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Nano TiO₂ as an efficient and reusable heterogeneous catalyst for the synthesis of 5-substituted 1*H*-tetrazoles

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Abstract

Nano TiO₂ is an effective heterogeneous catalyst for the [2+3] cycloaddition of sodium azide with nitriles to afford 5-substituted 1*H*-tetrazoles in good yields. This method has the advantages of high yields, simple methodology and easy work-up. The catalyst is recovered and reused for several cycles with consistent activity.

Keywords: 5-substituted 1*H*-tetrazole, [2+3] cycloaddition, nano TiO₂, heterogeneous catalyst

1. Introduction

The growth of tetrazole chemistry over the last 25 years has been significant, mainly as a result of the roles played by tetrazoles in coordination chemistry as ligands, in medicinal chemistry as stable surrogates for carboxylic acids and in materials' applications, including explosives, agriculture and photography (Bulter 1996; Herr 2002; Holland 1967; Figdor 1967; Rhonnstad 2002; Klapötke 2009; John 1989). Another important application of tetrazoles is preparation of imidoylazides (Modarresi-Alam 2007). The conventional method of synthesizing tetrazoles is by addition of azide ions to organic nitriles or cyanamides (Curran 1999; Habibi 2010; Huff 1993; Kadaba 1973; Modarresi-Alam 2009; Nasrollahzadeh 2009). Earlier reported methods for the synthesis of 5-substituted tetrazoles suffer from drawbacks such as the use of strong Lewis acids, or expensive and toxic metals, and the in situ generated hydrazoic acid which is highly toxic and explosive (Carini 1991; Duncia 1991; Sisido 1971; Wittenberger 1993). Recently, Sharpless and co-workers reported a relatively simple, convenient and safe procedure for the synthesis of tetrazoles by the addition of sodium azide to nitriles using stoichiometric amounts or 50 mol% of Zn(II) salts (Demko 2001). However, zinc(II) chloride or bromide being homogeneous Lewis acids could not be recycled from the reaction mixture.

Several syntheses of 5-substituted tetrazoles have been reported through the [2+3] cycloaddition of nitriles using NaN₃ or TMSN₃ in the presence of catalysts such as FeCl₃-SiO₂ (Nasrollahzadeh 2009), AlCl₃,^[9] (C₂H₅)₂O.BF₃ (Kumar 1996), TBAF (Amantini 2004), Pd(PPh₃)₄ (Gyoung 2000), and Zn/Al hydrotalcite (Kantam 2006).

Industry favors catalytic processes induced by heterogeneous catalysts over homogeneous processes in view of the ease of handling, simple work-up, and regenerability (Habibi 2011; Modarresi-Alam 2007; Modarresi-Alam 2008; Mohammadi 2010). Nanocrystalline metal oxides have attracted attention due to their unusual magnetic, physical and surface chemical and catalytic properties. These materials can exist with numerous surface sites with enhanced surface reactivity such as crystal corners, edges or ion vacancies (Choudary 2003; Choudary 2004; Guzman 2001; Richards 2000).

As a new material, nanosized TiO₂ is of great interests of many scientists in the recent years. Its small size

and large specific surface area allow for certain unique and unusual physico-chemical properties (Hua 2007; Zhang 2002). Titanium dioxide is a prominent material for various kinds of industrial applications related to catalysis, e.g. in the selective reduction of NO_x in stationary sources, photocatalysis for pollutant elimination or organic synthesis, photovoltaic devices, sensors, and paints (Forzatti 2000; Hoffman 1995; Maldotti 2002).

We herein report a new protocol for preparation of 5-substituted 1*H*-tetrazoles derivatives from nitriles using nano TiO₂ as an efficient heterogeneous catalyst (Scheme 1).

2. Experimental

2.1. General

All reagents were purchased from Merck and Aldrich and used without further purification. ¹³C NMR and ¹H NMR spectra were recorded on Bruker, 100 and 250 MHz using TMS as an internal standard. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. IR spectra were recorded on a Shimadzu 470 spectrophotometer. TLC was performed on Merck-precoated silica gel 60-F254 plates. Nano TiO₂ was prepared according to the literature (Hua 2007). Hua and co-workers studied the characterization of the Nano TiO₂ using powder XRD and TEM (Hua 2007).

