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Montmorillonite K-10 Clay as an Efficient Reusable Heterogeneous Catalyst for the Solvent-Free Microwave Mediated Synthesis of 5-Substituted 1*H*-Tetrazoles

Omid Marvi,[*] Abdolhamid Alizadeh,[†] and Saeid Zarrabi[‡]

Department of Chemistry, Faculty of Sciences, Payame Noor University (PNU), PO Box 19395-3697, Tehran, Iran
[*]E-mail: omid_marvi@pnu.ac.ir
[†]Faculty of Chemistry and Nanoscience & Nanotechnology Research Center (NNRC), Razi University, Kermanshah 67149, Iran
[‡]Department of Chemistry, Faculty of Sciences, Islamic Azad University, Lahijan Branch, Lahijan, Iran
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Various 5-substituted 1*H*-tetrazole derivatives were synthesized in a simple and environmentally benign method from the reaction of aryl and benzyl nitriles with sodium azide in solvent-free media using montmorillonite K-10 clay as solid recyclable heterogeneous acidic catalyst and microwave irradiation in good yields and short reaction times.

Key Words : Montmorillonite K-10 clay, 5-Substituted 1*H*-tetrazoles, Solvent-free, Microwave irradiation

Introduction

Tetrazoles, while not found in nature, have gained considerable popularity in drug discovery efforts.[1] 5-Substituted 1*H*-tetrazoles possess an acidic hydrogen at the N-1 position and have thus found use as carboxylic acid bioisosteres. While maintaining similar pK_a values to carboxylic acids, 5-substituted 1*H*-tetrazoles can benefit from improved cell permeability, bioavailability, and metabolic stability. Substitution of the N-1 nitrogen to give 1,5-disubstituted tetrazoles has also proven beneficial in drug discovery as *cis*-amide isosteres.[2a-e] Another important application of tetrazoles is in the preparation of imidoyl azides.[2f,g] The conventional method of synthesizing tetrazoles is by addition of azide ions to organic nitriles or cyanamides.[2h-l]

Extensive work on the synthesis of tetrazoles has been carried out in the field of material sciences, pharmaceuticals, explosives, and photography.[3] Sharpless and co-workers reported an innovative and safe procedure for the preparation of 5-substituted 1*H*-tetrazoles from the corresponding nitriles and NaN_3 in the presence of a stoichiometric amount or 50 mol % of Zn(II) salts.[4] Later, Pizzo and co-workers reported an efficient method for the synthesis of tetrazoles by the reaction of nitriles with $TMSN_3$ using 50 mol % of TBAF as catalyst.[5] Also, Lakshmi Kantam and co-workers efficiently synthesized tetrazoles by reaction of nitriles with NaN_3 using nanocrystalline ZnO or zinc hydroxyapatite as the catalyst at 120-130 ºC.[6a] More recently, Yamamoto and co-workers reported the [3+2] cycloaddition between various nitriles and trimethylsilyl azide proceeds smoothly in the presence of a CuI catalyst in DMF/MeOH, to give the corresponding 5-substituted 1*H*-tetrazoles in good to high yields.[6b] Also, application of solid acids such as Zn/Al hydrotalcite,[6c] modified montmorillonite K-10 including Cu^{2+}, Fe^{3+}, Ni^{2+}, and Zn^{2+} metal ions[6d] in the preparation of tetrazoles was investigated. Several variants of the procedure have also been employed.[7] However, all of these reported methods for the synthesis of tetrazoles suffer from drawbacks such as long reaction time, high temperature, poor selectivity, the use of strong Lewis acids, expensive and toxic metals or solvents, and the in situ-generated hydrazoic acid which is highly toxic and explosive.

