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ORIGINAL ARTICLE

Nano-TiO_2 an Efficient, Clean and Eco-friendly Catalyst for Synthesis of Naphthoxazinone Derivatives as High Potent Antibacterial Agents

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KEYWORDS

Antibacterial agents;
Naphthooxazinones;
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ABSTRACT: Oxazines naturally occurs and synthetically exhibit wide-ranging biological activity. In this study, a highly practical and efficient of 1,2-dihydro-1-phenylnaphtho[1,2-e][1,3]oxazine-3-one derivatives was developed via a multi-component reaction of 2-naphthol, aldehydes and urea in the presence of nano-titanium oxide as solid, recyclable catalyst at one-pot and solvent-free conditions. These synthetic compounds 2a-e were evaluated as potential antibacterial agents. The structures of products were confirmed by spectral analysis FT-IR and ^{1}H NMR. The antibacterial activity of the compounds was screened against *Staphylococcus aureus* and *Escherichia coli.* These results showed that these compounds exhibited significant to moderate activities against both Gram (+) and Gram (-) organisms.

INTRODUCTION

Oxazines, benzooxazines and naphthoxazine derivatives are an important category of heterocyclic compounds containing two heteroatoms (N, O). It is an important backbone in a large variety, which plays a significant role in pharmaceutical field and biologically active compounds [1, 2]. Additionally, naphthoxazines and their derivatives possess appearance biological activity such as 5-HT ligands [3], platelet fibrinogen receptor antagonists [4], protein kinas [5], HIV inhibitory [6], anti-viral [7], antimicrobial [8], antitumor [9], anti-malaria [10], hypertensive [11], Antiarrhythmic [12] and anticonvulsant [13].

Because of the importance of naphthoxazines the synthesis of new derivatives of these compounds is an important and useful task in organic chemistry. Recently diverse route for synthesis of naphthoxazine derivatives are reported as follows. The use of Carbamates [14], 2-hydroxyacetophenone [15] and hydrazine salisylaldehyde [16], Betti bases [17] and amino alcohols [18] with the yield moderate to good are reported. The most methods are known in literature for synthesis of aromatic oxazinones involves harsh conditions and use of toxic solvent and reagents, and longtime reaction [19-23].

In recent time, the use of nano-TiO_2 as catalyst has received a considerable attention in organic synthesis due to its environmentally compatibility, ease of handling, non-toxic nature, low cost and chemical stability even under high temperature [24]. In continuation of our investigation of using heterogeneous catalysts in organic synthesis in

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multi-component one-pot method [25-27], here in we want to report the convenient synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-one derivatives (2a-e) via the one-pot multi-component condensation reaction of aromatic aldehydes (1a-e), β-naphtol and urea and screen them for their level of antimicrobial activity. The reaction was realized in the presence of a catalytic amount of nano-TiO_2 under solvent-free conditions (Figure1).

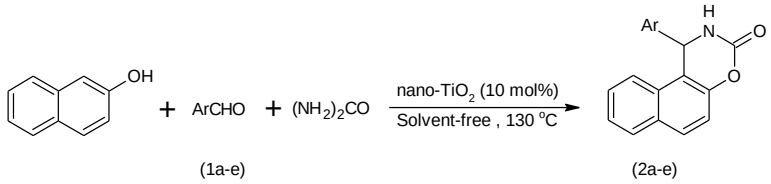


Figure 1. Nano-TiO_2 catalyzed synthesis of 1, 2-dihydro-1-aryl-naphtho[1,2-e][1,3]oxazine-3-ones.

MATERIALS AND METHODS

All commercial reagents were used as received without purification and all solvent were of reagent grade. The reaction was monitored by TLC using 0.25 mm Merck silica gel 60F254 pro-coated plates, which were visualized with UV light. The melting points were determined in open capillaries on an Electrothermal type 9100s melting point apparatus. The IR spectra were recorded on a Shimadzu 4300 spectrophotometer as KBr disk. The ^{1}H NMR spectra were recorded on a Bruker DRX-400 MHz instrument using TMS as the internal standard.

General experimental procedure for the synthesis of 1,2-dihydro-1-aryl-naphtho[1,2-e][1,3]oxazine-3-ones

A mixture of β-naphthol (2 mmol), aromatic aldehydes (2 mmol), urea (5 mmol) and nano-TiO_2 (0.2 mmol/ 10 mol%) was heated on the oil bath at 130 °C for an appropriate time (see later). The reaction was monitored by TLC using n-hexane ethylacetate (5:2) as an eluent. After completion of the reaction, the reaction mixture was cooled to room temperature, ethanol 96% was added and the mixture was heated for 10 min. After cooling the mixture to room temperature, the TiO_2 nanoparticles were filtered and the solvent evaporated. The crude product collected and recrystallized from 2-propanol to give compounds 2a-e in high good yields. All products were known and characterized by comparison of their physical and spectroscopic data with those of reported techniques.

