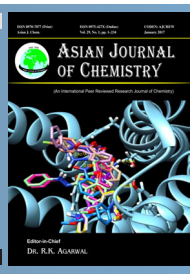
Asian Journal of Chemistry; Vol. 29, No. 4 (2017), 864-866

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2017.20337



Syntheses of 5-Substituted 1*H*-tetrazoles Catalyzed by Reusable Cu(II)-NaY Zeolite from Nitriles

K. SUDHAKAR*, B. PURNA CHANDRA RAO, B. PREM KUMAR, M. SURESH and S. RAVI

Rural Development Society, R & D Centre, Punjagutta, Hyderabad-500 082, India

*Corresponding author: E-mail: ksudhakarrds@gmail.com

Received: 10 October 2016; *Accepted*: 20 December 2016; *Published online*: 31 January 2017; AJC-18260

Cu(II)-NaY heterogeneous catalyst is used for the synthesis of 5-substituted 1*H*-tetrazoles by [2+3]-cycloaddition of sodium azide and nitriles. The salient features of this process are low reaction times, mild reaction conditions and high yields. The catalyst is recovered and reused for several cycles with consistent activity.

Keywords: 5-Substituted 1*H*-tetrazoles, Heterogeneous catalyst, Cu(II)-NaY zeolite, Additive free conditions, Green chemistry.

INTRODUCTION

Tetrazoles are nitrogen rich heterocycles, receiving considerable attention because of their wide range of applications in pharmaceuticals as lipophilic spacers and metabolically stable carboxylic acid surrogates, in materials as speciality explosives, photography and information recording systems, in coordination chemistry as ligands and also precursors to a variety of nitrogen containing heterocycles [1-4]. The most convenient route for the synthesis 5-substituted 1*H*-tetrazoles is [2+3] cycloaddition of azides and nitriles [5-11]. The earlier reports for this transformation use either expensive metal azides or strong Lewis acids, which suffers from the presence of highly hazardous hydrazoic acid and severe water sensitivity [12-17]. Sharpless and Demko [18] have reported an innovative and safe procedure for the preparation of 5-substituted 1*H*-tetrazoles starting from the corresponding nitriles, by using NaN_3 and stoichiometric amounts of Zn(II) salts in water. Later Pizzo and co-workers reported the synthesis of tetrazoles by addition of $TMSN_3$ to organic nitriles using 10 mol % TBAF as catalyst [19].

In recent years, there has been increasing emphasis on the use of environmental friendly solid catalysts to reduce the amount of toxic waste. In this view few heterogeneous catalysts are reported for the synthesis of 5-substituted 1*H*-tetrazoles [20]. Zeolites are stable solid materials and often found as useful catalysts in a large variety of reactions. They contain large number of Brønsted and Lewis acidic sites and transition metal ion supported zeolites act as bifunctional catalysts and more useful in synthesis of 5-substituted 1*H*-tetrazoles [21,22]. Recently recyclable copper catalyst systems attracted much attention due to their higher catalytic activity in a variety of organic transformations [23]. In this context we explore Cu-mediated zeolites for synthesis for clean synthesis of pharmaceutical compounds. Herewith we report an efficient method Cu(II)-NaY catalyzed synthesis of 5-substituted 1*H*-tetrazoles and application of this method in synthesis of antihypertensive drug irbesartan by the addition of sodium azide to corresponding organic nitrile. This catalyst is recovered and recycled for several times without loss of activity.

EXPERIMENTAL

All chemicals and solvents were of analytical grade and used as received without further purification.

Preparation of Cu(II)-NaY catalyst: Cu(II)-NaY zeolite was prepared by ion-exchange of zeolite NaY (10 g) with a solution of copper(II) acetate (2.86 g, 15.75 mmol in deionized water 150 mL) for 24 h at room temperature. The material was recovered by centrifugation, dried (110 °C) and calcined (550 °C) in a flow of air. The obtained atomic absorption spectroscopy analysis showed that the zeolite contains 6.84 wt % of Cu.

Typical procedure for the preparation of 5-substituted 1*H*-tetrazoles: Cu(II)-NaY (0.1 g) was added to a mixture of benzonitrile (0.206 g, 2.0 mmol) and sodium azide (0.169 g, 2.6 mmol) in DMF (5 mL) and mixture was stirred at 120 °C for 3 h. After completion of reaction (as monitored by TLC), the catalyst was centrifuged, washed with ethyl acetate and the centrifugate was treated with ethyl acetate (30 mL) and 5 N HCl (20 mL) and stirred vigorously. The resultant organic layer was separated and the aqueous layer was again extracted with ethyl acetate (20 mL). The combined organic layers were washed with water and concentrated to give the crude solid crystalline 5-phenyltetrazole. The product was characterized by ^{1}H NMR , ^{13}C NMR and mass spectroscopic analysis.