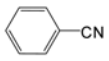
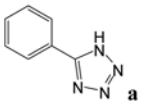
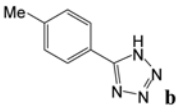
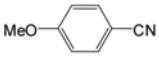
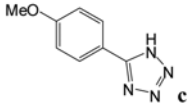
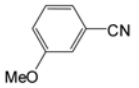
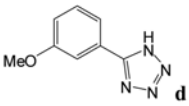
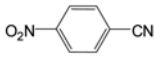
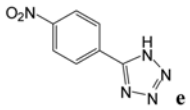
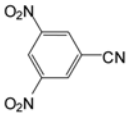
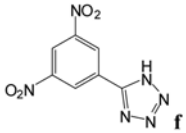
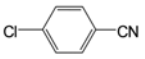
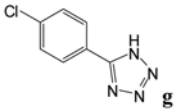
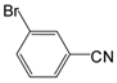
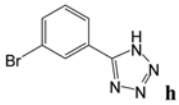
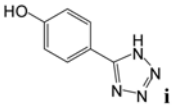
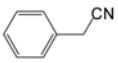
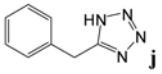
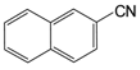
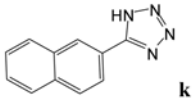
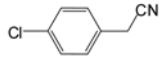
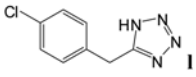
Consequently, it is desirable to develop an easy manipulative procedure, as well as to avoid using strong acids or bases and other corrosive media and replacing hazardous or expensive reactants and reagents by safer and economical ones. In achieving many of these goals, catalysts help the synthetic chemist in a big way. Catalysts are capable of making impracticable reactions to occur under the mildest possible conditions.The development of a catalytic synthetic method for tetrazoles still remains an active research area.

In recent years, heterogeneous catalysts have gained more importance due to enviroeconomic factors. They have successfully been utilized in several organic transformations to minimize undesirable waste causing environmental pollution. The use of solid acids as heterogeneous catalysts has received significant interest in different areas of organic synthesis.[8] Solid acids have many advantages such as ease of handling, decreasing reactor and plant corrosion problems, and environmentally safe disposal.[9] Also, wastes and by-products can be minimized or avoided by developing cleaner synthesis routes.[10] There is current research and general interest in heterogeneous systems because of their importance in industry and in developing technologies.[11] Heterogeneous solid acids are advantageous over conventional homogeneous acid catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be reused after or without activation, thereby making the process economically more viable. Montmorillonite is a clay mineral belonging to the group of the smectites. Montmorillonite K-10 (Mont K-10) clay is environmentally benign and economically feasible solid catalyst that offers several advantages, such as ease of handling and workup, strong acidity, non-corrosive properties, cheapness, mild reaction

conditions, high yields and selectivity, and regeneration. Mont K-10 is a solid acid of moderate acid strength.[12]

In addition, the use of microwaves in organic synthesis has gained importance. Microwave systems provide the opportunity to complete complex reactions in minutes. Selective absorption of microwave irradiation in conjunction with the use of catalysts or mineral supported reagents provide unique reaction environments leading to enhanced yield,

Table 1. The yields and reaction times for the K-10 clay supported microwave-induced synthesis of compounds **a-l**

Entry	Substrate	Product[a]	Reaction time (min)	Yield (%)[b] Fresh Clay/Recovered Clay	Ref.
1		 **a**	16	75/56	4a, 5, 6a, 19
2		 **b**	20	72/52	6b, 19a
3		 **c**	22	69/55	6b
4		 **d**	20	70/54	5
5		 **e**	15	87/73	4a, 5, 6b
6		 **f**	16	81/65	6b
7		 **g**	18	80/62	6a, 19b
8		 **h**	20	71/52	7e
9		 **i**	18	74/57	6b
10		 **j**	17	69/52	5, 6b, 19a
11		 **k**	15	72/53	4a, 6b
12		 **l**	20	68/50	6a, 19b

[a]All isolated products are known and their spectra and physical data have been reported in the literature.[4a,5,6,7e,19b] [b]Isolated yield.

reaction rate and easy work up of various organic reactions. Supported reagents on inorganic oxide surfaces like alumina, clays, silicas and zeolites in conjunction with microwave irradiation have received attention in recent years.[13-17]