2.2. General procedure for preparation of 5-substituted 1*H*-tetrazoles

Nano TiO₂ (0.1 g) was added to a mixture of nitrile (2 mmol), sodium azide (0.2 g, 3 mmol) and distilled dimethylformamide (6 mL) and stirred at 120 °C for the appropriate time (Table 1). After completion of the reaction (as monitored by TLC), the catalyst was centrifuged, washed with ethyl acetate and the centrifugate was treated with ethyl acetate (35 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 (25 mL). The combined organic layers were washed with water and concentrated to give the crude product. Column chromatography using silica gel gave pure product in high yield. The pure products were characterized by IR and NMR. All the products are known compounds and the spectral data and melting points were identical to those reported in the literature.

5-Phenyl-1*H*-tetrazole (**2a**):

¹H NMR δ 7.58-7.64 (m, 3H); 8.01-8.06 (m, 2H).

5-(4-Methylphenyl)-1*H*-tetrazole (**2c**):

¹H NMR δ 2.47 (s, 3H); 7.49 (d, *J* = 8.0 Hz, 2H); 8.01 (d, *J* = 8.0 Hz, 2H).

5-(Naphthalen-2-yl)-1*H*-tetrazole (**2f**):

¹H NMR δ 7.59-7.68 (m, 2 H); 7.98-8.18 (m, 4H); 8.65 (s, 1H).

4-(1*H*-tetrazole-5-yl)benzotrile (**2h**):

¹H NMR δ 7.76 (d, *J* = 7.3 Hz, 2H), 8.21 (d, *J* = 7.3 Hz, 2H), 10.96 (br, s, 1H).

3. Result and Discussion

The general synthetic method is depicted in Scheme 1. 5-Substituted 1*H*-tetrazoles were obtained from the reaction of nitrile with sodium azide in the presence of nano TiO₂ as an efficient heterogeneous catalyst at 120 °C for appropriate time in high yields.

First, we optimized the amount of nano TiO₂ catalyst required in the reaction between benzotrile and sodium azide (Table 1). Water was not a suitable solvent for this reaction. Not many organic solvents are stable at the high temperatures necessary for cycloaddition reactions (sometimes as high as 130 °C), and for this reason DMF is most commonly used for this purpose (Herr 2002; Kumar 1996; Kantam 2006). The optimum amount of nano TiO₂ was found to be 0.1 g in the presence of nitrile (2 mmol) and sodium azide

(3 mmol) in DMF (6 mL). We next examined a variety of structurally divergent benzonitriles possessing a wide range of functional groups to understand the scope and generality of the nano TiO₂-promoted [2+3] cycloaddition reaction to form 5-substituted 1*H*-tetrazoles and the results are summarized in Table 2. The nature of the substituent on the benzonitrile did not affect the reaction time. Interestingly 1,4-dicyanobenzene (Table 2, entry 8) afforded the mono-addition product, whereas in the reaction between sodium azide and 1,4-dicyanobenzene in the presence of Zn(II) salts the double-addition product was reported (Demko 2001). Reaction of the heteroaromatic nitrile, 3-pyridinecarbonitrile was complete at 120 °C after 6 h and gave the corresponding tetrazole in an excellent yield (Table 2, entry 9).

The simplicity, together with the use of inexpensive, non-toxic and environmentally benign catalyst under thermal condition are remarkable features of the procedure. The products were characterized by IR, ¹H NMR and ¹³C NMR spectroscopy and from melting points. The structure of the 5-substituted 1*H*-tetrazoles was in agreement with their IR and ¹H NMR spectra. The comparison of the IR spectra of nitriles with 5-substituted 1*H*-tetrazoles clearly confirmed the cyclization. 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. ¹³C NMR spectra display signals for tetrazole ring carbons of arylaminotetrazoles in the range of 154-157 ppm (Nasrollahzadeh 2009; Habibi 2010). On the other hand, 5-substituted 1*H*-tetrazoles contain one NH bond (NH of the tetrazole ring). In general, 5-substituted 1*H*-tetrazoles are acidic substances. Thus, signal of the NH of the tetrazole ring shifted downfield (¹H NMR data).

3.1. Catalyst reuse and stability

In a typical experiment, after the reaction was completed, Nano TiO₂ as a catalyst was isolated from the reaction mixture by simple filtration in the work-up stage. The reusability of the catalyst was assessed after activating the catalyst at 250 °C for 1 h. The nano TiO₂ was reused for five cycles with consistent activity. Moreover, even after five uses of the Nano TiO₂, there is no decrease in the reaction conversion of the product indicating high activity of the catalyst. This reusability demonstrates the high stability and turnover of Nano TiO₂ under operating condition. The reusability of the catalysts is one of the most important benefits and makes them useful for commercial applications.