5-Phenyl-1*H*-1,2,3,4-tetrazole (Table-2, entry 1): ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm): 8.04 (m, 2H), 7.61 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 124.17, 127.02, 129.45, 131.28, 155.2 (br). MS (ESI): M = 146, found 146 [M-H].

5-Benzyl-1*H*-1,2,3,4-tetrazole (Table-2, entry 5): ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm): 3.8 (s, 2H), 7.3- 7.5 (m, 5H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 155.2, 135.9, 128.7, 128.6, 127.0, 28.9. MS (ESI): M = 160, found 159 $[M-H]^-$.

5-(2-Methoxybenzyl)-1*H*-1,2,3,4-tetrazole (Table-2, entry 6): ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm): 3.6 (s, 2H), 3.85 (s, 3H), 6.8-7.0 (m, 2H), 7.2-7.4 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 23.9, 55.4, 111.0, 120.4, 123.6, 128.7, 130.1, 156.9. MS (ESI): M = 190, found 191 $[M+H]^+$.

4-(1*H*-1,2,3,4-Tetrazol-5-yl)benzaldehyde (Table-2, entry 10): ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm): 8.0 (d, 2H), 8.15 (d, 2H), 10.1 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 128.07, 130.00, 130.82, 138.07, 155.77, 193.13. MS (ESI): M = 173, found 173 [M-H].

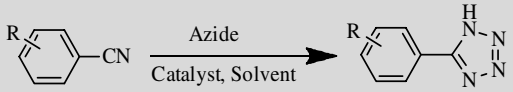
2-Butyl-3-({4-[2-(2*H*-1,2,3,4-tetrazol-5-yl)phenyl]-phenyl}methyl)-1,3-diazaspiro[4.4]non-1-en-4-one (Table-2, entry 14): White solid; m.p.: 180-181 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.83 (t, J = 7.4 Hz, 3H, CH_3), 1.41-1.20 (m, 2H, CH_2), 1.60-1.45 (m, 2H, CH_2), 2.0-1.59 (m, 8H, CH_2), 2.30 (t, J = 7.5 Hz 2H, CH_2), 4.57 (s, 2H, CH_2), 7.12(d, 2H, J = 8 Hz, ArH), 7.28-7.33 (m, 3H, ArH), 7.40-7.49 (m, 3H, ArH); ^{13}C NMR (300 MHz, $CDCl_3$); δ 14.0, 19.0, 26.1, 29.8, 37.6, 44.2, 72.7, 124.4, 127.7, 128.8, 130.2, 131.4, 131.5, 131.9, 134.9, 139.9, 141.8, 155.9, 172.5, 180.4; MS (ESI): M = 428, found 429 $[M+H]^+$.

RESULTS AND DISCUSSION

Initially, various reaction parameters were studied for the preparation of 5-phenyltetrazole by the reaction of benzonitrile with sodium azide and the results are summarized in Table-1. First we conducted this reaction using H-Y zeolite in DMF solvent at 120 °C afforded 19 % yield after 4 h and 15 % with NaY zeolite (Table-1, entries 1 and 2). Later the use of Zn(II)-NaY and Fe(II)-NaY catalysts resulted in 15 and 18 % yields, respectively (Table-1, entries 3 and 4). But with Cu(II)-NaY catalyst, the reaction was complete within 3.5 h and quantitative yields were obtained (Table-1, entry 5). When $TMSN_3$ was used as the azide source, the reaction gave 42 % yield (Table-1, entry 6). The homogeneous copper(II) acetate catalyst afforded 63 % yield (Table-1, entry 7). The solvent has pronounced effect in this reaction (Table-1, entries 8-11) in which DMSO provided better yields when compared to methanol and water while traces amount of the product was obtained in toluene. The used catalyst was recovered by centrifugation and reused for three cycles with consistent activity (Table-1, entry 5).

