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Highly Active and Reusable Cu/C Catalyst for Synthesis of 5-Substituted 1*H*-Tetrazoles Starting from Aromatic Aldehydes

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Abstract

A new, efficient and convenient method for the synthesis of 5-substituted 1*H*-tetrazole derivatives with a wide range of substituents in good to excellent yields has been developed. The synthesis was performed by the one-pot three-component [3+2]cycloaddition reaction between aldehyde, hydroxylamine and sodium azide in the presence of Cu/C. The reaction probably proceeds by the in situ formation of nitriles followed by successive [3+2]cycloaddition with sodium azide. A variety of aldehydes were used to obtain the corresponding tetrazoles. The catalyst was recovered by simple filtration and reused at least five times without significant loss of catalytic activity. The use of this method offers additional advantages for the synthesis of 5-substituted 1*H*-tetrazole derivatives, including the easy availability of starting materials, mild conditions, experimental simplicity and good yields.

Keywords: Heterogeneous catalyst, Cu/C nanoparticle, Tetrazoles, One-pot three component reaction, [3+2] Cycloaddition reaction

1. Introduction

Tetrazoles are a representative class of heterocyclic polyaza compounds, which are extensively investigated due to their broad range of applications. Tetrazoles exhibit potential biological activities such as antibiotic,[1] anti-allergic,[2] antagonist,[3] antihypertensive,[4] and antiviral activities.[5] These compounds have also been used as an important part of the number of modern drugs.[6] More recently, tetrazoles have been used to bind arylthiotetrazolylacetanilides with HIV-1 reverse transcriptase.[7] In medical chemistry, tetrazoles are considered lipophilic spacers and metabolically stable surrogates for carboxylic acid.[8] In addition, tetrazoles have been used in organometallic chemistry as effective stabilizers of metal peptide structures, as peptide chelating agents[9,10] and as ligands with different coordination modes in coordination chemistry.[11,12] Tetrazoles have also been used as plant growth regulators, herbicides and fungicides.[13] In addition, tetrazole compounds are used in photography,[14] in specialty explosives[15] and in organocatalysis.[16]

Due to their potential advantages and their wide range of applications, various and new synthesis methods for tetrazoles have been intensively developed.[17,18] The [3+2]-cycloaddition of nitriles with sodium azide is known as one of the most conventional methods for the synthesis of 5-substituted 1*H*-tetrazoles. This reaction was carried out by using catalysts such as copper triflates,[19] $CdCl_2$,[20] $Fe(OAc)_2$,[21] zinc(II) salts,[22] $AlCl_3$,[23] $BF_3\text{-}OEt_2$,[24] $FeCl_3\text{-}SiO_2$,[25] TBAF,[26] 4-(*N*,*N*-dimethylamino)pyridinium acetate,[27] $Cu(OAc)_2$,[28] $AgNO_3$,[29] CoY zeolites,[30] ZnS,[31] Cu_2O,[32] amberlyst 15,[33] $CuFe_2O_4$ nanoparticles,[34] cuttlebone,[35] Cu(II) immobilized on $Fe_3O_4@SiO_2@L\text{-}Arginine$[36] and Ag/sodium borosilicate nanocomposite.[37]

In general, toxic and expensive substituted phenylnitriles are used as precursors for the synthesis of tetrazoles. Therefore, the use of more available starting material instead of nitriles and the use of comparatively cheaper and easily accessible catalysts are the two motives that led us to do this work.

Previously, we have reported on copper nanoparticles on charcoal (Cu/C) as an excellent heterogeneous cat-

alyst for the synthesis of triazole,[38] propargylamine,[39] benzimidazole,[40] 2-amino-3-cyanopyridine,[41] indazole[42] and imidazole derivatives.[43]

In continuation of our studies on the synthesis of heterocycles and the use of heterogeneous catalysts in organic reactions,[44–56] we describe here a new strategy for the preparation of tetrazole derivatives. The strategy is based on a one-pot three-component [3+2]cycloaddition reaction between aldehydes, hydroxylamine hydrochloride and sodium azide using Cu/C as heterogeneous catalyst. The core of our new strategy for the synthesis of tetrazoles is the use of aldehydes instead of nitriles in a tandem process.

