-Journal of Applied Chemical Research, 10, 2, 69-84 (2016)

Journal of Applied Chemical Research
www.jacr.kiau.ac.ir

Application of Poly(*N, N′*- dibromo-*N*-ethyl-naphthyl-2, 7-disulfonamide) for the Regioselective Synthesis of New 3-Sulfenyl Indole Derivatives

Mahdieh Chegeni[1*], Ardeshir Khazaei [2], Maryam Kiani Borazjani[3], Shahnaz Saednia[4]

[1]*Department of Chemistry, Ayatollah ozma Boroujerdi University, Boroujerd, Iran*

[2]*Faculty of Chemistry, Bu-Ali Sina University,Hamedan, Iran*

[3]*Department of Chemistry, Faculty of Science, Payame Noor University (PNU), Tehran, Iran*

[4]*Young Researchers & Elites Club, Toyserkan Branch, Islamic Azad University, Toyserkan, Iran*

(Received 22 Jan. 2016; Final version received 20 Mar. 2016)

Abstract

Electron-rich aza-aromatic compounds such as indoles is structures of particular interest and importancein organic chemistry. A useful procedure for the preparation of new 3-sulfenyl indole derivatives using S-alkyl or S-arylthiophthalimides as sulfenylating agents and poly(*N, N′*-dibromo-*N*-ethyl-naphthyl-2,7-disulfonamide) as novel catalyst is described. The method represents an efficient preparation ofsulfenyl aza-aromatics, which are useful intermediates forimportant organic transformations, due to the great importanceof functionalized indoles among natural compoundsand pharmaceutical products.3-Arylthioindole apply as a block of compounds for the treatment of diseases. The direct 3-arylthiolation of 2-substituted indoles using poly(*N, N′*-dibromo-*N*-ethyl-naphthyl-2,7-disulfonamide) in CH_2Cl_2 with a wide variety of indole deraivatives has been accomplished.This method is effective even with 2-unsubstituted indoles.Simple methodology, easy workup procedure, regioselectivity and reusability of the catalyst are some advantages of this work.The reaction occurred under mild conditions,and the products were obtained in goodyields. The catalyst was recovered after completion of the reaction and re-used with minimum loss of activity over five cycles.

Keywords**:** *Regioselectivity, Sulfenylation, Indole, Poly(N,N′-dibromo-N-ethyl-naphthyl-2,7-disulfonamide), Thiophthalimide.*

Introduction

Indole compounds are present in structure drugs for treatment of diseases [1].3-Arylthioindoles are very useful as COX-2 inhibitors in medicinal chemistry [2].These motifs are very common in various drugs for the treatment of HIV,

***Corresponding author:** Dr. Mahdieh Chegeni, Department of Chemistry, Ayatollah ozma Boroujerdi University, Boroujerd, Iran. E-mail address: mahdiehchegeni@gmail.com, Tel.: +986642668320; fax: +986642668223.*

obesity, cancer, heart diseases and allergies[3]. Such compounds are generally prepared by means of electrophilic aromatic sulfenylation. The direct 3-arylthiolation of indoles has beenreported using various sulfenylating agents such asdisulfides, sulfenyl halides, quinone mono-O, *S*-acetalsand *N*-thioarylphthalimides [4–5]. However, most of these methods are often impractical due to the instability, scarcity and incompatibility of the reagents and the formation of bis-sulfides and chlorinated by-products. Sulfenylationsof indoles with thiols activated in situ by *N*-chlorosuccinimide, phenyliodine(III) bistrifluoroacetate and transition metal catalysts have been reported under mild conditions[1,6]. Some of these methods are only useful or sulfenylation of 2-carboxyindoles.

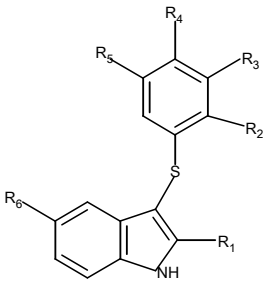
3-Arylthioindole is one of indole derivatives that apply as a block of compounds for the treatment of HIV; AIDS and obesity diseases [7]. 3-thioindole compounds are effective as inhibitors of tublin assembly (Figure 1) [8]. 3-Thioindole derivatives arealso often used as synthetic intermediates in the preparationof heterocyclic compounds of higher complexitywhich is known to have potent anti-HIV properties[9]. In particular, 3-sulfenyl indole is present as an inhibitor of 5-lipoxygenase [10],and can be prevented from growth of cancer cells [3].

It is necessary to develop a new procedure for the preparation of 3-thioindole. The electrophilic substituted of indole derivative is an important reaction in organic synthesis, due to they can be formed polymer [11-12]. The sulfur-sulfur and sulfur-nitrogen bonds have been prepared by using *N*-thiophthalimides [13-14]. Sulfenylation of indoles was obtained by using phenyliodine(III) bistrifluoroacetate, transition metal [15-16], Select fluor [17] and $CeCl_3$ [18-20]. Some of these methods are done by long reaction time, expensive metals, indirect and multistep reaction (For example by Pd/Cu) [21], and they need to microwave irradiation, high temperature [17,22]. Amounts of metal waste can be produced with methods that based on metals [15-16, 18-20]. This procedure suffers from several limitations due to the high reactivity, low stability, and difficulties in storing and handling of many sulfenyl halides.

Considering the synthetic utility of 3-thioindoles, methods to insert sulfide moieties into polyfunctionalized aza-aromatic molecules [9] are important, and the development of new procedures that can also be used for this purpose would be desirable. Therefore, *N*-halo reagents proved to be useful as catalysts for diverse organic reactions. A range of *N*-halo compounds can be viewed as a source of reactive intermediates [23]. Depending on the conditions, a number of highly reactive intermediates can be formed including halogen radicals, halogen cations, halogen anions, *N*-radicals, *N*-cations, *N*-anions, etc.

