

Biosynthesis of Fe₃O₄-magnetic nanoparticles using *Clover Leaf* aqueous extract: Green synthesis of oxazole derivatives

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Abstract: 1,3-oxazole derivatives were prepared *via* multicomponent reaction of α -bromo ketones, acid chlorides and ammonium thiocyanate in the presence of catalytic amount of Fe₃O₄ MNPs in water at 50°C in good yields. Also, the reaction of alkyl (aryl) isothiocyanates and γ -bromo ketones in the presence of catalytic amount of Fe₃O₄ MNPs in water at 50°C are investigated. The catalyst was reused five times with minor decrease in its catalytic activity. In addition, high yields, easy procedure, easy separation of catalyst from the mixture of reactions are the advantages of these reactions.

Keywords: Fe₃O₄ MNPs; 1,3-oxazole; Isothiocyanates; Ammonium thiocyanate; Alkyl (aryl) isothiocyanates.

Introduction

A multicomponent reaction is commonly described as a reaction in which three or more reactants join in one pot to produce one product that have fundamentally all of the atoms of the starting materials (with the elimination of products, such as H₂O, HCl or MeOH) [1-2]. Corresponding to the usual chemical reactions, the multicomponent reaction methods have the advantages such as simplicity and synthetic efficiency [3-4]. The finding of novel synthetic methods towards oxazole derivatives is a part of continued interest for organic chemists. The synthesis of functionalized oxazoles are attractive due to having many applications including biological activity such as antibacterial, anti-fungal [5], anti-tubercular [6] and anti-inflammatory activities [7] in addition to their applications as important precursors in many convenient synthetic transformations [8-10].

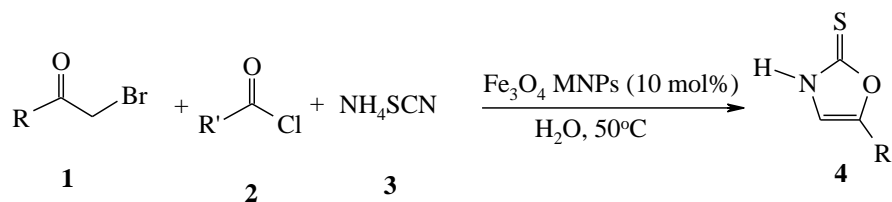
Oxazoles also are considered in colorant chemistry particularly as sparkling compounds and as fluorescent whitening agents for textiles [11-12]. Water is the inexpensive and environmentally kindly solvent. The employing of water as solvent in organic synthesis is of large attention [13]. The reaction of α -bromo ketones **1**, acid chlorides **2** and ammonium thiocyanate **3** in the presence of catalytic amount of Fe₃O₄ MNPs (10 mol%) lead to functionalized 1,3-oxazole derivatives **4** [14] in good yields (Scheme 1).

Results and discussion

For optimization of these reactions several catalysts and solvents were used. ZnO-NPs, TiO₂-NPs, KF/CP-NPs and Fe₃O₄-MNPs are used as catalyst. Among them Fe₃O₄-MNPs is the best because of easy separation of catalyst from the mixture of reaction and easy purification of product. Several solvents such as CH₂Cl₂, CH₃CN, toluene and H₂O are employed for these reactions. Among them H₂O is the best because

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of easy separation of product by filtration. The results of optimization are shown in Table 1. The Fe₃O₄MNPs are prepared according to literature procedure [15-16]. For confirming the structure of Fe₃O₄ MNPs, SEM (Figure 1) and XRD (Figure 2) spectra are given for nanostructure. Particles size of Fe₃O₄ MNPs has been found to be 21–23 nm [16].



