

Nano-Fe₃O₄/TiCl₂/cellulose as an Efficient and Green Magnetic Nanocatalyst for the Synthesis of 2,3-Dihydro-2-substituted-1*H*-naphtho[1,2-*e*][1,3]oxazine Derivatives

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(Received 10 October 2020, Accepted 27 April 2021)

Nano-Fe₃O₄/TiCl₂/cellulose as a green and recyclable nanocatalyst was synthesized and characterized by FT-IR, FESEM, TEM, XRF, BET, VSM, EDX and XRD. The prepared magnetic nanocatalyst was applied for the synthesis of 2,3-dihydro-2-substituted-1*H*-naphtho[1,2-*e*][1,3]oxazine under room temperature grinding condition. Short reaction time, high yield, green media, easy work-up, simple magnetic recovery and reusability of the catalyst are the important features of the present protocol.

Keywords: 1,3-Oxazines, Solvent-free reaction, Magnetic nanocatalyst, Grinding

INTRODUCTION

In recent years, cellulose as a natural biopolymer has been used for the preparation of heterogeneous catalytic systems. This bio-polymer is constituted of repeating β -D-glucopyranosyl units joined by β -1, 4-glycosidic linkages [1]. Cellulose has some important properties such as hydrophilicity, chirality, biocompatibility, biodegradability, environmentally-friendly and broad chemical-modifying capacity [2]. Manipulating cellulose molecules on the nanometer scale to create the nanocellulose of excellent properties has become a hotspot of cellulose science. By mechanical treatments or chemical modifications on cellulose pulp, nanometer-sized cellulose such as cellulose nanofibrils (CNFs) and cellulose nanocrystals (CNCs) can be produced. Unique properties of cellulose and its derivatives make them attractive supports for catalytic applications [3-5].

On the other hand, recently magnetic nanoparticles (MNPs) have received increasing attention as appealing and

sustainable supports for catalytic application due to several distinct properties such as high surface area, easy synthesis and functionalization, facile separation by magnetic forces and their chemical stability in various organic and inorganic solvents [6,7]. The most used and accessible magnetic particle is magnetite (Fe₃O₄) owing to its potential applications in catalysis, magnetic resonance imaging (MRI), hyperthermia and drug targeting [8].

1,3-Oxazines are an important class of heterocyclic compounds that exhibit a broad spectrum of biological and pharmacological activities such as such as antitumour [9], antimicrobial [10], anti-HIV [11], analgesic [12], antihypertensive [13], antithrombotic [14] and antiulcer [15] activities. Moreover, substituted naphthoxazines are used for the therapy of Parkinson disease [16]. In view of the importance of 1,3-oxazine derivatives, several methods have previously been reported for the synthesis of these compounds [17-19]. The Mannich reaction involving phenols, formalin and primary amines has been used as a common method for the synthesis of 2,3-dihydro-1,3-naphthoxazines. Various catalysts such as KAl(SO₄)₂·12H₂O (alum) [20], ZrOCl₂ [21], 1-benzyl-3-methyl imidazolium hydrogen sulphate [bnmim][HSO₄] [22], polyethylene

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glycol (PEG) [23], thiamine hydrochloride (VB₁) [24] and Fe₃O₄@nano-cellulose/TiCl₄ [25] have been reported to catalyze this reaction.

In continuation of our research on synthesis and application of supported Lewis acids in organic synthesis, herein, we wish to report synthesis of nano-Fe₃O₄/TiCl₄/cellulose as a recyclable and biodegradable magnetic nanocatalyst and its application for the synthesis of 2,3-dihydro-2-substituted-1*H*-naphtho[1,2-*e*][1,3]oxazines.

MATERIALS AND METHODS

General Remarks

All compounds were purchased from Merck, Aldrich and Fluka chemical companies and used without any additional purification. FT-IR spectra were run on a Bruker, Equinox 55 spectrometer. A Bruker (DRX-400 Avance) NMR was used to record the ¹H NMR and ¹³C NMR spectra. Melting points were determined by a Buchi melting point B-540 B.V.CHI apparatus and were uncorrected.

