Selective oxidation of thioureas in an ionic liquid by employing an ion-supported hypervalent iodine(III) reagent

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Several 2,4-dialkyl-3,5-bis(arylimino)-1,2,4-thiadiazolidines were synthesised under mild conditions in good yield by the selective oxidation of N-alkyl-N′-arylthioureas by using 1-(4-diacetoxyiodobenzyl)-3-methyl imidazolium tetrafluoroborate [dibmim]$^+$[BF_4]$^-$ in ionic liquids.

Keywords: hypervalent iodine reagent, thiourea, thiadiazolidine, oxidation, ionic liquid

Oxidation of N-alkyl-N'-arylthioureas is known to afford Dost's bases.[1] A large number of thiourea derivatives has been transformed into 1,2,4-thiadiazolidines because of their antibacterial and antifungal activities.[2] Various oxidants such as bromine,[3] hydrogen peroxide,[4] nitrous acid[2d,5] and benzoyl peroxide (BPO)[6] have been used but few reagents are environmentally benign or of good selectivity and recyclability. Hypervalent iodine reagents have been extensively used in organic syntheses due to their low toxicity, ready availability and easy handling.[7] Task-specific ionic liquids have been studied recently because of their high thermal stability, negligible vapour pressure, high loading capacity and tunable polarity.[8,9]

Very recently, we reported a highly selective oxidation of alcohols in ionic liquids employing an ion-supported hypervalent iodine reagent 1-(4-diacetoxyiodobenzyl)-3-methylimidazolium tetrafluoroborate [dibmim]$^+$[BF_4]$^-$ **1**.[10] This reagent can be easily dissolved in ionic liquids and water, and can be recycled and reused easily many times without decreasing its efficiency. Herein, we wish to report the selective oxidation of thioureas using the ion-supported hypervalent iodine reagent [dibmim]$^+$[BF_4]$^-$ **1** in ionic liquids.

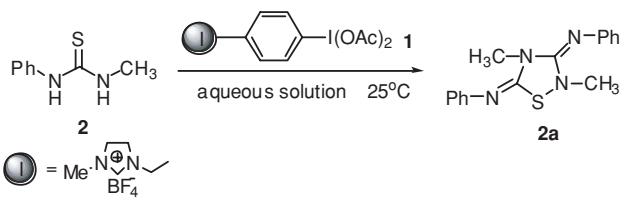
Water is an attractive reaction media.[11] We first examined the oxidation of *N*-methyl-*N'*-phenylthiourea **2** with 1.2 molar equiv. of **1** at room temperature in water, but there was almost no reaction after 40h, probably because of the low solubility of **2** in water. Organic solvents were added to increase the solubility of **2** in water. The reaction was carried out in a 1:1 mixture of water and acetone (Table 1, entry 1) at room temperature for 40h but there was still a lot of starting materials remaining. Fortunately, however, 2,4-dimethyl-3,5-diphenylimino-1,2,4-thiadiazolidine **2a** was produced without any other detectable side products. THF, ethanol and acetonitrile were also found to be effective (Table 1, entries 2–4).

Although the reaction performed in aqueous media had some disadvantages such as long reaction times and low yields, we were encouraged by the result that the reactant **2** could be oxidised selectively by [dibmim]$^+$[BF_4]$^-$ **1**. To accelerate the reaction, we decided to examine the reaction in various organic solvents in which the reactant **2** could be dissolved. Firstly, acetonitrile was chosen as a candidate at room temperature to provide **2a** in 53% yield (Table 2, entry 1). Then, acetone and THF were used at room temperature to give **2a** in 51% (Table 2, entry 2) and 88% (Table 2, entry 3) yields, respectively. Chloroform was used instead of alcohol and provided **2a** in 72% yield (Table 2, entry 4).

After the long reaction time, another product was found in entries 3 and 4 under above reaction conditions. The product was identified by IR, MS and NMR, as 4-methyl-5-methylimino-2-phenyl-3-phenylimino-1,2,4-thiadiazolidine **2b**.[6] No other side products were found in entries 1 and 2.

