Simple and Efficient Synthesis of 5-Substituted 1-*H*-Tetrazoles Using Metal-Modified Clay Catalysts

Alireza Najafi Chermahini,1 Abbas Teimouri,2 and Ali Moaddeli1

¹Department of Chemistry, Faculty of Science, Yasouj University, 75918-74831 Yasouj, Iran ²Department of Chemistry, Payame Noor University, Isfahan, P.O. Box 81395-671, Iran Received 3 April 2010; revised 26 November 2010

ABSTRACT: The synthesis of 5-substituted 1-Htetrazoles based on reaction of a series of aromatic nitriles with sodium azide was investigated. The reaction was catalyzed by modified montmorillonite K-10 including Cu^{2+} , Fe^{3+} , Ni^{2+} , and Zn^{2+} metal ions. The best results obtained by Mont-K10-Cu catalyst. The catalysts were reused several times without loss of their activity. The present procedure offers advantages such as a shorter reaction time, simple workup, recovery, and reusability of the catalyst. © 2011 Wiley Periodicals, Inc. Heteroatom Chem 22:168–173, 2011; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20672

INTRODUCTION

1-*H*-Tetrazoles are an important class of heterocyclic compounds and exhibit a wide range of applications in medicinal chemistry and the material sciences. For example, tetrazoles are regarded as isosteres of the carboxylic acid functionality in medicinal chemistry; they are applied in the material sciences and in chemical industry as propellants, explosives, and in photography and play an important role as ligands in coordination chemistry [1–8]. The [2+3] cycloaddition of nitriles and azides is a reliable method for the synthesis of tetrazole derivatives. Various synthetic approaches have been de-

veloped for this transformation. Most of them rely on the in situ generation of highly toxic and explosive hydrazoic acid through activation of the azide by strong Lewis acids [9,10], expensive and toxic metals [11–14], or amine salts [15]. The "click" chemistry approach utilizing zinc catalysis in aqueous solution is a magnificent improvement over previous methods [16,17], but sometimes still requires the tedious and time-consuming removal of zinc salts from the acidic products. Recently, application of solid acids such as Zn/Al hydrotalcite [18], ZnO [19], FeCl₃-SiO₂ [20], and Cu_2O [21] in the preparation of tetrazoles was investigated. Metal-modified montmorillonites were reported widely, and many metals, such as Cu, Zn, Mn, Fe, Cu, V, Mo, and Al [22-28] were commonly used to improve the catalytic abilities of montmorillonites. In these catalysts, the metal complexes are doped into the layered structure of montmorillonites and exist in more stable states. In any sense, these catalysts could keep excellent catalytic activity even after recycling and can be reused for many times. In continuing with our interest in tetrazole chemistry [29–31], herein we report a new process for the synthesis of 5-substituted 1-H-tetrazoles using modified clays as safe, environmentally benign, and inexpensive catalysts (Scheme 1).

RESULTS AND DISCUSSION

The preparation of metal-modified montmorillonite catalysts was carried out by the previously reported methods as those described in the literature [25–27]. The results of characterization of prepared catalysts

Correspondence to: Alireza Najafi Chermahini; e-mail: najafi@ mail.yu.ac.ir.

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using IR, XRD, and XRF methods are presented as the Supporting Information.

