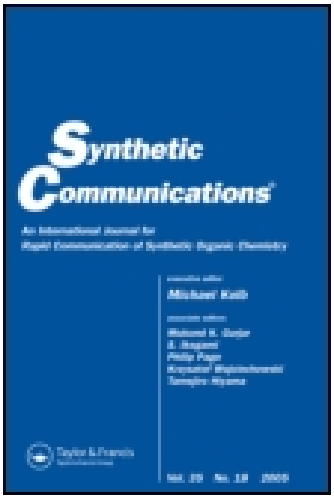

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Highly Efficient One-Pot Synthesis of 2-Aminobenzoxazoles Using Triflic Acid as a Cyclodesulfurizing Reagent

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HIGHLY EFFICIENT ONE-POT SYNTHESIS OF 2-AMINOBENZOXAZOLES USING TRIFLIC ACID AS A CYCLODESULFURIZING REAGENT

Gopal L. Khatik, Namita Dube, Anang Pal, and Vipin A. Nair
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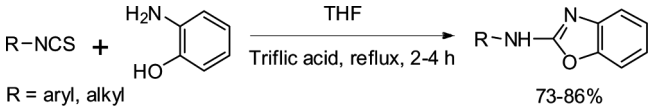
GRAPHICAL ABSTRACT



Abstract *An efficient one-pot synthetic strategy for 2-aminobenzoxazoles was developed from isothiocyanates and 2-aminophenol using triflic acid as a cyclodesulfurizing reagent.*

Keywords 2-Aminobenzoxazole; cyclodesulfurization; one-pot synthesis; triflic acid

INTRODUCTION

The 2-aminobenzoxazole moiety has been well explored as potential drug candidates for HIV, neurodegeneration, and inflammatory diseases.[1] There are various methods available for the synthesis of 2-aminobenzoxazoles, which suffer from one or more limitations because the reaction of an appropriately substituted 2-chlorobenzoxazole with an amine in the presence of base may require a multistep procedure.[2] A more general method for the synthesis of 2-aminobenzoxazole is through the cyclodesulfurization of *N*-substituted-2-hydroxy-phenylthioureas (Fig. 1). These thiourea intermediates can be prepared by the condensation of 2-aminophenol and isothiocyanates.[3,4] Various metallic reagents such as HgO,[5] NiO_2,[4] and $AgNO_3$[6] have been reported but are unsatisfactory for large-scale preparation because of the use of toxic heavy metals in excess amounts and longer reaction times.

Oxidative cyclodesulfurization of thiourea in the presence of KO_2 is exemplary;[7] however, this reagent has substrate limitation. Various salts of transition metals were also employed for this transformation,[8] but cyclodesulfurization required several days and removal of toxic metals from the product involved difficult procedures. Peptide coupling reagents were also employed[9] but are uneconomical,

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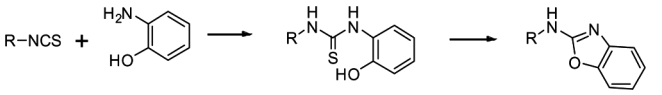


Figure 1. Synthetic strategy for the formation of 2-aminobenzoxazoles.

create difficult product isolation, and have poor yields. Cyclodesulfurization with TsCl/NaOH also has limitations because of the poor yield and undesired side products.[10] Recent reports have shown that LiOH in the presence of H_2O_2 in an excess amount can be used for the heterocyclization, though it is not tolerated by several functional groups.[11] There is an unmet need to develop a better methodology for the synthesis of 2-aminobenzoxazoles.

RESULTS AND DISCUSSION

For the synthesis of 2-aminobenzoxazoles, we assumed that a one-pot reaction involving 2-aminophenol and isothiocyanate followed by the addition of a desulfurizing agent to the reaction mixture would be a viable strategy to the desired compound and will circumvent the additional steps of isolation of the intermediate thiourea and its cyclization. To this end, a model reaction of 4-chlorophenyl isothiocyanate (**1b**) with 2-aminophenol (**2**) using various protic acids as given in Table 1 was tested to obtain *N*-4-chlorophenyl-2-aminobenzoxazoles (**3b**) (Scheme 1).