2. Experimental Section

2. 1. Instrumentation, Analysis and Raw Materials

The NMR spectra were recorded on a Bruker Advance DPX-250 (^{1}H NMR at 250 MHz and ^{13}C NMR at 62.5 MHz) in pure deuterated solvents with tetramethylsilane (TMS) as internal standard. Mass spectra were determined with a Shimadzu GCMS-QP 1000 EX instrument at 70 or 20 eV. Melting points were determined in open capillary tubes in a Buchi-535 melting point device. FT-IR spectroscopy (Shimadzu FT -IR 8300 spectrophotometer) was used to characterize the heterogeneous catalyst. Reaction monitoring was performed by TLC on silica gel Poly-Gram SILG/UV254 plates. Chemical materials were obtained from Fluka, Aldrich and Merck Companies.

2. 2. General Procedure

A mixture of aldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol), sodium azide (1 mmol) and catalytic amounts of Cu/C (5 mol%) in DMF (2 ml) was stirred at 120 °C for a reasonable time (Table 2). After completion of the reaction, as indicated by thin layer chromatography (TLC) with n-hexane/ethyl acetate (EtOAc) (1:2), the entire reaction mixture was passed directly through a celite and rinsed with EtOAc (3 × 15 mL). Then the reaction mixture was washed with distilled water (3 × 20 mL), extracted with EtOAc and the combined organic layers dried over anhydrous Na_2SO_4. It was then concentrated under vacuum and purified by recrystallisation in n-hexane/ ethyl acetate (1:1) to obtain tetrazoles of high purity.

5-Phenyl-1*H*-tetrazole (1)

White solid; m.p. 216–217 °C (Lit. 214–216 °C);[57] IR (KBr): υ 3078, 3056, 3000, 2400, 1610, 1478, 1466, 1150, 688 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.57–7.63 (m, 3H), 8.01–8.04 (m, 2H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 124.1, 126.9, 129.3, 131.1, 155.3; Anal. calcd. for $C_7H_6N_4$ (146.149): C, 57.53; H, 4.14; found: C, 57.39; H, 4.21.

5-(4-nitrophenyl)-1*H*-tetrazole (2)

Yellow solide; m.p. 217–218 °C (Lit. 218–220 °C);[58] IR (KBr): υ 3443, 2908, 1606, 2850, 1550, 1440, 1495, 1385, 712 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.14 (d, 1H, J = 7.0 Hz), 8.29 (dd, 2H, J_1 = 8.8, J_2 = 1.8 Hz), 8.43 (d, 1H, J = 8.9 Hz); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 123.7, 124.6, 128.2, 130.6, 148.7; Anal. calcd. for $C_7H_5N_5O_2$ (191.146): C, 43.98; H, 2.64; found: C, 44.09; H, 2.75.

Methyl 4-(1*H*-tetrazole-5-yl)benzoate (3)

White solid; m.p. 224–225 °C (Lit. 225 °C);[59] IR (KBr): υ 3450, 3101, 2649, 2554, 1750, 1431, 1505, 1550, 1610, 1163, 743 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$): δ 3.01 (s, 3H), 7.78 (d, 2H, J = 8.2 Hz), 8.21 (d, 2H, J = 8.1 Hz); ^{13}C NMR (62.5MHz, DMSO-d_6): δ 36.9, 117.9, 120.7, 130.5, 132.2, 163.4, 168.2; Anal. calcd. for $C_9H_8N_4O_2$ (204.185): C, 52.94; H, 3.95; found: C, 53.06; H, 4.07.

5-(4-Chloro-phenyl)-1*H*-tetrazole (4)

White solid; m.p. 261–263 °C (Lit. 261–263 °C);[60] IR (KBr): υ 3096, 3071, 1611, 1488, 1436, 1156, 820 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.68 (d, 2H, J = 8.5 Hz), 8.03 (d, 2H, J = 8.5 Hz); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 123.1, 128.6, 129.5, 135.8, 155.2; Anal. calcd. for $C_7H_5ClN_4$ (180.594): C, 46.55; H, 2.79; found: C, 46.63; H, 2.87.