In the reaction between benzonitrile 1a and sodium azide (Scheme 1), the effect of the catalyst amount was investigated. The results are presented in Table 1. The different amounts of montmorillonite K10-Cu catalyst were used, and it was found that the maximum reaction yield obtained using 5 mg of modified K10 in the presence of benzonitrile (1 mmol) and sodium azide (3 mmol) in DMF (10 mL). The same amounts were found for the K10-Fe, K10-Zn, and K10-Ni catalysts. To see whether the action of catalysts is truly catalytic, we reduced the amount of clays in the reaction between sodium azide and benzonitrile from 5 to 2.5 mg. Based on our results, it was found that a low loading of K10-M is still effective, although the reactivity was decreased consequently (see Table 1, entries 2,7,11, and 15). Even 2.5 mg of modified K10-Cu and K10-Fe afforded the desired product after 22 and 30 h in the DMF as the solvent. The variation of the reaction conversion with the amount of sodium azide was studied, and the experimental results are presented in Table 1. It is apparent that the reaction conversion increased as the mole ratio of benzonitrile to sodium azide increased from 1:1 to 1:3. With 1:1 benzonitrile to sodium azide ratio, the reaction was completed after 36 h (Table 1, entry 1); however, with using 1:3 ratio the reactions were completed after 2, 4, 6, and 6 h for the K10-Cu, K10-Fe, K10-Zn, and K10-Ni catalysts, respectively (Table 1, entries 3, 9, 12, and 15). The values less than 1:3 were not found suitable (see, e.g., entries 4, 8, 11, and 14 in Table 1). Further an increase in the mole ratio to 1:5, the benzenonitrile reaction times increased to 12, 10, 8, and 8 h for K10-Cu, K10-Fe, K10-Zn, and K10-Ni catalysts respectively (Table 1, entries 5, 10, 13, and 16). This observation suggests that the excess value of sodium azide may block active sites of catalysts. Water as a clean, inexpensive, and universal solvent is both economically and environmentally advantageous, but our results showed that DMF because of its higher boiling point is more efficient. For example, with using montmorillonite K-10 as a catalyst the reaction completed after 16 and 24 h. As can be seen from the table, the best results were obtained from the Mont-K10-Cu²⁺ catalyst. At the optimized condition with using 1:3 benzonitrile:sodium azide and 10 mg Mont-K10-Cu²⁺ as the catalyst, the reaction was completed after 2 h.

To show the advantages of modified clays as an efficient catalyst for the synthesis of tetrazole derivatives, we compared the reaction of benzonitrile

Entry	Catalyst	Solvent	Catalyst Amount (mg)	Benzonitrile: Sodium Azide	Time	
1	Mont-K10-Cu	DMF	5	1:1	_b	
2	Mont-K10-Cu	DMF	2.5	1:3	22	
3	Mont-K10-Cu	DMF	5	1:3	2	
4	Mont-K10-Cu	DMF	5	1:2	4	
5	Mont-K10-Cu	DMF	5	1:5	12	
6	Mont-K10-Cu	DMF	10	1:3	2	
7	Mont-K10-Fe	DMF	2.5	1:3	30	
8	Mont-K10-Fe	DMF	5	1:2	10	
9	Mont-K10-Fe	DMF	5	1:3	4	
10	Mont-K10-Fe	DMF	5	1:5	10	
11	Mont-K10-Zn	DMF	2.5	1:3	16	
12	Mont-K10-Zn	DMF	5	1:2	16	
13	Mont-K10-Zn	DMF	5	1:3	6	
14	Mont-K10-Zn	DMF	5	1:5	8	
15	Mont-K10-Ni	DMF	2.5	1:3	20	
16	Mont-K10-Ni	DMF	5	1:2	14	
17	Mont-K10-Ni	DMF	5	1:3	6	
18	Mont-K10-Ni	DMF	5	1:5	8	

TABLE 1 Initial Screening of Reaction Parameters for the Formation of Tetrazole Derivatives^a

^aThe times after completion of reaction.

^bReaction did not completed after 36 h.

Entry	Catalyst	Catalyst Amount (mg)	Solvent	Yield (%) ^a	Time (h)	
1	Mont-K10-Cu	5	DMF	85	2	
3	Mont-K10	50	DMF	50	12	
4	Mont-K10	50	H ₂ O	50	16	
5	Bentonite	50	DMF	44	12	
6	Kaolin	50	DMF	63	12	

TABLE 2 Comparison of Results of Different Catalysts with Mont-K10-Cu in the Formation of 5-Phenyl-1-H-Tetrazole

^alsolated yields

and sodium azide with unmodified montmorillonite K10, bentonite, and kaolin, in the DMF and water as the solvent. It is clear from Table 2 that the application of modified clays shows better results.

Several substituted nitriles reacted with sodium azide to give the corresponding tetrazoles in good yields. Heteroaromatic nitriles such as 2, 3, and 4-pyridinecarbonitriles gave the corresponding tetrazoles in the short time with good yields. Interestingly, phthalonitrile afforded the monoaddition product (Table 2, entry 9) whereas based on Sharpless's report on the reaction between sodium azide and 1,4-dicyanobenzene in the presence of Zn(II) salts, the double addition product was reported [15]. The nature of the substituents on the nitriles has a significant effect on the tetrazole formation; all attempts to synthesize 4-amino tetrazole have failed (Table 3, entry 10).

