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KF-ALUMINA IMMOBILIZED IN IONIC LIQUIDS: A NOVEL HETEROGENEOUS BASE FOR HETEROCYCLIZATION OF ALKYLSULFANYLPHENYLAMINES INTO 1,4-BENZOTHIAZINE

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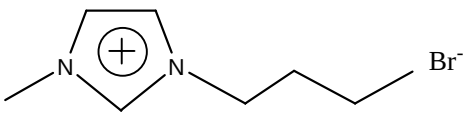
Abstract – A rapid and convenient synthetic methodology for the cyclocondensative transformation of various alkylsulfanylphenylamines with bromoacetyl bromide by supporting on KF-alumina in ionic liquids [bmim][Br] and [bmim][BF_4] has been developed to obtain 3-oxo-1,4-benzothiazine in good yields. The product is easily obtained by extraction with ethyl acetate and concentrating under vacuum. Easy recovery of ionic liquid and use in consecutive reactions is also reported.

INTRODUCTION

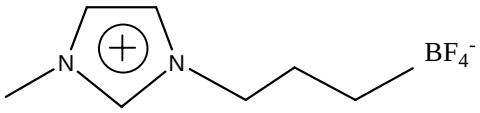
1,4-Benzothiazine is always a molecule of interest to chemists and biologists both, being a subunit of various tissues such as mammalian hair and feathers[1] and as a precursor in many synthetic transformations leading to biologically active heterocyclic molecules.[2] Biosynthetically obtained 1,4-benzothiazine derivatives, Luciferin and Rifamycin are well known for their pharmacological activity.[3] 1,4-Benzothiazine derivatives are found to possess a wide spectrum of biological activities such as antimicrobial, antifungal, anthelmintic activity[4] and aldose reductase inhibition property.[5] Various nitrogen sulfur bearing heterocycles in which benzothiazine is the central motif are recognized for their immunomodulating and anti-inflammatory properties.[6] 1,4-Benzothiazines are known for their utility as dyestuffs,[7] photographic developers,[8] UV light absorbers and anti-oxidant.[9] Semotiadil, a derivative of 1,4-benzothiazine is a well known widely used anti-hypertensive and anti-anginal drug.[10] Because of their widespread applications in diverse areas, synthesis of 1,4-benzothiazines has been a matter of an interest to organic chemists. Various methods have been reported for the synthesis of 1,4-benzothiazine such as

from 2-aminothiophenol,[11] by reductive cyclization of α–(*o*-nitrophenylthio) acids[12] and *o*-aminophenyl disulfides.[13] These methods involve the use of volatile organic solvents and the undesirable pyridine as a base. These reports do not mention any thing regarding solvent recovery and as the transformations are taking place at high temperature hence a huge loss of organic solvent was observed. The recent increased awareness about the detrimental effects of these organic solvents in the environment has led to rapid growth in research for alternative reaction media. Researchers have diverted their attention towards organic synthesis using eco-friendly, non-volatile solvents. More attention is being paid to reusability of solvent and catalyst in the reaction systems for the development of cost-effective protocol.

Considerable interest is being manifested in the use of room temperature ionic liquids as promising substitutes for volatile organic solvents.[14] These ambient temperature ionic liquids especially those based on 1,3-dialkylimidazolium cations have been emerging as promising green solvents for the past decades.[15] Their non-volatile nature without any detectable vapour pressure give them significant advantage in minimizing solvent consumption. They are highly polar yet weakly coordinating. This places them in an advantageous position as solvents for various organic, inorganic, polymeric and organometallic compounds. They have been employed as reaction media for several organic reactions namely alkylation,[16] hydrogenation,[17] Heck reaction,[18] Hetero-Diels-Alder cycloaddition,[19] Suzuki reaction,[20] oxidation[21] and Stille coupling.[22] They have unique properties such as excellent chemical and thermal stability and non-flammability which is the reason for their efficacy for repeated reusability.