5-(4-Methylphenyl)-1*H*-tetrazole (5)

White solid; m.p. 250–251 °C (Lit. 249–251°C);[61] IR (KBr): υ 3433, 3010, 2852, 1616, 1504, 1438, 1373, 1054, 824 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.35 (s, 3H), 7.37 (d, 2H, J = 7.6 Hz), 7.90 (d, 2H, J = 7.5 Hz); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 20.9, 121.2, 126.8, 129.8, 141.1, 154.9; Anal. calcd. for $C_8H_8N_4$ (160.176): C, 59.99; H, 5.03; found: C, 60.08; H, 4.91.

5-(3,5-dimethoxyphenyl)- 1*H*-tetrazole (6)

Brown solid; m.p. 204–205 °C (Lit. 204–205 °C);[35] IR (KBr): υ 3430, 3012, 2870, 2730, 1590, 1400, 911, 1250, 1035, 766 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6): δ 3.80 (s, 3H), 3.82 (s, 3H), 7.15 (d, 1H, J=8.7 Hz), 7.58–7.63 (m, 2H); ^{13}C NMR (62.5MHz, DMSO-d_6): δ 55.5, 109.9, 111.9, 116.1, 120.0, 149.0, 151.0, 154.8; Anal. calcd. for $C_9H_{10}N_4O_2$ (206.201): C, 52.42; H, 4.89; found: C, 52.29; H, 4.96.

N,N-dimethyl-4-(1*H*-tetrazole-5-yl)aniline (7)

White solid; m.p. 240–241 °C (Lit. 218–220 °C);[62] IR (KBr): υ 3461, 3274, 2926, 2877, 2713, 1600, 1430, 1530, 1377, 814, 751 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.96 (s, 6H), 6.81 (d, 2H, J = 8.5 Hz), 7.82 (d, 2H, J = 8.6 Hz); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 39.6, 110.4, 111.8, 127.9, 151.8, 154.9; Anal. calcd. for $C_9H_{11}N_5$ (189.217): C, 57.13; H, 5.86; found: C, 57.24; H, 5.97.

4-(1*H*-tetrazole-5-yl)benzene-1,3-diol (8)

White solid; m.p. 247–248 °C; IR (KBr): υ 3386, 3232, 2853, 2770, 2693, 1600, 1586, 1430, 1134, 974, 814,

748 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6): δ 6.41 (dd, 1H, J_1 = 8.5, J_2 = 2.3 Hz), 6.47 (d, 1H, J = 2.2 Hz), 7.79 (d, 1H, J = 8.6 Hz), 10.01 (s, 2H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 101.7, 102.4, 107.9, 130.0, 151.7, 156.8, 161.2; Anal. calcd. for C$_7$H$_6$N$_4$O$_2$ (178.148): C, 47.19; H, 3.39; found: C, 47.08; H, 3.26.

5-(2-Chloro-phenyl)-1*H*-tetrazole (9)

White solid; m.p. 178–180 °C (Lit. 175–177 °C);[57] IR (KBr): υ 3200, 3100, 2400, 1603, 1564, 1472, 1080, 784 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.37–7.45 (m, 1H), 7.50–7.53 (m, 2H), 7.74–7.78 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 124.4, 127.7, 130.4, 131.7, 131.9, 132.4, 153.6; Anal. calcd. for C$_7$H$_5$ClN$_4$ (180.594): C, 46.55; H, 2.79; found: C, 46.43; H, 2.68.

5-(2,4-dichlorophenyl)-1*H*-tetrazole (10)

White solid; m.p. 165–166 °C (Lit. 169–170 °C);[63] IR (KBr): υ 3455, 3200, 1481, 1590, 1030, 756, 566, 538 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.62 (dd, 1H, J_1 = 8.4, J_2 = 2.0 Hz), 7.82–7.86 (m, 2H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 116.8, 118.2, 124.9, 135.4, 138.5, 158.9; Anal. calcd. for C$_7$H$_4$Cl$_2$N$_4$ (215.039): C, 39.10; H, 1.87; found: C, 38.98; H, 1.75.

