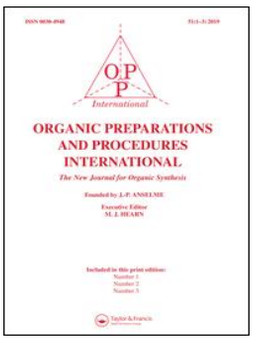

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EXPERIMENTAL PAPER

3-Mercapto-1,2,4-triazole Functionalized Fe_3O_4 Based Cu Nanoparticles: A Capable Catalyst for the Synthesis of Diverse Tetrazoles from Amino Acids

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Tetrazoles are an important class of heterocycles combining high nitrogen content with significant biological properties. Among these are activities as sedatives,[1] antibacterials,[2] anticancer drugs,[3] antidiabetic medications,[4] antifungals,[5] anti-inflammatories,[6] general antimicrobials,[7] antitumor compounds,[8] antivirals,[9] carboxylic acid isosteres,[10] diuretics[11] and herbicides.[12]

In continuation of our previous work on the application of magnetic nanoparticle metal complexes as heterogeneous catalysts for the synthesis of heterocyclic compounds,[13] we would now like to report the preparation of the novel title Cu nano-catalyst. Our motivation was to promote a new efficient nano-catalyst for greener methods and potentially lower costs for the synthesis of heterocycles. The catalyst preparation occurred via a multistep process including: the synthesis of the Fe_3O_4 magnetic nanoparticles, coating the latter with tetraethyl orthosilicate (TEOS) (Fe_3O_4/SiO_2), functionalization of Fe_3O_4/SiO_2 with 3-chloropropyltrimethoxysilane (CPTMS) and 3-mercapto-1,2,4-triazole (MT) ligands (Fe_3O_4/SiO_2/CPTMS/MT), and further complexation with $CuCl_2$ (Fe_3O_4/SiO_2/CPTMS/MT/Cu). In a demonstration of its utility for diversity in synthesis, the new Cu magnetic nano-catalyst was subsequently used for the synthesis of a variety of useful tetrazoles from the reaction of amino acids with sodium azide and triethyl orthoformate (TEOF) in H_2O at 40 °C (Scheme 1). To the best of our knowledge, this is the first such application.

The catalyst activity was optimized in a model reaction. This was the synthesis of 3-(1*H*-indol-3-yl)-2-(1*H*-tetrazol-1-yl)propanoic acid (**2c**) from the reaction of tryptophan with sodium azide and TEOF. The model was run under different conditions of temperature, amount of the catalyst and solvents. The best result was obtained with 10 mmole of amino acid, 10 mmole of sodium azide, 30 mmole of TEOF and 20 mg of the Cu nano-particle catalyst in H_2O at 407°C (Tables 1-3).

Applying the optimized results from the model, a number of tetrazoles were prepared with good to excellent yields (Table 4).

All of the compounds were fully characterized (see Experimental section).

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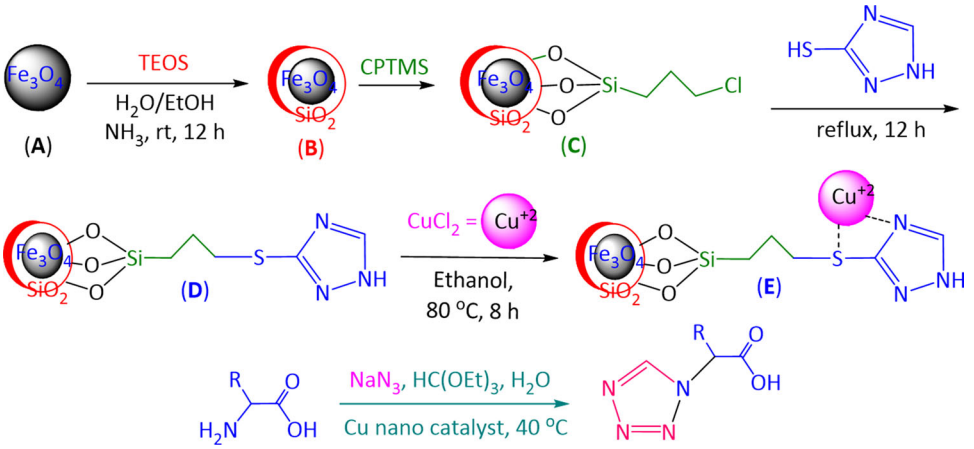


Scheme 1. Synthesis of the new Cu magnetic nano-catalyst and diverse tetrazoles.

Table 1 Effect of solvent on the synthesis of **2c** at 40 °C.