One of the most important advantages of heterogeneous catalysis over the homogeneous counterpart is the possibility of reusing the catalyst by simple filtration, without loss of activity. The recovery and reusability of the catalyst was investigated in the tetrazole formation with benzonitrile. After completion of the reaction, the catalyst was separated by filtration, washed three times with 5 mL of acetone, then with doubly distilled water several times, and dried at 110°C. Then the recovered catalyst was used in the next run. The results of three consecutive runs showed that the catalyst can be reused several times without significant loss of its activity (see Table 4).

The products were characterized by MS, IR, ¹H NMR, and ¹³C NMR spectroscopy and from melting points. The disappearance of one strong and sharp absorption band (the CN-stretching band), and the appearance of NH-stretching bands in the 2500–3000 cm⁻¹ in the IR spectra, evidenced the formation of 5-substituted 1-*H*-tetrazoles. In addition, observation of a M-28 peak in the mass spectra that resulted from the loss of N2 from a tetrazole ring supports the tetrazole formation.

CONCLUSION

In conclusion, we developed a simple, environmentally benign, and efficient method for the preparation of 5-substituted 1-H-tetrazoles using modified clay catalysts. Various nitriles reacted with NaN₃ at 100-130°C to yield the corresponding 5-substituted 1-Htetrazoles with moderate to good yields. Based on our results, the mont-K10-Cu²⁺ catalyst was found to be the best catalyst for this reaction. This methodology may find a widespread use in organic synthesis for the preparation of tetrazoles. The remarkable catalytic activity of modified clays is superior to the other reported catalytic methods with respect to shorter reaction times [9-16]. In addition, in comparison with other methods reported in the literature the advantages of this catalytic system are as follow: mild reaction condition, the low cost of reagents, high product yields, easy preparation of the catalysts, nontoxicity of the catalysts, and simple and clean workup of the desired products. However, it is noted that obtained yields for aromatic nitriles with electron-donating groups are less spectacular than reported for microwave heating of DMF solutions [32], using ionic liquid [14] and Cu_2O as the catalyst.

SYNTHESIS OF CATALYSTS

Solutions of 0.5 M ferric nitrate, zinc chloride, nickel chloride, and cuprous acetate were prepared by dissolving the equivalent amounts of the salts in deionized and distilled water. A diluted montmorillonite suspension was prepared by adding the montmorillonite powder (5 g) into the deionized and distilled water (200 mL). The pillaring reaction was carried out under continuous vigorous stirring by dropwise adding the pillaring solution into the montmorillonite suspension over a period of 10 min. The resulting slurry was refluxed for 8 h and then was stirred at room temperature for 24 h. The clays were filtered and washed with demineralized water until free from anions. The samples were dried at 100°C

			Time (h)			Yield (%) ^a					
	а	b	Cu	Fe	Ni	Zn	Cu	Fe	Ni	Zn	Melting Point (°C)
1	CN CN CN		2	4	6	6	85	80	75	80	214–216
2	NO ₂ CN		6	18	12	14	57	56	72	50	220
3			2	2	2	2	75	60	50	65	255–258
4	CN CN	N N N	6	12	12	10	80	78	78	70	226–228
5			6	8	8	10	65	56	45	70	211
6	CI		6	16	16	14	73	66	68	63	265
7		S N-N N N	6	8	14	10	85	70	65	65	205–207
8		H = N	8	12	8	10	68	70	65	73	183–185
9	CN	N NH CN	6	10	6	8	75	70	65	68	258–260
	CN	N=N N NH									
10	\tilde{I} NH ₂	$\stackrel{\uparrow}{NH}_2$	_	_	_	_	_	_	_	_	_

TABLE 3 Synthesis of 5-Substituted 1-H-Tetrazoles Catalyzed by Modified Clays

^alsolated yields

	Reused Cycle 1		Reused Cycle 2		Reused Cycle 3		Reused Cycle 4	
Catalyst	Time (h)	Yield ^a	Time	Yield	Time	Yield	Time	Yield
Mont-K10-Cu	4	65	4	68	5	65	5	60
Mont-K10-Fe	6	75	6	70	6	74	6	65
Mont-K10-Zn	8	66	8	60	8	64	8	63
Mont-K10-Ni	6	70	8	65	8	60	8	67

TABLE 4 Results Obtained from Catalyst Reuse Modified Montmorillonite K10 catalysts

^alsolated yields.

temperature then after grinding calcined for 3 h at 400° C under airflow.

