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Synthesis of Isoxazol-5-One Derivatives Catalyzed by Amine-Functionalized Cellulose

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Abstract: In this contribution, the propylamine-functionalized cellulose (Cell-Pr-NH_2) was employed as the catalyst in the three-component reaction between hydroxylamine hydrochloride, various type of aryl/heteroaryl aldehydes, ethyl acetoacetate/ethyl 4-chloroacetoacetate/ or ethyl 3-oxohexanoate. The results of these experiments were the formation of 3,4-disubstituted isoxazol-5(4*H*)-one heterocycles. The desired five-membered heterocyclic compounds were obtained in good to high yields at room temperature. The investigation of different solvents led us to the conclusion that water is the best solvent to perform the current one-pot, three-component reactions. Attempts to find the optimum catalyst loading clearly showed that 14 mg of Cell-Pr-NH_2 seems to be sufficient to carry out the reactions. This method has highlighted some principles of green chemistry including less waste generation, atom economy, use of water as an environmentally friendly solvent, and energy saving. Purification without chromatographic methods, mild reaction conditions, simple work-up, low-cost reaction medium, saving time, and obtainable precursors are other notable features of this one-pot fashion.

Keywords: Isoxazol-5(4*H*)-ones; propylamine-functionalized cellulose; β-keto ester; water

1. Introduction

Isoxazoles, as one of the most important five-membered *N,O*-containing heterocyclic compounds, display numerous pharmacological activities including anti-inflammatory, anti-obesity, antibacterial, anticonvulsant, antirheumatic, antifungal, antitumor, anti-mycobacterial, and antiviral [1]. Among the heterocyclic rings available in drugs, isoxazole ranks 33 [2], and among the drugs available in the market that have this attractive heterocyclic ring, we can mention oxacillin, cloxacillin, sulfisoxazole, sulfamethoxazole, isocarboxazid, leflunomide, valdecoxib, and dicloxacillin [3–5]. The arylideneisoxazol-5(4*H*)-one is present in vast variety of bioactive compounds, agrochemicals, and nonlinear optical (NLO) materials [6]. Additionally, these heterocycles act as promising drug candidates for anti-ulcer [7], anti-obesity [8], antioxidant [9], anti-Alzheimer [10], antimicrobial [11], anticancer [12], antifungal [13], antitubercular [13,14], enzyme inhibitor [15], larvicidal [16], antibacterial [17], and fungicide [18] applications (Figure 1). Furthermore, arylidenesoxazol-5-ones have been used as flexible building blocks for the synthesis of various heterocycles [19], alkynes [20], β-amido-*N*-allylated products [21], γ-functionalized ketones [22], and other functionalized molecules [23]. Because of the auspicious biological activities of the arylideneisoxazol-5(4*H*)-one and their technical applications, developing efficient and green procedures to synthesizing these heterocycles remains attractive to organic and medicinal chemists. In recent years, various catalysts have been reported for their synthesis, some of which include sodium acetate using 150 W halogen lamp in EtOH/H_2O [16], 2-aminopyridine [24], lipase [25], Stiglich's base [26], sodium acetate in EtOH [27], sodium malonate [28], guanidine hydrochloride [29], sodium acetate in EtOH under visible light [30], *N*-bromosuccinimide (NBS) [31], citrazinic acid [32], 2,2'-bipyridine]-1,1'-diium perchlorate [33], potassium hydrogen phthalate [34], piperazine [35], potassium phthalimide [36], salicylic acid [37], sulfanilic acid [38], hydantoin potassium salt [39], sodium cyclamate [40], NHC-precursor [41], malic acid [42], triphenylphosphine (TPP) [43], glycine [44], L-valine [45], boric acid [46], nickel(II) acetate [47], potassium iodide (KI) [48], 2-hydroxy-5-sulfobenzoic acid [49], succinic acid [50], eucalyptol [51], urea [52], vitamin B_1 [53], nano-SiO_2-H_2SO_4 [54], deep eutectic solvents (DESs) [55], nano-ZnO [56], nano-MgO [57], nano-SiO_2 [58], sodium benzoate using ultrasound 59], potassium bromide (KBr) under microwave irradiation [60], gluconic acid aqueous solution (50 wt % GAAS) [61], magnetic nanocomposite [62], sodium sulfide [63], pyridinium *p*-toluenesulfonate (PPTS) [64], fruit extracts [65], and NaCl [66]

