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ZrO_2 Nanoparticles-Supported Cu_2(II)-β-Cyclodextrin Mediated Synthesis of *N*-2 Substituted Tetrazoles by [2+3] Cycloaddition and Post Tetrazole Alkylation

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An efficient one-pot ZrO_2 nanoparticles-supported Cu_2(II)-β-cyclodextrin promoted [2+3] cycloaddition of benzonitriles and sodium azide followed by post tetrazole alkylation using aralkyl esters for the synthesis of *N*-2-substituted tetrazoles has been presented. One-pot operation, atom-economical, regioselectivity and good yields are the main advantages of this protocol. From the atom economy, it is clear that, catalyst can be reused up to four times without any appreciable changes in catalytic activity

Keywords: ZrO_2 Nanoparticles, [2+3] Cycloaddition, Alkylation, Tetrazoles, Benzonitriles.

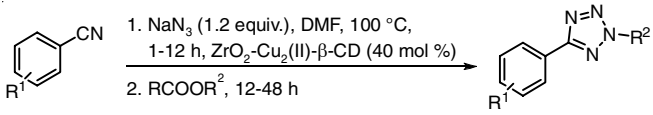
INTRODUCTION

Tetrazoles are important class of five membered nitrogen containing heterocycles which have considerable interest from the past two decades. Tetrazole moieties have wide spread applications such as in bioisosteres replacement for carboxylic acid group in drug industry [1], in coordination chemistry as ligands [2], as energetic materials [3,4], in laser flash photolysis [5], as effective adsorbents in clean energy application for adsorption of CO_2 by using microporous polymer with pending tetrazole moieties [6], in fluorescent chemo sensor for detection of multiple ions by bioimaging [7]. In addition tetrazole moiety is well explored in biological field as AT1-receptor antagonists (Losartan) in the regulation of blood pressure and fluid balance [8] as antimalarial and antiproliferative agents [9,10].

From past few years, several synthetic efforts have been made for the synthesis of bioactive nitrogen containing heterocycles and in that direction [11-15], we have been engaged in investigating the synthesis of various heterocycles using different catalysts [16,17]. Cu(II)-β-CD complex is well explored in the literature for various reactions [18,19] and recently we have reported ZrO_2-Cu_2(II)-β-CD catalyzed one-pot synthesis of N-2-substituted 1,2,3-triazoles *via* azide-chalcone oxidative cycloaddition and post-triazole alkylation [20]. To explore the further scope of the newly synthesized catalyst, we have used ZrO_2-Cu_2(II)-β-CD for the construction of N-2-alkylated tetrazoles *via* [2+3] cycloaddition and post tetrazole alkylation.

The conventional method for the synthesis of N-alkyalted tetrazoles is *via* [2+3] cycloaddition between an azide and nitrile results in the formation of 5-substituted 1*H*-tetrazole and followed by the subsequent treatment with base and alkyl halides [21,22]. Several research groups have attempted for the synthesis of 5-substituted 1*H*-tetrazole using various catalysts such as $TMSN_3$-TBAF [23], Zn/Al-hydrocalcite [24], Fe_2O_3 [25], Zn-hydroxyapatite [26], ionic liquid 1-N-butylimidazolium tetrafluoroborate [27], $FeCl_3$-SiO_2 [28], Cu_2O [29], $CuFe_2O_4$ nanoparticles [30], Amberlyst-15 [31], nano copper oxide [32], $AgNO_3$ [33] and ceric ammonium nitrate supported HY-zeolite [34]. It is noteworthy to mention that none of the above mentioned methods have reported the post tetrazole alkylation using esters as an alkylating agent.

Roh *et al*. [35] reported one-pot regioselective vinylation of tetrazoles using 1,2-dibromoethane and triethylamine at reflux temperature (**Scheme-I**, eqn 1). Gyoung *et al*. [36] have described improved reaction conditions for regiospecific synthesis of 2-allylated-5-substituted tetrazoles *via* palladium-catalyzed reaction of nitriles, allyl acetates and trimethylsilyl azide. However, the above said methods require harsh reaction conditions, use of toxic chemicals and long duration of time. To overcome these drawbacks we have developed an efficient one-pot protocol for the regioselective synthesis of N-2-substituted tetrazoles *via* [2+3] cycloaddition using an ZrO_2 nanoparticles supported Cu_2(II)-β-cyclodextrin complex (without any additives) followed by treatment with esters as an alkylating



Scheme-I: Strategy for the synthesis of 2,5-disubstituted tetrazoles

agent in DMF at 100 ºC. The main advantages of this protocol are the simple starting materials, one pot operation, easy work-up procedure and high regioselectivity.

