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Green synthesis of oxazole triazole derivatives: Application of Fe_3O_4@MWCNT MNCs

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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 Fe_3O_4@MWCNT MNCs in water at 50°C in good yields. Also, the reaction of alkyl (aryl) isothiocyanates and α-bromo ketones in the presence of catalytic amount of Fe_3O_4 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: Fe_3O_4@MWCNT MNCs; 1,3-oxazole; Isothiocyanates; Ammonium thiocyanate; Alkyl (aryl) isothiocyanates.

Introduction

Substituted 1,2,4-triazoles and their derivatives are key skeletons of many biologically active moleculers and important organic compounds, and they exhibit wide applications in pesticides, medicines, functional materials and organocatalysts. In addition, a number of natural products contain a 1,2,4- triazole motif. Owing to their important properties and applications, various methods for synthesis of 1,2,4-triazole derivatives have been developed. 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 H_2O, 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].

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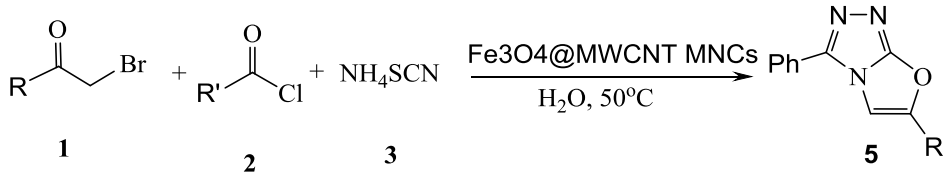
The finding of novel synthetic methods towards oxazole derivatives is a part of continued interest for organic chemists. The synthesis of functionalized oxazoles are attractive due to having many applications including biological activity such as antibacterial, anti-fungal [5], anti-tubercular [6] and 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 transition metal oxides nanostructures with high active surface area could be used as catalyst in these reactions. Also, these catalysts are employed as catalyst in technology and applied science. MWCNTs have been widely investigated, due to large surface area and high adsorption ability. Recently, the supported catalyst and bimetallic oxide or trimetallic oxide catalysts have

drawn attention owing to their high capabilities to carry out the high selectivity and efficiency organic reactions. Metal oxides possess great crystalline structure and catalytic efficiency. This is the reason why the mixture of two or more metals and their curing mechanisms allow the change in the properties of materials surface for the optimization the properties for particular goal. Accordingly, the combination of metal oxide catalysts and their nanocomposite structure have exhibited production of heterocyclic compounds according to green rules with high efficiency. Among the metal oxides nanoparticles, Fe_3O_4 magnetic nanoparticles (MNPs) are important because of high surface area, simple removing from reaction and their application in MCRs for several times.The employing of water as solvent in organic synthesis is of large attention [13]. The reaction of bromo ketones **1**, acid chlorides **2,** ammonium thiocyanate **3** and hydrazonoyl chloride **4** in the presence of catalytic amount of Fe_3O_4@MWCNT MNCs (0.02 g) lead to functionalized 1,3-oxazole-triazole derivatives **5** in good yields (Scheme 1).

Results and discussion



5	R	R'	Yied % of **5**
a	CO_2Et	4-MeO-C_6H_4	92
b	4-MeO-C_6H_4	4-NO_2-C_6H_4	87
c	4-Me-C_6H_4	^{t}Bu	90

Scheme 1: Synthesis of oxazole triazole derivatives **5**

For optimization of these reactions several catalysts and solvents were used. ZnO-NPs, TiO_2-NPs, KF/CP-NPs and Fe_3O_4@MWCNT MNCs are used as catalyst. Among them Fe_3O_4@MWCNT MNCs is the best because of easy separation of catalyst from the mixture of reaction and easy purification of product. Several solvents such as CH_2Cl_2, CH_3CN, toluene and H_2O are employed for these reactions. Among them H_2O is the best because of easy separation of product by filtration. The results of optimization are shown in Table 1. The Fe_3O_4@MWCNT MNCs are prepared according to literature procedure [15-16]. For confirming the structure of Fe_3O_4 MNPs, SEM (Figure 1) and XRD (Figure 2) spectra are given for nanostructure. Particles size of Fe_3O_4@MWCNT MNCs has been found to be 21–23 nm [16].