Preparation of nano-Fe₃O₄/TiCl₄/cellulose. In a well-ventilated system, TiCl₄ (5 ml) was added drop wise to the mixture of nanocellulose (5 g) and CH₂Cl₂ (20 ml). The mixture was stirred for one hour at room temperature. The resulted suspension was filtered, washed with CH₂Cl₂ and the resulted nano-TiCl₄/cellulose dried at room temperature. Then, Fe₃O₄ nanoparticles (0.25 g) were dispersed in 20 ml CH₂Cl₂ under ultrasound irradiation. Then, 0.25 g of nano-TiCl₄/cellulose was slowly added with vigorous stirring at 40 °C for 1 h. The resulted magnetic nano-Fe₃O₄/TiCl₄/cellulose particles were isolated through filtering, washing with CH₂Cl₂ and drying at 50 °C.

General procedure for synthesis of 2,3-dihydro-2-substituted-1*H*-naphtho[1,2-*e*][1,3]oxazines. A mixture of 2-naphthol (1 mmol), formalin (2 mmol), amine (1 mmol) and nano-Fe₃O₄/TiCl₄/cellulose (0.04 g) was ground at room temperature. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was dissolved in ethanol (3 ml) and the catalyst was separated magnetically, washed with ethanol and used for subsequent cycles. Finally, cold water was added to the reaction mixture and the solid product was collected by

filtration.

Spectral Data Analysis for Compounds

2-Benzyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine (Table 3, IV_g) Off-white solid, m.p.: 125-127 °C. FT-IR (ATR) $\bar{\nu}$ (cm⁻¹): 1623, 1597, 1461, 1223, 1058, 738. ¹H NMR (DMSO-*d*₆, 400 MHz)/ δ ppm: 7.05-7.71 (m, 11H, Ar-H), 4.89 (s, 2H, O-CH₂-N), 4.22 (s, 2H, -Ar-CH₂-N), 3.89 (s, 2H, -Ar-CH₂-N). ¹³C NMR (DMSO-*d*₆, 400 MHz)/ δ ppm: 46.55, 55.17, 81.55, 111.67, 118.32, 121.15, 123.37, 126.57, 127.19, 127.76, 128.34, 128.39, 128.49, 128.59, 131.53, 138.33, 151.41.

