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SHORT COMMUNICATION

N-Methylimidazole-promoted efficient synthesis of 1,3-oxazine-4-thiones under solvent-free conditions

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Abstract A novel method for oxazine ring formation is established using the reaction of ammonium thiocyanate and acid chlorides with napthols in the presence of *N*-methylimidazole to afford [1,3]oxazine-4-thione derivatives in excellent yields.

Keywords Oxazine · 1-Naphthol · 2-Naphthol · Benzoyl isothiocyanate · Acid chloride

Introduction

Oxazines constitute an important class of heterocycles, which have attracted considerable synthetic interest due to their wide range of biological activities [1–5]. Several oxazines exhibit diverse pharmacological properties, such as antagonism to progesterone receptor [6], antitumor [7], antiviral [8, 9], antithrombotic [10], antimycobacterial [11–13], anti-inflammatory [3], antidiabetic and hypolipidaemic [14] effects. Further to these applications, they have also been reported as inhibitors of human leucocyte elastase [15] and serotonin reuptake [16]. This prompted us to establish a novel oxazine ring formation method to find promising bioactive oxazine compounds.

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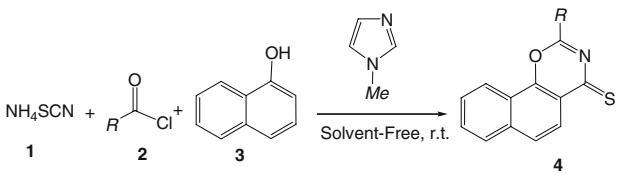
As part of our current studies on the development of new routes in heterocyclic synthesis [17, 18], we report an efficient synthesis of [1,3]oxazine-4-thiones.

Results and discussion

The reaction of ammonium thiocyanate (**1**) and acid chlorides **2** with 1-naphtol (**3**) in the presence of *N*-methylimidazole led to **4** in 65–95% yields (Scheme 1).

Structures of compounds **4a–4g** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. For example, the ^{1}H NMR spectrum of **4a** exhibited 11 proton resonances and 18 carbon resonances, in agreement with the proposed structure. The C=S group resonance in ^{13}C NMR spectra of **4a** appears at 198.5 ppm. The mass spectrum of **4a** displayed the molecular ion peak at $m/z = 289$.

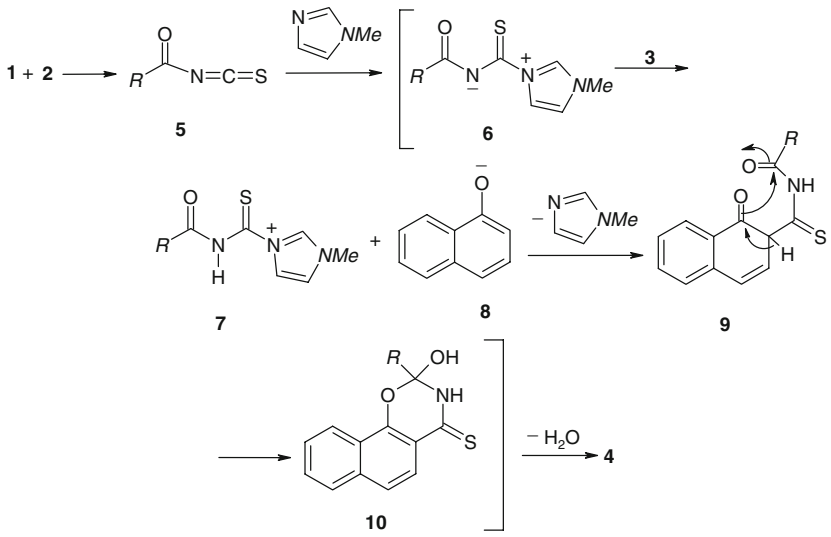
A tentative mechanism for this transformation is proposed in Scheme 2. It is conceivable that the reaction starts with formation of alkanoyl or aroyl isothiocyanate **5**,

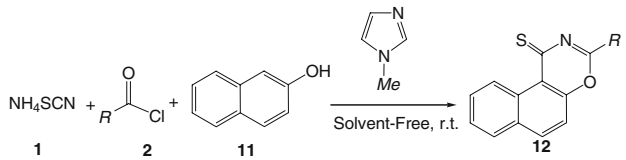


2, 4	R	Yield (%) of 4
a	*Ph*	95
b	4-NO_2-C_6H_4	93
c	4-Me-C_6H_4	92
d	4-Br-C_6H_4	98
e	4-Cl-C_6H_4	65
f	*^{t}Bu*	75
g	*Et*	78