To investigate and confirm the skeleton of organometallic nanocomposite, we used the image. SEM analysis can be applied to examine morphology, surface uniformity and the size of particles. Figure 2 exhibits the SEM images of Fe_3O_4@MWCNT MNCs. On the basis of the FE-SEM images, Fe_3O_4@MWCNT MNCs possess a spherical morphology, confirmed by the good spread of the nanoparticles in the makeup. Another analysis to confirm the structure of nanocatalyst is X-ray diffraction (XRD) utilized for measuring the size of synthesized Fe_3O_4@MWCNT MNCs (Fig. 3). The whole observed peaks at 2θ = 35.0°, 44.0°, 54.2°, 57.2° and 63.0° can be attributed to Fe_3O_4 (JCPDS No. 19-629) with the face-centered cubic phase. All of peaks are for the pure Fe_3O_4 and did not display any impurity in the structure of Fe_3O_4.

The typical peaks of MWNTs moiety (JCPDS No. 41-1487) were seen as broad peaks around 26.2° and 43.6°.

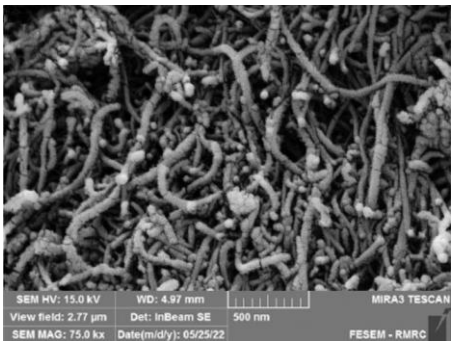


Figure 1: SEM image of Fe_3O_4@MWCNT MNCs

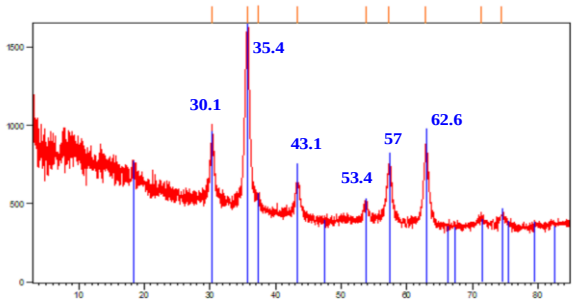
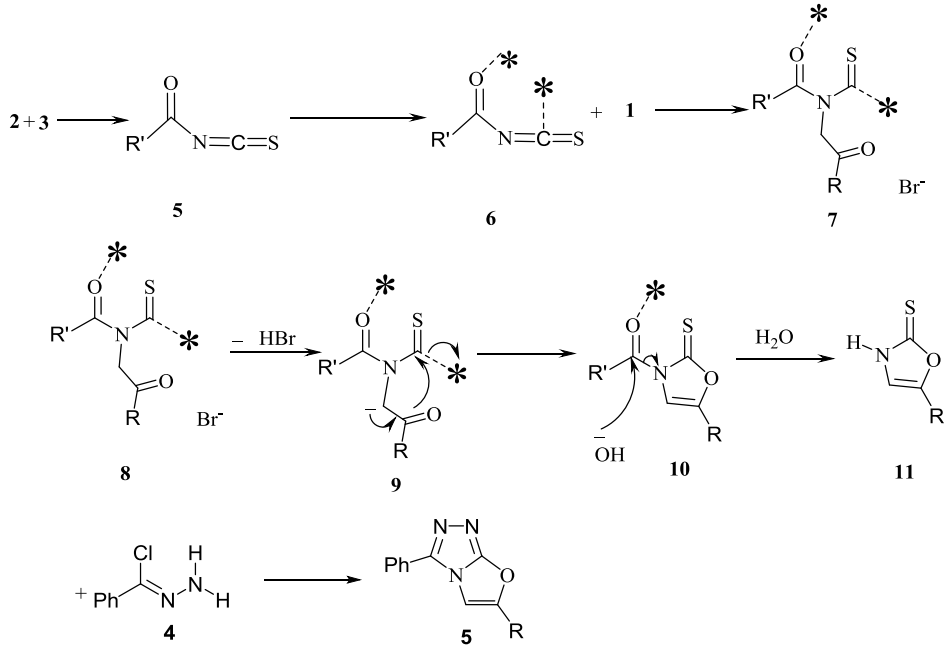