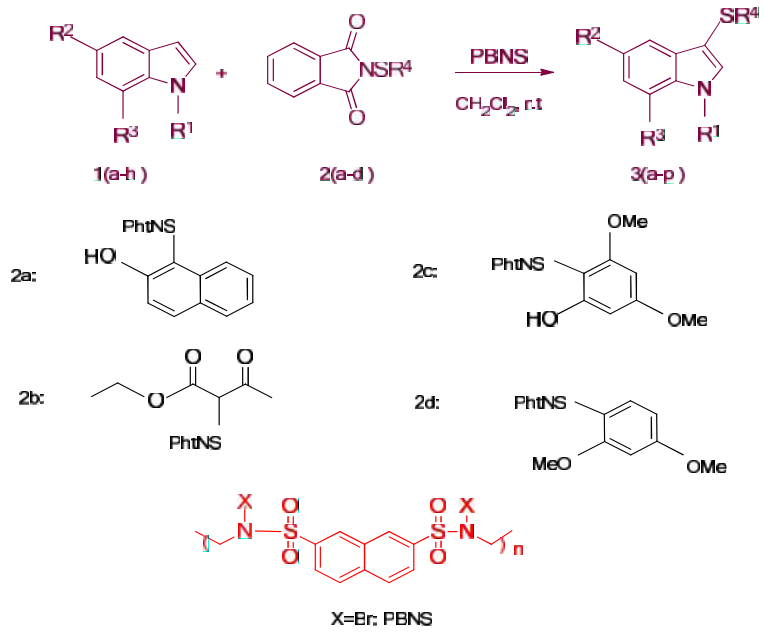
This context is first report by using PBNS:

Poly (*N,N′*-dibromo-*N*-ethyl-naphthyl-2,7-disulfonamide) [24] as a N-halo catalyst to produce new 3-sulfenyl indole derivatives. Compared to other methods, PBNS has advantages of stability for a long time, versatile catalyst with easy recovery, cheap preparation, no excessive catalyst loading, faster, simple and one pot reaction. We report the results of a study on the potential of different substituted S-aryl- or S-alkylthiophthalimides as sulfur-transfer reagents and Poly (*N, N′*-dibromo-*N*-ethyl-naphthyl-2,7-disulfonamide) as catalyst, direct reaction and new derivatives unlike the method reported (Scheme 1) [16-18].



R_1=ester/R_2-R_6:H, Cl, OMe

Figure 1. 3-Arylthioindole.



3a: 1a(R^1=R^2=R^3=H) + 2a
3b: 1a + 2b
3c: 1a + 2c
3d: 1a + 2d
3e: 1b(R^1=R^3=H, R^2=Br) + 2a
3f: 1b + 2c
3g: 1c(R^1=R^3=H, R^2=OMe) + 2d
3h: 1d(R^1=R^2=H, R^3=Et) + 2a
3i: 1d + 2c
3j: 1e((R^1=R^3=H, R^2=Me) + 2a
3k: 1e + 2b
3l: 1e + 2d
3m: 1f(R^1=R^3=H, R^2=NO_2) + 2b
3n: 1g(R^1=Me, R^2=R^3=H) + 2c
3o: 1h(R^1=R^3=H, R^2=CN) + 2c
3p: 1h + 2d

Scheme1.Synthesis of new 3-sulfenyl indole derivatives by PBNS.

Experimental

All commercially available chemicals were obtained from Merck and Fluka companies and used without further purifications. Melting points were measured on an Electrothermal 9100 apparatus and IR spectra were recorded on Perkin Elmer FT-IR spectrum Gx, KBr pellets were used for solid samples. ^{1}H, ^{13}CNMR spectra were recorded at Bruker Avance 300 and 500 MHz FT NMR spectrometers with $CDCl_3$ and $(CD_3)_2SO$ as solvent and 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 by 1100 Agilent Detector RI. The weight change curve in nitrogen was measured on a TA instrument of TGA Q50 V6.3 with maximum heating rate of 10°C/min.

Preparation of poly (N, N'-dibromo-N-ethyl-naphthyl-2,7-disulfonamide)

Poly (*N*-ethyl-naphthyl-2,7-disulfonamide) (0.003 mol) was dissolved in a solution of NaOH (3 mol L^{-1}) at room temperature then bromine (0.0584 mol) was added to the solution with vigorous stirring (at –10 ºC) and finally immediately precipitate was formed. The product was collected on a buchner funnel and it was washed with 30 ml distilled cold water. After that it was dried in a vacuum desiccator at room temperature for 5 h. Yellow Solid (90%) consists of mp: 225-235 °C, FT-IR (KBr) $\upsilon(cm^{-1})$= 3227, 1622, 1324, 1154. ^{1}H-NMR (300MHz, DMSO-d_6): 2.517-2.878 (t, 4H, CH_2), 7.046-8.746 (m, 6H, Ar). ^{13}C-NMR (300MHz, DMSO-d_6): 39.95, 40.57, 123.00, 125.24, 126.88, 127.69, 128.97, 130.01, 135.50, 135.75, 139.56. C 37.80, H 2.64, Br 18.60, N 7.35, S 16.82 %. Gel permeation chromatography (GPC) determined the number average molecular weight (Mn: 40291), the weight average molecular weight (Mw: 108107), the size average molecular weight (Mz: 264624) and polydispersity (PDI: 2.683176).

Typical procedure for the preparation of 3-sulfenyl indoles derivatives

To a stirred solution of indole (1 mmol), S-alkyl or S-arylthiophthalimides (1 mmol) in CH_2Cl_2 (10 mL) was added PBNS (0.01 mmol% in 10 mL CH_2Cl_2) at room temperature over 5 min .The reaction was monitored by TLC (9:1, carbon tetrachloride/acetone). After completion of the reaction, the catalyst was filtered and the organic phase was washed first with Na_2CO_3 solution (10 mL, 5%), then H_2O (10 mL) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the product. The pure product was obtained by using plate chromatography on silica gel with n-hexane–EtOAc (10:2) as eluent.