5-(furane-2-yl)-1*H*-tetrazole (11)

White solid; m.p. 203–204 °C (Lit. 203–204 °C);[64] ^{1}H NMR (250 MHZ, DMSO-d_6): δ 6.75 (s, 1H), 7.26 (s, 1H), 8.00 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 118.7, 126.4, 136.3, 141.2, 154.5, 141.2; Anal. calcd. for C$_7$H$_4$Cl$_2$N$_4$ (136.111): C, 44.12; H, 2.96; found: C, 44.25; H, 3.09.

5-(1-methyl-1*H*-pyrrol-2-yl)-1*H*-tetrazole (12)

White solid; m.p.: 240–241 °C; IR (KBr): υ 3450, 3185, 3115, 2895, 1600, 1512, 1421, 702, 802 cm^{-1}; ^{1}H NMR (250 MHZ, DMSO-d_6): δ 2.48 (s, 3H), 7.64 (dd, 1H, J_1 = 5.0, J_2 = 1.2 Hz), 7.80 (dd, 1H, J_1 = 5.0, J_2 = 2.9 Hz), 7.77 (dd, 1H, J_1 = 2.9, J_2 = 1.1 Hz); ^{13}C NMR (62.5MHz, DMSO-d_6): δ 46.1, 125.9, 127.4, 128.7; Anal. calcd. for C$_6$H$_7$N$_5$ (149.153): C, 48.32; H, 4.73; found: C, 48.25; H, 4.62.

5-(thiophen-3-yl)-1*H*-tetrazole (13)

White solid; m.p. 244–245 °C (Lit. 244–245 °C);[65] IR (KBr): υ 3286, 1600, 1512, 1460, 1100, 999, 750 cm^{-1}; ^{1}H NMR (250 MHZ, DMSO-d_6): δ 8.07 (d, 1H, J = 6.2 Hz), 8.21–8.27 (m, 2H). ^{13}C NMR (62.5MHz, DMSO-d_6): δ 125.8, 126.9, 128.5, 129.2, 154.3; Anal. calcd. for C$_5$H$_4$N$_4$S (152.177): C, 39.46; H, 2.65; found: C, 39.57; H, 2.78.

3. Results and Discussion

The copper nanoparticle on charcoal (Cu/C) as catalyst was synthesized according to our previously published methods (Scheme 1).[38]
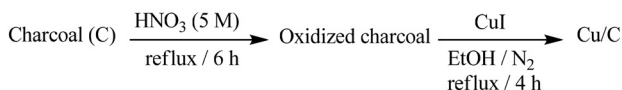
Scheme 1. Preparation of copper nanoparticle on charcoal (Cu/C)

The potential of Cu/C as a catalyst in tetrazole synthesis via a one-pot three-component [3+2] cycloaddition reaction between aldehyde, hydroxylamine hydrochloride and sodium azide was investigated. This methodology is based on the initial formation of an oxime derivative resulting from the reaction of an aldehyde with hydroxylamine hydrochloride in the presence of Cu/C. Subsequently, the oxime derivative is dehydrated, resulting in structurally different nitriles. Finally, the [3+2]cycloaddition of nitrile with sodium azide yields the required tetrazole derivatives (Scheme 2).
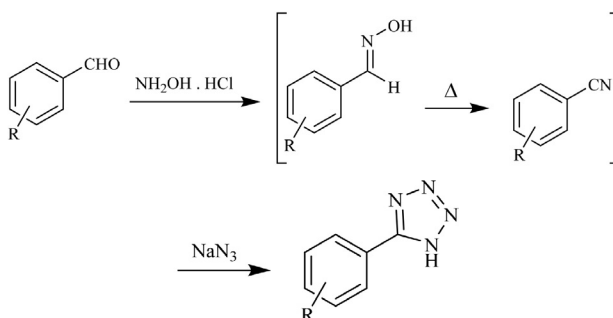
Scheme 2. Proposed reaction pathway for the synthesis of tetrazoles from aldehydes.

To search for optimal reaction conditions, a three-component reaction model between hydroxylamine hydrochloride, benzaldehyde and NaN$_3$ using Cu/C as catalyst was investigated. Different reaction parameters like solvent, temperature, different catalysts and the amount of catalyst were investigated. The corresponding results were summarized in Table 1.