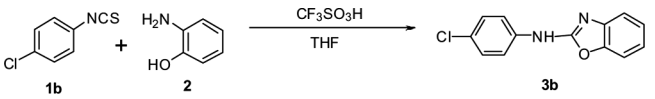
We observed that trifluoromethanesulfonic acid (triflic acid) has shown the best results among the various protic acid employed (entry 3, Table 1). The superiority of triflic acid over other protic acids may be due to its high proton-donor ability. Triflic acid is widely used as a catalyst and a precursor in organic chemistry.[12–14] To ascertain the concentration of the desulfurizing agent required, reactions were carried out by employing 0.2, 0.6, and 1.2 equivalents of triflic acid, and it was observed that 1.2 equivalent of protic acid afforded good yield of the product in short reaction time (entry 4, Table 1).

Table 1. Synthesis of *N*-4-chlorophenyl-2-aminobenzoxazole employing various regents[a]

Entry	Reagent	Time (h)	Isolated yield of **3b** (%)[b]
1	—	12	0
2	CF_3SO_3H (0.2 equiv.)	12	35
3	CF_3SO_3H (0.6 equiv.)	4	62
4	CF_3SO_3H (1.2 equiv.)	2	85
5	CH_3SO_3H (1.2 equiv.)	6	Trace
6	CH_3CO_2H (1.2 equiv.)	6	Trace
7	CF_3CO_2H (1.2 equiv.)	6	50
8	*p*-TsOH (1.2 equiv.)	6	25
9	$HClO_4$ (1.2 equiv.)	12	36
10	Conc. H_2SO_4 (1.2 equiv.)	12	20
11	Conc. HCl (1.2 equiv.)	12	30

[a]The reaction was carried out by stirring a mixture of 4-chlorophenyl isothiocyanate (1.83 mmol, 1.0 equiv) and 2-aminophenol (1.83 mmol, 1.0 equiv) in THF (10 mL) for 0.5 h for intermediate thiourea formation followed by the addition of the reagent and refluxing for the time indicated.

[b]The product was characterized by NMR and mass spectroscopic methods.



Scheme 1. One-pot synthesis of 2-aminobenzoxazoles.

Table 2. Effect of solvent for the synthesis of *N*-4-chlorophenyl-2-aminobenzoxazole using triflic acid[a]

Entry	Solvent	Time (h)	Isolated yield of **3** (%)[b]
1	Toluene	6	20
2	Benzene	6	24
3	Tetrahydrofuran	2	85
4	1,2-Dichloroethane	6	42
5	1,4-Dioxan	6	32
6	Acetonitrile	6	35
7	*N,N*-Dimethylformamide	6	28
8	Ethanol	6	0
9	Methanol	6	0

[a]The reaction was carried out by stirring a mixture of 4-chlorophenyl isothiocyanate (1.83 mmol, 1.0 equiv) and 2-aminophenol (1.83 mmol, 1.0 equiv) in solvent (10 mL) for 2 h for intermediate thiourea formation followed by the addition of the triflic acid (2.2 mmol, 1.2 equiv) and refluxing for the time indicated.

[b]The product was characterized by NMR and mass spectroscopic methods.

From a solvent study carried out, we found that nonpolar solvents as well as protic polar solvents were ineffective for the heterocyclization (entries 1, 2, 8, and 9; Table 2), while aprotic polar solvents such as tetrahydrofuran (THF) has indicated the best results for the reaction (entries 3 and 4–7; Table 2).

A plausible mechanism for the formation of the product is illustrated in Fig. 2. The reaction is expected to involve an initial reversible cyclization of the thiourea(III) to a tetrahedral thiol intermediate (IV) under the influence of triflic acid, which is finally desulfurized[15] to give the 2-aminobenzoxazole.

