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The Green Procedure for the Synthesis of 1,3-oxazine-4-thiones Using ZnO Nanoparticles

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Abstract

A novel method for oxazine derivatives formation is established using the reaction of ammonium thiocyanate and acid chlorides with 1-naphthol in the presence of Nanoparticle of ZnO to afford [1,3]oxazine-4-thione derivatives under solvent-free conditions at room temperature in excellent yields.

Keywords: *Oxazine, 1-Naphthol, Benzoyl isothiocyanate,OH-acid.*

Introduction

The development of simple synthetic routes to widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis [1]. Development of novel synthetic methods for the construction of new analogs of bioactive heterocyclic compounds represents a major challenge in synthetic organic and medicinal chemistry. Various oxazines have been found to show versatile bioactivities [2-6]. The synthesis of 1,3-oxazines has attracted attention in the past because of their potential as antibiotics [7-10], antitumor [11-13], analgesics [14,15], and anticonvulsants [16]. One present significant area of new synthetic chemistry is the expansion of effective workable procedures that diminish the necessary reagents, solvents, cost time and separation courses for the preferred conversion and also minimize the creation of waste [17]. Whereas the multi component reaction (MCR) tactic is identified as a strong method in the direction of this end, a catalytic reaction involving a MCR would be more beautiful to attain this purpose. Also, This procedure is performed under solvent free conditions and green conditions but more of procedure that is reported in the literature was performed in the hazardous solvents such as CH_2Cl_2 and $CHCl_3$ [18].

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Experimental

All chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV.

IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H, and ^{13}C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. ^{1}H, and ^{13}C, spectra were obtained for solutions in $CDCl_3$ using TMS as internal standard or 85% H_3PO_4 as external standard.

General Procedure for the Preparation of nanoparticle ZnO (NP-ZnO)

Sodium hydroxid (0.44 g) was disolved in distilled water (75 mL) at room temprature, zinc acetate dihydrate (0.6 g) was added to the mixture and the solution was refluxed for 1.5 h at 80 ◦C. The solution was then cooled at room temperature, the precipitate was assembled by filtration and washed with distilled water and ethanol (96%) several times. NP-ZnO was dried in the air at room temprature during 24 h.

General procedure for preparation of compounds **4**

To a stirred of amonium isothiocyanate (2 mmol) was added the acid chlorides (2 mmol). After five minutes, the acids (2 mmol) was added slowly. Finally, NP-ZnO (10 mol%) was added. The reaction mixture was then stirred for 12 h at room temperature. After completion of reaction (monitored by TLC), 15 mL H_2O was poured into the reaction mixture, and the solid residue was filtered and washed by cold diethylether (Et_2O) to afford **4**.

*2-phenyl-4H-naphtho[2,1-e][1,3]oxazine-4-thione (***4a***)*

Pale yellow powders; yield: 0.55 g (95%); m.p. 107-109°. IR (KBr): $\overline{\nu}$ = 1654, 1584, 1443, 1388, 1263 and 1215 cm^{-1}; EI-MS: 289 (M^+, 15); 149 (24); 105 (50); 77 (100); 51 (68); ^{1}H NMR: 7.56-7.64 (5 H, m, 5 CH), 7.72 (1 H, t, ^{3}J = 7.3, CH), 7.89 (1 H, d, ^{3}J = 7.3, CH), 8.00 (2 H, t, ^{3}J = 8.2, 2 CH), 8.16 (1 H, t, ^{3}J = 7.4, CH), 8.51 (1 H, d, ^{3}J = 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***)*

Yellow powders; yield: 0.62 g (93%); m.p. 167-169°. IR (KBr): $\overline{\nu}$ = 1657, 1592, 1512, 1391, 1345 and 1250 cm^{-1}; EI-MS: 334 (M^+, 15); 257 (46); 212 (74); 77 (68); 122 (100); ^{1}H NMR: 7.41 (1 H, d, ^{3}J = 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***)*

Pale brown powders; yield: 0.56 g (92%); m.p. 114-116°. IR (KBr): $\overline{\nu}$ = 1672, 1594, 1393, 1265, 1216 and 1179 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***)*

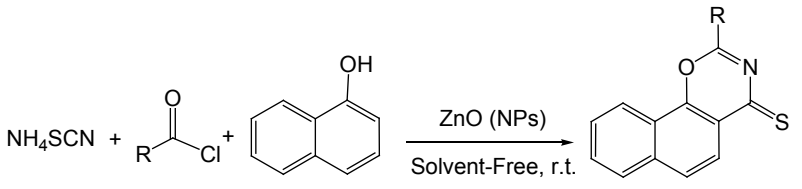
Yellow powders; yield: 0.72 g (98%); m.p. 122-124°. IR (KBr): $\overline{\nu}$ = 1663, 1573, 1390, 1240, 1214 and 1172 cm^{-1}; ^{1}H NMR: 7.39 (1 H, d, ^3J = 7.5, CH), 7.49-7.55 (2 H, m, 2 CH), 7.71 (2 H, d, ^3J = 8.1, 2 CH), 7.80 (1 H, d, ^3J = 7.5, CH), 7.90-7.93 (2 H, m, 2 CH), 8.20 (2 H, d, ^3J = 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). EI-MS: 334 (M+, 5), 257 (68), 142 (48), 179 (45), 155 (100) ppm.