Entry	Solvent	Time (h)	Yield (%)
1	**H_2O**	**3**	**87**
2	EtOH	3	83
3	MeOH	3	80
4	EtOAc	6	84
5	n-Hexane	4	79
6	Toluene	7	83
7	$CHCl_3$	5	85

Table 2 Effect of temperature on the synthesis of **2c** in H_2O.

Entry	Temp (°C)	Time (h)	Yield (%)
1	r.t.	1	84
2	**40**	**1**	**89**
3	60	1	85
4	80	1	87
5	reflux	1	85

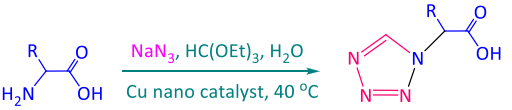
Table 3 Effect of amount of the catalyst on the synthesis of **2c** in H_2O at 40 °C.

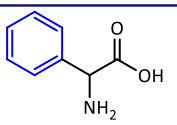
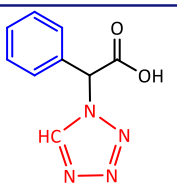
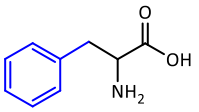
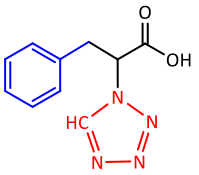
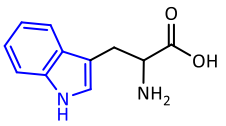
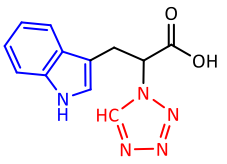
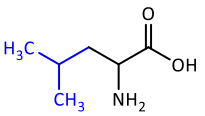
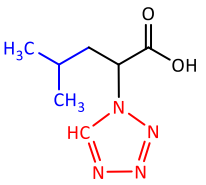
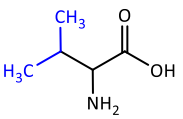
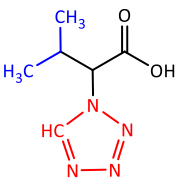
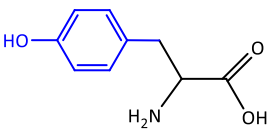
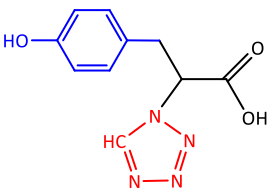
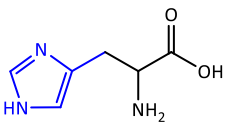
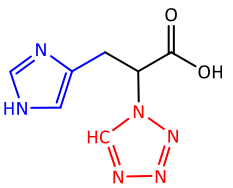
Entry	Catalyst (mg)	Time (h)	Yield (%)
1	No catalyst	1	Very low
2	5	1	85
3	10	1	86
4	**20**	**1**	**88**
5	30	1	86
6	50	1	86

The reusability of Fe_3O_4/SiO_2/CPTMS/MT/Cu was investigated with the model reaction to find the recycling capability of the catalyst. The catalyst was separated by filtration after the first run, washed with ethanol and dried under vacuum, then reused for the next successive runs under the same conditions. We found that the Cu nano-catalyst could be reused even after five runs; the catalytic activity in the fifth run was almost as same as the first for the preparation of the model tetrazole (97, 95, 92, 90 and 87%, respectively).

In conclusion, the novel heterogeneous Cu nano-catalyst was successfully prepared in five stages and used for the synthesis of diverse tetrazoles from the reaction of several

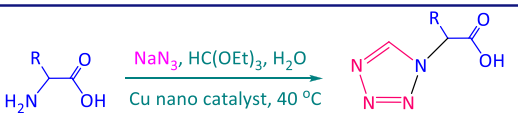
Table 4 Synthesis of tetrazoles (**2a-h**).

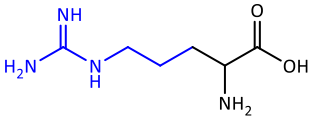
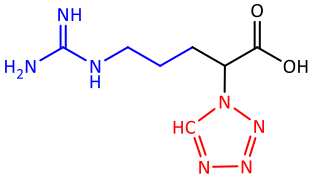


Entry	Amino acid	Product	Time (h)	Yield (%)
1			2	86
2			1	92
3			1	94
4			5	80
5			3	93
6			7	91
7			1	73

(*continued*)

Table 4 Continued.



Entry	Amino acid	Product	Time (h)	Yield (%)
8			2	75

amino acids with sodium azide and TEOF in water at 40 °C. Given its usefulness, it is our hope that other researchers will take up this catalyst for their syntheses of heterocyclic compounds.