Reusing and recycling of the catalyst

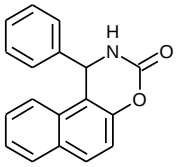
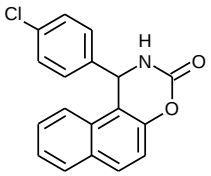
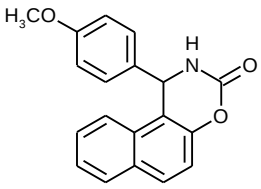
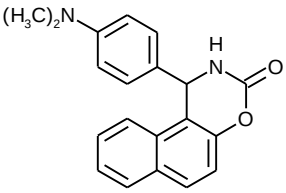
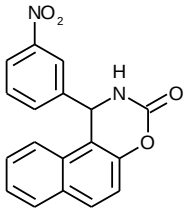
The recyclability of the catalyst in the reaction of β-naphthol, benzaldehyde and urea in the presence of nano-TiO_2 was checked. The separated catalyst can be reused after washing triple with boiling ethanol 95% drying at 95°C and reused in another reaction. It showed the same activity as fresh catalyst without any loss of in activity after six times (Table 1). The spectral data for some selected compounds are presented in Table 2.

Table 1. Recovery and reuse of nano TiO_2 for the synthesis of **2a**

Cycle	Yield[a]/%
1	80
2	80
3	80
4	79
5	79
6	78

[a]isolated yield

Table 2. Synthesis of naphthoxazines with use of *β*-naphthol, urea and aryl aldehydes in the presence of nano-TiO_2 as catalyst

Entry	Products	Physical information and quality of products
1		White Crystals, Yield: (80%), mp: 216-218 °C. IR (ν_{max}/cm^{-1})(KBr): 3211(NH Str.); 3152(CH_{arom}. Str.); 3052(CH_{alipha} Str.); 1736(C=O Str.); 1517(C=C Str.); 1419(C-N Str.); 1217(C-O Str.). ^{1}H-NMR (400.13 MHz DMSO-d_6)δ(ppm): 5.78(1H, s, H); 6.84-6.98(m, 6H_{arom}); 7.08(2H_{arom}, t, ^3J=6.8 Hz); 7.41(1H_{arom}, d, ^3J=7.9 Hz); 7.52-7.59(2H_{arom}, m); 8.44(1H , brs, NH).
2		White Crystals, Yield: (74%), mp: 210-212 °C. IR (ν_{max}/cm^{-1})(KBr): 3216(NH Str.); 3160(CH_{arom}. Str.); 3040(CH_{alipha}. Str.); 1722(C=O Str.); 1527(C=C Str.); 1420(C-N Str.); 1222(C-O Str.). ^{1}H-NMR (400.22 MHz DMSO-d_6)δ(ppm): 6.26(1H, s); 7.33-7.35(5H_{arom}, m); 7.80(2H_{arom}, d, ^3J=8.0 Hz); 7.97(1H_{arom}, d, ^3J=7.9 Hz); 8.01(2H_{arom}, d, ^3J=8.8 Hz); 8.93(1H , brs, NH).
3		White Crystals, Yield: (70%), mp: 190-193 °C. IR (ν_{max}/cm^{-1})(KBr): 3219(NH Str.); 3166(CH_{arom}, Str.); 3052(CH_{alipha}. Str.); 1736(C=O Str.); 1502(C=C Str.); 1380(C-N Str.); 1223(C-O Str.). ^{1}H-NMR (400.22 MHz DMSO-d_6)δ(ppm): 4.0(3H, s, OCH_3); 6.15(1H, s, CH_{alipha}); 6.90(2H_{arom}, d, ^3J=9.2 Hz); 7.25(2H_{arom}, d, ^3J=9.2 Hz); 7.37(1H_{arom}, d, ^3J=9.2 Hz); 7.45(2H_{arom}, d, ^3J=6.8 Hz, ^4J=1.2 Hz); 7.8(1H_{arom}, d, ^3J=8 Hz); 7.99(2H_{arom}, m); 8.80(1H, brs, NH).
4		White-yellow Crystals, Yield: (72%), mp: 224-226 °C. IR (ν_{max}/cm^{-1})(KBr): 3218(NH Str.); 3215(CH_{arom}. Str.); 3041(CH_{alipha}. Str.); 1729(C=O Str.); 1509(C=C Str.); 1390(C-N Str.); 1270(C-O Str.). ^{1}H-NMR (400.22 MHz DMSO-d_6)δ(ppm): 2.82(6H, s); 6.01(1H, s); 6.64(2H_{arom}, d, ^3J=8.8 Hz); 7.07(2H_{arom}, t, ^3J=9.2 Hz); 7.37(1H_{arom}, d, ^3J=9.2 Hz); 7.40(2H_{arom}, dd, ^3J=8.0 , ^4J=1.2 Hz); 7.80(2H_{arom}, d, ^3J=8.8 Hz); 7.94(2H_{arom}, m); 8.70(1H_{arom}, brs, NH).
5		White-yellow Crystals, Yield: (90%), mp: 228-230 °C. IR (ν_{max}/cm^{-1})(KBr): 3216(NH Str.); 3159(CH_{arom}. Str.); 3059(CH_{alipha}. Str.); 1732(C=O Str.); 1530, 1355(NO_2. Str.); 1522(C=C Str.); 1405(C-N Str.); 1225(C-O Str.). ^{1}H-NMR (400.22 MHz DMSO-d_6)δ(ppm): 5.55(1H, s, CH); 6.90-7.32(6H_{arom}, m); 7.16(1H_{arom}, d, ^3J=7.5 Hz); 7.22(1H_{arom}, dd, ^3J=7.5 Hz, ^3J=6.4 Hz); 7.55(1H_{arom}, d, ^3J=6.4 Hz); 8.15(1H_{arom}, s); 8.66(1H, brs, NH)