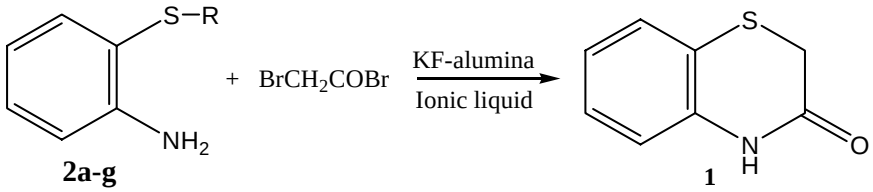
[bmim][Br]



[bmim][BF_4]

The use of room temperature ionic liquids has made a significant advancement in the development of clean chemical process in organic synthesis targeted to avoid or at least minimize the use of toxic or waste generating reagents and solvents. In recent years, use of solid supports such as clay, silica, and alumina has received considerable attention in different areas of organic synthesis because of their simplicity in operation, non-corrosiveness and ready availability at low cost. The KF-alumina has shown the potency in a number of reactions as reagent[23] and promoter in rearrangement reactions.[24] It has also been used as a good solid support for the synthesis of heterocyclic molecules.[25]

In our efforts to investigate the range of organic reactions possible in ionic liquid, while investigating the cyclization reaction for the synthesis of macrocyclic chelating agents, we observed the transformation of alkylsulfanylphenylamines into 3-oxo-1,4-benzothiazine (Scheme 2). Here we present the results of the transformation of various alkylsulfanylphenylamines into 3-oxo-1,4-benzothiazine using KF-alumina as base immobilized in ionic liquid (Scheme 1).

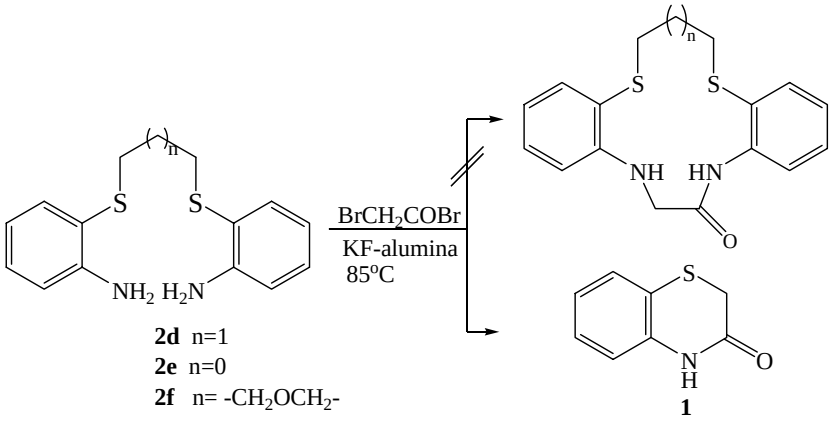


2a-g **1**

Scheme 1. Synthesis of 3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine in ionic liquids, [bmim][Br] and [bmim][BF_4]

RESULTS AND DISCUSSION

In view of emerging relevance of the imidazolium based ionic liquids as novel reaction media, we explored the cyclization reactions for the synthesis of macrocyclic chelating agents using ionic liquids as environment friendly and reusable reaction media. The alkylsulfanylphenylamines were synthesized by the substitution of 2-aminothiophenol with respective halides or diethyleneglycol ditosylate by slight modification of the reported procedure.[26] The varied transformation was observed in process of cyclization of 1,3-bis(2-aminophenylthio)propane (**2d**) with bromoacetyl bromide. Instead of obtaining the cyclized macrocycle, 3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine was found to be the sole product after spectroscopic analysis (Scheme 2).



2d n=1
2e n=0
2f n= -CH_2OCH_2-

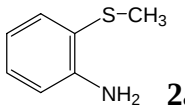
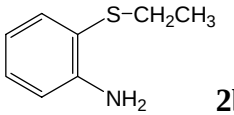
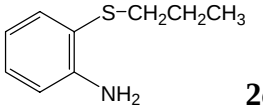
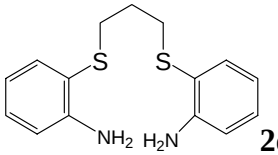
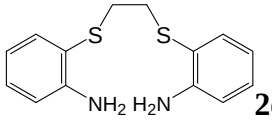
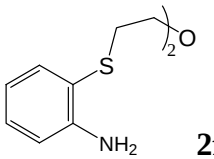
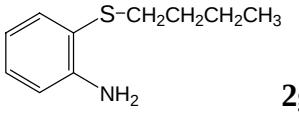
1

Scheme 2. Heterocyclization of diamines into 1,4-benzothiazine.