Finally, we performed the reaction in various ionic liquids at room temperature. Surprisingly we found that the reaction rate and the selectivity were improved significantly in some ionic liquids. The product **2a** was produced without any byproducts in [bmim]$^+$[BF_4]$^-$ (Table 3, entry 1) and [bpy]$^+$[BF_4]$^-$ (Table 3, entry 2) with only 1.2h and 4h, respectively. The ionic liquid [bmim]$^+$ [PF_6]$^-$ (Table 3, entry 3) provided **2b** in 83% yield

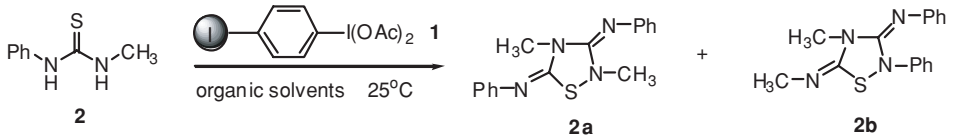
Table 1 Oxidation of *N*-methyl-*N'*-phenylthiourea **2** with [dibmim]$^+$[BF_4]$^-$ **1** in aqueous solution



2 **2a**

Entry	Solvent	Time/h	Yield/%
1	CH_3COCH_3:H_2O 1:1	40	40
2	THF:H_2O 1:1	40	36
3	CH_3CH_2OH : H_2O 1:1	40	18
4	CH_3CN : H_2O 1:1	40	33

Table 2 Oxidation of *N*-methyl-*N'*-phenylthiourea **2** with [dibmim]$^+$[BF_4]$^-$ **1** in organic solvents



2 **2a** **2b**

Entry	Solvent	Time/h	Products	Yield/%
1	CH_3CN	15	**2a**	53
2	CH_3COCH_3	15	**2a**	51
3	THF	15	**2a**+**2b**	88[a]
4	$CHCl_3$	15	**2a**+**2b**	72[a]

[a]Yield of **2a**.

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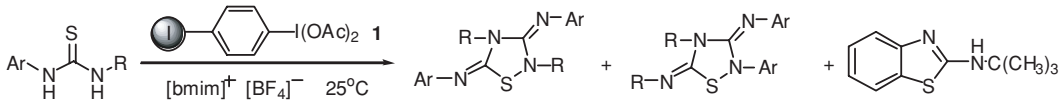
as sole product within 2h. Ionic liquids $[emim]^+[BF_4]^-$, $[hmim]^+[BF_4]^-$ and $[emim]^+[HSO_4]^-$ (Table 3, entries 4–6) were not suitable for this reaction. The results were shown in Table 3.

An extensive screening of solvents revealed that $[bmim]^+[BF_4]^-$ was the best solvent for this reaction. A variety of thioureas was then reacted with 1.2 molar equivlents of **1** in $[bmim]^+[BF_4]^-$ at room temperature within 3h to give the corresponding 1,2,4-thiadiazolidines, except for **11a**, in

Table 3 Oxidation of N-methyl-N′-phenylthiourea **2** with $[dibmim]^+[BF_4]^-$ **1** in ionic liquids

Entry	Solvent	Time/h	**2a** Yield/%	**2b** Yield/%
1	$[bmim]^+[BF_4]^-$	1.2	92	/
2	$[bpy]^+[BF_4]^-$	4	90	/
3	$[bmim]^+[PF_6]^-$	2	/	87
4	$[emim]^+[BF_4]^-$	3	45	30
5	$[hmim]^+[BF_4]^-$	2	60	30
6	$[emim]^+[HSO_4]^-$	5	20	/

