylenediamine **(3a–3c)** took place to produce the intermediate A, which reacted with 2 mol of indoles **(2a–2d, 5a–5b)** via the intermediate A to generate **4a–6f** in good yield.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus and infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR spectrum Gx; KBr pellets were used for solid samples. ^1H and ^{13}C spectra were recorded on Bruker Avance 300- and 500-MHz FT NMR spectrometers with $CDCl_3$ and $(CD_3)_2CO$ as solvent and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on a Shimadzu QP 1100 BX mass spectrometer. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer. Gel permeation chromatography (GPC) was taken on a 1100 Agilent Detector RI. Weight change curve in nitrogen was measured on a TA instrument of TGA Q50 V6.3 with



Scheme 4. Proposed mechanism.

maximum heating rate of 10 °C/min. All commercially available chemicals were obtained from Merck and Fluka companies and used without further purifications.

Typical Procedure for the Preparation of Bisindolylindeno[1,2-b]-quinoxaline and Bisindolylindeno[3,4-b]pyrazine Derivatives

A mixture of 0.178 g (1 mmol) indane-1,2,3-trione, 0.108 g (1 mmol) diamine aromatics, 0.234 g (2 mmol) indole, and 0.1 mmol% PBNS was heated at 80 °C. After completion of the reaction [monitored by thin-layer chromotography (9:1, carbon tetrachloride/acetone)], the mixture was cooled, filtered, and washed with methanol. The product was insoluble in methanol.

6,6-Bis-(1H-indol-3-yl)-6H-indeno[1,2-b]pyrido[3,2-e]pyrazine (6a)

Color yellow, mp = 274–278 °C. FT-IR (KBr)υ (cm^{-1}) = 3396, 1653, 1456, 766. ^{1}H NMR (300 MHz, DMSO-d^6) = 6.71–6.75 (t, J = 1.2 Hz, 2H), 6.88 (s, 2H), 6.97–7.06 (t, J = 2.7 Hz, 2H), 7.33–7.35 (d, J = 0.6 Hz, 2H), 3H), 7.58–7.66 (m, 3H), 7.92 (t, J = 0.6 Hz, 1H), 7.78–7.82 (t, J = 1.2 Hz, 1H), 7.90–7.92 (d, J = 0.3 Hz, 2H), 1H), 8.16–8.18 (d, J = 0.3 Hz, 1H), 8.28–8.30 (d, J = 0.2 Hz, 1H), 10.99 (s, 2H). ^{13}C NMR (300 MHz, DMSO-d^6) = 53.6, 112.19, 116.12, 120.12, 121.29, 121.47, 122.62, 125.20, 126.29, 126.88, 129.15, 129.26, 129.61, 129.76, 130.06, 132.42, 135.77, 137.52, 141.23, 142.09, 153.25, 153.77, 165.98. [Found: C, 80.18; H, 4.23; N, 15.50. $C_{30}H_{19}N_5$ requires C, 80.16; H, 4.26; N, 15.58]. MS: m/z = 405(5), 376(80), 319(80), 232(80), 176(35), 104(40), 90(80), 76(65), 43(70). HRMS (ESI) m/z 449.1900 ($M + H^+$) calcd. for $C_{16}H_{10}N_2O + H^+$ 449.1900.

11H-Indeno[1,2-b]quinoxaline-11-one (4H)[16]

Color yellow, mp = 218–220 °C. FT-IR (KBr)υ (cm^{-1}) = 1730, 1642, 1610, 1475, 741. ^{1}H NMR (300 MHz, DMSO-d^6) = 7.86 (m, 4H, Ar), 8.11 (m,4H, Ar). ^{13}C NMR (300 MHz, DMSO-d^6) = 126.51, 127.00, 128.91, 129.92, 130.22, 130.75, 133.15, 134.05, 134.51, 145.23, 146.11, 147.43, 147.51, 158.00, 185.00. [Found: C, 77.51; H, 3.43; N, 12.10. $C_{15}H_8N_2O$ requires C, 77.58; H, 3.47; N, 12.06; O, 6.89]. MS: m/z = 231.0000 (M^+).

SUPPORTING INFORMATION

Full experimental detail, ^{1}H and ^{13}C NMR, mass spectra, GPC, and TGA can be found via the Supplementary Content section of this article's Web page.

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