EXPERIMENTAL

General procedure for synthesis of N-2-substituted 1,2,3,4-tetrazoles: Aromatic benzonitriles (1 mmol), sodium azide (1.2 mmol), 40 mol % of ZrO_2-Cu_2(II)-β-CD (50 mg, 0.036 mmol) and 3 mL DMF were taken in a round bottom flask equipped with stirrer. The reaction mixture was agitated at 100 ºC for 1-12 h, then ester (1 mmol) was added to the mixture and the reaction continued at 100 ºC for 12-48 h. The reaction mixture was diluted with water (4 mL) and extracted with ethyl acetate (6 × 10 mL). The combined organic phases were washed with brine (4 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was subjected to column chromatography with hexane/EtOAc as eluent to get the desired product.

5-(4-Chlorophenyl)-2-methyl-2*H*-tetrazole (3a) [37]**:** White solid; m.p. 106-108 ºC (lit. 107-108 ºC); R_f = 0.4 (hexane: EtOAc 8:2); ATR-IR: 2968, 1727, 1606, 1448, 1439, 1415, 1163, 1114, 1048, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08-8.06 (d, *J* = 8.8 Hz, 2H, ArH), 7.47-7.45 (d, *J* = 8.4Hz, 2H, ArH), 4.39 (s, 3H, N-Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 136.3, 129.18, 129.15, 128.0, 125.8, 39.4; HRMS (ESI) *m/z*: Calculated for $C_8H_7N_4Cl$: 194.6220 $(M+1)^+$, 197.0330 $(M+3)^+$; Found: 195.0924 $(M+1)^+$, 197.0908 $(M+3)^+$.

5-(3,5-Dichlorophenyl)-2-methyl-2*H*-tetrazole (3b): White solid; m.p. 78-80 ºC; R_f = 0.5 (hexane: EtOAc 8:2); ATR-IR: 3028, 1856, 1742, 1512, 1447, 1386, 1106, 1100, 1029, 852 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 2H, ArH), 7.44 (s, 1H, ArH), 4.41 (s, 3H, N-Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 135.6, 130.17, 130.12, 130.07, 125.2, 125.1, 39.6; HRMS (ESI) *m/z*: Calculated for $C_8H_6N_4Cl_2$: 229.9940 $(M+1)^+$, 231.0630 $(M+3)^+$, 233.0630 $(M+5)^+$; Found: 229.0557 $(M+1)^+$, 231.0542 $(M+3)^+$, 233.0480 $(M+5)^+$.

5-(4-Bromophenyl)-2-methyl-2*H*-tetrazole (3c) [38]**:** White solid; m.p. 123-125 ºC; (lit. 124-126 ºC); R_f = 0.4 (hexane: EtOAc 8:2); ATR-IR: 3042, 1826, 1732, 1542, 1467, 1387, 1140, 1105, 1032, 785 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01-7.99 (d, *J* = 8.4 Hz, 2H, ArH), 7.47-7.45 (d, *J* = 8.8Hz, 2H, ArH), 4.39 (s, 3H, N-Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 132.1, 128.2, 126.3, 124.6, 39.5; HRMS (ESI) *m/z*: Calculated for $C_8H_7N_4Br$: 239.0760 $(M+1)^+$, 241.0326 $(M+3)^+$; Found: 239.0652 $(M+1)^+$, 241.0523 $(M+3)^+$.

5-(4-Fluorophenyl)-2-methyl-2*H*-tetrazole (3d) [37]**:** White solid; m.p. 88-89 ºC; (lit. 88-89 ºC); R_f = 0.52 (hexane: EtOAc 8: 2); ATR-IR: 3067, 1834, 1726, 1535, 1432, 1356, 1128, 1117, 1037, 792 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14-8.11 (m, 2H, ArH), 7.26-7.15 (m, 2H, ArH), 4.39 (s, 3H, N-Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 162.7, 128.8, 128.7, 123.6, 123.5, 116.1, 115.8, 39.4; HRMS (ESI) *m/z*: Calculated for $C_8H_7N_4F$: 179.0688 $(M+1)^+$; Found: 179.0521 $(M+1)^+$.