1-(1H-Indol-3-ylthio)naphthalen-2-ol (3a) [18]

Yield: 0.26 g (95%, 95×10^{-5} mol); brown oil, FT-IR (neat) υ(cm^{-1}) = 3328, 3010, 1550, 1430. ^{1}H-NMR (300MHz, DMSO-d_6) = 6.889 (t, *J*=3.3 Hz, 1H, OH), 7.046 (d, *J*=3.3 Hz, 1H), 7.338 (d, *J*=8.4 Hz, 2H, Ar-H), 7.620-7.662 (m, 2H, Ar-H), 7.699-7.717 (m, 2H, Ar-H), 7.820 (d, *J*=1.6 Hz, 2H, Ar-H), 7.909-7.29 (m, 2H, Ar-H), 8.306 (s, 1H, NH). ^{13}C-NMR (300MHz, DMSO-d_6) = 112.12, 116.17, 118.73, 121.24, 121.39, 122.47, 125.07, 128.22, 128.27, 128.82, 129.06, 129.22, 131.58, 132.22, 135.86, 137.44, 139.58 (Ar-C), 153.67 (C-OH). HRMS (ESI) *m/z* :calcd. for $C_{18}H_{14}NOS(M+H^+)$ 292.07; found 292.07.

Ethyl 2-(1H-Indol-3-ylthio)-3-oxobutanoate (3b) [18]

Yield: 0.23 g (85%, 85×10^{-5} mol); brown oil, FT-IR (neat)υ(cm^{-1}) = 3332, 2500, 1760, 1420. ^{1}H-NMR (300MHz, DMSO-d_6, in equilibrium with the enol form) = 1.993 (d, *J*=7.2 Hz, 3H, CH_3), 2.517 (t, *J*=7.2 Hz, 3H, CH_3), 2.521 (s, 3H, CH_3), 3.326 (d, *J*=4.2 Hz, 2H, CH_2), 3.350 (d, *J*=4.2 Hz, 2H, CH_2), 3.360 (s, 2H, CH), 7.191 (m, 2H, Ar-H), 7.231 (m, 2H, Ar-H), 7.506 (s, 2H), 7.680 (m, 4H, Ar-H), 7.814 (m, 3H, Ar-H), 8.207 (s, 1H, NH), 8.226 (s, 1H, NH). ^{13}C-NMR (300MHz, DMSO-d_6) = 14.20 (CH_3), 21.51 (CH_3), 39.92 (CH_2), 40.20, 118.58, 127.52, 128.19, 131.67, 134.73, 135.33, 135.40 (Ar-C), 165.96 (CO_2), 218.56 (=C-OH).HRMS (ESI) *m/z* :calcd. for $C_{14}H_{16}NO_3S(M+H^+)$ 278.08; found 278.08.

3,5-Dimethoxy-2-(1H-indol-3-ylthio)phenol (3c)

Yield: 0.26 g (85%, 85×10^{-5} mol); yellow oil, FT-IR (neat, cm^{-1}) = 3213, 2513, 1431, 1249. ^{1}H-NMR (300MHz, DMSO-d_6) = 2.567(s, 3H, OCH_3), 3.350 (s, 3H, OCH_3), 6.917 (d, *J*=4.9 Hz, 1H, OH), 7.191-7.231 (m, 2H, Ar-H), 7.560-7.563 (m, 2H, Ar-H), 7.524-7.814 (d, *J*=3.3 Hz, 2H, Ar-H), 8.036 (dd, *J*=2.3 Hz, *J'* 8.4 Hz, 1H, Ar-H), 8.226 (s, 1H, NH). ^{13}C-NMR (300MHz, DMSO-d_6)= 111.63 (OCH_3), 112.52 (OCH_3), 114.44, 114.87, 123.03, 123.61, 123.83, 124.22, 125.30, 126.89, 127.83, 129.89, 130.97, 139.91 (Ar-C), 145.28, 153.10 (C-OH).HRMS (ESI) *m/z* :calcd. for $C_{16}H_{16}NO_4S$ $(M+H^+)$318.08 found 318.07.

3-(2,4-dimethoxyphenylthio)-1H-indole (3d)

Yield: 0.23 g (82%, 82×10^{-5} mol). brown oil, FT-IR (neat, cm^{-1})= 3400, 1602, 1350. ^{1}H-NMR (300MHz, DMSO-d_6) = 3.140 (d, *J*=2.1 Hz, 3H, OCH_3), 3.357 (d, 3H, OCH_3), 6.714 (m, 2H, Ar-H), 6.815 (d, *J*=2.2 Hz, 2H, Ar-H), 6.922 (d, *J*=4.2 Hz, 1H, Ar-H), 6.974 (m, 2H, Ar-H), 7.001(s, 1H, Ar-H), 7.566 (d, *J*=2.2 Hz, 1H, Ar-H), 8.240 (s, 1H, NH). ^{13}C-NMR (300MHz, DMSO-d_6)= 53.44 (OCH_3), 59.49 (OCH_3), 111.33, 112.34, 113,51, 116.62, 118.62, 121.32, 121.66, 122.28, 124.75, 131.53, 132.48, 135.84, 152.88, 153.66 (Ar-

C). HRMS (ESI) *m/z* :calcd. for $C_{16}H_{16}NO_2S$ ($M+H^+$)286.09; found 286.09.

1-(5-Bromo-1H-Indol-3-ylthio)naphthalen-2-ol (3e)

Yield: 0.29 g (81%, 81×10^{-5} mol); yellow solid, mp: 120-124°C. FT-IR (KBr, cm^{-1}) = 3315, 3050, 1612, 1420. ^{1}H-NMR (300MHz, DMSO-d_6) = 6.420 (t, *J*=8.8Hz,1H, OH), 7.132-7.326 (m, 2H, Ar-H), 7.832-7.862 (m, 5H, Ar-H), 8.256-8.276 (dd, *J*=2.31Hz, 1H, Ar-H), 8.339-8.370 (s, 1H, NH). ^{13}C NMR (300MHz, DMSO-d_6)= 110.95, 111.22, 112.12, 118.56, 119.92, 120.01, 120.25, 122.30, 127.52, 128.19, 128.79, , 129.33, 131.67, 132.07, 132.22, 134.73, 135.40 (Ar-C), 165.96 (C-OH). HRMS (ESI) *m/z* :calcd. for $C_{18}H_{13}BrNOS$ ($M+H^+$)369.99; found 369.98.