To investigate the scope of the reaction, the standardized condition was employed on 2-aminophenol (**2**) and various isothiocyanates (**1a–k**).[16] All the reactions afforded the respective 2-aminobenzoxazoles (**3a–k**) in good yields; the results

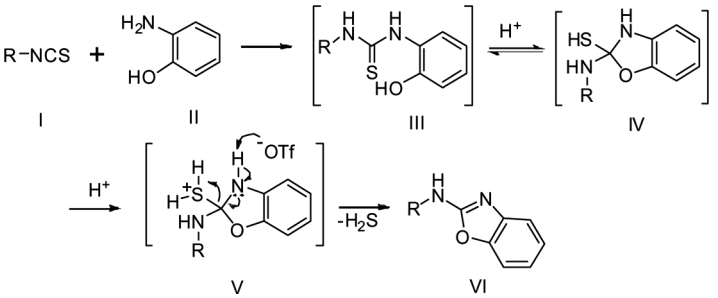
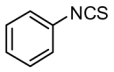
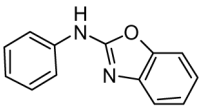
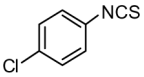
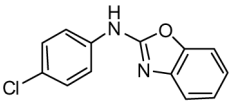
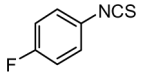
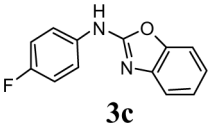
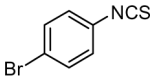
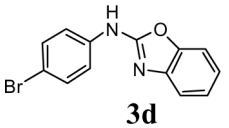
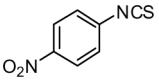
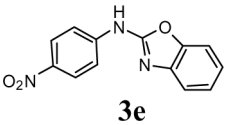
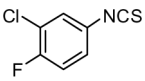
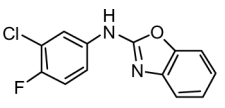
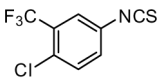
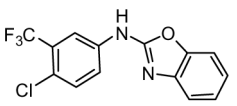
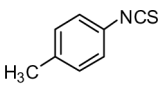
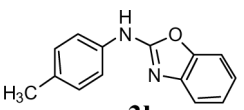
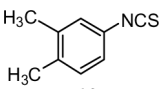
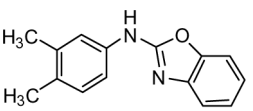


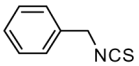
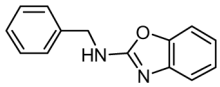
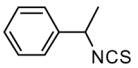
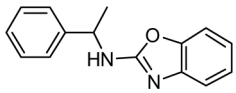
Figure 2. Plausible mechanism for the formation of 2-aminobenzoxazoles.

Table 3. Synthesis of various 2-aminobenzoxazoles[a]

Entry	Isothiocyanate	Reaction time (h)	Product	Isolated yield (%)[b]
1	 **1a**	2	 **3a**	80
2	 **1b**	2	 **3b**	85
3	 **1c**	3	 **3c**	86
4	 **1d**	3	 **3d**	83
5	 **1e**	4	 **3e**	77
6	 **1f**	3	 **3f**	82
7	 **1g**	2	 **3g**	79
8	 **1h**	2	 **3h**	74
9	 **1i**	3	 **3i**	76

(*Continued*)

Table 3. Continued

Entry	Isothiocyanate	Reaction time (h)	Product	Isolated yield (%)[b]
10	 **1j**	4[c]	 **3j**	74
11	 **1k**	4[c]	 **3k**	73

[a]The reaction was carried out by stirring a mixture of isothiocyanate (1.83 mmol, 1.0 equiv) and 2-aminophenol (1.83 mmol, 1.0 equiv) in THF (10 mL) for 0.5 h for intermediate thiourea formation followed by the addition of the triflic acid (2.2 mmol, 1.2 equiv) and refluxing for the time indicated.

[b]The product was characterized by NMR and mass spectroscopic methods.

[c]The reaction mixture was refluxed for 1 h for intermediate thiourea formation followed by the addition of the triflic acid (2.2 mmol, 1.2 equiv) and refluxing for the time indicated.

are summarized in Table 3. The yield of the product was influenced by the substituent on the aromatic ring (Table 3). Electron-withdrawing functional groups, which generally increase the electrophilicity of aryl isothiocyanate, provided better yields (entries 2–7; Table 3), whereas electron-donating groups led to longer reaction time with lesser yields (entries 8, and 9; Table 3). The reaction conditions were also compatible with disubstituted aryl isothiocyanates (entries 6–9; Table 3) and benzyl isothiocyanates (entries 10 and 11; Table 3).

