IRANIAN JOURNAL OF CATALYSIS

Montmorillonite KSF as a very efficient heterogeneous catalyst for the synthesis of 5-substituted 1*H*-tetrazoles

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Received 28 March 2017; received in revised form 6 October 2017; accepted 3 November 2017

ABSTRACT

Montmorillonite KSF has been used as an effective and non-toxic heterogeneous catalyst for one-pot synthesis of 5-substituted 1*H*-tetrazoles via [3+2] cycloaddition of sodium azide with a wide variety of nitriles. The reaction afforded high yields of the desired products in a short reaction time under mild reaction conditions. The catalyst can be recovered by simple filtration and reused for more consecutive trials without a significant decrease in activity. To avoid using toxic catalyst and catalyst recycling make this synthesis a truly green procedure.

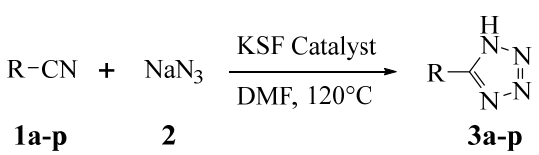
***Keywords**: Tetrazoles, [3+2] Cycloaddition, Sodium azide, Montmorillonite KSF, Nitriles, Heterogeneous catalyst.*

1. Introduction

Tetrazoles constitute an important class of heterocyclic compounds due to their application in pharmaceutical and material sciences including photography [1] and speciality explosives [2]. They are found in many biologically active compounds possessing antibacterial [3], antifungal [4], antiviral [5], analgesic [6], anti-inflammatory [7], antiulcer [8] and antihypertensive [9] activities. These compounds are being developed to act as isosteric replacements for carboxylic acids in drug design [1]. Various tetrazole-based compounds, which have also shown good coordination properties, are able to form stable complexes with several metal ions [10]. There are different methods for the synthesis of tetrazoles; these compounds are conventionally prepared by addition of azide ions to organic nitriles or cyanamides [11-13]. Several syntheses of 5-substituted 1*H*-tetrazoles have been reported through the [3+2] cycloaddition of nitriles using NaN_3 or $TMSN_3$ in the presence of catalysts such as $FeCl_3$–SiO_2 [14], $AlCl_3$ [15], $(C_2H_5)_2O.BF_3$ [16], tetrabutylammonium fluoride (TBAF) [17], $Pd(PPh_3)_4$ [18], Zn/Al hydrotalcite [19], nano ZnO [20], Kaolin [21], montmorillonite K-10 [21,22], montmorillonite K10-Cu [23], CoY Zeolite[24], $CuSO_4.5H_2O$ [25], $CdCl_2$ [26], Sb_2O_3 [27], diisopropyl ethylammonium acetate [28], diphenylphosphoryl azide [29], nickel zirconium phosphate nano particles [30], piperazinium dihydrogen sulfate [31], and *O*-phthalimide-N-sulfonic acid [32]. Some of these methods suffer from some disadvantages such as use of strong Lewis acids, expensive and toxic metals and the in-situ generated hydrazoic acid, which is highly toxic, explosive and volatile.

Consequently, it is desirable to develop an easy procedure to avoid using strong acids or bases and other corrosive media and to replace hazardous or expensive reactants and reagents by safer and economical ones. The use of environmentally friendly solid catalysts can reduce the amount of toxic waste and also facilitate the reactions to occur under milder conditions.

In this study, we developed a mild and convenient method for one-pot synthesis of 5-substituted 1*H*-tetrazoles obtained from the reaction of different nitriles with sodium azide using montmorillonite KSF as a safe, environmentally benign, inexpensive and efficient heterogeneous acidic catalyst (Scheme 1).



1a-p **2** **3a-p**

R= Aromatic, Aliphatic

Scheme 1. Synthesis of 5-substituted 1*H*-tetrazole.