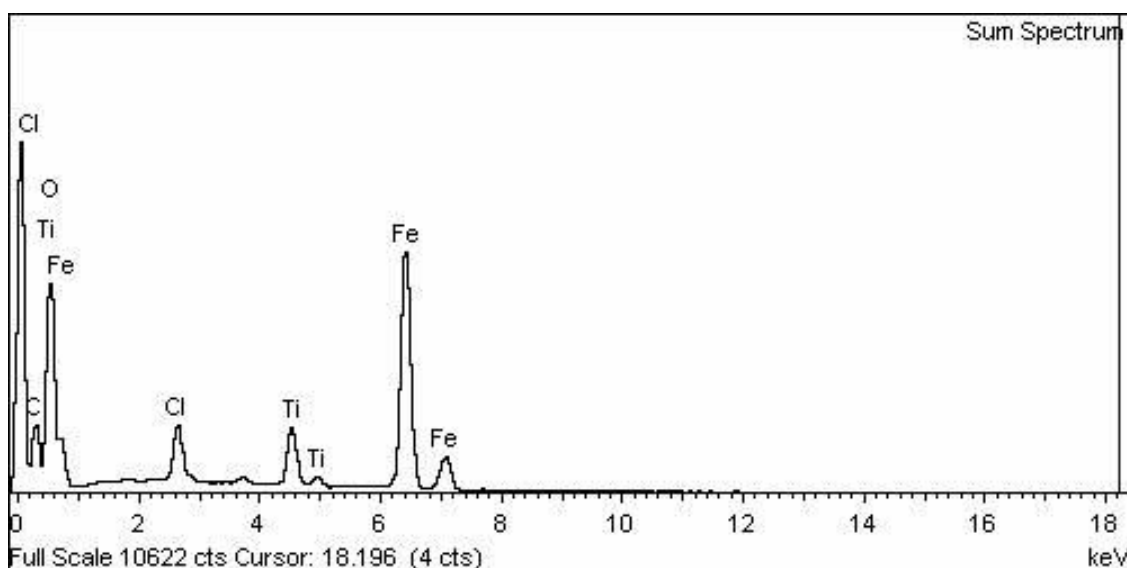
2-(Furan-2-ylmethyl)-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine (Table 3, IV_j) Pale-pink solid, m.p.: 98-100 °C. FT-IR (ATR) $\bar{\nu}$ (cm⁻¹): 1597, 1467, 1226, 1060. ¹H NMR (DMSO-*d*₆, 400 MHz)/ δ ppm: 7.71-8.02 (m, 4H, Ar-H), 7.36-7.61 (m, 2H, Ar-H), 7.04 (s, 1H, Ar-H), 6.32-6.52 (m, 2H, Ar-H), 4.89 (s, 2H, O-CH₂-N), 4.26 (s, 2H, -Ar-CH₂-N), 3.90 (s, 2H, furan-CH₂-N). ¹³C NMR (DMSO-*d*₆, 400 MHz)/ δ ppm: 46.37, 47.86, 81.22, 108.76, 110.42, 111.52, 118.27, 121.19, 123.43, 126.60, 127.80, 128.39, 128.50, 131.48, 142.70, 151.29, 151.79.

2-Butyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine (Table 3, IV_i) White solid, m.p.: 170 °C (d). FT-IR (ATR) $\bar{\nu}$ (cm⁻¹): 2954, 2864, 1597, 1433, 1225, 1056. ¹H NMR (DMSO-*d*₆, 400 MHz)/ δ ppm: 7.81 (m, 1H, Ar-H), 7.69 (m, 2H, Ar-H), 7.47 (m, 1H, Ar-H), 7.35 (m, 1H, Ar-H), 7.00 (m, 1H, Ar-H), 4.88 (s, 2H, O-CH₂-N), 4.25 (s, 2H, -Ar-CH₂-N), 2.69 (m, 2H, -CH₂-N), 1.53 (m, 2H, CH₂), 1.31 (m, 2H, CH₂), 0.87 (m, 3H, CH₃). ¹³C NMR (DMSO-*d*₆, 400 MHz)/ δ ppm: 13.80, 19.80, 29.64, 46.94, 50.84, 81.81, 112.08, 118.25, 121.31, 123.26, 126.45, 127.57, 128.32, 128.37, 131.54, 151.51.

2-Hexyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine (Table 3, IV_m) Brown solid, m.p.: 177 °C (d). FT-IR (ATR) $\bar{\nu}$ (cm⁻¹): 2927, 2854, 1597, 1467, 1225, 1057. ¹H NMR (DMSO-*d*₆, 400 MHz)/ δ ppm: 7.80 (m, 1H, Ar-H), 7.68 (m, 2H, Ar-H), 7.47 (m, 1H, Ar-H), 7.34 (m, 1H, Ar-H), 7.00 (m, 1H, Ar-H), 4.87 (s, 2H, O-CH₂-N), 4.25 (s, 2H, -Ar-CH₂-N), 2.68 (m, 2H, -CH₂-N), 1.53 (m, 2H, CH₂), 1.25 (m, 6H, 3CH₂), 0.84 (m, 3H, CH₃). ¹³C NMR (DMSO-*d*₆, 400 MHz)/ δ ppm: 14.77, 22.98, 27.23, 28.38, 32.02, 47.87, 52.09, 82.71, 112.97, 119.14, 122.18, 124.13, 127.32,

Table 1. XRF Analysis of Nano-Fe₃O₄/TiCl₂/cellulose

Sample	TiO ₂	NaCl	Catalyst	
KCPS	2318.4	516.5	149.8	58.1
	(TiO ₂)	(Cl)	(TiO ₂)	(Cl)
Amount of element (%)	60	60	3.9	6.75
	(Ti)	(Cl)	(Ti)	(Cl)

**Fig. 1.** EDS analysis diagram of nano-Fe₃O₄/TiCl₂/cellulose.

spectroscopy (EDS), Inductively Coupled Plasma Spectroscopy (ICP), vibrating sample magnetometry (VSM) and thermo-gravimetric analysis (TGA) [26].