2-Methyl-5-[4-(trifluoromethyl)phenyl]-2*H*-tetrazole (3e) [22]**:** White solid; m.p. 112-115 ºC; (lit. 113-115 ºC) R_f = 0.47(hexane:EtOAc 8: 2); ATR-IR: 3054, 1832, 1756, 1543, 1468, 1354, 1130, 1125, 1021, 767 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27-8.25 (d, *J* = 8.0Hz, 2H, ArH), 7.26-7.74 (d, *J* = 8.0 Hz, 2H, ArH), 4.42 (s, 3H, N-Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.03, 131.8, 130.6, 127.0, 125.8, 125.1, 39.5; HRMS (ESI) *m/z*: Calculated for $C_8H_7N_4F_3$: 229.1782 $(M+1)^+$; Found: 229.0124 $(M+1)^+$.

5-(3-Bromophenyl)-2-methyl-2*H*-tetrazole (3f) [39]**:** White solid; m.p. 121-123 ºC; (lit. 120-122 ºC); R_f = 0.5 (hexane: EtOAc 8:2); ATR-IR: 3016, 1822, 1739, 1538, 1456, 1390, 1147, 1104, 1023, 789 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H, ArH), 8.07-8.05 (d, *J* = 8.0Hz, 1H, ArH), 7.60-7.58 (d, *J* = 8.0 Hz, 1H, ArH), 7.37-7.33 (t, *J* = 7.8Hz, 1H, ArH), 4.39 (s, 3H, N-Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.00, 133.2, 130.4, 129.7, 129.2, 125.2, 122.9, 39.5; HRMS (ESI) *m/z*: Calculated for $C_8H_7N_4Br$: 239.0760 $(M+1)^+$, 241.0512 $(M+3)^+$; Found: 239.0652 $(M+1)^+$, 241.0451 $(M+3)^+$.

5-(5-Bromo-2-fluorophenyl)-2-methyl-2*H*-tetrazole (3g): Pale yellow needles; m.p. 85-87 ºC; R_f = 0.5 (hexane:EtOAc 8:2); ATR-IR: 3042, 1820, 1734, 1543, 1456, 1392, 1154, 1102, 1012, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04-8.01 (dd, *J* = 8.8 Hz, 1H, ArH), 7.74-7.71 (m, 1H, ArH), 7.53-7.49 (m, 1H, ArH, F coupling), 4.41 (s, 3H, N-Me); 13C NMR (100 MHZ, $CDCl_3$): δ 163.2, 133.7, 132.0, 129.5, 129.1, 125.7, 122.8, 40.1; HRMS (ESI) m/z:Calculated for $C_8H_6N_4BrF$: 257.0664 $(M+1)^+$, 259.0534 $(M+3)^+$; Found: 257.0521 $(M+1)^+$, 259.0454 $(M+3)^+$.

5-(3-Chloro-4-fluorophenyl)-2-methyl-2*H*-tetrazole (3h): Pink solid; m.p. 85-88 ºC; R_f = 0.4 (hexane:EtOAc 8: 2); ATR-IR: 3026, 1823, 1745, 1542, 1465, 1391, 1117, 1104, 1021, 852 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17-8.16 (d, *J* = 2.0 Hz, 1H, ArH), 8.07-8.04 (d, *J* = 10.4 Hz, 1H, ArH), 7.29-7.24 (t, 1H, ArH), 4.39 (s, 3H, N-Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 159.7, 139.0, 129.0, 126.18, 126.2, 125.0, 120.0, 39.5; HRMS (ESI) *m/z*: Calculated for $C_8H_6N_4ClF$: 213.6124 $(M+1)^+$, 215.4124 $(M+3)^+$; Found: 213.0154 $(M+1)^+$, 215.0361 $(M+3)^+$.