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2. **Experimental**

2.1. General

Melting points were determined with an Electrothermal 9100 apparatus. ^{1}H and ^{13}CNMR spectra were recorded on Bruker Avance 400 MHz spectrometer for solutions in d_6-DMSO. Montmorillonite KSF, sodium azide, nitriles and solvents were purchased from Fluka and Merck companies.

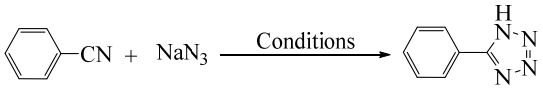
*2.2. General procedure for preparation of 5-substituted 1H-tetrazole (**3**)*

To a mixture of nitrile (1 mmol) and sodium azide (1 mmol), in DMF (7 mL), montmorillonite KSF (0.4 g) was added. The reaction mixture was heated at 120°C for the appropriate time with vigorous stirring. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to room temperature and then ethyl acetate (25 mL) was added to the reaction mixture. The mixture was filtered to remove the catalyst. The organic layer was treated with 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 dried over anhydrous Na_2SO_4 and concentrated by a rotary evaporator. The crude product was purified by recrystallization from CH_2Cl_2.

3. Results and Discussion

To optimize the reaction conditions, reaction between benzonitrile **1a** and sodium azide was chosen as a model reaction. When benzonitrile was treated with sodium azide in the presence of montmorillonite KSF (0.4 g) in DMF at 120°C, the corresponding tetrazole (**3a**) was obtained in 90% yield within 1.5 h. Various catalysts were examined in DMF at 120°C and results are presented in Table 1.

Table 1. Optimization of the reaction conditions.[a]



1a **2** **3a**

Entry	Catalyst (g)	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	$H_3PW_{12}O_{40}$ (0.4)	DMF	120	1.5	52
2	$H_3PMo_{12}O_{40}$ (0.4)	DMF	120	1.5	80
3	Al_2O_3 (0.4)	DMF	120	1.5	61
4	SiO_2 (0.4)	DMF	120	1.5	43
5	Amberlyst 15 (0.4)	DMF	120	1.5	48
6	MontmorilloniteK-10 (0.4)	DMF	120	1.5	57
7	Montmorillonite KSF (0.4)	DMF	120	1.5	90
8	-	DMF	120	4	5
9	Montmorillonite KSF (0.4)	DMSO	120	1.5	66
10	Montmorillonite KSF (0.4)	H_2O	Reflux	1.5	22
11	Montmorillonite KSF (0.4)	MeCN	Reflux	1.5	10
12	Montmorillonite KSF (0.4)	Dioxane	Reflux	1.5	63
13	Montmorillonite KSF (0.4)	THF	Reflux	1.5	15
14	Montmorillonite KSF (0.4)	MeOH	Reflux	1.5	trace
15	Montmorillonite KSF (0.4)	CH_2Cl_2	Reflux	1.5	trace
16	Montmorillonite KSF (0.4)	-	120	1.5	trace
17	Montmorillonite KSF (0.2)	DMF	120	1.5	75
18	Montmorillonite KSF (0.3)	DMF	120	1.5	81
19	Montmorillonite KSF (0.6)	DMF	120	1.5	90
20	Montmorillonite KSF (0.4)	DMF	70	1.5	26
21	Montmorillonite KSF (0.4)	DMF	25	1.5	5

[a]Reaction conditions: Benzonitrile (1 mmol) and sodium azide (1 mmol) in solvent (7 mL).
[b]Isolated yields.

As it is clear in the Table 1, montmorillonite KSF resulted in highest conversion to the desired product (Table 1, entries 1-7). When benzonitrile and sodium azide were reacted under similar conditions in the absence of the catalyst, only 5% of the desired product (**3a**) was obtained after 4 h (Table 1, entry 8). During further optimization of the reaction conditions, model reaction was carried out in different solvents such as CH_2Cl_2, THF, H_2O, MeCN, 1,4-dioxane, MeOH, DMF and under solvent free conditions. The best result in terms of reaction time and yield of the desired product **3a** was obtained, when the reaction was conducted in DMF (Table 1, entries 7 and 9-16). Decreasing the catalyst loading from 0.4 to 0.2 g lowered the yield of the reaction significantly (Table 1, entries 7 and 17-18). The best catalyst loading was found in 0.4 g, which gave an excellent yield of **3a** after only 1.5 h. Further increase in the catalyst amount did not improve the yield and the reaction time (Table 1, entry 19). It is worthwhile to mention that reaction temperature was optimized to be 120°C in DMF (Table 1, entries 7 and 20-21).