4	R	R'	Yield % of 4
a	CO ₂ Et	4-MeO-C ₆ H ₄	87
b	4-MeO-C ₆ H ₄	4-NO ₂ -C ₆ H ₄	80
c	4-Me-C ₆ H ₄	^t Bu	89

Scheme 1: Synthesis of oxazole derivatives **4**

Table 1: Optimization of reaction condition for the synthesis of compound **4a**

Entry	Catalyst	Solvent	Temp.	Time	Yield (%)
1	----	CH ₂ Cl ₂	r.t.	6	15
2	----	H ₂ O	r.t.	12	48
3	----	H₂O	50	8	55
4	----	H ₂ O	80	8	55
5	----	CH ₃ CN	r.t.	8	30
6	----	CH ₃ CN	50	8	45
7	----	toluene	r.t.	7	35
8	----	toluene	50	7	47
9	----	toluene	90	7	48
10	KF/CP (NPs)	CH ₂ Cl ₂	r.t.	8	38
11	KF/CP (NPs)	H ₂ O	r.t.	10	65
12	KF/CP (NPs)	H₂O	50	8	80
13	KF/CP (NPs)	CH ₃ CN	r.t.	8	42
14	KF/CP (NPs)	CH ₃ CN	50	8	45
15	KF/CP (NPs)	CH ₃ CN	80	8	45
16	KF/CP (NPs)	toluene	r.t.	8	48
17	KF/CP (NPs)	toluene	50	8	52
18	KF/CP (NPs)	toluene	80	8	54
19	ZnO (NPs)	H ₂ O	r.t.	10	47
20	ZnO (NPs)	H₂O	50	8	85
21	ZnO (NPs)	CH ₃ CN	50	8	70
22	ZnO-NR	CH ₂ Cl ₂	r.t.	12	35
23	ZnO-NR	H ₂ O	50	10	85
24	ZnO-NR	toluene	50	8	60
25	ZnO-NR	CH ₃ CN	50	10	80
26	TiO ₂ -NPs	CH ₂ Cl ₂	50	12	45
27	TiO ₂ -NPs	H ₂ O	50	8	78
28	TiO ₂ -NPs	CH ₃ CN	50	10	70
29	TiO ₂ -NPs	toluene	50	8	78
30	Fe₃O₄-MNPs	H₂O	50	6	87
31	Fe ₃ O ₄ -MNPs	CH ₃ CN	50	8	76
32	Fe ₃ O ₄ -MNPs	toluene	50	8	80

These reactions have low yield and busy mixture without catalyst. The sample reaction (synthesis of compound **4a**) have similar yield with ZnO-NPs and Fe₃O₄ MNPs (entry 20 and entry 30) but separation of catalyst from mixture of reaction after completing of reaction is easy in the presence of Fe₃O₄ MNPs.

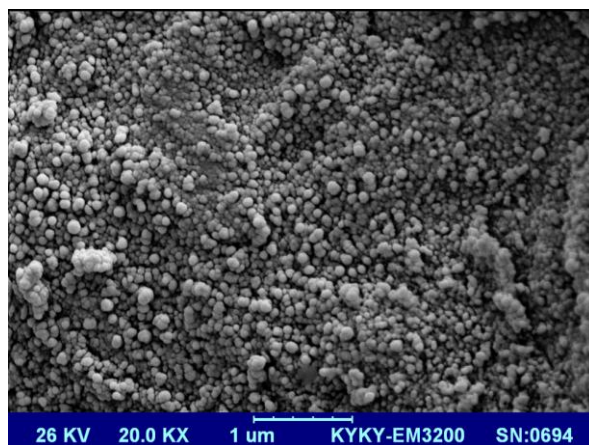


Figure 1: SEM image of Fe₃O₄ nanoparticles.