Experimental section

All reagents were purchased from Merck and Aldrich and used without further purification. The NMR spectra were recorded in the appropriate deuterated solvents, as noted in the individual procedures. ^{1}HNMR and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz instrument. FT-IR (KBr) spectra were recorded on a Perkin Elmer 781 spectrophotometer. Melting points were taken in open capillary tubes with a BUCHI 510 melting point apparatus and are uncorrected. Elemental analysis was performed using a Heraeus CHNO-Rapid analyzer. The inductively coupled plasma (ICP) measurements for the metal content evaluation were performed using a Perkin-Elmer ICP/6500. TLC was performed on silica gel polygram SIL G/UV 254 plates, using the mixture of AcOEt/n-hexane (40:60) as the moving phase. The TEM images were recorded on a Zeiss-EM10C-100 KV transmission electron microscope. The SEM images were recorded on a Philips XL-30 scanning electron microscope. The X-ray diffraction (XRD) measurements were done by a Bruker D8 Advance powder diffractometer, using Cu Kα ($\lambda = 1.54$ A) as the incident radiation. Dispersive X-ray spectroscopy (EDX) was determined on an Oxford instrument. Thermogravimetric-differential thermal analysis (TG-DTA) was determined by the Perkin Elmer Pyris Diamond instrument. Magnetic measurements were carried out at room temperature using an Iranian Meghnatis Daghigh Kavir Co. Vibrating Sample Magnetometer (VSM). TEM, XRD, EDX, TG-DTA and VSM data are available from the corresponding author upon request.

Preparation of the Cu nano-catalyst

Stage 1: Preparation of the Fe_3O_4 magnetic nanoparticles (Fe_3O_4 MNPs). The mixture of $FeCl_3{\cdot}6H_2O$ (11.44 g, 42 mmol) and $FeCl_2{\cdot}4H_2O$ (4.3 g, 21 mmol) was dissolved in water (100 mL), and the solution stirred for 0.5 h in 80 °C. A solution of 37% ammonia was then added dropwise with vigorous stirring. A black solid product was obtained when the

reaction medium reached pH 10. The mixture was heated for 0.5 h at 70 °C and the black magnetite solid product filtered, washed with water and dried at 80 °C for 12 h.

Stage 2: Coating of Fe_3O_4 MNPs with TEOS. Fe_3O_4 MNPs (0.2 g) were dispersed in EtOH/H_2O (250 mL, V/V = 4:1) with $NH_3{\cdot}H_2O$ (3 mL) solution under ultrasonication. Then, TEOS (2 mL) was slowly added dropwise and the mixture stirred for a further 6 h. Fe_3O_4/SiO_2 was obtained by centrifugation, washed with water and ethanol several times, and dried *in vacuo*.

Stage 3: Functionalization of Fe_3O_4/SiO_2 with the CPTMS ligand. The CPTMS ligand (1.0 mL, 5 mmol) was dissolved in dry toluene (100 mL) and Fe_3O_4/SiO_2 (1.0 g) added and stirred for 18 h at 60 °C. Then, the obtained product (Fe_3O_4/SiO_2/CPTMS) was separated with a strong magnet, washed with toluene and dried *in vacuo*.

Stage 4: Further functionalization with the MT ligand. The MT ligand (0.5 g, 5 mmol) and K_2CO_3 (0.69 g, 5 mmol) in toluene (60 mL) were added to Fe_3O_4/SiO_2/CPTMS (0.1 g) and refluxed for 12 h. Then, the obtained product (Fe_3O_4/SiO_2/CPTMS/MT) was separated with a strong magnet, washed repeatedly with ethanol and water and dried *in vacuo*.

Stage 5: Complexation of Fe_3O_4/SiO_2/CPTMS/MT with $CuCl_2$. Fe_3O_4/SiO_2/CPTMS/MT (0.1 g) was added to dispersed $CuCl_2$ (0.85 g, 5 mmol) in ethanol (20 mL) and stirred vigorously for 8 h at 80 °C. Then, the resulting Cu nano-catalyst (Fe_3O_4/SiO_2/CPTMS/MT/Cu) was separated with a strong magnet, washed with ethanol and air-dried (Scheme 1).

General procedure for the synthesis of tetrazoles

Amino acid (10 mmol), sodium azide (0.65 g, 10 mmol) and the Cu nano catalyst (20 mg) were added to a solution of TEOF (4.4 g, 5 mL, 30 mmol) in H_2O (5 mL). The solution was stirred and the mixture heated at 40 °C for 1-7 h depending on the substrate. Completion of the reaction was monitored by TLC. Then, H_2O (20 mL) was added, the Cu catalyst filtered, the filtrate concentrated and the solvent removed *in vacuo*. The obtained tetrazoles were recrystallized from ethanol and were fully characterized, including satisfactory elemental analyses.