As Ti(IV) is an active site in Fe₃O₄/TiCl₂/cellulose [27], Ti:Cl ratio was determined by XRF analysis. In order to obtain this ratio, Kilo Counts Per Seconds (KCPS) values of elements in catalyst were compared with KCPS values of the same elements in pure samples, NaCl and TiO₂. By this comparison, the ratio of Ti: Cl in catalyst is approximately 1:2 (Table 1).

Energy-dispersive X-ray spectroscopy (EDS) of nano-Fe₃O₄/TiCl₂/cellulose was also measured by EDS instrument (Fig. 1). According to this data, the weight

percentage of C, O, Cl, Ti and Fe is 21.2, 36.6, 2.44, 3.09 and 36.67, respectively.

According to the magnetization curve of nano-Fe₃O₄/TiCl₂/cellulose (Fig. 2), the most important feature of this catalyst is its super paramagnetic behavior. Saturation magnetization value of nano-Fe₃O₄/TiCl₂/cellulose (~30 emu g⁻¹) is lower than that of Fe₃O₄ (~50 emu g⁻¹). Even with this reduction in the saturation magnetization, the catalyst can still be efficiently separated from the reaction system by applying a magnetic field (as shown in the inset of Fig. 2).

In present study, the catalytic activity of nano-Fe₃O₄/TiCl₂/cellulose was investigated in the synthesis

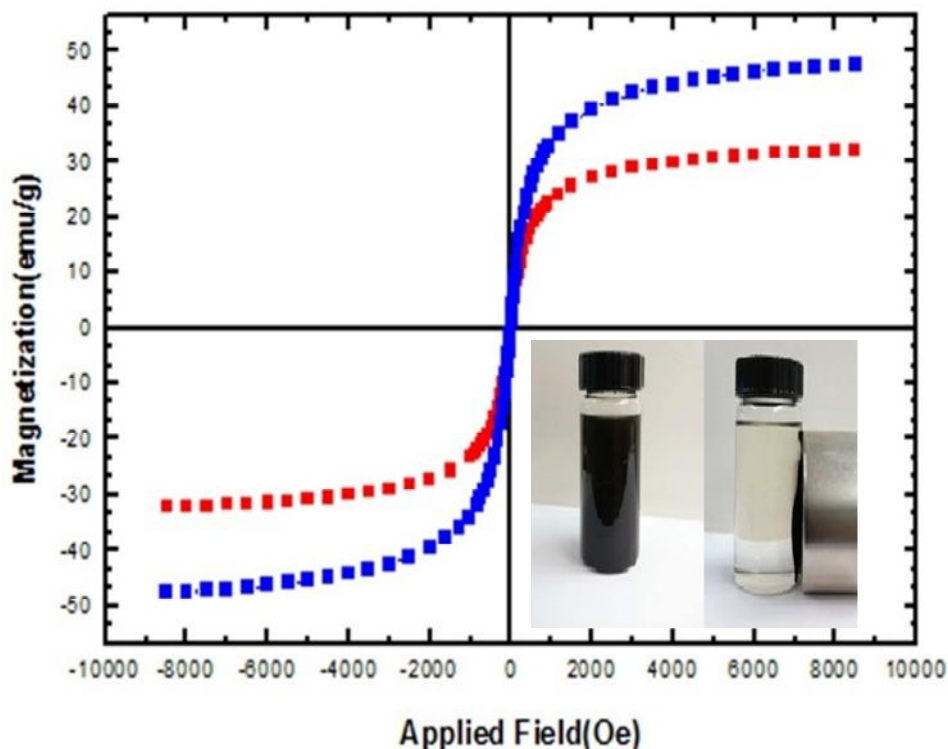


Fig. 2. Magnetization loops of (a) Fe₃O₄ (blue color) and (b) nano-Fe₃O₄/TiCl₂/cellulose (red color).