2-Methyl-5-(*p*-tolyl)-2*H*-tetrazole (3i) [37]**:** White solid; m.p. 104-105 ºC; (lit 104-105 ºC); R_f = 0.6 (hexane:EtOAc 8: 2); ATR-IR: 3036, 1853, 1725, 1532, 1467, 1392, 1123, 119, 1028, 778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01-7.99 (d, *J* = 8.0 Hz, 2H, ArH), 7.63-7.62 (d, *J* = 8.4 Hz, 2H, ArH), 4.37 (s, 3H, N-Me), 2.40 (s, 3H, P-Me); HRMS (ESI) *m/z*: Calculated for $C_9H_{10}N_4$: 175.2070 $(M+1)^+$; Found: 175.0325 $(M+1)^+$.

2-[5-(3-Bromophenyl)-2*H*-tetrazol-2-yl]ethyl 3-bromobenzoate (3j): Pale green solid; m.p. 75-77 ºC; R_f = 0.5 (hexane: EtOAc 8: 2); ATR-IR: 3034, 1834, 1726, 1547, 1437, 1352, 1120, 1109, 1054, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H, ArH), 8.09-8.07 (d, *J* = 7.6 Hz, 1H, ArH), 7.76-7.73 (t, *J* = 8.8 Hz, 1H, ArH), 7.64-7.59 (m, 2H, ArH), 7.38-7.32 (m, 3H, ArH), 5.08-5.05 (t, 2H, CH_2), 4.93-4.90 (t, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 164.2, 134.4, 133.3, 133.0, 131.6, 131.5, 130.7, 130.4, 129.8, 129.0, 127.2, 125.3, 122.95, 122.94, 62.0, 51.8 ; HRMS (ESI) *m/z*: Calculated for $C_{16}H_{12}N_4O_2Br_2$: 451.9307 $(M+1)^+$, 453.0652 $(M+3)^+$, 455.0546 $(M+5)^+$; Found: 451.0194 $(M+1)^+$, 453.0204 $(M+3)^+$, 455.0258 $(M+5)^+$.

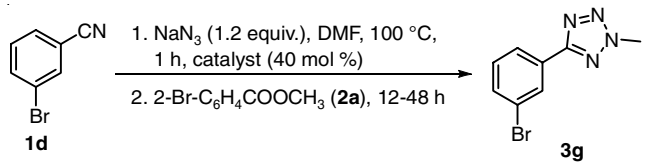
Ethyl 2-[5-(5-bromo-2-fluorophenyl)-2*H*-tetrazol-2-yl]acetate (3k): White solid; m.p. 78-80 ºC; R_f = 0.6 (hexane:

EtOAc 8:2); ATR-IR: 3046, 1829, 1754, 1532, 1456, 1392, 1128, 1100, 1037, 765 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (s, 1H, ArH),7.48-7.46 (d, *J* = 8.8 Hz, 1H, ArH), 6.46-6.43 (d, *J* = 8.8 Hz, 1H, ArH), 4.27-4.26 (q, 2H, CH_3), 3.96-3.95 (d, 2H, CH_2), 1.32-1.25 (t, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 148.1, 137.1, 134.7, 116.0, 112.4, 108.3, 98.2, 61.8, 44.9, 14.1; HRMS (ESI) *m/z*: Calculated for $C_{11}H_{10}N_4O_2BrF$: 329.1294 $(M+1)^+$, 331.0664 $(M+3)^+$; Found: 329.0452 $(M+1)^+$, 331.0564 $(M+3)^+$.

2-[5-(4-(Bromomethyl)phenyl)-2*H*-tetrazol-2-yl]ethyl 2-bromobenzoate (3l): Pale yellow liquid; R_f = 0.5 (hexane: EtOAc 8:2); ATR-IR: 3034, 1824, 1721, 1534, 1454, 1397, 1127, 1107, 1028, 745 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$): δ 8.17-8.15 (d, *J* = 8.0 Hz, 2H, ArH), 7.75-7.72 (t, *J* = 9.6 Hz, 1H, ArH), 7.63-7.61 (t, *J* = 8.8 Hz, 1H, ArH), 7.45-7.43 (d, *J* = 8.0 Hz, 2H, ArH), 7.33-7.27 (q, 2H, ArH), 5.08-5.05 (t, 2H, CH_2), 4.93-4.90 (t, 2H, CH_2), 4.41 (s, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 164.9, 137.6, 134.4, 133.0, 131.6, 130.8, 130.7, 128.7, 128.5, 127.2, 127.1, 127.0, 121.8, 62.1, 54.3, 51.7; HRMS (ESI) *m/z*: Calculated for $C_{17}H_{14}N_4O_2Br_2$: 465.1330 $(M+1)^+$, 467.3312 $(M+3)^+$, 469.4261 $(M+5)^+$; Found: 465.1298 $(M+1)^+$, 467.3902 $(M+3)^+$, 469.4869 $(M+5)^+$.