Scheme 1

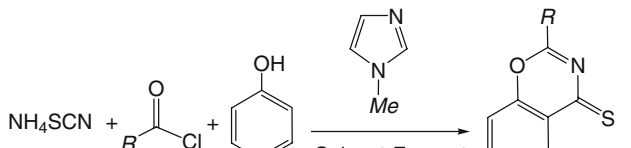
Scheme 2





2, 12	R	Yield (%) of 12
a	*Ph*	90
b	4-NO_2-C_6H_4	93
c	4-Me-C_6H_4	89
d	4-Br-C_6H_4	96
e	4-Cl-C_6H_4	56

Scheme 3



2, 14	R	Yield (%) of 14
a	*Ph*	85
b	4-NO_2-C_6H_4	90

Scheme 4

followed by formation of the 1:1 adducts **6** and its subsequent protonation by 1-naphthol to produce **7**. Then, the positively charged ion **7** is attacked by the anion of naphthol **8**. Intermediate **9** undergoes cyclization reaction and elimination of water to produce **4**.

Also, the reaction of ammonium thiocyanate and acid chlorides with 2-naphtol (**11**) in the presence of *N*-methylimidazole led to **12** in excellent yields (Scheme 3).

Structures of compounds **12a–e** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. For example, the ^{1}H NMR spectrum of **12a** exhibited 11 proton resonances and 18 carbon resonances in agreement with the proposed structure. The C=S group resonance in ^{13}C NMR spectra of **12a** appear at 200.1 ppm. The mass spectrum of **12a** displayed the molecular ion peak at $m/z = 289$. The reaction of ammonium thiocyanate, acid chlorides with phenol **13** in the presence of *N*-methylimidazole led to **14** in excellent yields (Scheme 4).

In conclusion, the reaction of ammonium thiocyanate and acid chlorides with naphthols in the presence of *N*-methylimidazole led to 1,3-oxazine derivatives in excellent yields. The present procedure has the advantage that the reaction is performed under neutral conditions and the starting material can be used without any activation or modification.

Experimental

N-methyl imidazole, 1-naphthol, 2-naphthol, phenol, acid chlorides and ammonium thiocyanate were obtained from *Fluka* and were used without further purification. Mp.: Electrothermal-9100 apparatus; uncorrected. IR Spectra: Shimadzu IR-460 spectrometer. ^{1}H-, ^{13}C-, and ^{31}P-NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500.1, 125.7, and 202.4 MHz, respectively; δ in ppm, J in Hz. EI–MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in *m/z*. Elemental analyses (C, H, N) were performed with a Heraeus CHN–O–Rapid analyzer.

*General procedure for the preparation of compounds **4**, **12** and **14***

To ammonium isothiocyanate (0.15 g, 2 mmol) in a 50-ml flask at r.t. was added acid chloride (2 mmol) via syringe. The reaction mixture was stirred in a water bath at about

90 °C for 5 min. Then, naphthol (2 mmol) was added at this temprature. The reaction mixture was allowed to cool to room temperature. Finally, 0.032 g *N*-methylimidazole (10 mol%) was added via syringe. The resulting mixture was stirred at r.t. for 12 h. The progress of the reaction was monitored by TLC analysis with 7:1 *n*-hexane-EtOAc as eluent and visualisation with UV (254 nm). After completion of the reaction, 15 ml distilled water was added over 5 min to the reaction mixture. The resulting precipitate was collected by filtration on a Buchner funnel and washed with 10 ml of cold (0 °C) diethyl ether to afford the pure title compounds.

2-Phenyl-4H-naphtho[2,1-e][1,3]oxazine-4-thione ***(4a,*** $C_{18}H_{11}NOS$***)***

Pale yellow powders, m.p. 107–109°; yield 0.55 g (95%); IR (KBr): $\bar{\nu}$ = 1,654, 1,584, 1,443, 1,388, 1,263 and 1,215 cm^{-1}; EI–MS: 289 (M^+, 5); 212 (65); 147 (64); 142 (42); 77 (100); ^{1}H NMR: 7.56–7.64 (5 H, *m*, 5 CH), 7.72 (1 H, *t*, ^3J = 7.3, CH), 7.89 (1 H, *d*, ^3J = 7.3, CH), 8.00 (2 H, *t*, ^3J = 8.2, 2 CH), 8.16 (1 H, *t*, ^3J = 7.4, CH), 8.51 (1 H, *d*, ^3J = 7.3, CH) ppm; ^{13}C NMR: 118.6 (CH), 121.6 (CH), 125.8 (CH), 126.3 (CH), 126.7 (CH), 126.8 (CH), 127.3 (C), 128.4 (CH), 128.9 (2 CH), 129.7 (C), 130.5 (2 CH), 134.0 (C), 135.0 (C), 147.2 (C), 165.4 (C), 198.5 (C=S) ppm.