A wide variety of nitriles were treated with sodium azide in the presence of montmorillonite KSF under optimized conditions (Table 2). As indicated in Table 2, benzonitrile and 2-naphthonitrile were smoothly reacted with montmorillonite KSF in DMF at 120°C and gave corresponding tetrazole products in 90 and 82% yields, respectively (Table 2, entries 1 and 16). Benzonitriles having an electron-withdrawing group and benzonitriles with electron-donating groups gave very good yields of desired products (Table 2, entries 2-8). However, substrates with high electron-donating groups on the benzene ring (such as OCH_3 and OH) also afforded tetrazole products but in slightly less yields and longer reaction times (Table 2, entries 5-6). Heteroaromatic nitriles such as 2-pyridine-, 3-pyridine- and 4-pyridine carbonitrile gave the corresponding tetrazoles in shorter reaction times with excellent yields (Table 2, entries 9-11). 2- Phenyl acetonitrile as an aliphatic nitrile provided a moderate yield of corresponding tetrazole (Table 2, entry 17). 1,3-Dicyanobenzene and 1,4-dicyanobenzene afforded mono-addition products with excellent yields (Table 2, entries 14-15).

Table 2. Preparation of 5-substituted 1*H*-tetrazoles mediated by montmorillonite KSF by the reaction of sodium azide and nitriles.[a]

Entry	Nitrile	Product	Time (h)	Yield (%)[b]	m.p. (°C)	Ref.
1	C_6H_5CN	**3a**	1.5	90	214- 216	[21]
2	4-ClC_6H_4CN	**3b**	2	91	258- 261[]	[24]
3	4-FC_6H_4CN	**3c**	2	89	111- 114	[33]
4	4-$CH_3C_6H_4CN$	**3d**	1.5	87	246- 248	[34]
5	4-$OCH_3C_6H_4CN$	**3e**	2.5	80	229- 230	[35]
6	4-OHC_6H_4CN	**3f**	3	70	242-243	[35]
7	4-$CHOC_6H_4CN$	**3g**	2.5	83	179- 182	[21]
8	4-$COCH_3C_6H_4CN$	**3h**	2.5	81	170- 171	[34]
9	2-PyridinylCN	**3i**	1.5	93	211-212	[21]
10	4-PyridinylCN	**3j**	1.5	95	255- 257	[21]
11	3-PyridinylCN	**3k**	2	92	238- 240	[21]
12	2-CNC_6H_4CN	**3l**	1.5	89	210- 212	[21]
13	2-CNC_6H_4CN	**3l′**	4	71	225- 227	[36]
14	3-CNC_6H_4CN	**3m**	1	94	215- 217	[21]
15	4-CNC_6H_4CN	**3n**	1	97	259- 261	[21]
16	2-NaphthylCN	**3o**	2	82	205- 207	[34]
17	$C_6H_5CH_2CN$	**3p**	4	53	122- 124	[24]

[a]Reactions were carried out with 1 mmol of nitrile, 1 mmol of NaN_3 in DMF at 120°C; except entry 13, was carried out with 1 mmol of nitrile and 2.5 mmol of NaN_3.

[b]Isolated yields; products were characterized by melting point, ^{1}H NMR, and ^{13}CNMR.