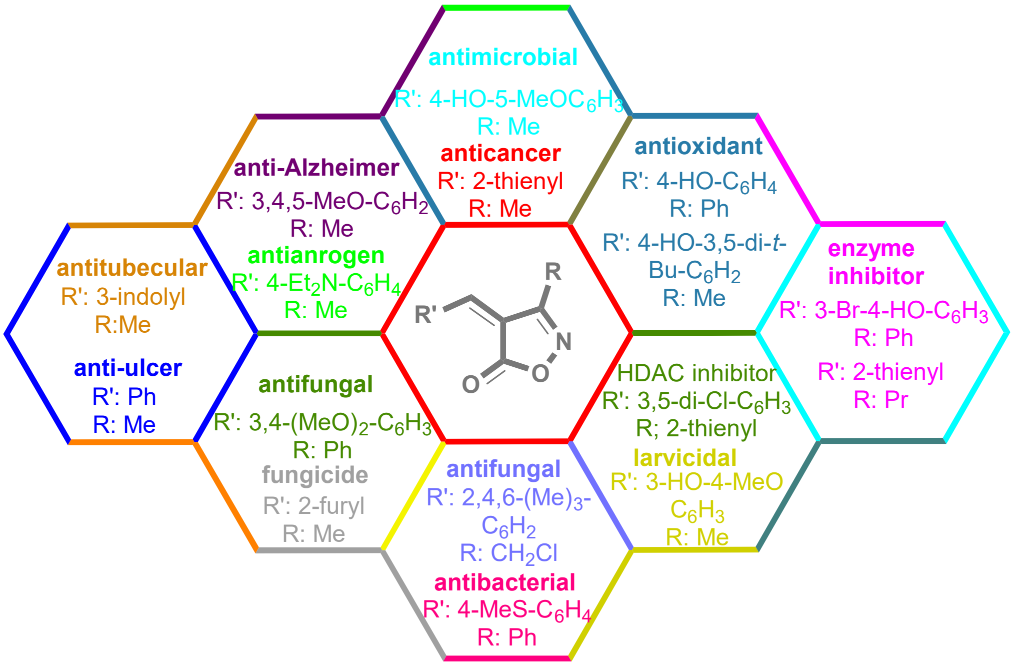
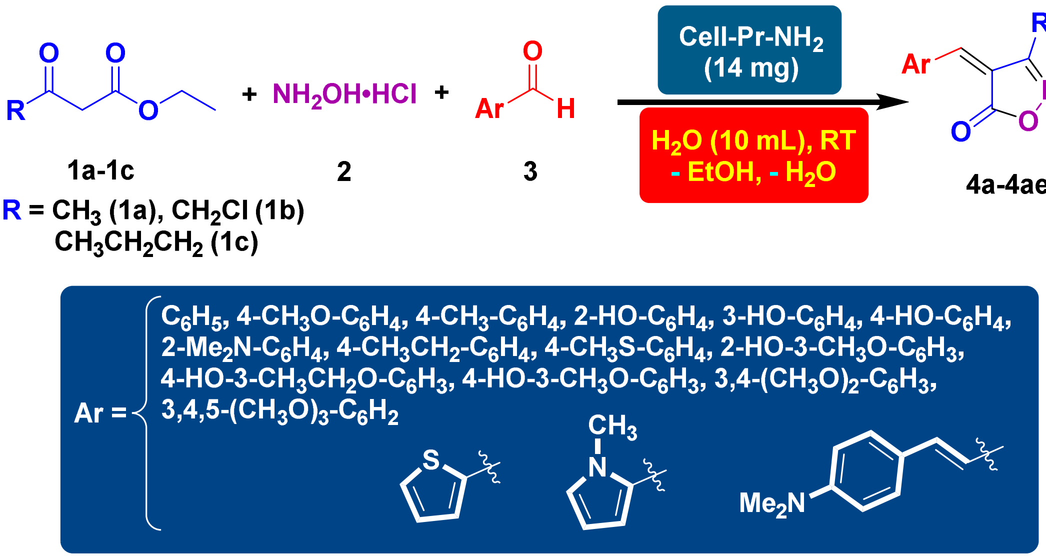


Figure 1. Representative some synthetically bioactive heterocycles with isoxazol-5(4*H*)-one skeleton.