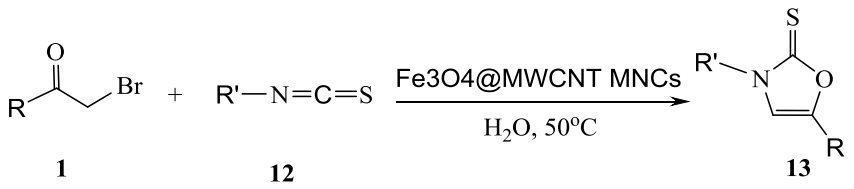
Figure 2: XRD spectra of Fe_3O_4@MWCNT MNCs

Structures of **5a**–**5c** are confirmed by IR, ^{1}H NMR, ^{13}C NMR mass spectra. For example, the ^{1}H NMR spectrum of **5a** exhibits one singlet for methin proton at δ = 7.82 ppm and one singlet at δ = 11.74 ppm for NH proton. The ^{13}C NMR spectra of **5a** 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 Fe_3O_4 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].

Under similar conditions, the reaction of □-bromo ketones **1** and isothiocyanate **11** in the presence of catalytic amounts of Fe_3O_4@MWCNT MNCs 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.



Scheme 2: Proposed mechanism for generation of oxazole triazoles **5**



1 **12** **13**

13	R	R'	Yied % of **13**
a	CO_2Et	4-MeO-C_6H_4	95
b	CO_2Et	4-NO_2-C_6H_4	90
c	CO_2Et	^{t}Bu	92
d	4-MeO-C_6H_4	^{t}Bu	92
e	4-Me-C_6H_4	4-MeO-C_6H_4	87

Scheme 3: Synthesis of oxazole triazole derivatives **13**

Conclusion

In summary, 1,3-oxazoletriazole derivatives are synthesized in good yields from the reaction of bromo ketones, acid chlorides and ammonium thiocyanate in the presence of catalytic amount of Fe_3O_4@MWCNT MNCs in water. Also, the reaction of bromo ketones and isothiocyanate in the presence of catalytic amount of Fe_3O_4@MWCNT MNCs 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. ^{1}H, 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.^{1}H, and ^{13}C, spectra are obtained for solutions in $CDCl_3$ using TMS as the internal standard.

General procedure for preparation of compounds 5:

To a magnetically stirred mixture of acid chloride **2** (2 mmol) and ammonium thiocyanate **3** in water (5 mL) at 50 ^{o}C, bromo ketones **1** (2 mmol) and Fe_3O_4@MWCNT MNCs (0.02 g) was added after 30 min.then hydrazonoyl chloride **4** (2 mmol) was added to final mixture. 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@MWCNT MNCs 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 (5a):

Pale yellow oil; yield: 0.30 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 1737, 1627, 1586, 1475, 1364 and 1295 cm^{-1}. ^{1}H 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 $C_6H_7NO_3S$ (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 (5b):

Yellow oil; yield: 0.33g (80%). IR (KBr): 1689, 1637, 1574, 1478, 1375 and 1294 cm^{-1}. ^{1}H 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 $C_{10}H_9NO_2S$ (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 (5c):

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 $C_{10}H_9NOS$ (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 13:

To a magnetically stirred mixture of isothiocyanate **12** (2 mmol) and bromo ketones **1** (2 mmol) in water was added Fe_3O_4@MWCNT MNCs (0.02 g) at 50 ^oC. After completion of the reaction (7 h; TLC control (hexane–AcOEt, 4:1), mixture is allowed to cool to room temperature. Fe_3O_4@MWCNT MNCs 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 (13a):

Yellow powders; yield: 0.53 g (95%). IR (KBr) (ν_{max}/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 $C_{13}H_{13}NO_4S$ (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 (13b):

Yellow powders; yield: 0.53 g (90%). IR (KBr) (ν_{max}/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 $C_{12}H_{10}N_2O_5S$ (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 (13c):

Yellow powders; yield: 0.42 g (92%). IR (KBr) (ν_{max}/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 $C_{10}H_{15}NO_3S$ (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 (13d):

Yellow powders; yield: 0.48 g (92%). IR (KBr) (ν_{max}/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 $C_{14}H_{17}NO_2S$ (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 (13e):

Pale yellow powders; yield: 0.52 g (87%). IR (KBr) (ν_{max}/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 $C_{17}H_{15}NO_2S$ (297.37): C, 68.66; H, 5.08; N, 4.71. Found: C, 68.78; H, 5.19; N, 4.83.

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