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Research Article

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Nano-TiO_2 as a new, green and recyclable catalyst for the synthesis of 2-aryl benzoxazole under solvent-free conditions

Bita Baghernejad

Department of Chemistry, School of Science, Payame Noor University (PNU), Iran

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ABSTRACT

A simple, convenient and general method has been developed for the synthesis of 2-arylbenzoxazole via condensation of o-aminophenols and benzoyl chloride derivatives under solvent-free condition in the presence of a catalytic amount of Nano-TiO_2 in good yields.

Keywords: Nano-TiO_2; o-aminophenols, benzoyl chloride, 2-arylbenzoxazole

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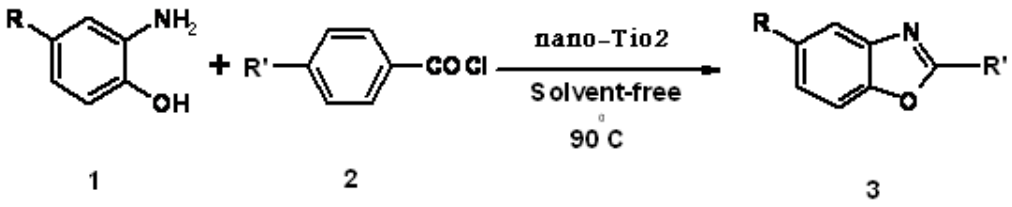
INTRODUCTION

Benz-fused azoles are an important class of molecules and are a common heterocyclic scaffold in biologically active and medicinally significant compounds. Benzoxazoles are found in a variety of natural products[1] and are important targets in drug discovery [1].

Benzoxazoles have been indicated as 5-HT_3 receptor partial agonists [2], HIV protease inhibitors[3], COX inhibitors[4], thrombin inhibitors[5], R2-antagonist/5-HT uptake inhibitors[6], and inhibitors of the human cyotmegalovirus protease[7]. 2-Arylbenzoxazoles posses the important biaryl pharmacophore and have exhibited a variety of biological activities, including antimicrobial and antitumor properties[8]. For example, a 2-arylbenzoxazole, AJI9561, was recently isolated as a cytotoxic metabolite from the extract of Streptomyces[9]. They have also found applications in industry as antioxidants, vulcanization accelerators, and as a dopant in a light-emitting organic electroluminescent device[10,11]. There are a few methods for the synthesis of these compounds. The most popular methods for the synthesis of 2-arylbenzoxazoles involves the reaction between a o-aminophenol and a carboxylic acid or benzoyl chloride or aldehyde[12-14]. But, many of these methods involve the use of expensive reagents, harsh conditions, extended reaction times, and also require tedious workup leading to the generation of a large amount of toxic waste. Consequently, there is a need to develop new methods to synthesis of these compounds. In our attempts to develop new catalyst systems, herein, we will describe a mild and efficient protocol for the synthesis of 2-arylbenzoxazoles via condensation of o-aminophenols and benzoyl chlorides under solvent-free condition in the presence of a catalytic amount of Nano-TiO_2 in good yields. (Scheme1)



Scheme 1

EXPERIMENTAL SECTION

Chemical and apparatus

All the chemicals were obtained from Merck Company. All products are known compounds and were characterized by mp, IR, ^{1}HNMR and GC/MS. Melting points were measured by using the capillary tube method with an electrothermal 9200 apparatus. ^{1}HNMR spectra were recorded on a Bruker AQS AVANCE-500 MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network Mass selective detector. Thin layer chromatography (TLC) on commercial aluminum- backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. All products were characterized by spectra and physical data.

Typical procedure for the synthesis of 2-arylbenzoxazole.

A mixture of o-aminophenol (1 mmol), benzoyl chloride (1 mmol) and Nano-TiO_2 (2 mol %) was stirred vigorously in oil bath at 90˚C for the indicated time (Table1). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with dichloromethane (3×10 mL) then, the reaction mixture was chromatographed over PTLC using petroleum ether–ethyl acetate (4:1) to afford the pure product.

Selected physical data

2- phenyl benzoxazol (3a): White solid; m.p. 102˚C (lit[27]. m.p. 102˚C); ^{1}H NMR ($CDCl_3$, 500 MHz): 8.1–8.3 (m, 2H), 7.2–7.8 (m, 7H); IR (KBr) (ν_{max}, cm^{-1}): 3060, 1620, 1560, 1460, 1450, 1330, 1240, 1040; GC/Ms: 195 (M^+).