2-(4-Nitrophenyl)-4H-naphtho[2,1-e][1,3]oxazine-4-thione ***(4b,*** $C_{18}H_{10}N_2O_3S$***)***

Yellow powders, mp 167–169°; yield 0.62 g (93%); IR (KBr): $\bar{\nu}$ = 1,657, 1,592, 1,512, 1,391, 1,345 and 1,250 cm^{-1}; EI–MS: 334 (M^+, 15), 257 (46), 212 (74), 77 (68), 122 (100); ^{1}H NMR: 7.41 (1 H, *d*, ^3J = 7.5, CH), 7.51–7.56 (2 H, *m*, 2 CH), 7.81 (1 H, *d*, ^3J = 7.5, CH), 7.88–7.93 (2 H, *m*, 2 CH), 8.32 (2 H, *d*, ^3J = 8.0, 2 CH), 8.43 (2 H, *d*, ^3J = 8.0, 2 CH) ppm; ^{13}C NMR: 118.1 (CH), 120.9 (CH), 123.8 (2 CH), 125.5 (C), 126.6 (CH), 126.7 (CH), 126.8 (C), 126.9 (CH), 128.3 (CH), 131.4 (2 CH), 134.7 (C), 134.8 (C), 146.5 (C), 151.0 (C), 163.4 (C), 197.5 (C=S) ppm.

2-(4-Methylphenyl)-4H-naphtho[2,1-e][1,3]oxazine-4-thione ***(4c,*** $C_{19}H_{13}NOS$***)***

Pale brown powders, mp 114–116°; yield 0.56 g (92%); IR (KBr): $\bar{\nu}$ = 1,672, 1,594, 1,393, 1,265, 1,216 and 1,179 cm^{-1}; EI–MS: 303 (M^+, 15), 226 (46), 213 (72), 77 (66), 90 (100); ^{1}H NMR: 2.50 (3 H, *s*, *Me*), 7.38 (1 H, *d*, ^3J = 7.3, CH), 7.41 (1 H, *d*, ^3J = 7.3, CH), 7.50 (1 H, *t*, ^3J = 7.4, CH), 7.53 (2 H, *d*, ^3J = 7.8, 2 CH), 7.80 (1 H, *d*, ^3J = 7.4, CH), 7.90 (1 H, *d*, ^3J = 7.3, CH), 7.98 (1 H, *d*, ^3J = 7.3, CH), 8.26 (2 H, *d*, ^3J = 7.8, 2 CH) ppm; ^{13}C NMR: 21.8 (Me), 118.3 (CH), 121.4 (CH), 125.5 (C), 126.0 (CH), 126.5 (CH), 126.6 (CH), 126.8 (C), 127.2 (C), 128.1 (CH), 129.5 (2 CH), 130.4 (2 CH), 134.8 (C), 144.7 (C), 147.0 (C), 165.3 (C), 198.1 (C=S) ppm.

2-(4-Bromophenyl)-4H-naphtho[2,1-e][1,3]oxazine-4-thione ***(4d,*** $C_{18}H_{10}BrNOS$***)***

Yellow powders, mp 122–124°; yield 0.72 g (98%); IR (KBr): $\bar{\nu}$ = 1,663, 1,573, 1,390, 1,240, 1,214 and 1,172 cm^{-1}; EI-MS: 334 (M^+, 5), 257 (68), 142 (48), 179 (45), 155 (100); ^{1}H NMR: 7.39 (1 H, *d*, ^3J = 7.5, CH), 7.49–7.55 (2 H, *m*, 2 CH), 7.71 (2 H, *d*, ^3J = 8.1, 2 CH), 7.80 (1 H, *d*, ^3J = 7.5, CH), 7.90–7.93 (2 H, *m*, 2 CH), 8.20 (2 H, *d*, ^3J = 8.1, 2 CH) ppm; ^{13}C NMR: 118.2 (CH), 121.2 (CH), 125.5 (CH), 126.3 (C), 126.6 (CH), 126.7 (CH), 126.9 (C), 128.2 (CH), 128.4 (C), 129.1 (C), 131.8 (2 CH), 132.2 (2 CH), 134.8 (C), 146.7 (C), 164.5 (C), 199.5 (C=S).