Table 4 Oxidation of thioureas with $[dibmim]^+[BF_4]^-$ in $[bmim]^+[BF_4]^-$



3, 4, 5, 6, 7
8, 9, 10, 11

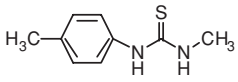
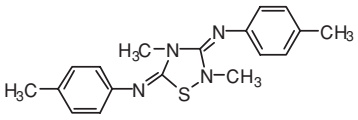
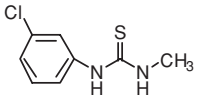
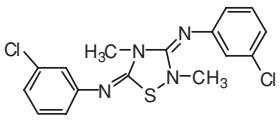
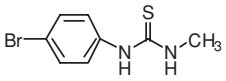
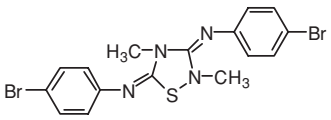
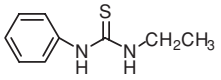
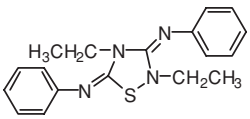
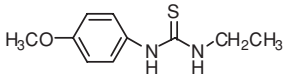
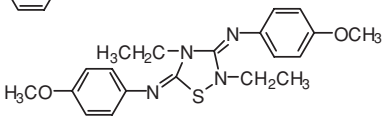
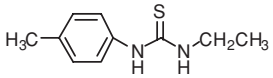
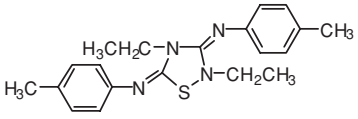
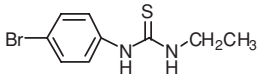
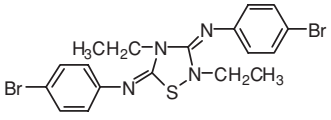
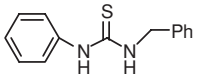
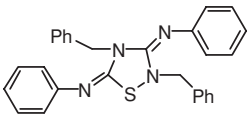
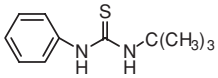
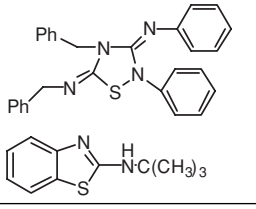
3a, 4a, 5a, 6a, 7a
8a, 9a, 10a

10b

11a

R=Me, Et, Benzyl, *t*-Butyl

Ar=Ph, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *p*-BrC_6H_4, *m*-ClC_6H_4

Entry	Substrate		Product		Time/h	Yield/%
1		**3**		**3a**	2	90
2		**4**		**4a**	1.5	87
3		**5**		**5a**	1	95
4		**6**		**6a**	2	92
5		**7**		**7a**	3	85
6		**8**		**8a**	2	90
7		**9**		**9a**	1	95
8		**10**		**10a** **10b**	1	57 25
9		**11**		**11a**	0.5	65

moderate to excellent yields (57–95%). The inductive effects of various substituted groups on the aryl ring in the reaction were evaluated in this system. The reaction of substrates **3**, **7** and **8** (Table 4, entries 1, 5–6) with **1** to give the corresponding products **3a**, **7a**, **8a** in 90%, 85% and 90% yields, respectively. Reactants **4**, **5** and **9** (Table 4, entries 2–3, 7), however, were oxidized by **1** to produce the corresponding products in even better yields. Electron-withdrawing functional groups were more favourable to this reaction. Different alkyl groups were also tested such as methyl (Table 4, entries 1–3), ethyl (Table 4, entries 4–7), benzyl (Table 4, entry 8) and *t*-butyl (Table 4, entry 9), which exerted different influence on this reaction because of their steric hindrance. Compound **2** (Table 3, entry 1) was oxidised to give the corresponding product 1,2,4-thiadiazolidine in 92% yield, so did compound **6**. Notably, N-benzyl-N'-phenylthiourea **10** (Table 4, entry 8) and N-*t*-butyl-N'-phenylthiourea **11** (Table 4, entry 9), which have larger alkyl groups, yielded other products **10b**[12] and **11a**,[13] respectively. The steric hindrance of the alkyl groups influenced the selectivity of the reaction. It should be mentioned that the oxidant **1** affect the selectivity of reaction at the same time. Compound **2** gave more than two products in this system when nitrous acid or hydrogen peroxide was used as oxidant.[4,5]

Compound **2** was chosen as a substrate to investigate the recycling of **1** (Table 5) in $[bmim]^+[BF_4]^-$. Excellent conversions were obtained for up to six consecutive cycles of recycling and reuse. Furthermore, the isolation of pure products was easily achieved by extraction with ether and the regeneration of **1** was conveniently accomplished by reaction with peracetic acid.

In summary, we have developed a new, mild and environmentally benign method for the synthesis of 1,2,4-thiadiazolidines by reaction of thiourea derivatives with hypervalent iodine reagent $[dibmim]^+[BF_4]^-$ **1** in ionic liquid $[bmim]^+[BF_4]^-$ with high yields. This procedure is simple to carry out and highly selective. The hypervalent iodine reagent **1** is readily recyclable and reusable. Further applications of this reagent in organic synthesis are being actively pursued in our laboratory.