The basic information about the transformation, prompted us to evaluate this reaction with different alkylsulfanylphenylamines in ionic liquids. The transformations were performed in two imidazolium ion based ionic liquids, 1-butyl-3-methylimidazolium bromide ([bmim][Br]) and 1-butyl-3-methyl-imidazolium tetrafluoroborate ([bmim][BF_4]). Both the ionic liquids were found to be equally compatible for this transformation. The advantage of the use of ionic liquids as novel reaction media for this transformation was the ease of base and product separation provided by solid supported heterogeneous base. The solid support base is good candidate for this transformation and for the recovery as well as reutilization of ionic liquid. KF-alumina is being used immensely for various transformations involved in organic synthesis.[25] As far as the stability of imidazolium ion is concerned at high temperature, the mild

base KF-alumina emerged the natural choice. In the presence of KF-alumina the transformation was carried out with high reaction kinetics and less time.

Table 1. Synthesis of 3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine in ionic liquid [bmim][Br].

Entry	Substrate	Equiv. of $BrCH_2COBr$	Reaction time (h)	Yield (%)
1	 **2a**	1.2	2.5	83 82[a]
2	 **2b**	1.15	2.5	83 83[a]
3	 **2c**	1.2	2.6	81
4	 **2d**	2.2	3	78
5	 **2e**	2.25	3	78
6	 **2f**	2.24	3.2	76
7	 **2g**	1.2	2.8	81

[a]Reaction performed in $[bmim][BF_4]$.

Interestingly the alkylsulfanylphenylamines that have smaller alkyl groups were converted to benzothiazine in shorter time and higher yields compared to that of larger alkyl groups (Table 1). This may be due to the steric factor involved at the time of cyclization with the nucleophilic substitution at thio group.

The ease of separation of benzothiazine product from the reaction media is the foremost advantage of this process in ionic liquids. The products were easily separated by simple extraction with ethyl acetate. The remaining ionic liquid was filtered and washed with ethyl acetate. The recovered ionic liquid was reused in subsequent reactions. The products obtained were of same purity as in the first run and there was appreciable consistency in the product yields (Table 2).

Table 2. Benzothiazine obtained in recycled ionic liquid [bmim][Br] with 2-methylsulfanylphenylamine.

Cycle	1	2	3	4
Yield (%)	82	82	80	80

The present paper demonstrates an elegant and simple methodology for the cyclocondensative transformation of various alkylsulfanylphenylamines at ambient temperature on KF-alumina in ionic liquid [bmim][Br] and [bmim][BF_4] as the reaction media. This procedure shares the advantage of improved yields, easier separation of the product, small volume of organic solvent consumption and last but not the least recyclability of the ionic liquid giving approximately constant yield of the product in consecutive cycles. The simple experimental and product isolation procedures combined with the ease of recovery and reuse of the novel reaction media is of broader interest to the chemical community for the synthesis of heterocyclic 1,4-benzothiazines.

EXPERIMENTAL

All chemicals and reagents were of analytical grade. Ionic liquids [bmim][Br] and [bmim][BF_4] were prepared according to the literature procedure.[27] TLC was run on the silica gel coated aluminum sheets (Silica gel 60 F_{254}, Emerck, Germany) and visualised in UV light 254nm. Melting point was determined at Buchi B540 instrument. IR spectra were recorded on the FT-IR Perkin Elmer Spectrum BX spectrophotometer. NMR spectral characterization was carried out on Bruker 400 MHz NMR instrument operating near 400 (^{1}H) and 100 (^{13}C) MHz and Bruker 300 MHz NMR instrument operating near 300 (^{1}H) and 75 (^{13}C) MHz. The FAB-MS spectra were recorded from Central Drug Research Institute, India on JEOL SX 102/DA-6000 mass spectrometer using *m*-nitrobenzyl alcohol matrix. EI-MS spectra were recorded on a JEOL SX102 / DA (KV 10 mA) instrument. Elemental analysis was done on Elementar Analysensysteme GmbH VarioEL system.