2-Phenyl-2-(1H-tetrazol-1-yl)acetic acid (2a)

White crystals, mp 158-160 °C; IR (KBr) 3127 ($CH_{tetrazole}$), 2970 ($CH_{stretch}$), 1752 (C = O) (cm^{-1}). ^1H NMR (300 MHz, acetone-d_6): δ 6.85 (s, 1 H, CH), 7.46-7.55 (m, 5 $H_{aromatic}$), 9.20 (s, 1 $H_{tetrazole}$). ^{13}C NMR (75 MHz, acetone-d_6): δ 63.10 (CH), 127.83 ($CH_{p\text{-aromatic}}$), 127.83 (2 $CH_{m\text{-aromatic}}$), 128.25 (2 $CH_{o\text{-aromatic}}$), 131.63 ($C_{aromatic}$), 141.93 ($CH_{tetrazole}$), 166.58 (C = O).

Anal. Calcd for $C_9H_8N_4O_2$: C, 52.94; H, 3.95; N, 27.44. Found: C, 52.71; H, 3.87; N, 27.34.

3-Phenyl-2-(1H-tetrazol-1-yl)propanoic acid (2b)

White crystals, mp 156-158 °C; IR (KBr): 3443 (COOH), 3130 ($CH_{tetrazole}$), 1725 (C = O) (cm^{-1}). ^1H NMR (300 MHz, acetone-d_6): δ 3.09 (m, 2 H, CH_2), 5.44 (m, 1 H,

CH), 6.85 (s, 5 $H_{aromatic}$), 8.95 (s, 1 $H_{tetrazole}$). ^{13}C NMR (75 MHz, acetone-d_6): δ 36.31 (CH_2), 61.64 (CH), 126.89 ($CH_{p\text{-aromatic}}$), 128.36 (2 $CH_{m\text{-aromatic}}$), 128.70 (2 $CH_{o\text{-aromatic}}$), 135.57 ($C_{aromatic}$), 144 ($CH_{tetrazole}$), 168.87 (C = O).

Anal. Calcd for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68. Found: C, 55.06; H, 4.63; N, 25.57.

3-(1H-indol-3-yl)-2-(1H-tetrazol-yl)propanoic acid (2c)

Yellow crystals, mp 82-85 °C; IR (KBr) 3387 (COOH & NH), 3129 ($CH_{tetrazole}$), 1725 (C = O) (cm^{-1}). ^{1}H NMR (300 MHz, acetone-d_6): δ 3.78-3.86 (m, 2 H, CH_2), 5.97 (q, 1 H, CH), 6.96 (m, 4 $H_{aromatic}$), 7.287.45 (m, 1 $H_{aromatic}$), 9.08 (s, 1 $H_{tetrazole}$), 10.02-10.2 (d, 1 H, NH). ^{13}C NMR (75 MHz, acetone-d_6): δ 27.48 (CH_2), 61.55 (CH), 108.04 ($C_{3\text{-aromatic}}$), 111.25 ($CH_{7\text{-aromatic}}$), 117.64 ($CH_{4\text{-aromatic}}$), 118.89 ($CH_{5\text{-aromatic}}$), 121.44 ($CH_{6\text{-aromatic}}$), 123.53 ($CH_{2\text{-aromatic}}$), 126.92 ($C_{aromatic}$), 136.34 ($C_{aromatic}$), 143.29 ($CH_{tetrazole}$), 168.41 (C = O).

Anal. Calcd for $C_{12}H_{11}N_5O_2$: C, 56.03; H, 4.31; N, 27.22. Found: C, 56.08; H, 4.25; N, 27.14.

4-Methyl-2-(1H-tetrazol-1-yl)pentanoic acid (2d)

White crystals, mp 220-222 °C; IR (KBr) 3475 (COOH), 3105 ($CH_{tetrazole}$), 2961 ($CH_{stretch}$), 1725 (C = O) (cm^{-1}). ^{1}H NMR (300 MHz, D_2O-acetone-d_6): δ 0.74-1.01 (m, 6 H, 2 CH_3), 1.84 (m, 1 H, CH), 5.17 (t, 1 H, CH), 9.17 (s, 1 $H_{tetrazole}$). ^{13}C NMR (75 MHz, acetone-d_6): δ 21.62 (CH_3), 23.28 (CH_3), 25.91 (CH), 42.25 (CH_2), 64.01 (CH), 144.69 ($CH_{tetrazole}$), 174.00 (C = O).