2-(p-tolyl) benzoxazol (3b): White solid; m.p. 112–113˚C (lit[27]. m.p. 113–114˚C); ^{1}H NMR ($CDCl_3$, 500 MHz): 8.05–8.39 (m, 2H), 7.07–7.60 (m, 6H), 2.45 (s, 3H); IR (KBr) (ν_{max}, cm^{-1}): 3056, 1630, 1545, 1455, 1240, 1050; GC/Ms: 209 (M^+).

5-methyl 2- phenyl benzoxazol (3d): White solid; m.p. 103˚C (lit[27]. m.p. 103 ˚C); ^{1}H NMR ($CDCl_3$, 500 MHz): 8.20–8.40 (m, 2H), 7.05–7.60 (m, 6H); 2.43 (s, 3H); IR (KBr) (ν_{max}, cm^{-1}): 3055, 1640, 1555, 1470, 1330, 1250, 1050; GC/Ms: 209 (M^+).

Synthesis of nano-TiO_2

A 500 mL three-necked flask containing 5 mL of titanium tetrachloride was equipped with a condenser, a gas trap and a water steam producer. The titanium tetrachloride was heated to 130 8C. By adding water steam to hot titanium tetrachloride for 15 min, a milky solution was formed. After washing the condenser, the milky solution was filtered to obtain a white solid. By heating of the white solid in oven at 400 ˚C for 7 h, the TiO_2 nanoparticle as a white crystalline powder was formed.

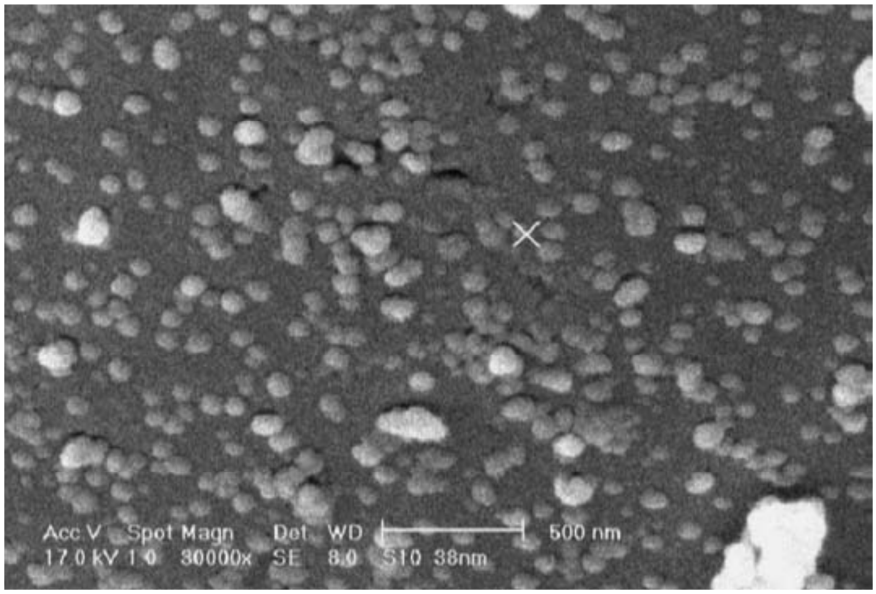


Fig.1. SEM photograph of nano-TiO2

RESULTS AND DISCUSSION

At first we focused on the reaction of o-aminophenol and benzoyl chloride. In a typical procedure, o-aminophenol (1 mmol) with benzoyl chloride (1 mmol) in the presence of a catalytic amount Nano-TiO_2 under solvent-free condition afforded the desired 2-phenyl-benzoxazole in 94% yield (Entry 1, Table 1). The reaction then was applied to a variety of benzoyl chloride and o-aminophenol . Most of these reactions proceeded in relatively short times, and pure products were obtained by recrystallization or preparative thin layer chromatography (PTLC). The synthesis from readily available benzoyl chloride and o-aminophenol seems to be generally applicable and tolerant of a variety of functional groups, and is, to the best of our knowledge, the first time, the Nano-TiO_2 as a catalyst has been used for the synthesis of 2-arylbenzoxazoles.