Experimental

^{1}H NMR spectra were measured in $CDCl_3$ at 400MHz using tetramethylsilane as the internal standard. IR spectra were recorded on a Bruker Vector-22 infrared spectrometer. Mass spectra were obtained with a single quadrapole and fitted with an electrospray sourece. All melting points were uncorrected. The columns were handpacked with silica gel H60 (-400). The progress of reactions was monitored by thin layer chromatography (TLC) on silica gel 60_{P254}. Reactions were carried out in air and most solvents were purchased and used without further purification.

Preparation of thioureas **2, 3, 4, 5, 6, 7, 8, 9, 10** *and* **11**: Substituted aryl thioureas were prepared as described in the literature[14] or acquired from commercial sources.

General procedure for thioureas oxidations: $[dibmim]^+[BF_4]^-$ (303mg, 0.6mmol) was added to a solution of thiourea (0.5 mmol) in 1.5g of given solvent. The reaction mixture was stirred at ambient temperature for a given time. Then, the mixture was extracted with ether (3 × 8ml) and concentrated under reduced pressure. The product was purified by flash column chromatography using petroleum ether and ethyl acetate as eluent.

Recycling and resue of $[dibmim]^+[BF_4]^-$ **1** *in* $[bmim]^+[BF_4]^-$: The mixture was extracted with ether (3 × 8ml) after the reaction finished and to be sure that no product remained in the ionic liquid. Extra ether was removed under reduced pressure. Peracetic acid (6 mmol 0.46g) was slowly added with stirring to the mixture keeping temperature below 20 °C. After the addition, the mixture was stirred 4h at 40 °C and then it was extracted with ether (3 × 8ml) and extra peracetic acid and ether were removed with oil pump. Finally, thiourea could be directly added into the mixture to reaction without additional oxidants to be added.

Table 5 Recyclability of **1** in oxidation of thiourea **2**

Substrate	Product	Cycle	Yield/%
2	2a	1	92%
2	2a	2	91%
2	2a	3	92%
2	2a	4	92%
2	2a	5	92%
2	2a	6	90%

2,4-Dimethyl-3,5-diphenylimino-1,2,4-thiadiazolidine (*product* **2a**): White solid, m.p. 135–136 °C; lit[6a] 137.5 °C. ^{1}H NMR (ppm): δ 7.34–7.30 (m, 2H; Ar–H), 7.27–7.23 (m, 2H; Ar–H), 7.13–7.10 (m, 1H; Ar–H), 7.00–6.94 (m, 5H; Ar–H), 3.46 (s, 3H, CH_3), 2.68 (s, 3H, CH_3). IR (KBr): 1623, 1587, 763, 699 cm^{-1}. MS(70eV): *m/z*(%): 296 (53) [M$^+$], 77 (100), 91 (61.2), 104 ((86.4), 132 (54.3).

4-Methyl-5-methylimino-2-phenyl-3-phenylimino-1,2,4-thiadiazolidine (*product* **2b**)**:** White solid, m.p. 102 °C; lit[6b] 103.5 °C. ^{1}H NMR (ppm): δ 7.38–7.34 (m, 2H; Ar–H), 7.30–7.26 (m, 2H; Ar–H), 7.19–7.16 (m, 1H; Ar–H), 7.09–7.05 (m, 3H; Ar–H), 6.94–6.92 (m, 2H; Ar–H), 3.31 (s, 3H, CH_3), 2.97 (s, 3H, CH_3). IR (KBr): 1649, 1588, 759, 697 cm^{-1}. MS(70eV): *m/z*(%): 296 (0.53) [M$^+$] 57 (100), 43 (79), 41 (57.5), 132 (50.5).

2,4-Dimethyl-3,5-bis(4-methylphenylimino)-1,2,4-thiadiazolidine (*product* **3a**): White solid, m.p. 129–130.5 °C; lit[6a] 136 °C. ^{1}H NMR (ppm): δ 7.12 (d, *J* = 7.6Hz, 2H; Ar–H), 7.05 (d, *J* = 7.6Hz, 2H; Ar–H), 6.90–6.86 (m, 4H; Ar–H), 3.44 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.29 (s, 3H, CH_3). IR (KBr): 1621, 1597, 923, 817, 714, 688cm^{-1}. MS(70eV): *m/z*(%): 324 (43) [M$^+$], 104 (100), 61 (97), 77 (81), 132 (56.5).