Anal. Calcd for $C_7H_{12}N_4O_2$: C, 45.64; H, 6.57; N, 30.42. Found: C, 45.39; H, 6.58; N, 30.40.

3-Methyl-2-(1H-tetrazol-1-yl)butanoic acid (2e)

White crystals, mp 201-203 °C; IR (KBr) 3427 (COOH), 3170 ($CH_{tetrazole}$), 3097, 2969, 2875 ($CH_{stretch}$), 1626 (C = O) (cm^{-1}). ^{1}H NMR (300 MHz, D_2O-acetone-d_6): δ 1.08 (m, 6 H, 2 CH_3), 2.71 (m, 1 H, CH), 5.25 (m, 1 H, CH), 9.49 (s, 1 $H_{tetrazole}$). ^{13}C NMR (75 MHz, acetone-d_6): δ 18.94 (CH_3), 20.25 (CH_3), 24.72 (CH), 71.92 (CH), 145.06 ($CH_{tetrazole}$), 173.27 (C = O).

Anal. Calcd for $C_6H_{10}N_4O_2$: C, 42.35; H, 5.92; N, 32.92. Found: C, 42.39; H, 5.88; N, 32.81.

3-(4-Hydroxyphenyl)-2-(1H-tetrazol-1-yl)propanoic acid (2f)

White crystal, mp 221 °C; IR (KBr) 3445 (OH), 3265 (COOH), 3153 ($CH_{tetrazole}$), 1605 (C = O) (cm^{-1}). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.38 (m, 3 H, CH_2 & OH), 5.11 (dd, 1 H, CH), 6.58 (d, 2 $H_{aromatic}$), 6.76 (d, 2 $H_{aromatic}$), 9.19 (s, 1 $H_{tetrazole}$). ^{13}C NMR (75 MHz, acetone-d_6): δ 37.57 (CH_2), 66.13 (CH), 115.60 (2 $CH_{o\text{-phenol}}$), 127.51 ($C_{p\text{-phenol}}$), 129.86 (2 $CH_{m\text{-phenol}}$), 143.95 ($CH_{tetrazole}$), 156.79 ($C_{ipso\text{-}OH}$), 171.69 (C = O).

Anal. Calcd for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.22; H, 4.23; N, 23.85.

3-(1H-imidazol-4-yl)-2-(1H-tetrazol-1-yl)propanoic acid (2g)

White crystals, mp 138-140 °C; IR (KBr) 3381 (COOH & NH), 3021 ($CH_{tetrazol}$), 1691 (C = O) (cm^{-1}). ^1H NMR (300 MHz, DMSO-d_6): δ 3.40 (m, 2 H, CH_2), 4.70 (NH), 5.20 (dd, 1 H, CH), 6.48 (s, 1 $H_{aromatic}$), 7.38 (s, 1 $H_{aromatic}$), 9.22 (s, 1 $H_{tetrazole}$). ^{13}C NMR (75 MHz, acetone-d_6): δ 30.32 (CH_2), 64.47 (CH), 117.25 ($C_{5\ imidazole}$), 133.22 ($C_{4\ imidazole}$), 134.81 ($CH_{2\ imidazole}$), 143.44 ($CH_{tetrazole}$), 174.99 (C = O).

Anal. Calcd for $C_7H_8N_6O_2$: C, 40.39; H, 3.87; N, 40.37. Found: C, 40.25; H, 3.81; N, 40.29.

2-(1H-tetrazol-1-yl)-5-(1H-tetrazole-1-carboximidamido)pentanoic acid (2h)

Yellow crystals, mp 183-185 °C; IR (KBr) 3350 (COOH & NH_2), 3117 ($CH_{tetrazole}$), 3012, 2924, 2879 ($CH_{stretch}$), 1681 (C = O) (cm^{-1}). ^1H NMR (300 MHz, DMSO-d_6): δ 1.43 (m, 2 H, CH_2), 1.72 (2 H, CH_2), 2.20 (m, 3 H, CH_2 & NH), 5.02 (m, 1 H, CH), 7.88 (bs, NH_2), 9.07 (bs, =NH), 9.41 (s, 1 $H_{tetrazole}$). ^{13}C NMR (75 MHz, acetone-d_6): δ 25.43 (CH_2), 29.19 (CH_2), 39.43 (CH_2), 63.47 (CH), 143.54 ($CH_{tetrazole}$), 157.35 (=C), 171.03 (C = O).

Anal. Calcd for $C_7H_{13}N_7O_2$: C, 34.29; H, 4.32; N, 49.98. Found: C, 34.30; H, 4.30; N, 49.90.

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