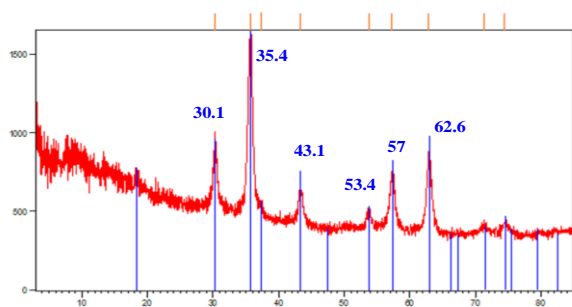
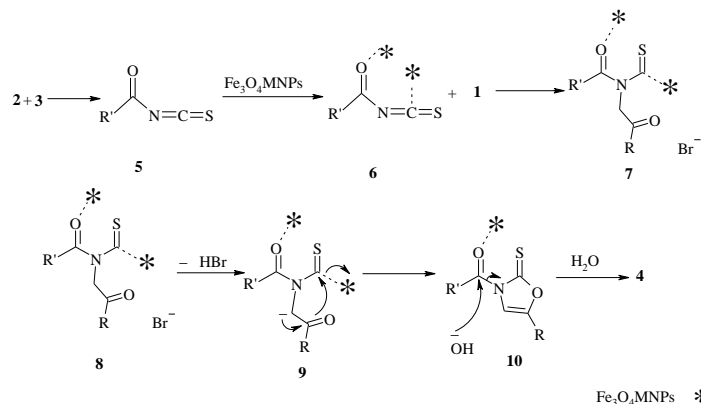


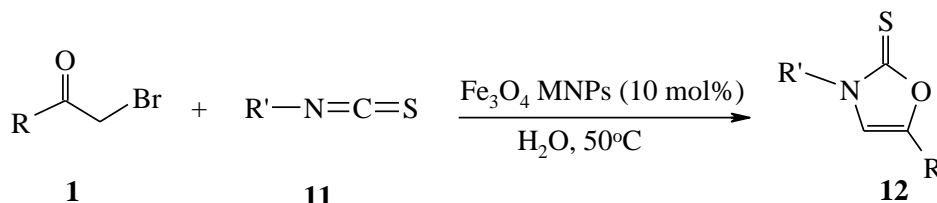
Figure 2: XRD spectra of Fe₃O₄ nanoparticles.

Structures of **4a–4c** are confirmed by IR, ¹H NMR, ¹³C NMR mass spectra. For example, the ¹H NMR spectrum of **4a** exhibits one singlet for methin proton at δ = 7.82 ppm and one singlet at δ = 11.74 ppm for NH proton. The ¹³C NMR spectra of **4a** show resonance of carbonyl and thionyl group at 161.7 (C=O) ppm and 172.3 (C=S) ppm respectively. A proposed mechanism for this transformation is given in Scheme 2. The reaction starts with formation of isothiocyanate **5** that followed by activation in the presence of Fe₃O₄ MNPs to generate intermediate **6**. Alkyl bromides **1** react with intermediate **6** and produced intermediate **7** that finally intermediate **10** generate by intermolecular cyclization. In water compound **10** converted to **4** by elimination R'COOH [17].



Scheme 2: Proposed mechanism for generation of thiazole derivatives **5**

Under similar conditions, the reaction of α-bromo ketones **1** and isothiocyanate **11** in the presence of catalytic amounts of Fe₃O₄ MNPs in water as a solvent produce 1,3-oxazole derivatives **12** in good yields (Scheme 3). The amount of catalyst in these reactions is 10 mol%. By increasing of catalyst from 10 to 25 mol% wasn't seen any change in yield of reaction.



12	R	R'	Yield % of 12
a	CO ₂ Et	4-MeO-C ₆ H ₄	95
b	CO ₂ Et	4-NO ₂ -C ₆ H ₄	90
c	CO ₂ Et	^t Bu	92
d	4-MeO-C ₆ H ₄	^t Bu	92
e	4-Me-C ₆ H ₄	4-MeO-C ₆ H ₄	87
f	4-Br-C ₆ H ₄	4-NO ₂ -C ₆ H ₄	83

Scheme 3: Generation of oxazole derivatives **4**.

Conclusion

In summary, 1,3-oxazole derivatives are synthesized in good yields from the reaction of α -bromo ketones, acid chlorides and ammonium thiocyanate in the presence of catalytic amount of Fe_3O_4 MNPs in water. Also, the reaction of α -bromo ketones and isothiocyanate in the presence of catalytic amount of Fe_3O_4 MNPs lead to 1,3-oxazole derivatives in good yields. Performing these reactions in water as green solvent and simplicity of separation of catalyst and product with present procedure makes it an interesting alternative to the complex multistep approaches.