3,5-Dimethoxy-2-(5-Bromo-1H-indol-3-ylthio) phenol (3f)

Yield: 0.30 g (77%, 77×10^{-5} mol); white solid, mp: 140-143°C. FT-IR (KBr, cm^{-1}) =3430, 1626, 1458, 795. ^{1}H-NMR (300MHz, DMSO-d_6) = 3.333 (s, 3H, OCH_3), 4.990 (s, 3H, OCH_3), 6.046 (d, *J*=4.2 Hz, 1H), 7.338-7.359 (m, 1H, Ar-H), 7.584-7.717 (m, 2H, Ar-H), 7.735-7.799 (m, 2H, Ar-H), 8.169 (d, *J*=2.6 Hz, 1H, Ar-H), 8.306 (s, 1H, NH). ^{13}C-NMR (300MHz, DMSO-d_6)= 79.79, 116.62, 118.60, 121.32, 121.66, 124.75, 126.52, 128.28, 129.04, 129.79, 131.53, 135.84, 139.25, 141.52, 152.88 (Ar-C), 165.56 (C-OH). HRMS (ESI) m/z :calcd. for $C_{16}H_{15}BrNO_3S$ ($M+H^+$)379.99; found 379.99.

5-Methoxy-3-(2,4-Dimethoxyphenylthio)-1H-indole (3g)

Yield: 0.25 g (80%, 80×10-5 mol); yellow oil, FT-IR (neat, cm^{-1}) =3437, 1731, 1586, 942. ^{1}H-NMR (300MHz, DMSO-d_6) = 2.480 (s, 3H), 3.140 (s, 3H), 3.357 (s, 3H), 6.66-6.714 (d, *J*=2.1 Hz, 1H), 6.947 (d, *J*=2.14 Hz, 2H), 7.499-7.589 (m, 2H), 7.771 (s, 1H), 7.928 (d, *J*=3 Hz, 1H), 8.240 (s, 1H). ^{13}C-NMR (300 MHz, DMSO-d_6)= 50.833, 64.168, 77.008, 77.214, 117.165, 121.551, 123.716, 127.741, 128.267, 128.998, 128.665, 129.666, 133.929, 138.622, 151.809, 154.678, 155.989. HRMS (ESI) m/z :calcd. for $C_{17}H_{18}NO_3S$ ($M+H^+$)316.10; found 316.10.

1-(7-Ethyl-1H-Indol-3-ylthio)naphthalen-2-ol (3h)

Yield: 0.28 g (84%, 84×10^{-5} mol); yellow oil, FT-IR (neat, cm^{-1}) = 3402, 3051, 1590, 1340, 782. ^{1}H-NMR (300MHz, $CDCl_3$) =1.157 (t, 3H, CH_3), 2.270 (q, 2H, CH_2), 5.738(t, *J*=8.1 Hz, 1H, OH), 7.024 (t, *J*=8.1 Hz, 3H, Ar-H), 7.270-7.274 (m, 2H, Ar-H), 7.812-7.853 (m, 2H, Ar-H), 8.239-8.262 (m, 2H, Ar-H), 8.269 (s, 1H, NH). ^{13}C-NMR (300MHz, $CDCl_3$)= 16.241 (CH_3), 29.472 (CH2), 116.978, 125.566, 127.769, 128.063, 128.870, 128.373, 129.518, 129.530, 129.802, 129.118, 129.239,

133.682, 134.629, 141.805, 152.332, 155.012 (Ar-C), 156.634 (COH). HRMS (ESI) m/z :calcd. for $C_{20}H_{18}NOS$ ($M+H^+$) 320.11; found 320.11.

3,5-Dimethoxy-2-(7-Ethyl-1H-indol-3-ylthio) phenol (3i)

Yield: 0.26 g (81%, 81×10^{-5} mol); yellow oil, FT-IR (neat, cm^{-1}) = 3402, 1590, 1261, 782. ^{1}H-NMR (300MHz, DMSO-d_6) (ppm) = 1.157 (t, 2H, CH_3), 2.285 (q, 2H, CH_2), 3.153 (s, 3H, OCH_3), 3.174(s, 3H, OCH_3), 5.738 (dd, *J*=1.7 Hz, 1H, OH), 7.024 (d, *J*=2.14 Hz, 2H, Ar-H), 7.028(d, *J*=8.55 Hz, 2H, Ar-H), 7.274 (d, *J*=1.8 Hz, 1H, Ar-H), 7.812-7.853 (m, 2H, Ar-H), 8.269 (s, 1H, NH). ^{13}C-NMR (300MHz, DMSO-d_6) = 18.618, 34.664, 106.599, 118.618, 127.026, 127.128, 127.742, 127.975, 128.695, 128.717, 128.815, 128.991, 129.106, 134.509, 133.522, 136.394, 150.859 (Ar-C), 154.299 (COH). HRMS (ESI) *m/z* :calcd. for $C_{18}H_{20}NO_3S$ ($M+H^+$)298.12; found 298.12.

Ethyl 2-(5-Methyl-1H-Indol-3-ylthio)-3-oxobutanoate (3k)

Yield: 0.24 g (85%, 85×10^{-5} mol); yellow oil, FT-IR (neat, cm^{-1}) = 3427, 2498, 1764, 731. ^{1}H-NMR (300MHz, $CDCl_3$, in equilibrium with the enol form) = 1.129 (t, *J*=4.8 Hz, 3H, CH_3), 1.205(t, J=4.8 Hz, 3H, CH_3), 2.356 (s, 3H, CH_3), 2.389 (s, 3H, CH_3), 2.450 (q, 2H, CH_2), 3.153 (q, 2H, CH_2), 3.323 (s, 2H, CH), 5.706 (d, *J*=6.8 Hz, 1H, Ar-H), 7.350 (m, 2H, Ar-H), 7.861 (s, 1H, Ar-H), 7.891-7.903 (m, 4H, Ar-H), 7.931 (m, 3H, Ar-H), 8.362 (s, 1H, NH), 8.392 (s, 1H, NH). ^{13}C-NMR (300MHz, $CDCl_3$)= 16.170 (CH_3), 18.173 (CH_3), 25.070 (CH_2), 40.090 (CH_2), 53.13, 112.12, 116.170, 118.731, 121.242, 121.393, 122.470, 120.061, 131.580, 132.221 (Ar-C), 153.571(CO_2), 202.12 (=C-OH). HRMS (ESI) *m/z* :calcd. for $C_{15}H_{18}NO_3S$ ($M+H^+$)292.10; found 292.10.