2-(4-Chlorophenyl)-4H-naphtho[2,1-e][1,3]oxazine-4-thione ***(4e,*** $C_{18}H_{10}ClNOS$***)***

Yellow powders, mp 120–122°; yield 0.42 g (65%); IR (KBr): $\bar{\nu}$ = 1,598, 1,575, 1,397, 1,256, 1,225 and 1,183 cm^{-1}; EI–MS: 323 (M^+, 10), 286 (74), 212 (66), 126 (56), 77 (64), 111(100); ^{1}H NMR: 7.35 (1 H, *d*, ^3J = 7.4), 7.40–7.48 (2 H, *m*, 2 CH), 7.70 (2 H, *d*, ^3J = 7.6, 2 CH), 7.83 (1 H, *d*, ^3J = 7.4, CH), 7.91–7.94 (2 H, *m*, 2 CH), 8.22 (2 H, *d*, ^3J = 7.6, 2 CH) ppm; ^{13}C NMR: 118.3 (CH), 121.5 (CH), 125.7 (CH), 126.4 (C), 126.7 (CH), 126.9 (CH), 127.1 (C), 128.4 (CH), 128.5 (C), 129.5 (C), 132.0 (2 CH), 132.4 (2 CH), 135.0 (C), 145.2 (C), 164.4 (C), 199.1 (C=S) ppm.

2-(Tert-butyl)-4H-naphtho[2,1-e][1,3]oxazine-4-thione ***(4f,*** $C_{16}H_{15}NOS$***)***

Yellow powders, mp 120–122°; yield 0.40 g (75%); IR (KBr): $\bar{\nu}$ = 1,625, 1,570, 1,389, 1,265, 1,220 and 1,100 cm^{-1}; EI–MS: 269 (M^+, 10), 212 (82), 192 (62), 77 (47), 57 (100); ^{1}H NMR: 1.18 (9 H, *s*, 3 *Me*), 7.30 (1 H, *d*, ^3J = 7.4, CH), 7.40–7.46 (2 H, *m*, 2 CH), 7.80 (1 H, *d*, ^3J = 7.6, CH), 7.91 (1 H, *d*, ^3J = 7.5, CH), 8.75 (1 H, *d*, ^3J = 7.6, CH) ppm; ^{13}C NMR: 27.0 (3 *Me*), 41.5 (C), 122.5 (CH), 123.8 (CH), 124.1 (C), 124.9 (CH), 125.8 (CH), 126.4 (C), 128.2 (CH), 131.4 (CH), 138.4 (C), 150.8 (C), 180.6 (C), 201.4 (C=S) ppm.

2-Ethyl-4H-naphtho[2,1-e][1,3]oxazine-4-thione ***(4 g,*** $C_{14}H_{11}NOS$***)***

Yellow powders, mp 118–120°; yield 0.38 g (78%); IR (KBr): $\bar{\nu}$ = 1,632, 1,582, 1,391, 1,265, 1,321 and 1,254 cm^{-1}; EI–MS: 241 (M^+, 15), 212 (68), 164 (78), 77 (62), 29 (100); ^{1}H NMR: 1.35 (3 H, *t*, ^3J = 7.5, *Me*); 2.65 (2 H, *q*, ^3J = 7.5, OCH_2); 7.41 (1 H, *d*, ^3J = 7.5, CH), 7.47–7.54 (2 H, *m*, 2 CH), 7.74 (1 H, *d*, ^3J = 7.8, CH), 7.84 (1 H, *d*, ^3J = 7.5, CH), 8.72 (1 H, *d*, ^3J = 7.8, CH) ppm; ^{13}C NMR: 9.25 (Me); 21.4 (CH_2), 123.2 (CH), 124.0 (CH), 124.4(C), 125.3 (CH), 126.7 (CH), 127.1 (C), 127.9 (CH), 132.2 (CH), 137.5 (C), 149.8 (C), 177.6 (C), 202.4 (C=S) ppm.