First, different solvents for the preparation of 5-substituted 1*H*-tetrazole were screened. No product was formed during the reaction in H$_2$O, CH$_3$CN and ethanol (Table 1, entries 1–3). In another attempt to synthesize the tetrazole ring, benzaldehyde, hydroxylamine and NaN$_3$ were used in PEG 200 at 120 °C, which provided the desired tetrazole in very low yield (Table 1, entry 4). When the model reaction was carried out in DMSO at 120 °C, the desired product was obtained in moderate yield as indicated in Table 1, entry 5. The solvent has a noticeable effect in this reaction, in which dimethylformamide (DMF) was the best solvent to achieve the highest yields of the desired tetrazole (Table 1, entry 6).

Next, we investigated the influence of temperature on the model reaction. A temperature increase from 120 to 140 °C had no significant effect on the yield and the reac-

Table 1. Optimization for the synthesis of tetrazole from aldehyde.[a]

Entry	Solvent	Catalyst (mol%)	Temperature (°C)	Time (h)	Yield (%)[b]
1	H_2O	Cu/C (5)	Reflux	9	–
2	MeCN	Cu/C (5)	Reflux	9	–
3	EtOH	Cu/C (5)	Reflux	9	–
4	PEG 200	Cu/C (5)	120	9	12
5	DMSO	Cu/C (5)	120	9	48
6	DMF	Cu/C (5)	120	9	87
7	DMF	Cu/C (5)	140	9	89
8	DMF	Cu/C (5)	100	9	48
9	DMF	Cu/C (5)	r.t	9	–
10	DMF	Cu/C (2)	120	9	68
11	DMF	Cu/C (10)	120	9	90
12	DMF	–	120	9	–
13	DMF	Charcoal	120	9	17
14	DMF	$Cu(OAc)_2$ (5)	120	9	48
15	DMF	CuI (5)	120	9	53
16	DMF	$CuSO_4$	120	9	41

[a] Reaction conditions: benzaldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol), sodium azide (1 mmol) and Cu/C (5 mol%) in solvent (2 mL). [b] Isolated yields.
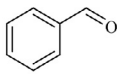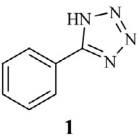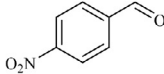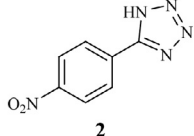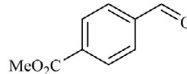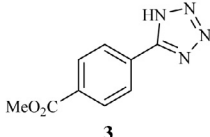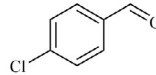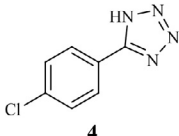
tion time (Table 1, entry 7). By lowering the temperature to 100 °C only a yield of 48% of the target product was obtained (Table 1, entry 8). Furthermore, no reaction took place at room temperature in the presence of the catalyst (Table 1, entry 9).
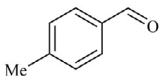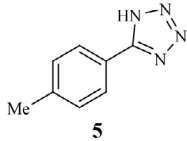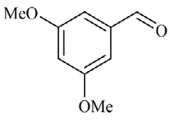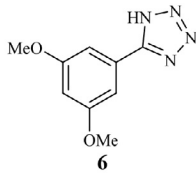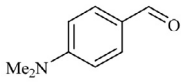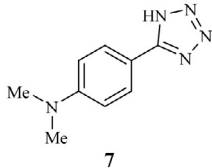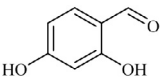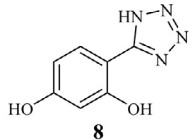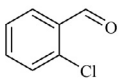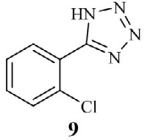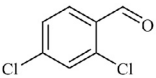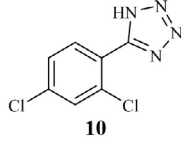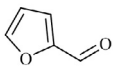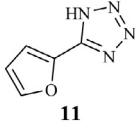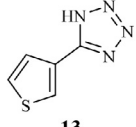
Then the different amounts of catalyst were tested to find the optimum state. The yield was reduced to 68% by reducing the amount of catalyst to 2 mol% (Table 1, entry 10). A further increase in the catalyst quantity did not significantly increase the product yield (Table 1, entry 11). A mixture of aldehyde, hydroxylamine hydrochloride and sodium azide in the absence of Cu/C catalyst was heated to 120 °C for 9 h, but the starting materials were recovered (Table 1, entry 12). To study the catalytic activity of copper, activated carbon was used as a catalyst to reach the target product. The low yield was achieved with activated carbon (Table 1, entry 13). As can be seen from Table 1, the presence of Cu was essential for substrate conversion, and in the absence of Cu, activated carbon did not catalyze the model reaction (entry 13).