5-Methyl-3-(2, 4-Dimethoxyphenylthio)-1H-indole (3l)

Yield: 0.25 g (84%, 84×10^{-5} mol); brown oil, FT-IR (neat, cm^{-1}) = 3404, 2900, 1508, 784. ^{1}H-NMR (300MHz, $CDCl_3$) = 1.299 (s, 3H, CH_3), 3.394 (s, 3H, OCH_3), 3.458 (s, 3H OCH_3), 6.420 (d, *J*=2.14 Hz, 1H, Ar-H), 7.132 (d, *J*=7.8, 1H , Ar-H), 7.276 (d, 2H, Ar-H), 7.299 (d, 2H, Ar-H), 7.832-7.862 (m, 2H, Ar-H), 8.370 (s, 1H, NH). ^{13}C-NMR (300MHz, DMSO-d_6)= 29.742 (CH_3), 51.241 (OCH_3), 77.570 (OCH_3), 93.637, 99.434, 116.978, 125.988, 127.768, 128.063, 128.373, 128.530, 128.802, 128.870, 129.118, 129.239, 133.682, 134.629 (Ar-C). HRMS (ESI) *m/z* :calcd. for $C_{17}H_{18}NO_2S$ ($M+H^+$)300.10; found 300.10.

Ethyl 2-(5-nitro-1H-Indol-3-ylthio)-3-oxobutanoate (3m)

Yield: 0.24 g (79%, 79×10^{-5} mol); yellow oil, FT-IR (neat, cm^{-1}) = 3392, 1760, 1400, 1321; ^{1}H-NMR (300MHz, DMSO-d_6) =1.993 (t, *J*=6.4 Hz, 3H, CH_3), 2.517 (t, *J*=6.4 Hz, 3H,

CH_3), 2.521 (s, 3H, CH_3), 3.326 (dd, *J*=6.8 Hz, 2H, CH_2), 3.350 (dd, *J*=6.8 Hz, 2H, CH_2), 7.191 (m, 4H, Ar-H), 7.506-7.587 (s, 1H, Ar-H), 7.710-7.952 (m, 4H, Ar-H), 7. 680 (m, 3H, Ar-H), 8.036 (s, 1H, NH), 8.226 (s, 1H, NH). ^{13}C-NMR (300MHz, DMSO-d_6)= 39.66 (CH_3), 39.94 (CH_3) , 40.21 (CH_2), 53.45 (CH2), 112.12, 116.17, 118,73, 121.24, 125.07, 132.22, 135.86, 137.44, 142.07, 153.13 (Ar-C), 153,67 (CO_2), 208.73 (=C-OH). HRMS (ESI) m/z :calcd. for $C_{14}H_{15}N_2O_5S$ ($M+H^+$)323.07; found 323.06.

3,5-Dimethoxy-2-(1-Methyl-1H-indol-3-ylthio) phenol (3n)

Yield: 0.27 g (86%, 86×10^{-5} mol); yellow solid, mp : 140-143 °C. FT-IR (KBr, cm^{-1}) = 3210, 1610, 1400. ^{1}H-NMR (300MHz, DMSO-d_6) = 2.567 (s, 3H, CH_3), 3.350 (s, 3H, OCH_3), 3.793 (s, 3H, OCH_3), 6.917 (d, *J*=3.40 Hz, 1H, OH), 7.191-7.231 (m, 1H, Ar-H), 7.506-7.587 (m, 2H, Ar-H), 7.710 (dd, *J*=2.40 Hz, 2H, Ar-H), 8.226 (s, 1H, NH). ^{13}C-NMR (300MHz, DMSO-d_6)= 34.87 (CH_3),79.71, 111.83, 112.58, 114.44, 114.87, 123.03, 123.61, 125.30, 129.89, 134.20, 134.87, 139.91, 145.28, 147.20, 153.10 (Ar-C). HRMS (ESI) *m/z* :calcd. for $C_{17}H_{18}NO_3S$ ($M+H^+$)316.10; found 316.10.

3,5-Dimethoxy-2-(5-cyano-1H-indole-3-ylthio) phenol (3o)

Yield: 0.25 g (83%, 83×10^{-5} mol); yellow solid, mp:151-153 °C. FT-IR (KBr, cm^{-1}) = 3220, 2250, 1320. ^{1}H-NMR (300MHz, DMSO-d_6) = 3.394 (s, 3H, OCH_3), 3.458 (s, 3H, OCH_3) , 6.420 (d, *J*=3.40 Hz,1H, OH), 7.132 (m, 3H, Ar-H), 7.832 (m, 2H, Ar-H), 8.256 (dd, *J*=2.14 Hz,J' 8.56 Hz, 1H, Ar-H), 8.339 (s,1H, NH). ^{13}C-NMR (300MHz, DMSO-d_6)= 78.720 (OCH_3), 107.54 (OCH_3), 110.48, 114.18, 122.44, 124.12, 124.87, 126.87, 131.97, 133.85, 135.80, 137.42, 137.60, 138.10, 140.75, 145.76 (Ar-C), 150.10 (C-OH). HRMS (ESI) m/z :calcd. for $C_{17}H_{15}N_2O_3S$(M+H+)327.08; found 327.08.