of 2,3-dihydro-2-substituted-1*H*-naphtho[1,2-*e*][1,3]oxazine derivatives. In order to obtain the optimal reaction conditions, initially, the reaction of 2-naphthol, formaldehyde and aniline was selected as model reaction. The effect of various parameters such as temperature, solvent and catalyst loading were screened on the model reaction. According to the experimental results as summarized in Table 2, the best reaction condition for this transformation is solvent-free grinding at room temperature using 0.04 g of the catalyst (Table 2, entry 12). In addition, low yield of the product in the blank reaction, without catalyst, approved the important role of the catalyst in this reaction (Table 2, entry 15).

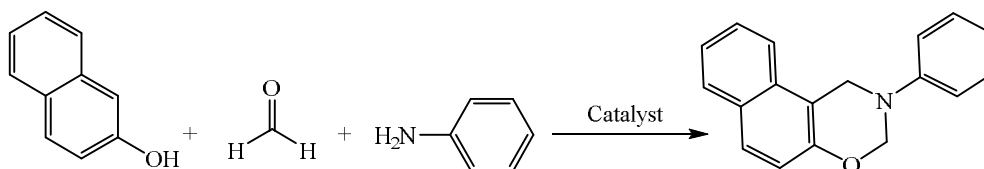
Reusability of the catalyst was also investigated on the model reaction. The heterogeneous nature of the catalyst allowed its facile recovery by an external magnet, washing with ethanol and drying at 80 °C to provide an opportunity for recycling experiments. Recycling experiments showed that nano-Fe₃O₄/TiCl₂/cellulose catalyst retained its activity for at least ten consecutive runs (Fig. 3). Meanwhile, FT-IR,

XRD, VSM spectra and ICP analysis of recovered catalyst were identical with the original catalyst spectra indicating no considerable leaching of catalyst in reaction medium.

Turn over number (TON) and turn over frequency (TOF) of the catalyst in model reaction were also calculated with respect to the total of product and the total number of moles of Ti in the catalyst. The TON and TOF calculated are 110.6×10^6 and $22.12 \times 10^6 \text{ min}^{-1}$, respectively. (The Ti content in the catalyst was measured by Inductively Coupled Plasma Spectroscopy (105 mg g^{-1}), since it is assumed that Ti is an accessible active site.)

Using the optimized reaction conditions (Table 2, entry 12), the scope and generality of the present method was explored by using a variety of aromatic and aliphatic amines to prepare a series of 2,3-dihydro-2-substituted-1*H*-naphtho[1,2-*e*][1,3]oxazines (Table 3). In most cases, the reactions proceeded cleanly and the desired products were obtained in good to excellent yields.

An important aspect of this reaction was the high purity of the products. All of the products were characterized by

Table 2. Reaction of 2-Naphthol, Formaldehyde and Aniline in the Presence of Nano-Fe₃O₄/TiCl₂/cellulose under Various Conditions^a

Entry	Solvent	Catalyst (g)	Condition	Time (min)	Yield (%) ^b
1	EtOH	^c Catalyst (0.06)	R. T	45	66
2	MeOH	^c Catalyst (0.06)	R. T	45	50
3	EtOH/MeOH (1:1)	^c Catalyst (0.06)	R. T	45	63
4	H ₂ O	^c Catalyst (0.06)	R. T	45	50
5	CHCl ₃	^c Catalyst (0.06)	R. T	45	40
6	CH ₃ CN	^c Catalyst (0.06)	R. T	45	45
7	-	^c Catalyst (0.06)	R. T (Grinding)	5	93
8	-	^c Catalyst (0.06)	50 °C	50	25
9	-	^c Catalyst (0.06)	60 °C	50	15
10	-	^c Catalyst (0.06)	80 °C	50	-
11	-	^c Catalyst (0.05)	R. T (Grinding)	5	95
12	-	^c Catalyst (0.04)	R. T (Grinding)	5	97
13	-	^c Catalyst (0.03)	R. T (Grinding)	5	92
14	-	^c Catalyst (0.02)	R. T (Grinding)	5	86
15	-	-	R. T (Grinding)	60	10