To identify the role of Cu/C in this reaction, the catalytic activities of different copper sources were investigated under the same optimal experimental conditions. All alternative copper species produced the desired product in lower yields than Cu/C (Table 2, entries 14–16). Furthermore, separation and reuse of the catalyst was problematic due to its complete dissolution in DMF. The application of this protocol, which is based on the in-situ generation of nitriles, allowed us to efficiently produce tetrazole derivatives.

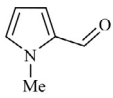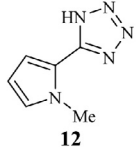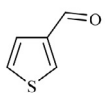To determine the generality of this conversion, the reaction of different aldehydes with a multitude of substituents on the aromatic part in the presence of nanocopper on charcoal was investigated. It was found that the reaction is quite general and that it tolerates a large number of

Table 2. Sequential one-pot synthesis of 5-substituted 1*H*-tetrazoles from aldehydes via in-situ generation of nitriles followed by [2+3] cycloaddition with sodium azide using nano-Cu/C as a catalyst.[a]

Entry	Aldehyde	Product	Time (h)	Yield (%)[b]
1		**1**	9	87
2		**2**	9	89
3		**3**	15	88
4		**4**	9	84

Entry	Aldehyde	Product	Time (h)	Yield (%)[b]
5		**5**	9	82
6		**6**	9	79
7		**7**	9	78
8		**8**	15	80
9		**9**	15	76
10		**10**	15	74
11		**11**	9	83
12		**12**	9	85
13		**13**	9	81

[a] Reaction conditions: aldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol), sodium azide (1 mmol) and Cu/C (5 mol%) in DMF (2 mL) at 120 °C. [b] Isolated yields.

substituted benzaldehydes (Table 2). All reactions took place in less than 15 h, and tetrazole derivatives were isolated in good or even high yields (74–89%) without the need to isolate the aryl nitriles as an intermediate. In general, electronic and steric modifications did not have a remarkable effect on the reactivity of the aldehyde.

The influence of the withdrawing groups on the aromatic ring of benzaldehyde was also investigated. The reactions with nitro and ester groups were carried out in the isolated yields of 88–89% and the carbonyl functionality remained unaffected (Table 2, entries 2–3).

The [3+2] cycloaddition process was also extended to nitriles with electron donating groups such as methyl, methoxy and *N,N*-dimethyl. Using the optimal reaction conditions, the corresponding 5-substituted 1*H*-tetrazoles **5–7** were prepared in 9 h and isolated in good yield (Table 1, entries 5–7).

Benzaldehydes with electron donating groups at the ortho positions of the aromatic rings yielded the corresponding tetrazoles in good yield. However, sterically hindered ortho-substituted benzaldehydes required a longer reaction time (Table 2, entries 8–10).

The above results showed that this reaction can be applied to benzaldehyde for a wide range of functional groups. The reaction proceeded well, regardless of the position and electronic nature of the substituents on the aromatic ring. Next, the reactivity of acid-sensitive heterocyclic aldehydes was investigated. The reaction of furfural, *N*-methylpyrrole-2-carbaldehyde and thiophene-3-carbaldehyde resulted in the desired tetrazoles 11–13 in good yields (Table 2, entries 11–13).