CONCLUSION

In conclusion, an efficient and viable one-pot synthetic strategy for 2-aminobenzoxazoles has been demonstrated.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively on a Bruker Avance DPX 400 (400-MHz) spectrometer in $CDCl_3$/$(CD_3)_2SO$ using tetramethylsilane (TMS) as an internal standard. The chemical shifts (δ) for ^{1}H and ^{13}C are given in parts per million (ppm) relative to residual signals of the solvent. Coupling constants are given in hertz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; m, multiplet; and bs, broad signal. Mass spectra were recorded on Finnigan LCQ LCMS instrument, and the elemental analyses were done on a Vario-EL elemental analyzer. The reactions were monitored by thin-layer chromatography (TLC; Merck). Evaporation of solvents was performed under reduced pressure using a Buchi rotary evaporator. Melting points are uncorrected.

Commercial-grade reagents and solvents were used without further purification: hydrochloric acid (Renkem); α-methyl benzylamine, 4-aminobenzonitrile, 4-chloro-3-trifluoromethylaniline (Aldrich); perchloric acid, aniline, bromoaniline, 4-fluoroaniline, triflic acid, methane sulfonic acid, *p*-toluene sulfonic acid (*p*-TsOH), 4-methylaniline, 3,4-dimethylaniline, thiophosgene, 1,4-dioxan, THF (Spectrochem); sulfuric acid, 4-chloroaniline, methanol, toluene (Merck); sodium hydrogen carbonate, acetonitrile, ethanol, benzene (CDH); trifluoroacetic acid, DCE (Loba Chemie); DMF (SISCO); and 4-nitroaniline and benzylamine (SD Fine Chemical).

General Procedure for the Synthesis of 2-Aminobenzoxazole

To a solution of 4-chlorophenyl isothiocyanate (0.25 g, 1.83 mmol, 1.0 equiv) in THF (10 mL) was added 2-aminophenol (0.2 g, 1.83 mmol, 1.0 equiv), the and the mixture was stirred at room temperature for 30 min. Triflic acid (0.19 mL, 2.2 mmol, 1.2 equiv) was then added to it and refluxed for 2 h. The reaction mixture was cooled, extracted with ethyl acetate, and washed with aqueous $NaHCO_3$ solution; the organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford the crude product. It was dissolved in a minimum amount of dichloromethane, precipitated with excess of hexane, filtered, and dried to get the desired product as a white solid (0.26 g, 85%). The compound was identified by spectral and analytical methods.

***N*-Phenyl-2-aminobenzoxazole (3a).** Yield: 80%, white solid; mp 119–121 °C; ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 7.01–7.05 (m, 1H), 7.11–7.15 (m, 1H), 7.20–7.24 (m, 1H), 7.32–7.39 (m, 2H), 7.44–7.49 (m, 2H), 7.76 (d, 2H), 10.61 (s, 1H, NH); ^{13}C NMR [100 MHz, $(CD_3)_2SO$] δ 109.40, 117.05, 118.01, 122.12, 122.57, 124.85, 129.43, 139.17, 142.87, 147.44, 158.42; MS (*m*/*z*): 211.53 (M^{+1}). $C_{13}H_{10}N_2O$ calcd. C, 74.27; H, 4.79; N, 13.33. Found: C, 74.29; H, 4.84; N, 13.37.

***N*-(4-Chlorophenyl)benzoxazol-2-amine (3b).** Yield: 85%, white solid; mp 216–219 °C; ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 7.15–7.19 (m, 1H), 7.32–7.35 (m, 1H), 7.41 (d, 2H), 7.61 (d, 1H), 7.82 (d, 3H), 10.60 (s, 1H, NH); ^{13}C NMR [100 MHz, $(CD_3)_2SO$]: δ 119.65, 119.82, 121.58, 122.96, 125.87, 126.41, 129.29, 130.44, 139.98, 152.37, 161.76; MS (*m*/*z*): 245.27 (M^{+1}). $C_{13}H_9ClN_2O$ calcd. C, 63.81; H, 3.71; N, 11.45. Found: C, 63.80; H, 3.72; N, 11.48.