The synthesis of these compounds was carried out using various common solvents such as CCl_4, acetonitrile, methanol, ethylacetate and THF. With using Nano-TiO_2 as a catalyst, the highest yield of products was obtained under solvent-free condition. In addition, the time required for completion of the reaction was found to be less in this condition.

Aminophenols with electron-withdrawing groups, which were predicted to be less reactive toward benzoyl chlorides, gave comparable results (entries 7–9, Table 1). Electron-donating substituents on the aromatic ring of benzoyl chlorides decrease the yield and increase the time of the reaction (entries 2,5,8, Table 1). The insolubility of Nano-TiO_2 in different organic solvents provides an easy method for separation of the catalyst and the product. The catalyst was separated by filtration and reused after activation with only a gradual decrease in activity observed. The amount of catalyst has been optimized to 2 mol%; however, lesser amount (1 mol%) would also work with longer reaction times. The effect of temperature was studied by carrying out the reactions at different temperatures [25˚C, 60 ˚C and 90˚C]. As it shown in Tables 1 by raising the reaction temperature to 90˚C, the yield of reactions increased.

From these results, it was decided that 90˚C would be the best temperature for all reactions.

Table1. Synthesis of 2-arylbenzoxazoles catalyzed by Nano-TiO_2

Entry	R	R'	Product	Time (min)	Yield(%)[a]		
					25˚C	60˚C	90˚C
1	H	H	3a	17	55	85	94
2	H	CH_3	3b	20	45	75	87
3	H	Cl	3c	15	40	70	97
4	CH_3	H	3d	15	45	72	95
5	CH_3	CH_3	3e	20	50	79	88
6	CH_3	Cl	3f	12	50	77	97
7	Cl	H	3g	30	43	70	90
8	Cl	CH_3	3h	33	50	77	85
9	Cl	Cl	3i	30	43	70	91

[a]*Yields of isolated products*

CONCLUSION

In conclusion, Nano-TiO_2 as a reusable catalyst was found to be a mild and effective catalyst for the one-pot reactions of o-aminophenols with benzoyl chlorides to afford 2-substitued benzoxazole derivatives in excellent yields. The use of this inexpensive, recyclable and easily available catalyst under essentially neutral reaction and workup conditions and the cleaner reaction make this protocol practical and economically attractive.

REFERENCES

[1] M Ueki; K Ueno; S Miyadoh; K Abe; K Shibata; M Taniguchi; S Oi., *J. Antibiot.* **1993**, 46, 1089-1094.
[2] Y Sato; M Yamada; S Yoshida; T Soneda; M Ishikawa; T Nizato; K Suzuki; F Konno, *J. Med. Chem.* **1998**, 41, 3015-3021.
[3] P Chen; PTW Cheng; M Alam; BD Beyer; GS Bisacchi *J. Med. Chem.* **1996**, 39, 1991-2007.
[4] R Paramshivappa; PP Kumar; PV Subba; A Srinivase Rao, *Bioorg. Med. Chem. Lett*. **2003**, 13, 657–660.
[5] MJ Costanzo; BE Maryanoff; LR Hecker; MR Schott; SC Yabut, *J. Med. Chem.* **1996**, 39, 3039-3043.
[6] MD Meyer; AA Hancock; K Tietje; KB Sippy; R Prasad; DM Stout; DL Arendsen; BG Donner, *J. Med. Chem.* **1997**, 40, 1049-1062.
[7] W Ogilvie ; M Bailey; MA Abraham; C Yoakim, *J. Med. Chem.* **1997**, 40, 4113-4135.
[8] O Temiz; I Rren; E Sener; I Yalcin; N Ucarturk, *Farmaco* **1998**, 53, 337.
[9] S Sato; T Kajiura; M Noguchi; K Takehana; T Kobayashi; T Tsuji, *J. Antibiot*. **2001**, 54, 102-105.
[10] SKN Ivanov; VS Yuritsyn, Inhibity action of organic sulfur compounds during cumene oxidation. *Chem. Abstr*. **1971**, 74, 124487m.
[11] C Monsanto, Benzothiazole sulfenamides for use as vulcanization accelerators. *Chem. Abstr*. **1968**, 68, 96660t.
[12] M Terashima; M Ishii, *Synthesis* **1982**, 1484-1490.
[13] RS Varma; RK Saini; O Prakash, *Tetrahedron Lett*. **1997**, 38, 2621-2626.
[14] RS Varma; D Kumar, *J. Heterocyclic Chem*. **1998**, 35, 1539-1542.