General Procedure for Preparation of Tetrazoles under Reflux Condition

The procedure for the synthesis of the tetrazole **1a** is a representative one. In a round-bottom flask, benzonitrile (0.2 g, 2 mmol), sodium azide (0.4 g, 6 mmol), modified montmorillonite K-10 (5 mg), and DMF (20 mL) were charged. Then the reaction mixture was refluxed. The progress of reaction was followed by TLC (75:25 ethylacetat:*n*-hexane). After completion of the reaction, the reaction was cooled to room temperature and insoluble material was filtered and washed with doubly distilled water and acetone to separate the catalyst. The solution was acidified with HCl (2 mL, 12 M). The precipitate was collected, dried, and recrystallized from water/ethanol to afford pure 5-phenyltetrazole as a white powder, yield: 0.26 g, 85%. mp ($^{\circ}$ C) = 214–216 (215–216 [15]). ¹H NMR (DMSO-*d*₆, 400 MHz): 7.6– 8.1 ppm (m, 5H); ¹³C NMR (DMSO-*d*₆, 400 MHz); 124.5, 127.4, 129.9, 131.7. 155.8; MS (70 eV) m/z: 146, 118, 103, 91, 77, 63, 39; IR, (KBr), 3054, 2981, 2914, 2837, 2794, 2701, 2610, 1608, 726 cm⁻¹

5-(4-Nitrophenyl)-1H-tetrazole (**2b**). White solid; mp°C = 218–220 (219–220 [21]); ¹H NMR (DMSO- d_6 , 400 MHz): 8.1 (d, J = 8 Hz, 2H), 8.2 (d, J = 8 Hz, 2H) ppm; ¹³C NMR (DMSO- d_6 , 100 MHz); 156, 130, 128, 124 ppm; MS (70 eV) m/z: 191, 163, 149, 134, 90, 63; IR (KBr) ν : 3103, 2914, 2853, 2752, 2621, 1605, 1526, 1487, 861 cm⁻¹

4-(*1*-*H*-tetrazole-5-yl)pyridine (**3b**). White solid; mp°C = 254–256 (253–255 [33]); ¹H NMR (DMSO- d_6 , 400 MHz): 8.0 (d, J = 7.8 Hz, 2H), 8.8 (d, J = 7.8 Hz, 2H) ppm; ¹³C NMR (DMSO- d_6 , 100 MHz); 165, 149, 134, 121 ppm; MS (70 eV) m/z: 147, 119, 92, 78, 62, 50. IR (KBr) ν : 3080, 3060, 3028, 2955, 2917, 2832, 2751, 2689, 1608, 1581, 1492, 1065, 784 cm⁻¹. 3-(1-H-Tetrazole-5-yl)pyridine (**4b**). White solid; mp°C = 238–240 (239–240 [15]); ¹H NMR (DMSO- d_6 , 400 MHz): 9.1 (s, 1H), 8.8 (d, J = 3.8 Hz, 1H), 8.3(d, J = 3.8 Hz, 1H), 7.6 (1H, m); ¹³C NMR (DMSO- d_6 , 100 MHz); 165, 153, 150, 136, 126, 123. IR (KBr) v: 3080, 2950, 2890, 2850, 2761, 1480, 1200, cm⁻¹.

2-(*1*-*H*-*Tetrazole-5-yl*)*pyridine* (**5b**). White solid; mp°C = 208–210 (211 [16]); ¹H NMR (DMSO-*d*₆, 400 MHz): 7.4 (t, J = 6.4 Hz, 1H), 7.8 (t, J = 6.4 Hz, 1H) 8.0 (t, J = 8.0 Hz, 1H) 8.5 (d, J = 3.2 Hz, 1H) ppm; ¹³C NMR (DMSO-*d*₆, 100 MHz); 167, 158, 149, 137, 124, 121 ppm; MS (70 eV) *m*/*z*: 147, 119, 105, 91, 78, 51, IR (KBr) ν : 3278, 3181, 2929, 1662, 1578, 1390, 923 cm⁻¹.