To check the reusability of the catalyst, the reaction was carried out with benzaldehyde, hydroxylamine hydrochloride and sodium azide under the optimized reaction conditions. After completion of the reaction, the catalyst was separated from the reaction mixture by simple filtration, washed with ethyl acetate and dried for reuse under air atmosphere. As shown in Figure 1, five recoveries of catalyst were found without significant loss of catalytic activity.
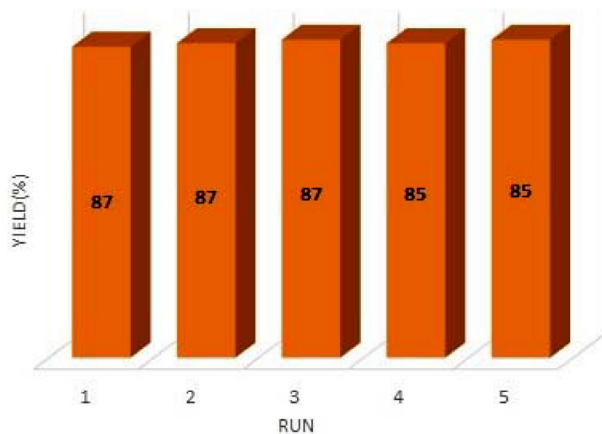
Figure 1. Recovery and reuse of Cu/C nanoparticles for the synthesis of 5-phenyl-1*H*-tetrazole from benzaldehyde via benzonitrile.

The plausible mechanism for the synthesis of 5-substituted 1*H*-tetrazoles from aldehydes was shown in Scheme 3 using Cu/C as catalyst. First, oxime is formed on the aldehyde according to the activation of the carbonyl group of the aldehyde and the nucleophilic attack of the
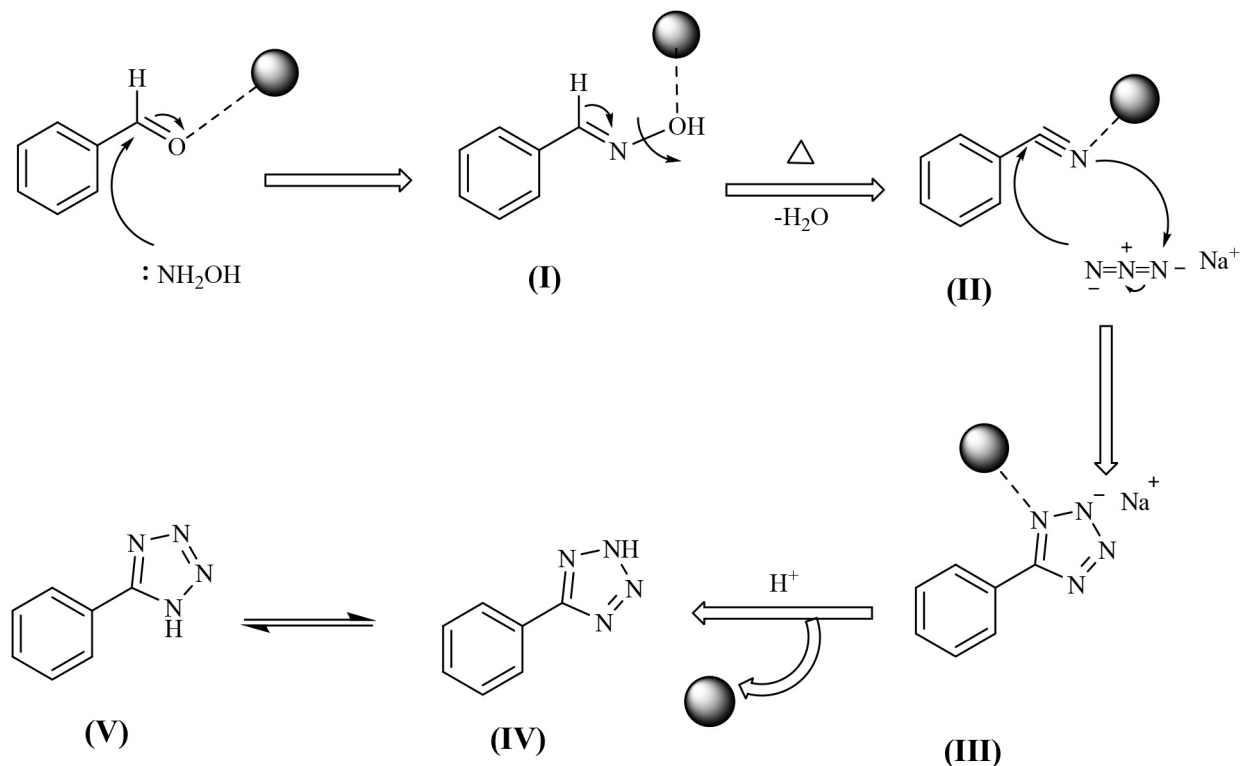
Scheme 3: Plausible mechanism for the synthesis of 5-substituted 1*H*-tetrazoles from aldehydes catalyzed by Cu/C.