RESULTS AND DISCUSSION

Initially, we have selected 3-bromobenzonitrile (**1d**) as a model substrate to screen the reaction using different catalysts such as CuO, α-Fe_3O_4, ZrO_2-β-CD, ZrO_2-Cu_2(II)-β-CD, $CuFe_2O_4$, sulfated ZrO_2, ZnO and β-cyclodextrin (**Scheme-II**, Table-1). Among all the catalysts, ZrO_2-Cu_2-β-CD was found to be better for cyclization and only catalyst to effect the post tetrazole alkylation. Then the reaction was screened using ZrO_2-Cu_2(II)-β-CD as a catalyst by varying solvent, temperature and mol % of catalyst. Initially 40 mol % of ZrO_2-Cu_2(II)-β-CD in DMF at 110 ºC gave only 84 % of yield even after 18 h (entry 9, Table-1). A decrease in temperature to 100 ºC resulted in increase of product yield up to 86 % (entry 10, Table-1). Later with optimal temperature and catalyst load, we have screened the reaction in shorter time 16 h and noticed the increase in product yield of 88 % (entry 11, Table-1). A decrease in catalyst load percentage doesn't improve the product yield (entry 12, Table-1).



Scheme-II: Strategies for the synthesis of 2,5-disubstituted tetrazoles

Then the reaction was screened using DMSO as solvent which gave a moderate yield of 78 % (entry13, Table-1).

Furthermore, diverse nitriles possessing wide range of functional groups were used to investigate the substrate tolerance under the given reaction condition and the results obtained are summarized in Table-2. Nitriles bearing chloro, dichloro, bromo, fluoro, trifluoro methyl, alkyl bromo and methyl groups at different position on the benzene ring underwent reaction smoothly to produce desired product in good yield within 12-48 h (entry 1-9, Table-3). Since halogens having α-hydrogen atoms are very good leaving group, when we used 2-chloroethyl-3-bromobenzoate and ethylbromoacetate (entry 10-12, Table-2) for alkylation, triazole anion undergoes substitution at α-carbon of the halogens instead of α-carbon of the ester leading to the formation of highly substituted tetrazole derivatives.

With the optimized reaction conditions in hand, we explored the generality and scope of the protocol by keeping nitrile component as common and used various substituted alkyl/aralkyl esters for alkylation. The reaction of tetrazole anion with an methyl ester containing bromine atom at the O-position of the aryl group proceeded smoothly and regioselectively produced the corresponding *N*-2-methylated tetrazole with an excellent yield (entry 3, Table-3). Inspired by this, we went on to examine different alkyl esters like ethyl, isopropyl, *t*-butyl, *n*-butyl and isoamyl groups, unfortunately none of the groups promoted the reaction (entries 4-8, Table-3).

Conclusion

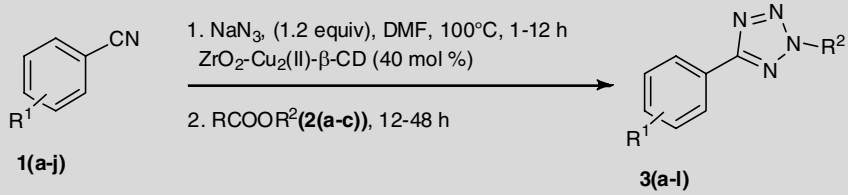
An efficient ZrO_2 nanoparticles-supported Cu_2(II)-β-cyclodextrin complex catalyzed protocol for regioselective synthesis of *N*-2-substituted tetrazoles in moderate to excellent yields starting from aromatic benzonitrilesand sodium azide *via* [2+3] cycloaddition and post-tetrazole alkylation using different aryl-