5-(4-Chlorophenyl)-1H-tetrazole (**6b**). White solid; mp°C = 258–260 (263–264 [34]); ¹H NMR (acetone- d_6 , 400 MHz): 7.65 (d, J = 8.4 Hz, 2H), 8.15 (d, J = 8.4 Hz, 2H) ¹³C NMR (acetone- d_6 , 100 MHz); 136, 130, 128, 124 ppm; IR (KBr) ν : 3060, 2460, 1900, 1608, 1486, 1435, 1100 cm⁻¹.

5-(*Thiophen-2yl*)-1*H*-tetrazole (**7b**). White solid; mp°C = 201–203 (210–213 [35], 205 [36]); ¹H NMR (DMSO- d_6 , 400 MHz): 7.1 (t, J = 4 Hz, 1H), 7.6 (d, J = 4Hz, 1H), 7.7 (d, J = 4 Hz, 1H) ppm; ¹³C NMR (DMSO- d_6 , 100 MHz); 149, 134, 130, 125 ppm; MS (70 eV) m/z: 154, 152, 124, 109, 97, 69, 45; IR (KBr) ν : 3108, 3093, 3076, 2952, 2890, 2789, 2685, 1505, 1434, 964 cm⁻¹.

4-(1H-Tetrazole-5-yl)benzaldehyde (**8b**). White solid; mp°C = 180–182; ¹H NMR (DMSO- d_6 , 400 MHz): 7.9 (d, J = 7.2 Hz, 2H), 8.0 (d, J = 7.2 Hz, 2H) 9.1 (s, 1H) ppm; ¹³C NMR (DMSO- d_6 , 100 MHz); 188, 156, 138, 131, 129, 128 ppm; MS (70 eV)/g/z: 174, 146, 130, 116, 102, 90, 57, 43 IR (KBr) ν : 3015, 2924, 2854, 2713, 2612, 1667, 1440, 776 cm⁻¹.

4-(1*H*-Tetrazole-5-yl)benzonitrile (**9b**). White solid; $mp^{\circ}C = 258-260 \text{ d} (300 > d [37])$; ¹H NMR (DMSO-*d*₆, 400 MHz): 8.0 (d, J = 7.8 Hz, 2H),

8.2 (d, J = 7.8 Hz, 2H) ppm; ¹³C NMR (DMSO- d_6 , 100 MHz); 160, 135, 132, 130, 126, 114 ppm; MS (70 eV) m/z: 171, 143, 129, 103, 62; IR (KBr) v: 3100, 2848, 2750, 2250, 1480, 781 cm⁻¹.

SUPPORTING INFORMATION

Results of characterization of prepared catalysts using IR, XRD, and XRF methods are available from the corresponding author (najafi@mail.yu.ac.ir) on request.

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REFERENCES

- Meier, H. R.; Heimgartner, H. In Methoden der Organischen Chemie; Houben-Weyl; Schumann, E. (Ed.); Georg Thieme: Stuttgart, Germany, 1994; Vol. E8d, p 664.
- [2] Herr, R. J. Bioorg Med Chem 2002, 10, 3379.
- [3] Butler, R. N. In Comprehensive Heterocyclic Chemistry II; Katritzky, A. R., Rees, C. W., Scriven, E. F. V. (Eds.); Pergamon Press: New York, 1996; Vol. 4, p 621.
- [4] Yu, K. L.; Johnson, R. L. J Org Chem 1987, 52, 2051.
- [5] Zabrocki, J.; Smith, D.; Dunbar, J. B., Jr.; Iijima, H.; Marshall, G. R. J Am Chem Soc 1988, 110, 5875.
- [6] Davis, B.; Brandstetter, T. W.; Smith, C.; Hackett, L.; Winchester, B. G.; Fleet, G. W. J. Tetrahedron Lett 1995, 36, 7507.
- [7] Burg, D.; Hameetman, L.; Filippov, D. V. van der Marel, G. A.; Mulder, G. J Bioorg Med Chem Lett 2002, 12, 1579.
- [8] Hayashi, R.; Jin, X.; Cook, G. R. Bioorg Med Chem Lett 2007, 17, 6864.
- [9] Dunica, J. V.; Pierce, M. E.; Santella, J. B. J Org Chem 1991, 56, 2395.
- [10] Kumar, K.; Narayanan, R.; Shechter, H. J Org Chem 1996, 61, 4462.
- [11] Curran, D. P.; Hadida, S.; Kim, S. Y. Tetrahedron 1999, 55, 8997.