***N*-(4-Fluorophenyl)benzoxazol-2-amine (3c).** Yield: 86%, white solid; mp 167–169 °C; ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 7.11–7.14 (m, 1H), 7.19–7.23 (m, 3H), 7.42–7.44 (m, 1H), 7.46–7.48 (m, 1H), 7.72–7.75 (m, 2H), 10.63 (s, 1H, NH); ^{13}C NMR [100 MHz, $(CD_3)_2SO$]: δ 109.42, 115.91, 116.14, 117.03, 119.67, 122.16, 124.49, 135.60, 142.75, 147.46, 158.47; MS (*m*/*z*): 229.33 (M^{+1}). $C_{13}H_9FN_2O$ calcd. C, 68.42; H, 3.97; N, 12.27. Found: C, 68.45; H, 3.99; N, 12.30.

***N*-(4-Bromophenyl)benzoxazol-2-amine (3d).** Yield: 83%, white solid; mp 217–219 °C; ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 7.13–7.15 (m, 1H), 7.20–7.24 (m, 1H), 7.44–7.49 (m, 2H), 7.54 (d, $J = 8.6$ Hz, 2H), 7.72 (d, $J = 8.6$ Hz, 2H), 10.79 (s, 1H, NH); ^{13}C NMR [100 MHz, $(CD_3)_2SO$]: δ 109.51, 114.02, 117.20, 119.91, 122.37, 124.54, 132.19, 138.59, 142.64, 147.42, 158.08; MS (*m*/*z*): 289.33 (M^{+1}), 291.33 (M^{+2}). $C_{13}H_9BrN_2O$ calcd. C, 54.00; H, 3.14; N, 9.69. Found: C, 54.04; H, 3.16; N, 9.71.

***N*-(4-Nitrophenyl)benzoxazol-2-amine (3e).** Yield: 77%, yellow solid; mp 168–170 °C; ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 7.10–7.22 (m, 3H), 7.25–7.36 (m, 2H), 7.60–7.63 (m, 1H), 8.07 (d, $J = 9.2$ Hz, 1H), 8.35 (d, $J = 9.2$ Hz, 1H), 11.75 (s, 1H, NH); ^{13}C NMR [100 MHz, $(CD_3)_2SO$]: δ 109.92, 110.23, 117.72, 122.27, 124.22, 125.78, 130.76, 141.72, 143.75, 154.83, 157.35; MS (m/z): 256.60 (M^{+1}). $C_{13}H_9N_3O_3$ calcd. C, 61.18; H, 3.55; N, 16.46. Found: C, 61.21; H, 3.57; N, 16.49.

***N*-(3-Chloro-4-fluorophenyl)benzoxazol-2-amine (3f).** Yield: 82%, white solid; mp 201–203 °C; ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 7.14–7.16 (m, 1H), 7.21–7.23 (m, 1H), 7.43 (t, $J = 9.0$ Hz, 1H), 7.48–7.51 (m, 2H), 7.60–7.64 (m, 1H), 8.06–8.08 (m, 1H), 10.85 (s, 1H, NH);^{13}C NMR [100 MHz, $(CD_3)_2SO$]: δ 109.57, 117.33, 117.57, 117.79, 118.24, 119.04, 119.82, 120.00, 122.49, 124.61, 142.44, 147.42, 158.01; MS (m/z): 263.27 (M^{+1}). $C_{13}H_8ClFN_2O$ calcd. C, 59.44; H, 3.07; N, 10.66. Found: C, 59.47; H, 3.09; N, 10.69.