Antibacterial activity

The compounds **2a-e**, was evaluated for their efficacy an antibacterial *in vitro* by disc diffusion method against various bacterial strains. The antibacterial activity has been compared to some standard antibacterial agents like sulfanilamide and sulfadiazine that contain a ρ-amino benzene sulfonamide moiety. From the results in Table 3 compound **(2a-e)** exhibited activity to ward *E. coli* and *S. aureus* as test grams.

Table 3. *In vitro* antibacterial activity of 1-aryl naphtha [1,2-e][1,3]oxazin-3-ones (2a-e)

Comp.	MIC (µg/ml)	
	***E. coli* MTCC 448** Gram (-)	***S. aureus* MTCC 432** Gram (+)
2a	10	8
2b	8	9
2c	22	16
2d	26	22
2e	10	21
SA	>128	>128
SZ	14	20

SA: Sulfanilamide; SZ: Sulfadiazine

RESULTS AND DISCUSSION

Due to the increasing demand in modern organic processes for reusability of catalysts, we decided to investigate the efficacy of nano TiO_2 as heterogeneous catalyst in the synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones **2a-e** thoroughly a mixture of *β*-naphthol appropriate aromatic aldehydes, urea and nano TiO_2 as catalyst in the mole ratio 2:2:5:02 followed by direct heating on an oil-bath at 130 °C in solvent free conditions. Products of **2a-e** were afforded in good yield (Figure 1 and Table 2).

A mixture of above-named compounds was heated on the oil bath at different temperature in the presence of various amounts of nano-TiO_2 as heterogeneous catalyst (Table 4). As can be seen from this table, the yield of compounds **2a** was affected by the catalyst amount and reaction temperature. No product was obtained in the absence of the catalyst (Entry 1, Table 4) or in the presence of the catalyst at room temperature (Entry 2, Table 4) indicating that the catalyst and temperature are necessary for the reaction. Increasing the amount of catalyst

and reaction temperature up to 10 mol% and 130 °C, respectively, increased the yield of the product **2a**. Further increase in both catalyst amount and temperature did not increase the yield noticeably (Entry 15-16, Table 4). The principle advantage of the use of heterogeneous solid acid catalyst in organic transformation is their reusability. Hence, we decided to study the catalytic activity of recycled nano-TiO_2 in the synthesis of compounds **2a**. After the completion of the reaction, the catalyst was recovered according to the procedure mentioned in experimental part and reused for a similar reaction. The catalyst could be reused at least six times with only slight reduction in the catalytic activity (Table 1). The proposed mechanism for synthesis of **2a-e** has been shown in Figure 2.

Table 4. Effect of nano-TiO_2 amount and temperature on the model reaction[a]

Entry	Amount of Catalyst (mol%)	T (°C)	Time (min)	Yield[b] (%)
1	None	100	60	None
2	10	r.t	60	None
3	2	120	60	30
4	2	130	60	35
5	4	120	60	45
6	4	130	60	52
7	4	130	80	52
8	6	130	60	58
9	6	140	60	58
10	8	120	60	60
11	8	130	60	64
12	8	140	60	64

Table 4. Continued.