Table-2 summarizes the scope and the generality of the Cu(II)-NaY promoted formation of 5-substituted 1*H*-tetrazoles. A variety of structurally divergent benzonitriles possessing a wide range of functional groups are studied in this regard. All the nitriles gave the corresponding tetrazoles in quantitative yields. 2-Chloro-, 4-chloro- and 4-methoxybenzonitriles are converted to the corresponding tetrazoles in quantitative yields within 4 h (Table-2, entries 1-4), which shows that there is no effect of substitution on benzonitrile. Phenylacetonitrile and 4-methoxyphenyl acetonitrile are also provided quantitative yields in shorter reaction times (Table-2, entries 5 and 6), whereas the previous reported longer reaction times. This catalytic system provided good compatibility to other functional groups (Table-2, entries 7 and 8) and mono addition product was obtained when 1,3-dicyanobenzene and 1,4-dicyanobenzene are used (Table-2, entries 9 and 10,). Heteroaromatic nitriles such as 2-pyridinecarbonitrile and cyanopyrazine gave corresponding tetrazoles in quantitative yields in shorter reaction times (Table-2, entries 11 and 12,). Interestingly simple acetonitrile is also converted to 5-methyltetrazole in quantitative yields in 3 h (Table-2, entry 13). Irbesartan nitrile intermediate (Table-2, entries 14) gave corresponding final API in good yield. Irbesartan marketed under the trade name Avapro, a tetrazole derivative, is an antihypertensive drug which is a potent, long acting non pepetide Ang II receptor antagonist with high selectivity for the AT1 sub type [24].

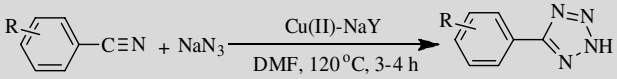
TABLE-1
SCREENING OF REACTION PARAMETERS FOR THE FORMATION OF 5-PHENYL TETRAZOLE[a]

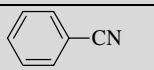
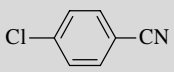
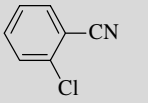
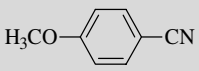
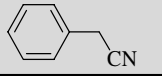


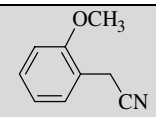
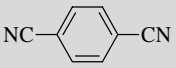
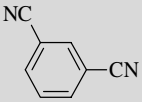
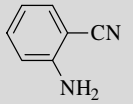
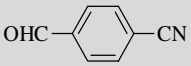
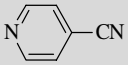
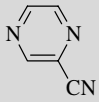
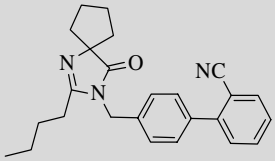
Entry	Catalyst	Azide	Solvent	Yield[b] (%)
1	H-Y	NaN_3	DMF	19.0
2	Na-Y	NaN_3	DMF	15.7
3	Zn Na-Y	NaN_3	DMF	15.0
4	Fe Na-Y	NaN_3	DMF	18.0
5	Cu Na-Y	NaN_3	DMF	99, 99[c]
6	Cu Na-Y	$TMSN_3$	DMF	42.0
7	$Cu(OAc)_2$	NaN_3	DMF	63.0[d]
8	Cu Na-Y	NaN_3	DMSO	47.0
9	Cu Na-Y	NaN_3	H_2O	9.0
10	Cu Na-Y	NaN_3	CH_3OH	17.0
11	Cu Na-Y	NaN_3	$C_6H_5CH_3$	Trace

[a]Reaction condition: Nitrile (2.5 mmol), NaN_3 (2.75 mmol) catalyst 0.1 g, solvent (5 mL); Reaction time (4 h); Temperature (120 °C); [b]Isolated yield; [c]Yield after third cycle; [d]$Cu(OAc)_2$, 2.5 mol %

TABLE-2
Cu(II) Na-Y MEDIATED PREPARATION OF 5-SUBSTITUTED 1*H*-TETRAZOLES[a]



Entry	Substrate	Time (h)	Yield[b] (%)
1		3.5	99
2		4.0	99
3		4.0	98
4		3.0	99
5		3.0	99

6		4.0	98
7		3.0	99
8		3.0	99
9		4.0	98
10		4.0	99
11		1.0	99
12		1.0	99
13	CH_3CN	3.0	99
14		4.0	86

[a]Reaction condition: Nitrile (2.5 mmol), NaN_3 (2.75 mmol), Cu(II)Na-Y (0.1 g), DMF (5 mL); Reaction time (4 h); Temperature (120 °C); [b]Isolated yield.

Conclusion

In conclusion, we developed a simple and efficient method for the preparation of 5-substituted 1*H*-tetrazoles using Cu(II)-NaY heterogeneous catalyst. Various nitriles are studied and found corresponding 5-substituted 1*H*-tetrazoles are formed in quantitative yields. The catalyst can be readily recovered and reused. This methodology may find widespread use in organic synthesis for the preparation of 5-substituted 1*H*-tetrazoles including irbesartan an antihypertensive drug.

ACKNOWLEDGEMENTS

One of the authors (KSR) thanks the Rural Development Society (RDS) and DST, New Delhi, India, for financial support.

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