3-Phenyl-1H-naphtho[1,2-e][1,3]oxazine-4-thione ***(12a, $C_{18}H_{11}NOS$)***

Pale yellow powders, mp 103–105°; yield 0.52 g (90%); IR (KBr): $\bar{\nu}$ = 1,637, 1,616, 1,583, 1,497, 1,441 and 1,352 cm^{-1}; EI–MS: 289 (M^+, 10), 212 (46); 147 (86), 142 (64), 77 (100); ^{1}H NMR: 7.50–7.54 (2 H, *m*, 2 CH), 7.56 (2 H, *d*, $^3J_{HH}$ = 7.9, 2 CH), 7.66 (1 H, *t*, $^3J_{HH}$ = 7.4, CH), 7.75 (1 H, *d*, $^3J_{HH}$ = 7.6, CH), 7.86 (1 H, *d*, $^3J_{HH}$ = 7.5, CH), 7.90 (1 H, *d*, $^3J_{HH}$ = 7.4, CH), 7.93 (1 H, *d*, $^3J_{HH}$ = 7.5, CH), 8.31 (2 H, *d*, $^3J_{HH}$ = 7.9, 2 CH) ppm; ^{13}C NMR: 118.8 (CH), 121.3 (CH), 125.8 (CH), 126.7 (CH), 127.8(C), 127.9 (CH), 128.7 (2 CH), 129.5 (C), 129.8 (CH), 130.3 (2 CH), 131.6 (CH), 133.7 (C), 134.0 (C), 148.8 (C), 165.4 (C), 200.1 (C=S) ppm.

3-(4-nitrophenyl)-1H-naphtho[1,1-e][1,3]oxazine-4-thione ***(12b, $C_{18}H_{10}N_2O_3S$)***

Yellow crystals, mp 169–171°; yield 0.62 g (93%); IR (KBr): $\bar{\nu}$ = 1,630, 1,618, 1,593, 1,514, 1,344 and 1,273 cm^{-1}; EI–MS: 334 (M^+, 5), 257 (66), 212 (82), 77 (42), 122 (100); ^{1}H NMR: 7.49–7.55 (2 H, *m*, 2 CH), 7.71 (1 H, *d*, ^3J = 7.5, 2 CH), 7.82 (1 H, *d*, ^3J = 7.6, 2 CH), 8.88 (1 H, *d*, ^3J = 7.6, CH), 7.92 (1 H, *d*, ^3J = 7.5, CH), 8.35 (2 H, *d*, ^3J = 8.1, 2 CH), 8.40 (2 H, *d*, ^3J = 8.1, 2 CH) ppm; ^{13}C NMR: 118.6 (CH), 120.7 (CH), 123.8 (2 CH), 126.1 (C), 126.9 (CH), 127.8 (CH), 127.9 (C), 129.7 (CH), 131.3 (2 CH), 131.7 (CH), 133.8 (C), 135.0 (C), 148.2 (C), 151.0 (C), 163.5 (C), 199.8 (C=S) ppm.

3-(4-Methylphenyl)-1H-naphtho[1,1-e][1,3]oxazine-4-thione ***(12c, $C_{19}H_{13}NOS$)***

Yellow powders, mp 132–134°; yield 0.54 g (89%); IR (KBr): $\bar{\nu}$ = 1,647, 1,593, 1,495, 1,264, 1,232 and 1,166 cm^{-1}; EI–MS: 303 (M^+, 15), 226 (52), 213 (94), 77 (86), 90 (100); ^{1}H NMR: 2.48 (3 H, *s*, *Me*), 7.35 (2 H, *d*, ^3J = 7.2, 2 CH), 7.50–7.56 (2 H, *m*, 2 CH), 7.76 (1 H, *t*, ^3J = 7.8, CH), 7.87 (1 H, *d*, ^3J = 7.5, CH), 7.91 (1 H, *d*, ^3J = 7.5, CH), 7.93 (1 H, *d*, ^3J = 7.6, CH), 8.21 (2 H, *d*, ^3J = 7.6, 2 CH) ppm; ^{13}C NMR: 21.8 (Me), 118.8 (CH), 121.5 (CH), 125.8 (CH), 126.6 (CH), 127.0 (C), 127.8 (CH), 127.9 (CH), 129.4 (2 CH), 129.5 (C), 130.4 (2 CH), 131.6 (C), 134.0 (C), 144.5 (C), 148.9 (C), 165.5 (C), 198.9 (C=S) ppm.