3-(2,4-Dimethoxyphenylthio)-1H-indol-5-carbonitrile (3p)

Yield: 0.25 g (80%, 80×10^{-5} mol); brown oil, FT-IR (neat, cm^{-1}) =3213, 2225, 1410. ^{1}H-NMR (300MHz, DMSO-d_6) = 3.323 (s, 3H, OCH_3), 3.361 (s, 3H, OCH_3), 5.706 (m, 1H, Ar-H), 7.305 (d, *J*=2.1 Hz 2H, Ar-H), 7.861 (d, *J*=8.5 Hz, 2H, Ar-H), 7.891-7.916 (m, 2H, Ar-H), 7.918 (s, 1H, Ar-H), 7.931(d, *J*=2.5 Hz, 2H, Ar-H), 8.376 (s, 1H, NH). ^{13}C-NMR (300MHz, $CDCl_3$)= 51.241 (OCH_3), 77.570 (OCH_3), 93.677, 99.434, 116.978, 125.988, 127.768, 128.063, 128.373, 128.530, 128.802, 128.870, 129.118, 129.239, 133.682, 134.629 (Ar-C). HRMS (ESI) m/z :calcd. for $C_{17}H_{15}N_2O_2S$($M+H^+$)311.08; found 311.08.

Results and discussion

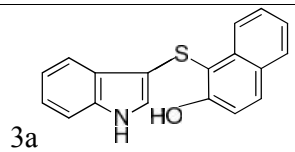
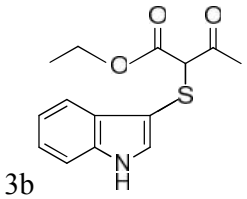
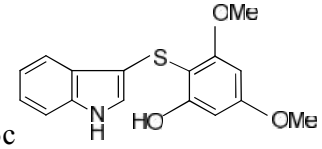
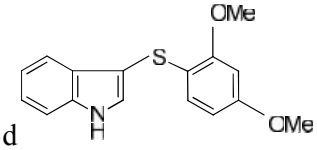
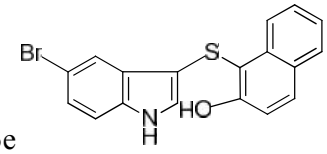
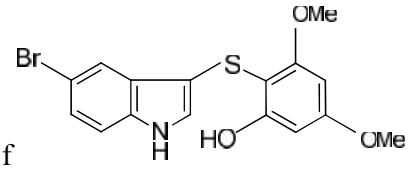
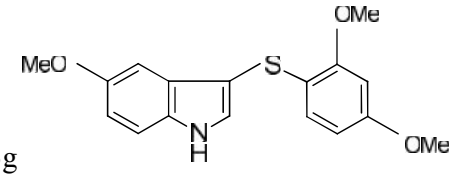
As part of studies on the design of new routes

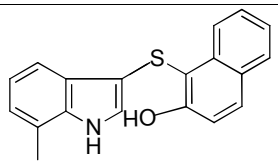
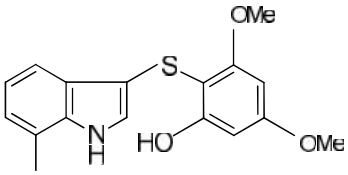
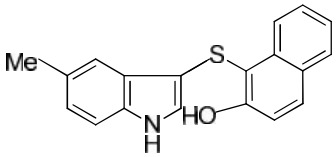
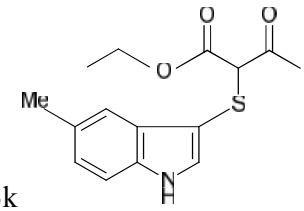
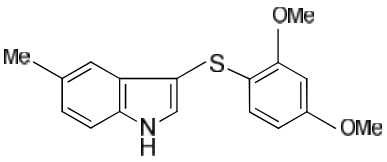
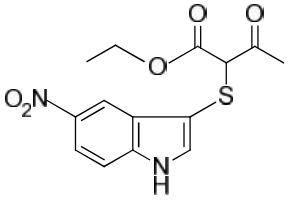
for the preparation of biologically active heterocyclic compounds; herein, we describe a simple and convenient method for the efficient synthesis of new 3-sulfenyl indole derivatives by the synthesized PBNS with high yields. A series of substituted indoles with electron-donating or electron-withdrawing groups attaching S-alkyl- and *S*-arylthiophthalimides were investigated. 3-Sulfenyl indoles with electron-donating or electron-withdrawing groups gave high yields of the desired products (Table1).

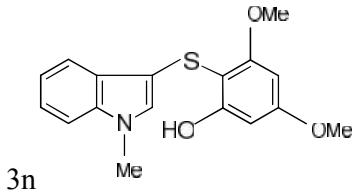
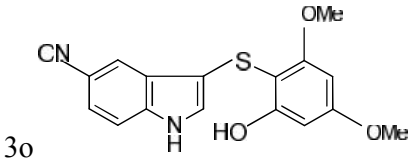
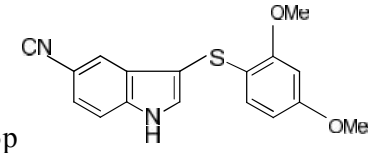
The advantages to use Poly(*N, N′*-dibromo-*N*-ethyl-naphthyl-2, 7-disulfonamide) (PBNS) as catalyst are: (1) The preparation of PBNS is easy and not expensive. (2) It is a versatile catalyst and which can be separated by a simple method. (3) The present methodology offers simple procedure. The Friedel-Crafts reaction of indole derivatives observed at C-3 position and no protection of indole ring did not need. The electron-withdrawing and electron-donating groups show an effect on yield and time reactions (Table 1). 3-sulfenyl indoles containing electron-withdrawing groups have been achieved in a longer reaction time rather than electron-donating group substitute compounds (Table 1, 3m and 3j). Then we examined several substratesusing a variety of functionalized indoles and *S*-alkyl- and *S*-arylthiophthalimides. The results are shown in Table 1.The substitution on the indole nucleus occurred exclusivelyat the 3-position, and the indole nitrogen did not requireprior protection. Under our conditions, the indole moietiesare reactive substrates, and even indolyl rings bearing electron-withdrawing groups gave the corresponding 3-sulfenylindolesin satisfactory yields (Table 1, entries 13, 15,and 16).