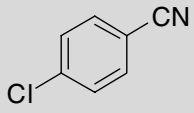
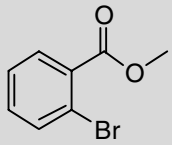
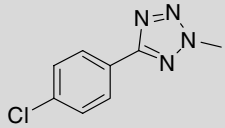
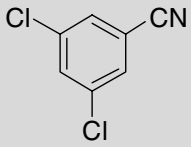
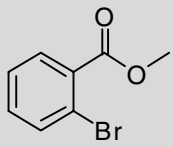
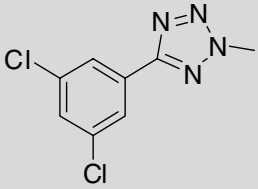
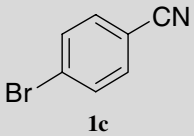
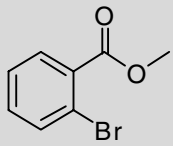
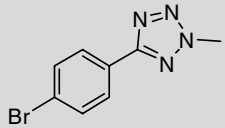
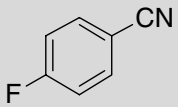
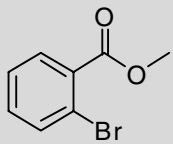
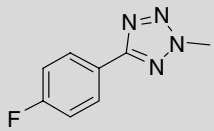
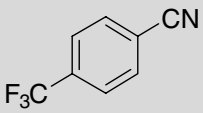
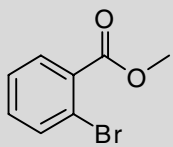
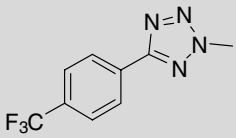
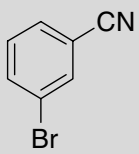
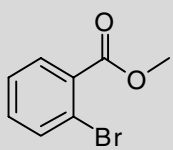
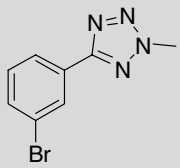
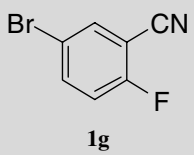
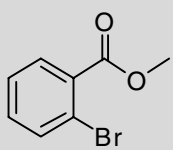
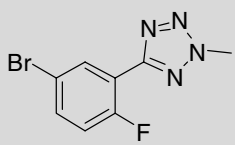
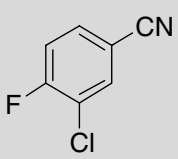
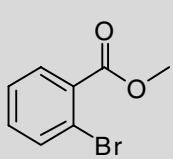
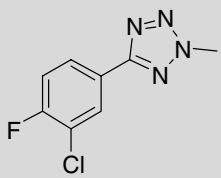
TABLE-1
EFFECT OF CATALYST AND SOLVENT ON THE REACTION

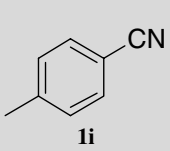
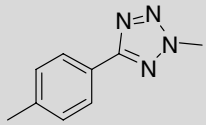
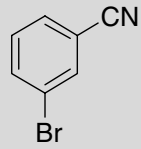
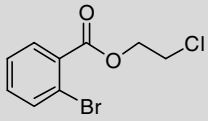
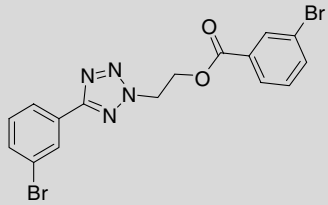
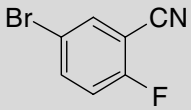
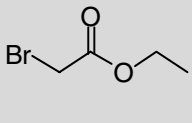
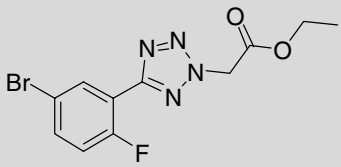
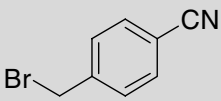
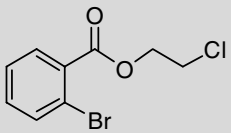
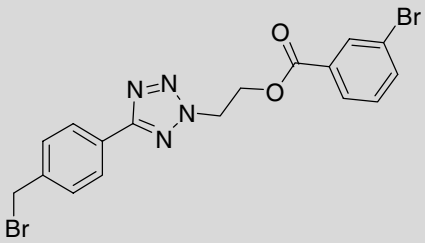
Entry[a]	Catalyst	Temp. (°C)	Mol (%)	Solvent	Time (h)	Yield (%)
1	–	125	–	DMF	24	–
2	CuO	110	40	DMF	10	–
3	α-Fe_3O_4	110	40	DMF	20	–
4	ZrO_2-β-CD	110	40	DMF	1:30	–
5	$CuFe_2O_4$	110	40	DMF	12	–
6	Sulfated ZrO_2	110	40	DMF	24	–
7	ZnO	110	40	DMF	14	–
8	β-CD	110	40	DMF	1:45	–
9	ZrO_2-Cu_2(II)-β-CD	110	40	DMF	18	84
10	ZrO_2-Cu_2(II)-β-CD	100	40	DMF	18	86
11	**ZrO_2-Cu_2(II)-β-CD**	**100**	**40**	**DMF**	**16**	**88**
12	ZrO_2-Cu_2(II)-β-CD	100	30	DMF	16	80
13	ZrO_2-Cu_2(II)-β-CD	**100**	**40**	DMSO	16	78