2,4-Dimethyl-3,5-bis(3-chlorophenylimino)-1,2,4-thiadiazolidine (*product* **4a**): White solid, m.p. 78–79 °C; lit[2c] ^{1}H NMR (ppm): δ 7.27–7.23(m, 1H; Ar–H), 7.20–7.16 (m, 1H; Ar–H), 7.11–7.08 (m, 1H; Ar–H), 7.01–6.93 (m, 1H; Ar–H), 6.89–6.84 (m, 2H; Ar–H), 3.43 (s, 3H, CH_3), 2.74 (s, 3H, CH_3). IR (KBr): 1615, 1576, 863, 789cm^{-1}. MS(70eV): *m/z*(%): 364 (30.5) [M$^+$], 366 (20.2) [M$^+$+2], 57 (100).

2,4-Dimethyl-3,5-bis(4-bormophenylimino)-1,2,4-thiadiazolidine (*product* **5a**): White solid, m.p. 123–125 °C; lit[6a] 128.5 °C. ^{1}H NMR (ppm): δ 7.42 (d, *J* = 8.4Hz, 2H; Ar–H), 7.35 (d, *J* = 8.4Hz, 2H; Ar–H), 6.88–6.84 (m, 4H; Ar–H), 3.42 (s, 3H, CH_3), 2.71 (s, 3H, CH_3). IR (KBr): 1621, 1577, 923, 833, 708cm^{-1}. MS(70eV): *m/z*(%): 452 (5.62) [M$^+$], 454 (10.42) [M$^+$+2], 61(100).

2,4-Diethyl-3,5-diphenylimino-1,2,4-thiadiazolidine (*product* **6a**): White solid, m.p. 70–71 °C; lit[6a] 77.5 °C. ^{1}H NMR (ppm): δ 7.34–7.30 (m, 2H; Ar–H), 7.25–7.23 (m, 2H; Ar–H), 7.12–7.08 (m, 1H; Ar–H), 7.02–6.93 (m, 5H; Ar–H), 4.06 (q, *J* = 6.8Hz, 2H; CH_2), 2.95 (q, *J* = 6.8Hz, 2H; CH_2), 1.37 (t, *J* = 6.8Hz, 3H; CH_3), 0.92 (t, *J* = 6.8Hz, 3H; CH_3). IR (KBr): 1619, 1583, 756, 695 cm^{-1}. MS(70eV): *m/z*(%): 324 (100) [M$^+$], 77 (29).

2,4-Diethyl-3,5-bis(4-methoxyphenylimino)-1,2,4-thiadiazolidine (*product* **7a**): White solid, m.p. 73–75 °C; lit[6a] 80.5 °C. ^{1}H NMR (ppm): δ 6.95–6.92 (m, 4H; Ar–H), 6.86 (d, *J* = 8.8Hz, 2H; Ar–H), 6.82 (d, *J* = 8.8Hz, 2H; Ar–H), 4.04 (q, *J* = 6.8Hz, 2H; CH_2), 3.80 (s, 3H; CH_3), 3.78 (s, 3H; CH_3), 2.96 (q, *J* = 6.8Hz, 2H; CH_2), 1.36 (t, *J* = 6.8Hz, 3H; CH_3), 0.93 (t, *J* = 6.8Hz, 3H; CH_3). IR (KBr): 1616, 1575, 1504, 1239, 831, 688 cm^{-1}. MS(70eV): *m/z*(%): 384 (47.5) [M$^+$],153 (100), 176 (64), 133 (57).

2,4-Diethyl-3,5-bis(4-methylphenylimino)-1,2,4-thiadiazolidine (*product* **8a**): White solid, m.p. 87.5 °C; lit[6a] 93 °C. ^{1}H NMR (ppm): δ 7.12 (d, *J* = 7.2Hz, 2H; Ar–H), 7.05 (d, *J* = 7.2Hz, 2H; Ar–H), 6.91–6.87 (m, 4H; Ar–H), 4.49 (q, *J* = 6.8Hz, 2H; CH_2), 2.96 (q, *J* = 6.8Hz, 2H; CH_2), 2.32 (s, 3H; CH_3), 2.29 (s, 3H; CH_3), 1.35 (t, *J* = 6.8Hz, 3H; CH_3), 0.92 (t, *J* = 6.8Hz, 3H; CH_3). IR (KBr): 1621, 1596, 1506, 827, 783, 688 cm^{-1}. MS(70eV): *m/z*(%): 352 (45) [M$^+$], 91 (100), 131 (76), 65 (52), 164 (49).