We also investigated the electronic effects of substituents on the nitrogen of the indole ring, and here, the presence of an electron-donating group (in **1e**) resulted in the formation of the corresponding product in a shorter reaction time than when an electron-withdrawing group was present (in 1h) (Table 2, entries 6 and 10). It can, therefore, safely be asserted that the reaction proceeded in good yield, even for less reactive. The interaction of the indolyl derivative with the catalyst with our system, was much reduced. 3-sulfenyl indole structures were confirmed by using IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectra data.

Table 1. Formation of 3-sulfenyl indoles with PBNS under room temperature.

Entry	Product	Time (h)	Yield[a](%)
1	 3a	3	95
2	 3b	1	85
3	 3c	3	85
4	 3d	12	82
5	 3e	4	81
6	 3f	2	77
7	 3g	16	80

Entry	Product	Time (h)	Yield[a](%)
8	 3h	2	84
9	 3i	1	81
10	 3j	1	83
11	 3k	2	85
12	 3l	16	84
13	 3m	8	79

Entry	Product	Time (h)	Yield[a](%)
14	 3n	1	86
15	 3o	50	83
16	 3p	19	80

[a]Isolated yield

The results of the synthesis (3a) by using a variety of N-halo compounds and an acid catalyst are shown (Table 2). We employed Trichloroisocyanuric acid (TCCA), N-Bromosaccharin (NBSa), Silica sulfuric acid (SSA) and Al $(HSO_4)_3$. Comparison of thesecompounds showed that the higher activity and yields could be achieved by using PBNS. Some of these compounds were not carried out under room temperature. PBNS can be separated by a simpler method rather than others and gave the highest yield of the desired product (Table 2).

The reaction of indole (**3j**) with S-arylthiophthalimide **2a** was carried out using PBNS as catalyst in dichloromethane, at room temperature,the desired 3-sulfenylindole (i.e., 3j) was produced in 83% yield after 1 h (Table 1, entry 10). Changing the temperatureto 60 °C, only traces of the desired product wererecovered, along with several by-products (Table 1, entry 10). A variety of solvents were examined, and the efficiencybased on the yields of 3j showed that dichloromethane was thesolvent of choice. In fact, the order, in terms of efficiency,was as follows (yields in parentheses): CH_2Cl_2 (83 %),$CHCl_3$ (68 %), MeOH (55 %),acetonitrile (53 %), n-Hexane (47 %), and solvent-free (71 %)(Table 3).

When the same reaction was carried out by

using different amounts of the catalyst, the highest yield was obtained in the presence of 0.1 mmol%.A lower and higher amount of the catalyst was not improved the yield of the product even after longer reaction time (Table 2).

Table 2. Comparison of different compounds employed for preparation of 3a after 3 hours.

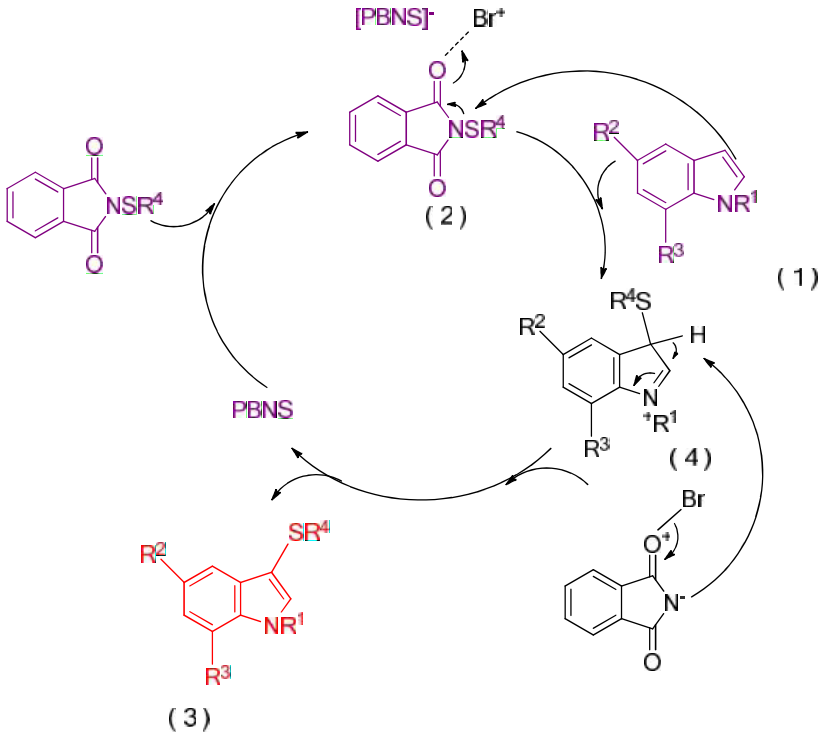
Entry	Conditions	Catalyst amount (mmol %)	Yield (%)
1	NBSa/65 ˚C	0.20	48
2	TCCA	0.10	63
3	SSA	0.10	65
4	$Al(HSO_4)_3$	0.10	50
5	$CeCl_3 \cdot 7H_2O$/NaI[18]	0.30	85
6	la PBNS	0.05	82
7	PBNS	0.10	95
8	PBNS	0.15	92
9	PBNS	0.2	88

Table 3. Evaluation of solvents and temperature for **3j**.

Entry	Conditions	Time(h)	Temperature	Yield[a] (%)
1	CH_2Cl_2	1	r.t	83
2	$CHCl_3$	1	r.t	68
3	CH_3OH	3	60 ˚C	55
4	CH_3CN	3	60 ˚C	53
5	n-Hexane	4	80 ˚C	47
6	solvent-free	1	60 ˚C	71

[a]Isolated yield

The catalyst releases Br^+ in situ can act as an electrophilic spice. A plausible mechanism for the synthesis of 3-sulfenyl indole derivatives with PBNS is shown (Scheme 2). A nucleophilic substitution of the indole C-3 at the sulfur of the sulfenyl group moiety gave intermediate 4. Aromatization of indole derivativesoccurs by deprotonation of 4, releasing the catalyst and 3-sulfenyl indoles [18].



Scheme 2. A plausible mechanism for the synthesis of 3-sulfenyl indole derivatives with PBNS.