- [12] Hajra, S.; Sinha, D.; Bhowmick, M. J Org Chem 2007, 72, 1852.
- [13] Kantam, M. L.; Balasubrahmanyam, V.; Shiva Kumar, K. B. Synth Commun 2006, 36, 1089.
- [14] Schmidt, B.; Meid, D.; Kieser, D. Tetrahedron 2007, 63, 492.
- [15] Amantini, D.; Beleggia, R.; Fringuelli, F.; Pizzo, F.; Vaccoro, L. J Org Chem 2004, 69, 2896.
- [16] Demko, P. Z.; Sharpless, K. B. J Org Chem 2001, 66, 7945.
- [17] Himo, F.; Demko, P. Z.; Noodleman, L.; Sharpless, K. B. J Am Chem Soc 2002, 124, 12210.
- [18] Kantam, M. L.; Shiva Kumar, K. B.; Phani Raja, K. J Mol Catal A: Chem 2006, 247, 186.
- [19] Kantam, M. L.; Shiva Kumar, K. B.; Sridhar, C. Adv Synth Catal 2005, 347, 1212.
- [20] Nasrollahzadeh, M.; Bayat, Y.; Habibi, D.; Moshaee, S. Tetrahedron Lett 2009, 50, 4435.
- [21] Jin, T.; Kitahara, F.; Kamijo, S.; Yamamoto, K. Tetrahedron Lett 2008, 49, 2824.
- [22] Ben Achma, R.; Ghorbel, A.; Dafinov, A.; Medina, F. Appl Catal A 2009, 349, 20.
- [23] Varma, R. S. Tetrahedron 2002, 58, 1235.
- [24] Shinde, A. B.; Shrigadi, N. B.; Samant, S. D. Appl Catal A 2004, 276, 5.
- [25] Clark, P. D.; Mesher, S. T. E.; Primak, A.; Yao, H. Catal Lett 1997, 43, 79.
- [26] Yin, W.; Shi, M. Tetrahedron 2005, 61, 10861.
- [27] Gue'lou, E.; Barrault, J.; Fournier, J.; Tatibouet, J. M. Appl Catal B: Environ 2003, 44, 1.
- [28] Caudo, S.; Centi, G.; Genovese, C.; Perathoner, S. Appl Catal B: Environ 2007, 70, 437.
- [29] Dabbagh, H. A.; Chermahini, A. N.; Banibairami, S. Tetrahedron Lett 2006, 47, 3929.
- [30] Dabbagh, H. A.; Chermahini, A. N.; Teimouri, A. Heteroatom Chem 2006, 17, 416.
- [31] Chermahini, A. N.; Esfahani, M. N.; Dalirnasab, Z.; Dabbagh, H. A.; Teimouri, A. J Mol Struct (Theochem) 2007, 820, 7.
- [32] Alterman, M.; Hallberg, A. J Org Chem 2000, 65, 7984.
- [33] Zhou, Y.; Yao, C.; Ni, R.; Yang, G. Synth Commun 2010, 40, 2624.
- [34] Rostamizade S.; Ghaieni, H.; Aryan, R.; Amani, A. Chinese Chem Lett 2009, 20, 1311.
- [35] Shie, J.; Fang, J. J Org Chem 2003, 68, 1158.
- [36] Elpern, B.; Nachod, F. C. J Am Chem Soc 1950, 72, 3379.
- [37] Finnegan, W. A.; Henry, R. A.; Lofquist, R. J Am Chem Soc 1958, 80, 3908.