[a]Reaction condition 3-bromo benzonitrile **1d** (1 mmol), NaN_3 (1.2 mmol), 40 mol % of ZrO_2-Cu(II)-β-CD (50 mg) in DMF (3 mL) at 100 °C in air for 1 h first, then 2-Br-$C_6H_4COOCH_3$ (1 mmol), was added to mixture and the reaction continued for 12-48 h.

TABLE-2
SUBSTRATE SCOPE OF DIFFERENT BENZONITRILES AND ESTERS

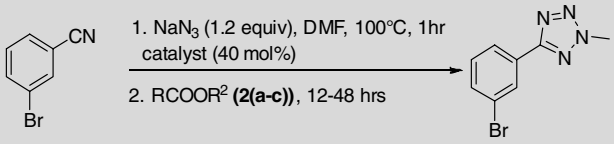


Entry	Substrate	Ester	Product	Time (h)	Yield[a,b] (%) [Ref.]
1	 **1a**	 **2a**	 **3a**	24	90 [37]
2	 **1b**	 **2a**	 **3b**	30	85
3	 **1c**	 **2a**	 **3c**	16	94 [38]
4	 **1d**	 **2a**	 **3d**	48	65 [37]
5	 **1e**	 **2a**	 **3e**	48	82 [22]
6	 **1f**	 **2a**	 **3f**	15	87 [39]
7	 **1g**	 **2a**	 **3g**	24	50
8	 **1h**	 **2a**	 **3h**	48	40

9	 **1i**	 **2a**	 **3i**	12	50 [37]
10	 **1f**	 **2b**	 **3j**	16	60
11	 **1g**	 **2c**	 **3k**	32	70
12	 **1j**	 **2b**	 **3l**	24	60

[a]Isolated yields; [b] Literature reported compounds.

TABLE-3
N-ALKYLATION USING DIFFERENT ESTERS



1d **3(a-i)**

Entry	R	R^2	Yield (%)	Product
1	CH_3	CH_2CH_3	–	–
2	C_6H_5	CH_3	56	3g
3	**2-BrC_6H_4**	**CH_3**	**88**	**3g**
4	2-BrC_6H_4	CH_2CH_3	Trace	–
5	2-BrC_6H_4	Isopropyl	–	–
6	2-BrC_6H_4	*t*-Butyl	–	–
7	2-BrC_6H_4	*n*-Butyl	–	–
8	2-BrC_6H_4	Isoamyl	–	–

alkyl esters without any additives is reported. The ZrO_2-Cu_2(II)--β-CD nanoparticles were collected easily by filtration and the reusability of the prepared nanocatalyst was successfully examined up to four cycles without appreciableloss of catalytic activity (Table-4). Hence, the present method proved to be an economical and very much useful in the synthesis of bioactive tetrazole derivatives.

TABLE-4
RECYCLABILITY STUDY OF
ZrO_2-SUPPORTED Cu_2(II)-β-CYCLODEXTRIN

Recycles	Catalyst recovery (wt%)	Yield of **3a** (%)
1	90	90
2	86	85
3	84	82
4	82	74

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