Results and Discussion

In continuation of our efforts on the microwave-assisted reactions on solid surfaces under the solvent free conditions,[18] herein, we have described a fast, convenient and simple method for the synthesis of 5-substituted 1*H*-tetrazole derivatives from the reaction of different nitriles with sodium azide in solvent-free media using montmorillonite K-10 clay as an efficient heterogeneous acidic catalyst and microwave irradiation. We examined a variety of structurally divergent benzonitriles possessing a wide range of functional groups to understand the scope and generality of the montmorillonite K-10 -promoted [2+3] cycloaddition reaction to form 5-substituted 1*H*-tetrazoles and the results are summarized in Table 1. These results clearly prove the scope and generality of the reaction with respect to the various benzonitriles. The reactions were completed in 15-22 min under microwave irradiation affording the corresponding tetrazoles in 68-87% yields. It seems that the nature of the substituents on the aromatic ring of benzonitriles has different influences. It is of interest to note that the presence of the electron-withdrawing groups such as nitro which increase the polarity of the cyanide group inductively (Table 1, entries 5 and 6), give high yields of products compared to the electron-donating groups like methyl, and methoxy (Table 1 entries 2-4). Using of the solid acid catalyst in this method offers high yields of products compared to the conventional procedures, probably due to the more molecular interactions.

The applied K-10 clay in the first cycle, was filtered off, washed with methanol (2 × 25 mL) and dried at 120 °C for 10 h under the reduced pressure to be reused in the subsequent reactions which showed the gradual decrease in activity.

The products were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and from melting points. The disappearance of one strong and sharp absorption band (CN stretching band), and the appearance of an NH stretching band in the IR spectra, were evidence for the formation of 5-substituted 1*H*-tetrazoles.

Experimental Section

Chemicals were purchased from Aldrich and Merck chemical companies and used without further purification. Montmorillonite K-10 clay [surface area: (200 ± 10) m^2/g; surface acidity 0.65 meq. H^+/g (determined in our laboratory by temperature programmed desorption of ammonia gas (NH_3-TPD); chemical composition (average value): SiO_2 (73.0%), Al_2O_3 (14.0%), Fe_2O_3 (2.7%), CaO (0.2%), MgO (1.1%), Na_2O (0.6%), K_2O (1.9%)] was purchased from Fluka chemical company.

Melting points were measured on an Electro thermal 9100 apparatus. The ^{1}H NMR and ^{13}C NMR spectra were recorded on FT-NMR JEOL FX 90Q spectrometer using TMS as internal standard (δ/ppm). The IR spectra were obtained on a Perkin Elmer FT IR GX instrument in KBr discs. The relevant products were characterized by comparison of their spectral and physical data with the authentic samples.

In a typical experiment (entry 5), *p*-nitrobenzonitrile (0.39 g, 2 mmol), sodium azide (0.2 g, 3 mmol), and montmorillonite K-10 clay (1.0 g) mixed and placed in a quartz tube, and introduced into a Synthewave 402® (Prolabo, France) single mode focused microwave reactor for 15 min at 130 °C (monitored temperature)[20] with continuous rotation. After completion of the reaction (as indicated by TLC), the reaction mixture was allowed to cool to room temperature, the montmorillonite K-10 clay was removed by filtration and the filtrate was treated with ethyl acetate (40 mL) and 6 N HCl (20 mL) and stirred vigorously. The resultant organic layer was separated and the aqueous layer was extracted with ethyl acetate (30 mL). The combined organic layer was washed with water (10 mL) and concentrated to give a crude product. Column chromatography using silica gel gave pure product 5-(*p*-nitrophenyl)-1*H*-tetrazole (**e**), mp 214-217 °C, in 87% yield with the fresh K-10 clay and 73% with the recovered K-10 clay, (lit. mp 219-220 °C in 96% yield).[6b] IR (KBr): 3200-3300 (br), 1527, 1359, 1164, 1032, 753 cm^{-1}. δ_H (90 MHz, DMSO-d_6): 7.92 (d, 2H), 8.28 (d, 2H), 10.48 (br s, 1H). δ_C (22.5 MHz, DMSO-d_6): 123.52, 128.68, 139.08, 149.21, 158.74.

All the products are known compounds and the spectral data and melting points were identical to those reported in the literature.

Using of the solid acid catalyst in this method offers high yields of products compared to the conventional procedures, probably due to the more molecular interactions.

Conclusion

In summary, we have described a new, simple, easy and highly efficient procedure for the synthesis of 5-substituted 1*H*-tetrazole derivatives using environmentally acceptable montmorillonite K-10 clay. The catalyst is inexpensive, nontoxic and reusable which makes the process convenient, more economic and benign. The recyclability detail of the K-10 clay, which is another advantage of our method, has been explained in caption of the Table 1 and the relevant data is tabulated.

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