***N*-(4-Chloro-3-trifluoromethylphenyl)benzoxazol-2-amine (3g).** Yield: 79%, white solid; mp 199–200 °C; ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 7.15–7.19 (m, 1H), 7.23–7.27 (m, 1H), 7.49–7.53 (m, 2H), 7.72 (d, 1H), 8.03–8.06 (m, 1H), 8.27–8.28 (m, 1H), 11.11 (s, 1H, NH); ^{13}C NMR [100 MHz, $(CD_3)_2SO$]: δ 109.71, 116.59, 116.65, 117.52, 122.70, 122.77, 123.02, 124.71, 127.57, 132.80, 138.74, 142.27, 147.41, 157.70; MS (m/z): 313.27 (M^{+1}). $C_{14}H_8ClF_3N_2O$ calcd. C, 53.78; H, 2.58; N, 8.96. Found: C, 53.80; H, 2.61; N, 8.99.

***N*-(4-Methylphenyl)benzoxazol-2-amine (3 h).** Yield: 74%, white solid; mp 180–181 °C; ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 2.26 (s, 3H), 7.10–7.12 (m, 1H), 7.15–7.17 (m, 2H), 7.19–7.21 (m, 1H), 7.41–7.46 (m, 2H), 7.61–7.63 (m, 2H), 10.47 (s, 1H, NH); ^{13}C NMR [100 MHz, $(CD_3)_2SO$]: δ 20.82, 109.32, 116.92, 118.05, 121.95, 124.39, 129.81, 131.45, 136.66, 142.98, 147.45, 158.55; MS (m/z): 225.47 (M^{+1}). $C_{14}H_{12}N_2O$ calcd. C, 74.98; H, 5.39; N, 12.49; Found: C, 75.01; H, 5.40; N, 12.48.

***N*-(3,4-Dimethyl phenyl)benzoxazol-2-amine (3i).** Yield: 76%, white solid; mp 150–151 °C; ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 2.08 (s, 6H), 7.06–7.13 (m, 2H), 7.19–7.24 (m, 1H), 7.43–7.52 (m, 4H), 10.40 (s, 1H, NH); ^{13}C NMR [100 MHz, $(CD_3)_2SO$]: δ 19.15, 20.18, 109.27, 115.60, 116.91, 119.26, 121.88, 124.36, 125.61, 130.29, 137.04, 136.89, 143.05, 147.46, 158.58; MS (m/z): 239.33 (M^{+1}). $C_{15}H_{14}N_2O$ calcd. C, 75.61; H, 5.92; N, 11.76. Found: C, 75.63; H, 5.95; N, 11.77.

***N*-Benzyl-2-aminobenzoxazole (3j).** Yield: 74%, white solid; mp 104–106 °C; ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 4.50 (d, $J = 6.0$ Hz, 2H), 6.94–6.98 (m, 1H), 7.07–7.11 (m, 1H), 7.21–7.25 (m, 2H), 7.30–7.37 (m, 5H), 8.48 (t, $J = 6.0$ Hz, 1H, NH); ^{13}C NMR [100 MHz, $(CD_3)_2SO$]: δ 46.10, 109.04, 115.97, 119.97, 120.74, 124.12, 127.62, 128.84, 139.45, 143.48, 148.52, 162.88; MS (m/z): 225.20 (M^{+1}). $C_{14}H_{12}N_2O$ calcd. C, 74.98; H, 5.39; N, 12.49. Found: C, 75.02; H, 5.43; N, 12.51.

***N*-(1-Phenylethyl)benzoxazol-2-amine (3k).** Yield: 73%, white solid; mp 49–52 °C; ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 1.49 (d, $J = 6.8$ Hz, 3H), 4.89–4.97 (m, 1H), 6.96 (t, $J = 7.6$ Hz, 1H), 7.08 (t, $J = 7.8$ Hz, 1H), 7.19–7.25 (m, 2H), 7.33 (t, $J = 7.8$ Hz, 3H), 7.42 (d, $J = 7.6$ Hz, 2H), 8.50 (d, 1H, NH); ^{13}C NMR [100 MHz, $(CD_3)_2SO$]: δ 23.48, 52.69, 108.97, 115.93, 120.70, 124.05, 126.04, 127.33, 128.81,

143.45, 144.93, 148.34, 161.98; MS (m/z): 239.07 (M^{+1}). $C_{15}H_{14}N_2O$ calcd. C, 75.61; H, 5.92; N, 11.76. Found: C, 75.65; H, 5.95; N, 11.79.

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