On the other hand, multicomponent reactions (MCRs) are among the most extensive and diverse chemical transformations in organic synthesis and medicinal chemistry, which enable the rapid synthesis of various heterocyclic compounds from at least three starting materials [67]. The majority of the atoms from starting materials are incorporated into final products [68]. Due to the economic cost issue, high efficiency, mild conditions, atom-, step, and pot-economy, as well as following principles of green chemistry, MCRs can be considered as significant, environmentally friendly, cost-effectiveness, and the most successful processes in organic synthesis [69].

Cellulose-derived materials are used in numerous fields such as biology, medicine, tissue engineering, ultraviolet (UV) protection, and artificial blood vessels due to wide availability, biodegradability, biocompatibility, and inexpensiveness [70]. Nano-cellulose-grafted amines are also used in catalytic organic transformations [71]. Based on the above considerations, finding a sustainable and environmentally friendly catalyst for the synthesis of heterocycles is desirable for synthetic chemistry scholars, not only from the synthetic point of view but also for observing aspects of green chemistry principles. For this purpose, we tried to use a useful and efficient catalyst for the synthesis of isoxazol-5(4*H*)-one derivatives (Scheme 1).



Scheme 1. Synthesis of isoxazol-5(4*H*)-ones (**4a-4ae**) using Cell-Pr-NH_2 (**C**) as the catalyst.

2. Materials and Methods

The mixture of β-keto esters (**1a-1c**, 1 mmol), hydroxylamine hydrochloride (**2**, 1 mmol), aldehyde derivatives (**3**, 1 mmol), and catalytic amount of Cell-Pr-NH_2 (**C**, 14 mg) in water (10 mL) were stirred at room temperature. After the completion of the reaction, monitored through TLC analysis, the precipitates formed were filtered off, washed with ethanol (3 × 10 mL), and air-dried to provide the heterocyclic products (**4a-4ae**).

4-(3-Hydroxybenzylidene)-3-methylisoxazol-5(4H)-one (4e) ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H, CH_3), 7.08 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.39 (t, 1H, *J* = 8.0 Hz, Ar-H), 7.79 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.85 (s, 1H, H-vinyl), 7.95 (s, 1H, Ar-H), 9.96 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.7 (H-vinyl), 118.9, 119.9, 121.8, 125.8, 130.2, 134.1, 152.3, 157.8, 162.6 (C=N), 168.2 (C=O).

3-Methyl-4-(4-(methylthio)benzylidene)isoxazol-5(4H)-one (4i) ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.30 (s, 3H, CH_3), 2.55 (s, 3H, SCH_3), 7.30 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.33 (s, 1H, H-vinyl), 8.32 (d, *J* = 8.6 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.6 (CH_3), 14.5 (SCH_3), 125.1, 125.3, 128.8, 134.2, 148.6, 148.9, 161.1 (C=N), 167.9 (C=O).

4-(2-Hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4H)-one (4j) ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.24 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.89 (t, *J* = 8.1 Hz, 1H, Ar-H), 7.26 (dd, *J* = 1.2, 8.1 Hz, 1H, Ar-H), 8.11 (s, 1H, H-vinyl), 8.32 (dd, *J* = 1.2, 8.4 Hz, Ar-H), 10.34 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.5 (CH_3), 58.4 (OCH_3), 116.8, 118.6, 119.8, 139.3, 145.0, 147.6, 149.5, 152.9, 162.2 (C=N, 176.1 (C=O).