General procedure for the synthesis of alkylsulfanylphenylamine (2a, 2b, 2c, 2d, and 2g):

The alkyl halide (20-40 mmol) was added dropwise to a refluxing solution of 2-aminothiophenol (5 g, 40 mmol) and sodium methoxide (3.2 g, 50 mmol) in dry methanol (20 mL). The refluxing reaction mixture was stirred for 6-7 h and it was monitored by TLC. On completion of reaction the solvent was removed *in vacuo* and the reaction mixture was cooled to 0^{o}C. Water (50 mL) was added and reaction mixture was extracted with dichloromethane (20 mL × 4). The organic layer was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to get a crude product, which was further purified by column chromatography [column of SiO_2 (100 g); pre-adsorbtion of the residue at SiO_2 (*ca*. 8 g) with ethyl acetate; elution with petroleum ether/ethyl acetate=60:40 (v/v)].

2-Methylsulfanylphenylamine (2a): It was synthesized by above procedure using methyl iodide (5.64 g, 40 mmol) as alkylating agent. The resulting compound was purified by silica gel column chromatography to obtain transparent liquid (5.25 g, 94%). IR (NaCl plates, ν/cm^{-1}) 3447, 3350, 3015, 2990, 2919, 1606, 1479, 1447, 1301, 748. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.30 (d, J=7.6 Hz, 1H, ArH), 7.02 (t, J=7.5 Hz, 1H, ArH), 6.66 (t, J=7.5 Hz, 1H, ArH), 6.60 (d, J=8.0 Hz, 1H, ArH), 4.10 (br s, 2H, NH_2, exchanged with D_2O), 2.26 (s, 3H, S-CH_3). Anal. Calcd for C_7H_9NS: C 60.39; H 6.52; N 10.06; S 23.03. Found C 60.42; H 6.42; N 9.89; S 23.00. FAB-MS: Found m/z 140 $[M+H]^+$; calcd for C_7H_9NS: 139.

2-Ethylsulfanylphenylamine (2b): It was synthesized by above procedure using ethyl bromide (4.32 g, 40 mmol) as alkylating agent. The resulting crude product was purified by silica gel column chromatography to obtain violet colored liquid product (5.68 g, 94%). IR (NaCl plates, ν/cm^{-1}) 3454, 3355, 3063, 3015, 2973, 2924, 1606, 1478, 1447, 748. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.30 (d, J=6.8 Hz, 1H, ArH), 7.00 (t, J=7.6 Hz, 1H, ArH), 6.60 (d, J=7.6 Hz, 2H, ArH), 4.30 (br s, 2H, NH_2, exchanged with D_2O), 2.70 (q, J=7.3 Hz, 2H, S-CH_2-), 1.20 (t, J=7.3 Hz, 3H, S-C-CH_3). Anal. Calcd for $C_8H_{11}NS$: C 62.70; H 7.24; N 9.14; S 20.92. Found C 62.54; H 7.08; N 9.92; S 20.70. FAB-MS: Found m/z 154 $[M+H]^+$; calcd for $C_8H_{11}NS$: 153.

2-Propylsulfanylphenylamine (2c): It was synthesized by above procedure using propyl bromide (4.9 g, 40 mmol) as alkylating agent. The resulting crude product was purified by silica gel column chromatography to obtain dark viscous liquid (6.1 g, 92%). IR (NaCl plates, ν/cm^{-1}) 3456, 3357, 3063, 3014, 2977, 2934, 1607, 1477, 1446, 748. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.29 (d, J=7.8 Hz, 1H, ArH), 7.04 (t, J=7.4 Hz, 1H, ArH), 6.70 (d, J=7.6 Hz, 2H, ArH), 4.32 (br s, 2H, NH_2, exchanged with D_2O), 2.70 (t, J=7.3 Hz, 2H, S-CH_2-), 1.20 (m, 2H, S-C-CH_2-), 0.90 (merged t, J=7.4 Hz, 3H, S-C-C-CH_3). Anal. Calcd for $C_9H_{13}NS$: C 64.62; H 7.83; N 8.37; S 19.17. Found C 64.58; H, 7.64; N 8.47; S 19.27. FAB-MS: Found m/z 168 $[M+H]^+$; calcd for $C_9H_{13}NS$: 167.