^aThe amount ratio of 2-naphthol (mmol), formaldehyde (mmol) and aniline (mmol) are equal to 1:2:1.

^bIsolated yield. ^cNano-Fe₃O₄/TiCl₂/cellulose.

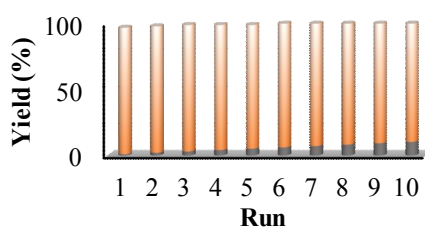
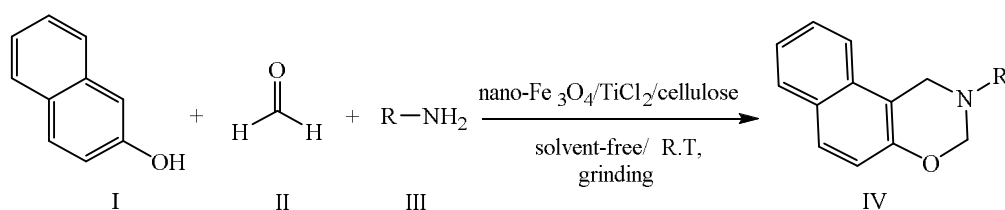
**Fig. 3.** Recycling experiment.

Table 3. Synthesis of 2,3-Dihydro-2-substituted-1*H*-naphtho[1,2-*e*][1,3]oxazine Derivatives (IV_{a-m}) in the Presence of Nano-Fe₃O₄/TiCl₂/cellulose under Solvent-free Condition at Room Temperature Grinding^a

Entry	R	Product	Time (min)	Yield (%) ^b	M.P. (°C) [Ref.]
1	Ph-	IV _a	5	97	46-48 [20]
2	4-Me-Ph-	IV _b	6	90	87-89 [20]
3	4-Et-Ph-	IV _c	6	90	43-46 [25]
4	4-Br-Ph-	IV _d	5	93	118-120 [20]
5	4-Cl-Ph-	IV _e	5	93	100-104 [25]
6	4-OMe-Ph-	IV _f	5	95	76-78 [20]
7	Ph-CH ₂ -	IV _g	6	88	125-127 [26]
8	2-Cl-C ₆ H ₄ -CH ₂ -	IV _h	7	84	70-75 [26]
9	Ph-CH ₂ -CH ₂ -	IV _i	5	93	232 (d) [25]
10	2-Furyl-CH ₂ -	IV _j	5	92	98-100 [25]
11	Cyclohexyl-	IV _k	8	90	248 (d) [25]
12	n-Butyl-	IV _l	8	93	170 (d) [25]
13	n-Hexyl-	IV _m	8	90	177 (d) [25]