To clarify this issue, we established a set of experiments for the synthesis of 3j by using the PBNS catalyst. After the completion of the first reaction, the reaction mixture was centrifuged for 5 min. Then, the catalyst was separated and the residue was finally dried at 30 ˚C. Poly (*N, N′*-dibromo-*N*-ethyl-naphthyl-2,7-disulfonamide) can be reusable for five runs without decrease of activity (Table 4).

Table 4. Reaction of 3j in the presence of recycled PBNS under room temperature.

Entry	Cycle	Time (min)	Yield[a] (%)
1	1st run	60	83
2	2st run	70	83
3	3st run	80	78
4	4st run	90	75
5	5st run	100	71

[a] Isolated yield.

Conclusion

In summary, we have been able to synthesize some 3-sulfenyl indoles with poly (*N, N′*-dibromo-*N*-ethyl-naphthyl-2,7-disulfonamide) as heterogeneous catalyst. By using this methodology, the preparation of 3-sulfenyl indoles are simple, time-saving, high yields and has the reusability of the catalyst.

References

[1] L.D. Quin, J. A.Tyrell, *Fundamentals of Heterocyclic Chemistry*, John Wiley & Sons, Hoboken, New Jersey, chapters 8–9, 196 (2010).

[2] B.S. Lane, M.A. Brown, D. Sames, *J. Am. Chem. Soc.,* 127, 8050 (2005).

[3] W. Ge, Y. Wei, *Synthesis*, 44, 934 (2012).

[4] G. Bartoli, E. Marcantoni, L. Sambri, *Synlett*., 2101–2166 (2003).

[5] Z. Li, J. Hong, X. Zhou, *Tetrahedron*, 67, 3690 (2011).

[6] G. La Regina, M. C. Edler, A. Brancale, S. Kandil, A. Coluccia, F. Piscitelli, E. Hamel, G.De Martino, R. Matesanz, J.F. Díaz, A.I. Scovassi, E. Prosperi, A. Lavecchia, E. Novellino, M. Artico, R. Silvestri, *J. Med. Chem*. 50, 2865 (2007).

[7] K. Manabe, N. Aoyama, S. Kobayashi, Adv. Synth. Catal., 343, 174 (2001); Y. Mori, K. Kakumoto, K.Manabe, S. Kobayashi, Tetrahedron Lett., 41, 3107 (2000); K. Manabe, Y. Mori, T. Wekabayashi, S. Nagayama, S. Kobayashi, *J. Am. Chem*. Soc.,122, 7202 (2000).

[8] G.C. De Martino, M.La. Edler, G. Regina, A. Coluccia, M. Chiara, D. I.Barbera, R. Barrow, G. Nicholson, A. Chiosis,E. Brancale, M. Hamel Artico, R. Silvestri, *J. Med. Chem.,* 49(3), 947 (2006).

[9] T.M. Williams, T.M. Ciccarone, S.C. Mac Tough, C.S. Tooney, S.K. Balani, J.H. Sardana, W.A. Schleif, A.D. Theoharidas, O.S. Anderson, *J. Med. Chem*., 36, 1291 (1993).

[10] F. Cianchi, C. Cortesini, L. Magnelli, E. Fanti, L. Papucci, N. Schiavone, L. Masserini, A. Vannacci, S.Capaccioli, F. Perna, M. Lulli, V. Fabbroni, G. Perigli, P. Mechi, E. Masini, *Mol. Cancer Ther*., 5, 2716 (2006).

[11] B. S. Lane, M. A. Brown, D. Sames, *J. Am. Chem. Soc*., 127, 8050 (2005).

[12] S.D. Young, S.F. Britcher, L.S. Payne, L.O. Tran, J.W.C. Lumma, *Chem. Abstr*., 21, 5519021 (1996).

[13] D.N. Harpp, G.T. Back, J. Org. Chem., 36, 3828–3829 (1971); K.B. Boustany, A. Sullivan, *Tetrahedron Lett*., 11, 3557 (1970).

[14] J. Bures, C. Isart, J.Vilarrasa, Org. Lett. 9, 4635 (2007); D.N. Harpp, G.T. Back, *Tetrahedron Lett*.,12, 4953 (1971).

[15] Y. Maeda, M. Koyabu, T. Nishimura, S. Uemura, J. Org. Chem., 69, 7688 (2004); J. A. Campbell, C.A. Broka, L. Gong. K.A.M. Walker, J. H.Wang, *Tetrahedron Lett*.,45, 4073 (2004).

[16] K.M. Schlosser, A. .Krasutsky, H.W. Hamilton, E. Reed, K. Sexton, *Org. Lett*.6, 819 (2004).

[17] J.S. Yadav, B.V. Subba Reddy, Y. Jayasudhan Reddy, *Tetrahedron Lett*.,48, 7034 (2007).

[18] E. Marcantoni, R. Cipolletti, L. Marsili, S. Menichetti, R. Properzi, C. Viglianisi, Eur. J. *Org. Chem*., 1, 132 (2013).

[19] C. Silveira, S.R. Mendes, L.G. Wolf, M. Martins, *Tetrahedron Lett*.,51, 2014 (2010).

[20] C.M. Tudge, M. Tamiya, C. Savarin, G. R. Humphrey, *Org. Lett*.,8, 565 (2006).

[21] Yu. Chen, C-H. Cho, F. Shi, R.C. Larock, *J. Org. Chem*., 74(17), 6802 (2009).

[22] Y.A.N. Chen, C. Markina, R. Larock, *Tetrahedron*,8908 (2009).

[23] H. Veisi, R. Ghorbani-Vaghei, S.Akbari Dadamahaleh, *J. Heterocycl. Chem.*,48, 669 (2011).

[24] A. Khazaei, A. Massoudi, M. Chegeni,Synth. Commun., 44(5), 633 (2014);A. Khazaei, S.Shahnaz, L.Roshani, M.Kazem-Rostami, Z.Abdolkarim, *Letters in Organic Chemistry,* 11(3),159 (2013).

[25] G. Bartoli, G. Di Antonio, S. Giuli, E. Marcantoni, M. Marcolini, M. Paoletti, *Synthesis*, 320 (2008).