1,3-Bis(2-aminophenylthio)propane (2d): It was synthesized by above procedure using 1,3-dibromopropane (4.02 g, 20 mmol) as alkylating agent. The resulting crude product was purified by silica gel column chromatography to obtain transparent oily liquid (4.5 g, 82%). IR (NaCl plates, ν/cm^{-1}) 3434, 3355, 3018, 2988, 2925, 1606, 1478, 1448, 1301, 748. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.20 (dd, J_{ab}=7.5 Hz, J_{ac}=1.5 Hz, 2H, ArH), 7.00 (dt, J_{ab}=7.6 Hz, Jac=1.4 Hz, 2H, ArH), 6.68 (dd, J_{ab}=8.0 Hz, Jac=1.2 Hz, 2H, ArH), 6.64 (dt, J_{ab}=7.6 Hz, J_{ac}=1.2 Hz, 2H, ArH), 4.10 (br s, 4H, 2 x NH_2, exchanged with D_2O), 2.80 (t, J=7.1 Hz, 4H, 2 x S-CH_2-), 1.75 (quintet, J=7.1 Hz, 2H, S-C-CH_2-). Anal. Calcd for $C_{15}H_{18}N_2S_2$: C 62.03; H 6.25; N 9.64; S 22.08. Found C 62.14; H 6.26; N 9.82; S, 21.88. FAB-MS: Found m/z 290 $[M]^+$; calcd for $C_{15}H_{18}N_2S_2$: 290. EI-MS: 290, 166, 138, 124 (base peak), 94.

2-Butylsulphanylphenylamine (2g): It was synthesized by above procedure using butyl bromide (5.48g, 40 mmol) as alkylating agent. The resulting crude product was purified by silica gel column

chromatography to obtain viscous liquid (6.66 g, 92%). IR (NaCl plates, ν/cm^{-1}) 3437, 3356, 3018, 2988, 2925, 1606, 1478, 1448, 1301, 748. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.30 (d, J=7.6 Hz, 1H, ArH), 7.02 (t, J=7.5 Hz, 1H, ArH), 6.60 (d, J=7.9 Hz, 2H, ArH), 4.20 (br s, 2H, NH_2, D_2O exchanged), 2.30 (t, J=7.6 Hz, 2H, S-CH_2-), 1.20 (m, 4H, S-C-CH_2-CH_2-), 0.89 (t, J=7.3 Hz, 3H, S-C-C-C-CH_3). Anal. Calcd for $C_{10}H_{15}NS$: C 66.25; H 8.34; N 7.73; S 17.69. Found C 66.45; H 8.24; N 7.62; S 17.62. FAB-MS: Found m/z 182 $[M+H]^+$; calcd for $C_{10}H_{15}NS$: 181.

1,2-Bis(2-aminophenylthio)ethane (2e): The 1,2-dibromoethane (3.7 g, 20 mmol) was added dropwise to a refluxing solution of 2-aminothiophenol (5 g, 40 mmol) and sodium ethoxide (3.7 g, 50 mmol) in dry ethanol (20 mL). The refluxing reaction mixture was stirred for 6-7 h and it was monitored by TLC. On completion of reaction the solvent was removed *in vacuo* and the reaction mixture was cooled to 0^{o}C. Water (50 mL) was added and reaction mixture was extracted with dichloromethane (20 mL × 4). The organic layer was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to get a solid product, which on recrystallization from ethanol gave white colored solid (4.3 g, 78%), mp 72-73 ^{o}C. IR (KBr pallets, ν/cm^{-1}) 3385, 3356, 3290, 3018, 2988, 2925, 1617, 1582, 1479, 1446, 749. ^{1}H NMR (60 MHz, $CDCl_3$) δ ppm 6.70-7.50 (m, 8H, ArH), 4.30 (br s, 4H, 2 x NH_2, exchanged with D_2O), 2.80 (s, 4H, 2 x S-CH_2). Anal. Calcd for $C_{14}H_{16}N_2S_2$: C 60.83; H 5.83; N 10.13; S 23.20. Found C 60.63; H, 5.76; N 10.60; S 23.01 FAB-MS: Found m/z 276 $[M]^+$; calcd for $C_{14}H_{16}N_2S_2$: 276. EI-MS: 276, 138, 124 (base peak), 94.