Table 3: Comparison between the efficiency of Cu/C as catalyst and some other catalysts for the synthesis of 5-substituted 1*H*-tetrazole derivatives.

Entry	Reaction Condition	Time (h)	Yield (%)	Ref.
1	Ni(OH)$_2$ Nanoparticles, H$_2$O, Reflux	10	98	66
2	Cu(OAc)$_2$, DMF, 120 °C	12	96	67
3	Cu-MCM-41, DMF, 140 °C	12	90	68
4	(NH$_4$)$_2$Ce(SO$_4$)$_4$.2H$_2$O, DMF, 140 °C	5	72	69
5	Bi(OTf)$_3$, DMF, 120 °C	24	87	70
6	Cu/C, DMF, 120 °C	9	87	This work

nitrogen atom of the hydroxylamine. In the next step, the nitrile product is formed by splitting off water. Then the nitrile group is activated by Cu/C, which accelerates the cyclization step. The cycloaddition between the nitrile group and the azide ion takes place immediately to form the intermediate product III. After removal of the catalyst by simple filtration and acidic processing, IV and V tautomers are obtained. The more stable tautomer V (5-substituted-1*H*-tetrazole) is accepted as the significant product.

The efficiency of Cu/C as a catalyst for the synthesis of 5-substituted 1*H*-tetrazoles starting from aldehydes was compared with that of other catalysts reported in the literature. The results were summarized in Table 3. It is clear that Cu/C is the most effective catalyst for the synthesis of 5-substituted 1*H*-tetrazole derivatives.

4. Conclusion

In summary, we have developed an efficient direct route for the synthesis of tetrazole derivatives from aromatic aldehydes, hydroxylamine hydrochloride and sodium azide. The reaction was carried out by copper-catalyzed [3+2]cycloaddition to produce 5-substituted 1*H*-tetrazole in a sequential one-pot three-component reaction without isolation of the nitrile intermediate. The main advantage of this method is the replacement of toxic nitrile precursors by aldehydes. This method demonstrates the potential of the nanocatalyst Cu/C as a very user-friendly, cost-effective and efficient catalyst for the production of 5-substituted 1*H*-tetrazoles. The catalyst can be easily recovered and reused.

Acknowledgement

5. References

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Povzetek

Razvita je nova, učinkovita in priročna metoda za sintezo 5-substituiranih derivatov 1*H*-tetrazola s široko paleto substituentov in z dobrimi izkoristki. Sinteza je bila izvedena z enostopenjsko trikomponentno reakcijo [3+2] cikloadicije med aldehidom, hidroksilaminom in natrijevim azidom v prisotnosti Cu/C kot katalizatorja. Reakcija verjetno poteka z *in-situ* tvorbo nitrila, čemur sledi nadaljnja [3+2] cikloadicija z natrijevim azidom. Za pridobitev ustreznih tetrazolov so uporabili različne aldehide. Katalizator so rekuperirali s preprosto filtracijo in ponovno uporabili v najmanj petih poskusih, brez večje izgube katalitične aktivnosti. Uporaba te metode ponuja nove možnosti za sintezo 5-substituiranih derivatov 1*H*-tetrazola, vključno z lahko dostopnimi vhodnimi snovmi, blagimi reakcijskimi pogoji, enostavno izvedbo reakcije in dobrimi izkoristki.