2,4-Diethyl-3,5-bis(4-bormophenylimino)-1,2,4-thiadiazolidine (*product* **9a**): White solid, m.p. 155–156 °C; lit[6a] 161 °C. ^{1}H NMR (ppm): δ 7.44–7.42 (m, 2H; Ar–H), 7.37–7.34 (m, 2H; Ar–H), 6.89–6.86 (m, 4H; Ar–H), 4.02 (q, *J* = 7.2Hz, 2H; CH_2), 2.99 (q, *J* = 7.2Hz, 2H; CH_2), 1.34 (t, *J* = 7.2Hz, 3H; CH_3), 0.95 (t, *J* = 7.2Hz, 3H; CH_3). IR (KBr): 1609, 1576, 833, 821, 779 cm^{-1}. MS(70eV): *m/z*(%): 480 (7.5) [M$^+$], 482 (13) [M$^+$+2], 75(100), 97 (64), 90 (59).

2,4-Dibenzyl-3,5-diphenylimino-1,2,4-thiadiazolidine (*product* **10a**): Oil. ^{1}H NMR (ppm): δ 7.60–7.58 (m, 2H; Ar–H), 7.36–7.28 (m, 4H; Ar–H), 7.25–7.18 (m, 6H; Ar–H), 7.06–7.01 (m, 5H; Ar–H), 7.96–7.88 (m, 3H; Ar–H), 5.20 (s, 2H; CH_2), 4.16 (s 2H; CH_2). ^{13}C NMR (ppm): δ 152.96, 149.68, 148.74, 147.53, 137.06, 135.43, 129.72, 129.58, 129.40, 128.88, 128.65, 128.58, 128.53, 127.83,

124.70, 122.75, 121.99, 121.32, 55.82, 47.99. IR (film): 1620, 1583, 755, 695cm^{-1}. MS(70eV): *m/z*(%): 448 (9) [M$^+$], 91(100). Anal. calcd. for $C_{28}H_{24}N_4S$: C74.97, H5.39, N12.49. Found: C74.79, H5.28, N12.32.

4-Benzyl-5-benzylimino-2-phenyl-3-phenylimino-1,2,4-thiadiazolidine (*product* **10b**): Light yellow solid, m.p. 42–45 °C. ^{1}H NMR (ppm): δ 7.36–7.34 (m, 8H; Ar–H), 7.24–7.11 (m, 9H; Ar–H), 6.90–6.82 (m, 3H; Ar–H), 4.35 (s, 2H, CH_2), 4.25 (s, 2H, CH_2). ^{13}C NMR (ppm): δ 153.02, 147.51, 139.39, 136.98, 135.67, 129.41, 129.25, 129.20, 129.01, 128.82, 128.59, 128.47, 127.88, 127.51, 127.11, 122.39, 122.13, 120.37, 57.32, 55.71. IR (film): 1630, 1589, 754, 694 cm^{-1}. MS(70eV): *m/z*(%): 448 (3.8) [M$^+$], 91 (100). Anal. calcd. for $C_{28}H_{24}N_4S$: C74.97, H5.39, N12.49. Found: C74.72,H5.24, N12.27.

2-(t-Butylamino)benzothiazole (*product* **11a**): Light yellow solid, m.p. 70–72 °C. ^{1}H NMR (ppm): δ 7.58–7.52 (m, 2H; Ar–H), 7.29–7.26 (m, 1H; Ar–H), 7.09–7.05 (m, 1H; Ar–H), 5.19 (s, 1H, NH), 1.50 (s, 9H, CH_3). ^{13}C NMR (ppm): δ 164.67, 152.51, 130.84, 125.79, 121.56, 120.50, 119.12, 53.39, 29.18. IR (KBr): 3383, 3053, 2959, 2925, 1595, 1529, 751 cm^{-1}. MS(70eV): *m/z*(%): 206 (2.6) [M$^+$], 57 (100). Anal. calcd. for $C_{11}H_{14}N_2S$: C64.04, H6.84, N13.58. Found: C64.19, H6.97, N13.32.

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