*2-(4-chlorophenyl)-4H-naphtho[2,1-e][1,3] oxazine-4-thione (***4e***)*

Yellow powders; yield: 0.42 g (65%); m.p. 120-122°. IR (KBr): $\overline{\nu}$ = 1598, 1575, 1397, 1256, 1225 and 1183 cm^{-1}; EI-MS: 323 (M$^+$, 10); 286 (74); 212 (66); 126 (56); 77 (64); 111(100); 1H 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.

Results and discussion

The reaction of ammonium thiocyanate 1, acid chlorides 2 with 1-naphtol 3 in the presence of ZnO nanoparticles led to 4 in 90-95% yields (Scheme1).



1 2 3 4

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

Scheme 1. Synthesis of Oxazine derivatives 4.

As shown in Table 1, the reaction did not take place without any catalyst (Table 1, entry 1) and the yield of the preferred product was increased when NP-ZnO was utilized (Table 1, entry 6). The yield increased effortlessly with catalyst fill up to 15% but further increase led to diminish of product exchange. To know the position of solvent, we checked several solvent systems, such as CH_3CN, H_2O, CH_2Cl_2, $CHCl_3$, Et_2O, n-hexane and solvent-free conditions (Table 2). The results were shown the quantity of preferred product was set up to be greater in solvent-free condition.

Table 2. Optimization of Solvent.

Entry	Solvent	Temperature (°C)	Yeild (%)
1	CH_3CN	r.t.	83
2	CH_3CN	70	83
3	H_2O	r.t.	54
4	CH_2Cl_2	r.t.	35
5	$CHCl_3$	r.t.	40
6	Et_2O	r.t.	-----
7	n-Hexane	r.t.	------
8	Toluene	r.t.	65
9	**Solvent-free**	r.t.	**85**
9	Solvent-free	70	85

The SEM image and XRD pattern of NP-ZnO shows in Figure 1 and Figure 2 respectively. The average crystal size for NP-ZnO is about 30 nm.

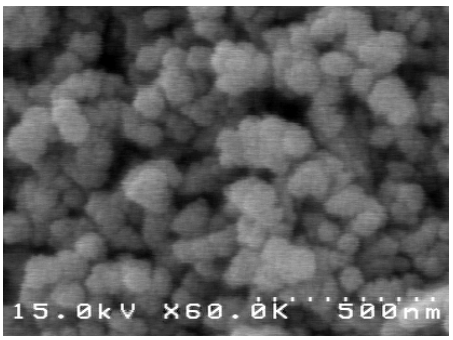


Figure 1. SEM image of NP-ZnO.

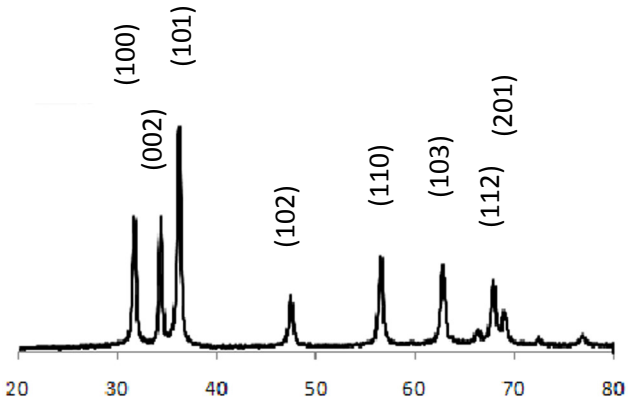
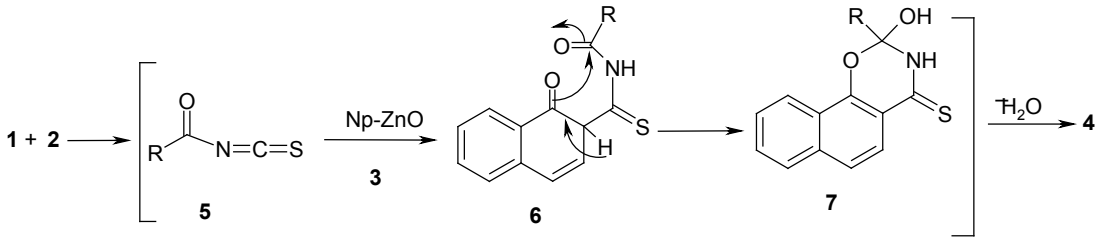


Figure 2. XRD spectra of NP-ZnO.

The catalyst can be resolved five times without significant loss of activity. Structures of compounds **4a–4e** 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 agreement with the structure. The C=S group resonance in ^{13}C NMR spectra of **4a** appear 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 isothiocyanate **5**, followed by formation of the 1:1 adducts **6** to produce **7**. Intermediate **7** undergoes cyclization reaction and elimination of water to produce **4**.



Scheme 2. Proposed mechanism for synthesis of **4**.

Conclusion

In conclusion, the reaction of ammonium thiocyanate, acid chlorides with OH-acids in the presence of NP-ZnO led to 1,3-oxazine derivatives in excellent yields. The present procedure had the advantage that the reaction was performed under neutral conditions so that the starting material could be used without any activation or modification.

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