In contrast to other reported results [37], no bis-tetrazole products were formed even at higher temperature and the higher mole ratio of sodium azide. Under optimum reaction conditions, 1,2-dicyanobenzene also provided mono-addition products (Table 2, entry 12) but when treated with 2.5 mmol of sodium azide in DMF at 130°C, bis-tetrazole product was obtained in 71% yield after 4 h (Table 2, entry 13).

The catalyst can be recovered at the end of the reaction and can be used several times without losing its activity. To recover the catalyst, after completion of the reaction, the mixture was filtered and the catalyst was washed with EtOH. After activating the catalyst at 100°C, it was used for the further reaction. This process was repeated for four cycles and the yield of product **3a** did not change significantly (The yields were 90, 88, 85 and 83%, respectively).

Due to acidic characteristic of montmorillonite KSF and on the basis of the proposed mechanism by others [21,38], a plausible mechanism for the formation of 5-substituted-(1*H*)-tetrazoles can be suggested. Initially, nitrogen atom of nitrile interacts with Lewis acid sites of the montmorillonite KSF to form an activated fragment which facilitates the attack of the azide on the carbon of the nitrile by increasing its electrophilic character. The resulting imidoyl azide was then converted to 5-substituted-(1*H*)-tetrazole derivatives.

To show the merits and drawbacks of this catalyst, our results were compared with other catalysts reported in the literature (Table 3). In this table 5-Phenyl-1*H*-tetrazole (**3a**) has been considered. Although the present protocol gives a higher yield of the product in much shorter reaction times in comparison with most other methods, in our method there is no need for any metal catalysts (Table 3, entries 2, 4, 7, 10) and without using additional instrument (Table 3, entry 3) or expensive nano catalysts (Table 3, entries 10, 13-15, 19); this advantage is very important. However, in this method tetrazoles are prepared under benign conditions in the recyclable heterogeneous catalyst.

Table 3. Comparison of montmorillonite KSF with other catalysts for the synthesis of tetrazole **3a**.

Entry	Catalyst	Reaction Conditions	Time (h)	Yield (%)	Ref.
1	Montmorillonite KSF	DMF/120°C	1.5	90	This work
2	$CuSO_4.5H_2O$	DMSO/120°C	1	98	[25]
3	Kaolin	DMF-H_2O/ultrasonic irradiation	2	90	[21]
4	Montmorillonite K10-Cu	DMF/Reflux	2	85	[23]
5	$H_3Mo_{12}O_{40}P$	DMF/80°C	4	89	[39]
6	SiO_2-H_2SO_4	DMF/Reflux	5	88	[33]
7	$CdCl_2$	DMF/80°C	6	91	[26]
8	Sb_2O_3	DMF/120°C	8	86	[27]
9	Py. HCl	DMF/110°C	8	84	[40]
10	$CuFe_2O_4$ nanoparticles	DMF/120°C	12	82	[41]
11	$FeCl_3$-SiO_2	DMF/120°C	12	79	[14]
12	Zinc hydroxyapatite	DMF/120°C	12	78	[37]
13	CoY Zeolite	DMF/120°C	14	90	[24]
14	Nano TiO_2	DMF/120°C	14	82	[42]
15	Nano ZnO	DMF/120°C	14	72	[20]
16	$Al(HSO_4)_3$	DMF/120°C	18	91	[43]
17	Montmorillonite K-10	DMF/Reflux	24	90	[21]
18	Zeolite	DMF/110-120°C	24	90	[44]
19	Mesoporous ZnS nanospheres	DMF/HNO_3/120°C	36	96	[45]

4. Conclusions

In summary, we have described an efficient procedure for the one-pot synthesis of 5-substituted 1*H*-tetrazoles using montmorillonite KSF as a solid acid, reusable and non-toxic catalyst. The main advantages of this procedure include high yields, simple experimental procedure, short reaction times, use of various substrates, easy work-up and easy recovering and reusing of the catalyst, which make it a useful, attractive and green strategy for the preparation of tetrazole derivatives.

Acknowledgements

We gratefully acknowledge financial support of the Research Council of University of Mazandaran.

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