3-(4-Bromophenyl)-1H-naphtho[1,1-e][1,3]oxazine-4-thione ***(12d, $C_{18}H_{10}BrNOS$)***

Yellow powders, mp 123–125°; yield: 0.64 g (96%); IR (KBr): $\bar{\nu}$ = 1,618, 1,574, 1,264, 1,152 and 1,064 cm^{-1}; EI-MS: 334 (M^+, 10), 257 (88), 142 (54), 179 (48), 155 (100); ^{1}H NMR: 7.48–7.53 (2 H, *m*, 2 CH), 7.66 (2 H, *d*, ^3J = 7.6, 2 CH), 7.68 (1 H, *d*, ^3J = 7.3, CH), 7.82 (1 H, *d*, ^3J = 7.4, CH), 7.87 (1 H, *d*, ^3J = 7.4, CH), 7.90 (1 H, *d*, ^3J = 7.3, CH), 8.01 (2 H, *d*, ^3J = 7.6, 2 CH) ppm; ^{13}C NMR: 118.7 (CH), 121.1 (CH), 125.9 (C), 126.7 (CH), 127.7 (CH), 127.9 (CH), 128.6 (C), 128.9 (C), 129.6 (CH), 131.6 (C), 131.7 (2 CH), 132.0 (2 CH), 133.9 (C), 148.5 (C), 164.7 (C), 199.6 (C=S) ppm.

3-(4-Chlorophenyl)-1H-naphtho[1,2-e][1,3]oxazine-4-thione ***(12e, $C_{18}H_{10}ClNOS$)***

Yellow powders, mp 121–123°; yield 0.36 g (56%), IR (KBr): $\bar{\nu}$ = 1,615, 1,572, 1,200, 1,169 and 1,154 cm^{-1}; EI–MS: 323 (M^+, 5), 286 (65), 212 (42), 126 (54), 77 (86), 111 (100); ^{1}H NMR: 7.52–7.57 (2 H, *m*, 2 CH), 7.64 (2 H, *d*, ^3J = 7.5, 2 CH), 7.71 (1 H, *d*, ^3J = 7.4, CH), 7.84 (1 H, *d*, ^3J = 7.3, CH), 7.91 (1 H, *d*, ^3J = 7.4, CH), 7.96 (1 H, *d*, ^3J = 7.3, CH), 8.22 (2 H, *d*, ^3J = 7.5, 2 CH) ppm; ^{13}C NMR: 118.6 (CH), 122.4 (CH), 126.1 (C), 126.8 (CH), 128.2 (CH), 128.4 (CH), 129.1 (C), 129.8 (C), 130.2 (CH), 131.4 (C), 131.9 (2 CH), 132.7 (2 CH), 134.1 (C), 149.5 (C), 165.7 (C), 198.9 (C=S) ppm.

2-Phenyl-4H-[1,3]-benzoxazine-4-thione ***(14a, $C_{14}H_9NOS$)***

Yellow powders, mp 114–116°; yield 0.41 g (85%); IR (KBr): $\bar{\nu}$ = 1,658, 1,579, 1,443, 1,387, 1,258 and 1,210 cm^{-1}; EI–MS: 239 (M^+, 5), 187 (60), 162 (85), 77 (100), 54 (42); ^{1}H NMR: 7.31–7.42 (4 H, *m*, 4 CH), 7.74 (2 H, *t*, ^3J = 7.5, CH), 8.12 (2 H, *d*, ^3J = 8.5, 2 CH), 8.64 (1 H, *d*, ^3J = 7.6, CH) ppm; ^{13}C NMR: 118.2 (CH), 122.0 (CH), 124.2 (C), 127.1 (CH), 128.4 (2 CH), 129.6 (2 CH), 131.7 (CH), 131.9 (C), 135.1 (CH), 151.7 (C), 167.3 (C), 200.1 (C=S) ppm.

2-(4-Nitrophenyl-4H-[1,3]-benzoxazine-4-thione ***(14b, $C_{14}H_8N_2O_3S$)***

Yellow powders, mp 120–122°; yield 0.51 g (90%); IR (KBr): $\bar{\nu}$ = 1,578, 1,592, 1,440, 1,375, 1,241 and 1,151 cm^{-1}; EI–MS: 284 (M^+, 10), 230 (60), 164 (72), 120 (100), 54 (36); ^{1}H NMR: 7.32–7.45 (3 H, *m*, 3 CH), 8.35 (2 H, *d*, ^3J = 8.2, 2 CH), 8.41 (2 H, *d*, ^3J = 8.2, 2 CH), 8.74 (1 H, *d*, ^3J = 7.6, CH) ppm; ^{13}C NMR: 119.3 (CH), 126.1 (2 CH), 127.4 (2 CH), 127.8 (CH), 128.5 (C), 129.2 (CH), 131.2 (CH), 136.3 (C), 150.0 (C), 152.7 (C), 168.4 (C), 199.2 (C=S) ppm.

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