Experimental

All chemicals used in this work are prepared from Fluka (Buchs, Switzerland) and employed without further purification. We prepared Fe_3O_4 MNPs through literature method [16-17]. Melting points are measured on an Electrothermal 9100 apparatus. IR spectra are measured on a Shimadzu IR-460 spectrometer. ^1H , and ^{13}C NMR spectra are obtained using a BRUKER DRX-400 AVANCE spectrometer at 400.1 and 100 MHz, respectively. Mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV. ^1H , and ^{13}C , spectra are obtained for solutions in CDCl_3 using TMS as the internal standard.

General procedure for preparation of compounds 4:

To a magnetically stirred mixture of acid chloride **2** (2 mmol) and ammonium thiocyanate **3** in water (5 mL) at 50 °C, α -bromo ketones **1** (2 mmol) and Fe_3O_4 MNPs (10 mol %) was added after 30 min. After completion of the reaction (8 h; TLC control (hexane–AcOEt, 6:1), mixture is allowed to cool to room temperature. The Fe_3O_4 MNPs were separated by external magnet. After removing solvent, the residue was purified by column chromatography (6:1 hexane/EtOAc) to afforded pure title compounds.

Ethyl 2-thioxo-2,3-dihydro-1,3-oxazole-5-carboxylate (**4a**):

Pale yellow oil; yield: 0.30 g (87%). IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 1737, 1627, 1586, 1475, 1364 and 1295 cm^{-1} . ^1H NMR: δ 1.28 (3 H, t, $^3J = 7.4$ Hz, Me), 4.25 (2 H, q, $^3J = 7.4$ Hz, CH_2O), 7.82 (1 H, s, CH), 11.74 (1 H, s, NH) ppm. ^{13}C NMR: δ 13.8 (Me), 62.4 (CH_2O), 117.4 (CH), 138.2 (C), 161.7 (C=O), 172.3 (C=S) ppm. MS, m/z (%): 173 (M^+ , 10), 128 (86), 45 (100). Anal. Calcd for $\text{C}_6\text{H}_7\text{NO}_3\text{S}$ (173.19): C, 41.61; H, 4.07; N, 8.09. Found: C, 41.73; H, 4.23; N, 8.24.

5-(4-methoxyphenyl)-1,3-oxazole-2(3H)-thione (**4b**):

Yellow oil; yield: 0.33g (80%). IR (KBr): 1689, 1637, 1574, 1478, 1375 and 1294 cm^{-1} . ^1H NMR: δ 3.87 (3 H, s, MeO), 6.92 (2 H, d, $^3J = 7.6$ Hz, 2 CH), 7.18 (2 H, d, $^3J = 7.6$ Hz, 2 CH), 7.67 (1 H, s, CH), 11.83 (1 H, s, NH) ppm. ^{13}C NMR: δ 55.6 (MeO), 103.8 (CH), 115.8 (2 CH), 128.2 (C), 129.3 (2 CH), 148.6 (C), 158.6 (C), 176.2 (C=S) ppm. MS, m/z (%): 207 (M^+ , 15), 100 (84), 107 (100). Anal. Calcd for $\text{C}_{10}\text{H}_9\text{NO}_2\text{S}$ (207.25): C, 57.95; H, 4.38; N, 6.76. Found: C, 58.12; H, 4.53; N, 6.82.

5-(4-methylphenyl)-1,3-oxazole-2(3H)-thione (**4c**):

Yellow oil; yield: 0.34g (89%). IR (KBr): 1962, 1642, 1583, 1462, 1368 and 1274 cm^{-1} . ^1H NMR: δ 2.32 (3 H, s, Me), 7.10 (2 H, d, $^3J = 7.5$ Hz, 2 CH), 7.16 (2 H, d, $^3J = 7.5$ Hz, 2 CH), 7.73 (1 H, s, CH), 12.04 (1 H, s, NH) ppm. ^{13}C NMR: δ 21.8 (Me), 102.7 (CH), 126.3 (2 CH), 127.5 (2 CH), 132.7 (C), 135.6 (C), 148.6 (C), 174.5 (C=S) ppm. MS, m/z (%): 191 (M^+ , 15), 104 (78), 91 (100). Anal. Calcd for $\text{C}_{10}\text{H}_9\text{NOS}$ (191.25): C, 62.80; H, 4.74; N, 7.32. Found: C, 62.94; H, 4.86; N, 7.45.