1,5-Bis(2-aminophenylthio)-3-oxapentane (2f): The diethyleneglycolditosylate (8.2 g, 20 mmol) was added dropwise to a refluxing solution of 2-aminothiophenol (5 g, 40 mmol) and sodium methoxide (3.2 g, 50 mmol) in dry methanol (20 mL). The refluxing reaction mixture was stirred for 6-7 h and it was monitored by TLC. On completion of reaction the solvent was removed *in vacuo* and the reaction mixture was cooled to 0^{o}C. Water (50 mL) was added and reaction mixture was extracted with dichloromethane (20 mL × 4). The organic layer was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to get a crude product, which was further purified by column chromatography [column of SiO_2 (100 g); pre-adsorbtion of the residue at SiO_2 (*ca*. 8 g) with ethyl acetate; elution with petroleum ether/ethyl acetate=60:40 (v/v)] to obtain viscous liquid (4.56 g, 72%). IR (KBr pallets, ν/cm^{-1}) 3432, 3349, 3058, 2921, 2855, 1607, 1479, 1105, 748. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.30 (d, J=7.5 Hz, 2H, ArH), 7.10 (t, J=7.5 Hz, 2H, ArH), 7.00 (d, J=7.5 Hz, 2H, ArH), 6.60 (t, J=7.8 Hz, 2H, ArH), 4.00 (br s, 4H, 2 x NH_2, exchanges with D_2O), 3.30 (t, J=7.1 Hz, 4H, 2 x O-CH_2-), 2.73 (t, J=7.0 Hz, 4H, 2 x S-CH_2). ^{13}C NMR ($CDCl_3$) δ ppm 32.15, 67.32, 112.71, 114.06, 114.97, 127.81, 133.97, 148.19. Anal. Calcd for $C_{16}H_{20}N_2OS_2$: C 59.96; H 6.29; N 8.74; O 4.99; S 20.01. Found C 59.66; H 6.08; N 8.44; S, 20.00. EI-MS: 320, 319, 227, 195, 136 (base peak), 166, 94, 57.

Representative procedure for the synthesis of benzothiazine: Methylsulfanylphenylamine (**2a**) (139 mg, 1 mmol) was added to a mixture of KF-alumina (0.5 g) and ionic liquid [bmim][Br] (3 mL) in a RB

flask and the reaction temperature was slowly raised to 85^{o}C, followed by dropwise addition of bromoacetyl bromide (241 mg, 1.2 mmol) with efficient stirring. On completion of reaction (TLC, 2.5 h), the reaction mixture was cooled to rt and extracted with ethyl acetate (4 x 5 mL). The organic layer was concentrated *in vacuo* to afford the crude product which on purification by column chromatography (silica gel, AcOEt/Hexane=50:50 v/v eluent) gave crystalline benzothiazine product (136 mg, 83%). The cyclization of **2(a-b)** were performed using same reaction condition as mentioned above with [bmim][BF_4]. The by product methyl bromide, ethyl bromide and propyl bromide being volatile escaped during the work-up procedure. The respective alkyl bromides obtained from substrate **2(d-g)** were separated by column chromatography in 40-60 % yield.

3-Oxo-3,4-dihydro-2*H*-1,4-benzothiazine (1): White crystalline solid. mp 181^{o}C. IR (KBr pallets, ν/cm^{-1}): 3313-3114, 3057, 2971, 2911, 1662, 1583, 1479, 1385, 740. ^{1}H NMR ($CDCl_3$, 400MHz) δ ppm 9.20 (s, 1H, N-H), 7.31 (d, 1H, J=7.6 Hz, ArC5-H), 7.10 (t, 1H, J=7.5 Hz, ArC6-H), 7.00 (t, 1H J=7.5 Hz, ArC7-H), 6.92 (d, 1H, J=7.5 Hz, ArC8-H), 3.40 (s, 2H, -CH_2-). ^{13}C NMR ($CDCl_3$, δ ppm): 166.5, 136.4, 127.7, 127.2, 123.9, 120.0, 117.4, 21.9. EI-MS (m/z): 164, 135 (100%). Anal. Calcd for C_8H_7NOS: C 58.18, H 4.24, N 8.40. Found C 58.29, H 4.23, N 8.22.

Procedure to recover the ionic liquid: The reaction mixture was filtered to recover ionic liquid through the Whatman no. 3 filter paper under suction. The filtrate was extracted with ethyl acetate (2 x 3 mL). The ionic liquid left after the extraction was concentrated *in vacuo* to remove traces of organic solvent and used as such in the subsequent reactions.

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