4. Conclusion

In conclusion, we have developed a simple and highly efficient method for the preparation of 5-substituted 1*H*-tetrazoles via [2+3]-cycloaddition using nano TiO₂ as a heterogeneous catalyst. The significant advantages of this methodology are high yields, elimination of dangerous and harmful hydrazoic acid and a simple work-up procedure. The catalyst can be recovered by simple filtration and reused without loss of activity. It also has excellent activity on an industrial scale and in most cases can be recovered from reaction mixtures and reused. This methodology may find widespread use in organic synthesis for the preparation of tetrazoles.

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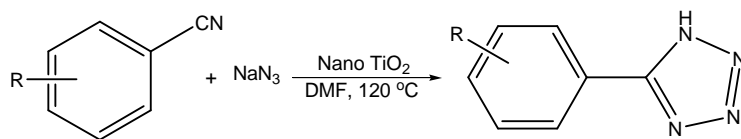
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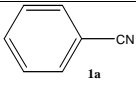
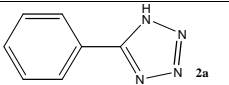
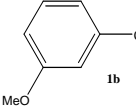
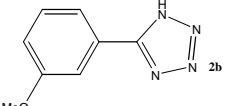
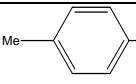
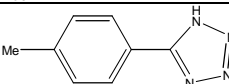
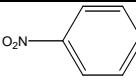
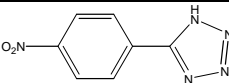
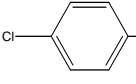
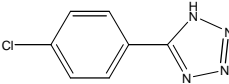
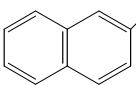
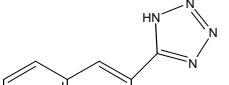
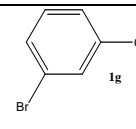
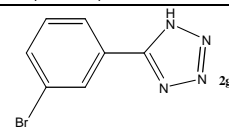
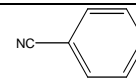
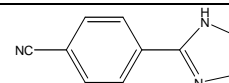
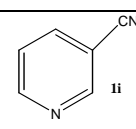
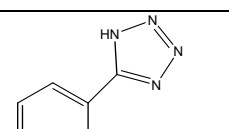
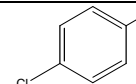
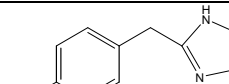
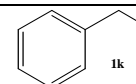
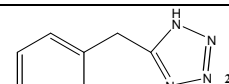
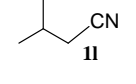
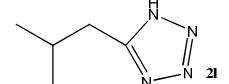
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Scheme 1. Conversion of nitriles to the corresponding 5-substituted 1H-tetrazoles using nano TiO₂

Table 1. Synthesis of various 5-substituted 1*H*-tetrazoles in the presence of nano TiO₂ by reaction of sodium azide and nitriles at 120 °C

Entry	Substrate	Product	Time [h]	Yield [%] ^a	Ref.
1			14	82	(Nasrollahzadeh 2009)
2			14	80	(Nasrollahzadeh 2009)
3			14	81	(Nasrollahzadeh 2009)
4			14	82	(Nasrollahzadeh 2009)
5			14	78	(Nasrollahzadeh 2009)
6			14	83	(Nasrollahzadeh 2009)
7			14	80	(Nasrollahzadeh 2009)
8			22	80	(Nasrollahzadeh 2009)
9			6	83	(Nasrollahzadeh 2009)
10			24	75	(Nasrollahzadeh 2009)
10			24	74	(Nasrollahzadeh 2009)
12			30	66	(Mihina 1950)

^aYield refer to the pure isolated product.

Table 2. Preparation of 5-phenyltetrazole using varying amounts of nano TiO₂ under thermal conditions at 120 °C^a

Entry	Nano TiO ₂ (g)	Solvent	Yield% ^b
1	0.15	DMF	82
2	0.11	DMF	81
3	0.1	DMF	81
4	0.09	H ₂ O	10
5	0.1	DMSO	80
6	0.07	DMF	77
7	0	DMF	0 ^c

^aReaction conditions: nitrile (2 mmol), NaN₃ (3 mmol), nano TiO₂ (0.1 g), DMF (6 mL), reaction time (14 h) at 120 °C.

^bIsolated yield.

^cIn the absence of catalyst at 120 °C, no reaction occurred after 20 h.

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