General procedure for preparation of compounds 12:

To a magnetically stirred mixture of isothiocyanate **11** (2 mmol) and α -bromo ketones **1** (2 mmol) in water was added Fe_3O_4 MNPs (10 mol %) at 50 °C. After completion of the reaction (7 h; TLC control (hexane–AcOEt, 4:1), mixture is allowed to cool to room temperature. Fe_3O_4 MNPs were separated by external magnet and the solid was separated by filtration to afforded pure title compounds.

Ethyl 3-(4-methoxyphenyl)-2-thioxo-2,3-dihydro-1,3-oxazole-5-carboxylate (**12a**):

Yellow powders; yield: 0.53 g (95%). IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): 1739, 1692, 1587, 1467, 1374 and 1284 cm^{-1} . ^1H NMR: δ 1.32 (3 H, t, $^3J = 7.3$ Hz, Me), 3.78 (3 H, s, MeO), 4.26 (2 H, q, $^3J = 7.3$ Hz, CH_2O), 6.93 (2 H, d, $^3J = 7.8$ Hz, 2 CH), 7.24 (2 H, d, $^3J = 7.8$ Hz, 2 CH), 7.62 (1 H, s, CH) ppm. ^{13}C NMR: δ 14.2 (Me), 55.6 (MeO), 62.5 (CH_2O), 115.8 (2 CH), 117.2 (CH), 129.6 (2 CH), 131.3 (C), 138.3 (C), 158.6 (C), 160.6 (C=O), 170.5 (C=S) ppm. MS, m/z (%): 279 (M^+ , 15), 234 (64), 45 (100). Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_4\text{S}$ (279.31): C, 55.90; H, 44.69; N, 5.01. Found: C, 56.04; H, 44.83; N, 5.17.

Ethyl 3-(4-nitrophenyl)-2-thioxo-2,3-dihydro-1,3-oxazole-5-carboxylate (**12b**):

Yellow powders; yield: 0.53 g (90%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 1742, 1695, 1592, 1478, 1382 and 1273 cm^{-1} . ^1H NMR: δ 1.28 (3 H, t, $^3J = 7.4$ Hz, Me), 4.23 (2 H, q, $^3J = 7.4$ Hz, CH_2O), 7.63 (2 H, d, $^3J = 7.8$ Hz, 2 CH), 7.68 (1 H, s, CH), 8.23 (2 H, d, $^3J = 7.8$ Hz, 2 CH) ppm. ^{13}C NMR: δ 14.3 (Me), 62.4 (CH_2O), 117.3 (CH), 121.7 (2 CH), 127.4 (2 CH), 130.8 (C), 145.2 (C), 148.4 (C), 161.4 (C=O), 171.3 (C=S) ppm. MS, m/z (%): 294 (M^+ , 10), 249 (74), 45 (100). Anal. Calcd for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_5\text{S}$ (294): C, 48.98; H, 3.43; N, 9.52. Found: C, 49.18; H, 3.56; N, 9.68.

Ethyl 3-(tert-butyl)-2-thioxo-2,3-dihydro-1,3-oxazole-5-carboxylate (12c):

Yellow powders; yield: 0.42 g (92%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 1738, 1634, 1545, 1462, 1363 and 1247 cm^{-1} . ^1H NMR: δ 1.25 (3 H, t, $^3J = 7.4$ Hz, Me), 1.68 (9 H, s, Me_3C), 4.26 (2 H, q, $^3J = 7.4$ Hz, CH_2O), 7.52 (1 H, s, CH) ppm. ^{13}C NMR: δ 14.2 (Me), 28.7 (Me_3C), 52.6 (Me_3C), 62.4 (CH_2O), 116.3 (CH), 125.6 (C), 161.4 (C=O), 177.6 (C=S) ppm. MS, m/z (%): 229 (M^+ , 15), 172 (78), 57 (100). Anal. Calcd for $\text{C}_{10}\text{H}_{15}\text{NO}_3\text{S}$ (229.29): C, 52.38; H, 6.59; N, 6.11. Found: C, 52.53; H, 6.73; N, 6.26.