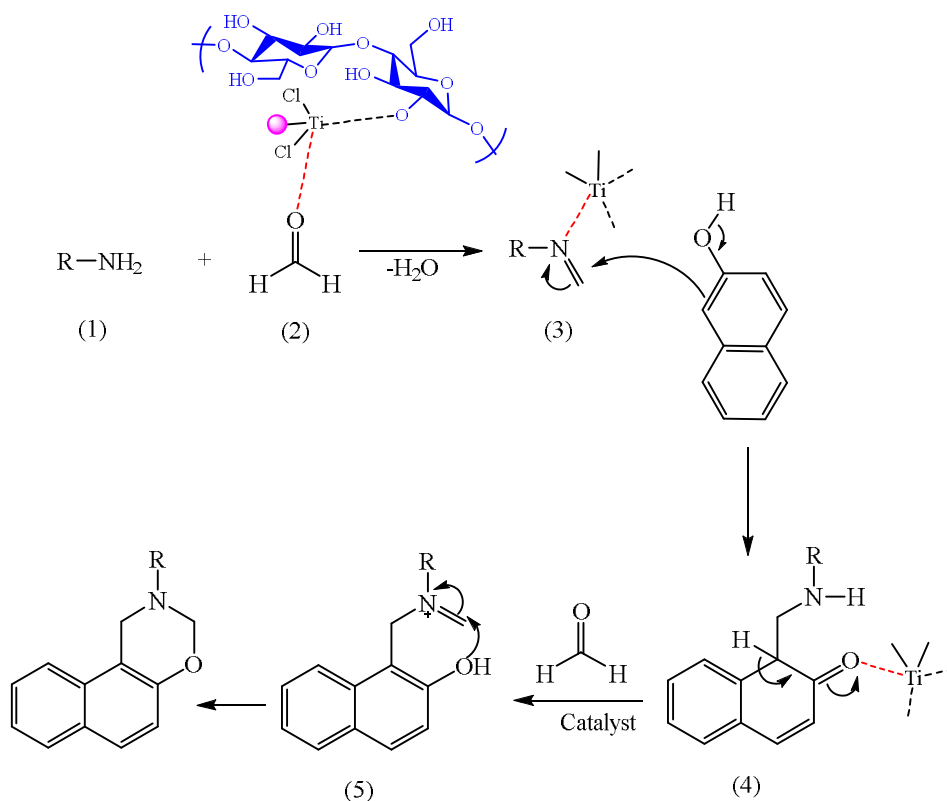
^aI (mmol): II (mmol): III (mmol): nano-Fe₃O₄/TiCl₂/cellulose (g) is equal to 1:2:1:0.04. ^bIsolated yield. d = decompose.

¹H NMR, ¹³C NMR and IR spectroscopy. The ¹H NMR spectra of compounds IV_{a-m} showed two singlet peaks in the region of 4.22-5.06 ppm and 4.87-5.54 ppm, which are due to protons of -Ar-CH₂-N- and -O-CH₂-N- of oxazine ring, respectively.

Suggested mechanism for the synthesis of 2,3-dihydro-2-substituted-1*H*-naphtho[1,2-*e*][1,3]oxazines catalyzed by nano-Fe₃O₄/TiCl₂/cellulose has been shown in Scheme 2

[28]. Ti(IV) in nano-Fe₃O₄/TiCl₂/cellulose operates as a Lewis acid and first activates carbonyl functional group in aldehyde.

Mannich-type condensation of amine with formaldehyde gives imine 3 which was then attacked by the electron-rich centre of 2-naphthol to form intermediate 4. Intermediate 4 activated by Ti(IV), *via* a second Mannich-type condensation with a second molecule of formaldehyde,



Scheme 2. Plausible mechanism for the synthesis of 2,3-dihydro-2-substituted-1H-naphtho[1,2-e][1,3]oxazines catalyzed by nano-Fe₃O₄/TiCl₂/cellulose

gives intermediate 5 which through intramolecular cyclization afforded 1,3-oxazine derivatives.

CONCLUSIONS

In summary, we have developed a simple, clean and highly efficient procedure for the synthesis of 2,3-dihydro-2-substituted-1H-naphtho[1,2-e][1,3]oxazines using nano-Fe₃O₄/TiCl₂/cellulose as a bio-based magnetic nanocatalyst in a green media. Short reaction times, high yields, green reaction conditions, easy work-up procedure, product purity, magnetic separation and reusability of nanocatalyst are among the advantages of this protocol.

ACKNOWLEDGEMENTS

The Research Council of Yazd University gratefully

acknowledged for the financial support for this work.

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