13	10	120	60	70
14	10	130	10	80
15	10	130	30	80
16	12	130	30	74
17	12	140	60	72

[a] 2 mmol *β*-naphthol, 2 mmol benzaldehyde, 5 mmol urea under solvent-free condition; [b] Isolated yields

As shown in Figure 2, the nano-TiO_2 motives the activation of the aldehyde by non-bonding interaction, thereafter, the nucleophilic attack of nitrogen and remove of water case formation of active inline intermediate. Then *β*-naphthol, with Michael addition reaction in reasonable mechanism and remove of NH_3 give the **2a**. In Table 5 the efficient of our method for the synthesis of 1,2-dihydro-1-aryl naphtha[1,2-e][1,3] oxazine-3-ones are compared with some other published works in the literature. Each of these methods have their own advantages, but they often suffer from troubles inclusive of use of organic solvent, high load of catalyst, long reaction time and employing of expensive catalyst.

Table 5. Comparison of efficiency of various catalysts in synthesis of 1,2-dihydro-1-phenylnaphtho[1,2-e][1,3]oxazine-3-ones

Entry	Condition	T (°C)	Time (min)	Yield[b] (%)	Reference
1	Montmorillonite K10 clay/neat	160	30	89	[28]
2	$HClO_4/SiO_2$/neat	150	60	85	[29]
3	Phosphomolybdic acid/DMF	100	180	87	[30]
4	I_2/Hot plate	80	5	96	[31]
5	*p*-TSA/neat	160	90	58	[32]
6	[bmim]Br/*p*-TSA	160	180	76	[33]
7	Nano Cu/PEG-400	r.t	45	93	[34]
8	TCT	150	12	87	[35]
9	$LaCl_3/ClCH_2COOH$/Solvent-free	125	55	94	[36]
10	Perlite-SO_3H NPs/MW/Solvent-free	110	45	53	[37]
11	Nano TiO_2/Sovent-free	130	30	80	This study

The synthesized compounds were tested for the antibacterial activity by measuring the inhibition area on agar plates with *S. aureus* and *Escherichia coli* as test grams (Table 3). The results of antibacterial screening indicated that good activity was shown by compounds **2d**, **2e** against *S. aureus* and compounds **2c**, **2d** shows good activity towards *E. coli* while the compounds **2a**, **2b** have less activity against *S. aureus* and compounds **2a**, **2b**, **2e** have less activity against *E. coli* other compounds showed moderate activity against both bacteria strains the MIC results are summarized in Table 3. The structure activity relationship (SAR) of 1,2-dihydro-1-phenylnaphtho[1,2-e][1,3]oxazine-3-ones demonstrates that substitution of the methoxy, dimethylamine and nitro groups at the position para and meta in the naphtha oxazine generally increased the activity profile.

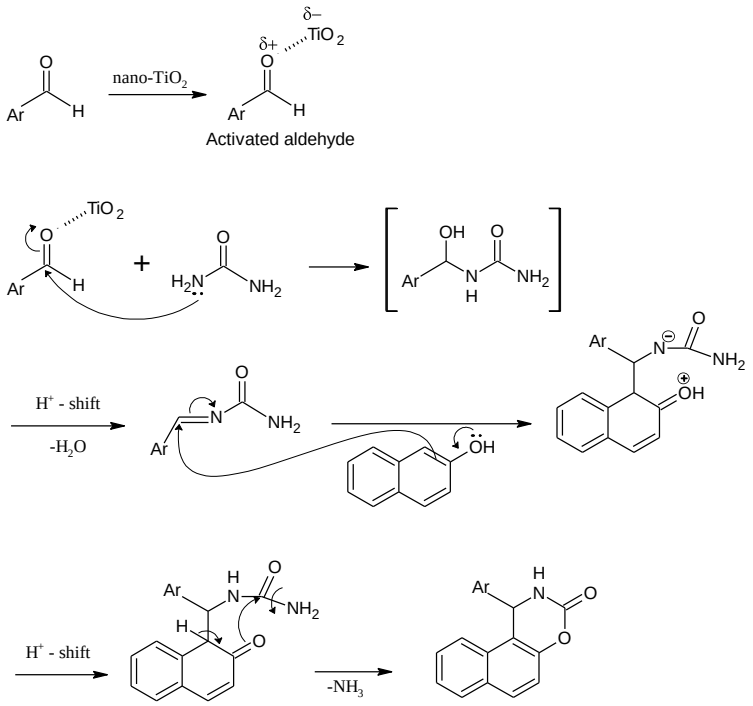


Figure 2. Plausible mechanism

CONCLUSIONS

The simplicity of methodology, ease of the product isolation, good yields, low case of catalyst solvent-free conditions and easy of recovery and reuse of catalyst could make this process a useful and reliable method for the synthesis of the described compounds. In addition, it is consistent with a green chemistry approach, since no organic solvent is needed. The synthesized compounds are known as high potent antibacterial agents.

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