3-(tert-butyl)-5-(4-methoxyphenyl)-1,3-oxazole-2(3H)-thione (12d):

Yellow powders; yield: 0.48 g (92%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 1695, 1593, 1486, 1368 and 1295 cm^{-1} . ^1H NMR: δ 1.68 (9 H, s, Me_3C), 3.76 (3 H, s, MeO), 6.95 (2 H, d, $^3J = 7.6$ Hz, 2 CH), 7.18 (1 H, s, CH), 7.28 (2 H, d, $^3J = 7.6$ Hz, 2 CH) ppm. ^{13}C NMR: δ 28.9 (Me_3C), 52.3 (Me_3C), 55.7 (MeO), 102.4 (CH), 116.8 (2 CH), 127.4 (C), 129.2 (2 CH), 138.6 (C), 159.3 (C), 179.5 (C=S) ppm. MS, m/z (%): 263 (M^+ , 10), 206 (68), 57 (100). Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_3\text{S}$ (263.36): C, 63.85; H, 6.51; N, 5.32. Found: C, 63.96; H, 6.63; N, 5.44.

3-(4-methoxyphenyl)-5-(4-methylphenyl)-1,3-oxazole-2(3H)-thione (12e):

Pale yellow powders; yield: 0.52 g (87%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 1687, 1568, 1474, 1365 and 1273 cm^{-1} . ^1H NMR: δ 2.34 (3 H, s, Me), 3.78 (3 H, s, MeO), 6.92 (2 H, d, $^3J = 7.5$ Hz, 2 CH), 7.15 (2 H, d, $^3J = 7.6$ Hz, 2 CH), 7.23 (2 H, d, $^3J = 7.6$ Hz, 2 CH), 7.32 (2 H, d, $^3J = 7.5$ Hz, 2 CH), 7.52 (1 H, s, CH) ppm. ^{13}C NMR: δ 21.6 (Me), 55.6 (MeO), 101.8 (CH), 115.6 (2 CH), 125.8 (2 CH), 128.2 (2 CH), 129.6 (2 CH), 133.2 (C), 134.6 (C), 139.7 (C), 143.8 (C), 158.9 (C), 175.4 (C=S) ppm. MS, m/z (%): 297 (M^+ , 15), 206 (54), 190 (78), 77 (100). Anal. Calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_2\text{S}$ (297.37):

C, 68.66; H, 5.08; N, 4.71. Found: C, 68.78; H, 5.19; N, 4.83.

3-(4-nitrophenyl)-5-(4-bromophenyl)-1,3-oxazole-2(3H)-thione (12f):

Yellow powders; yield: 0.52 g (83%). IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 1692, 1576, 1484, 1367 and 1283 cm^{-1} . ^1H NMR: δ 7.18 (2 H, d, $^3J = 7.6$ Hz, 2 CH), 7.38 (2 H, d, $^3J = 7.6$ Hz, 2 CH), 7.48 (1 H, s, CH), 7.63 (2 H, d, $^3J = 7.8$ Hz, 2 CH), 8.12 (2 H, d, $^3J = 7.8$ Hz, 2 CH) ppm. ^{13}C NMR: δ 102.7 (CH), 121.3 (C), 122.2 (2 CH), 127.5 (2 CH), 128.2 (2 CH), 132.2 (2 CH), 134.2 (C), 143.6 (C), 144.8 (C), 149.3 (C), 176.3 (C=S) ppm. MS, m/z (%): 377 (M^+ , 15), 255 (46), 77 (100). Anal. Calcd for $\text{C}_{15}\text{H}_9\text{BrN}_2\text{O}_3\text{S}$ (377.21): C, 47.76; H, 2.40; N, 7.43. Found: C, 47.87; H, 2.56; N, 7.55.

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