4-(3-Ethoxy-4-hydroxybenzylidene)-3-methylisoxazol-5(4H)-one (4k) ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.41 (t, *J* = 6.9 Hz, 3H, $\underline{CH_3}CH_2$), 2.27 (s, 3H, CH_3), 4.14 (q, *J* = 6.9 Hz, 2H, CH_2O), 6.99 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.80 (s, 1H, H-vinyl), 7.90 (dd, *J* = 2.1, 8.4 Hz, 1H, Ar-H), 8.54 (d, *J* = 2.1 Hz, 1H, Ar-H), 10.72 (s, 1H, OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 11.8 (CH_3), 15.1 ($\underline{CH_3}CH_2$), 64.3 (CH_2O), 114.1, 116.3, 118.1, 125.5, 132.0, 147.1, 152.4, 154.5, 162.8 (C=N), 169.5 (C=O).

4-(4-Hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4H)-one (4l)

^{1}H NMR (500 MHz, DMSO-d_6): δ 2.28 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 6.98 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.90 (s, 1H, H-vinyl), 7.93 (dd, *J* = 1.8, 8.4 Hz, 1H, Ar-H), 8.56 (d, *J* = 1.8 Hz, 1H, Ar-H), 10.81 (s, 1H, OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 11.9 (CH_3), 55.8 (OCH_3), 114.1, 116.2, 117.3, 125.6, 132.2, 148.1, 152.3, 154.4, 162.9 (C=N), 169.6 (C=O).

4-(3,4-Dimethoxybenzylidene)-3-methylisoxazol-5(4H)-one (4m) ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.29 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 7.22 (d, *J* = 9.0 Hz, 1H, Ar-H), 7.87 (s, 1H, Ar-H), 8.03 (d, *J* = 9.0 Hz, 1H, Ar-H), 8.51 (s, 1H, H-vinyl); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.8 (CH_3), 55.9 (OCH_3), 56.5 (OCH_3), 112.1, 115.5, 116.1, 126.5, 131.5, 148.8, 152.2, 154.8, 162.8 (C=N), 169.3 (C=O).

3-Methyl-4-(3,4,5-trimethoxybenzylidene)isoxazol-5-(4H)-one (4n) ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.30 (s, 3H, CH_3), 3.96 (s, 6H, OCH_3), 3.99 (s, 3H, OCH_3), 7.32 (s, 1H, H-vinyl), 7.84 (s, 2H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.8 (CH_3), 56.6 (OCH_3), 60.8 (OCH_3), 112.4, 117.5, 128.5, 143.5, 152.3, 152.8, 162.6 (C=N), 168.8 (C=O).

3-Methyl-4-(thiophen-2-ylmethylene)isoxazol-5(4H)-one (4o) ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.29 (s, 3H, CH_3), 7.39-7.42 (m, 1H, Ar-H), 8.24 (d, J = 3.0 Hz, 1H, Ar-H), 8.27 (s, 1H, H-vinyl), 8.34 (d, J = 6.0 Hz, 1H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.6 (CH_3), 113.5, 129.5, 136.7, 141.6, 142.1, 143.5, 162.1 (C=N), 169.0 (C=O).

3-Methyl-4-((1-methyl-1H-pyrrol-2-yl)methylene)isoxazol-5(4H)-one (4p) ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.26 (s, 3H, CH_3), 3.84 (s, 3H, N-CH_3), 6.41 (dd, J = 2.3, 4.5 Hz, 1H, Ar-H), 7.13 (t, J = 2.0 Hz, 1H, Ar-H), 7.16 (s, 1H, H-vinyl), 8.56 (dd, J = 1.5, 4.5 Hz, 1H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO-d_6): δ 11.1 (CH_3), 34.2 (N-CH_3), 112.2, 126.0, 129.2, 131.6, 134.9, 160.9 (C=N), 169.2 (C=O).

3-(Chloromethyl)-4-(4-(dimethylamino)benzylidene)isoxazol-5(4H)-one (4v) ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.22 (s, 6H, $N(CH_3)_2$), 4.54 (s, 2H, CH_2Cl), 6.78 (d, J = 8.6 Hz, 2H, Ar-H), 7.55 (s, 1H, H-vinyl), 8.47 (d, J = 7.2 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.6 ($N(CH_3)_2$), 40.4 (CH_2Cl), 111.8, 121.6, 125.5, 138.4, 150.5, 154.7, 160.8 (C=N), 169.7 (C=O).

3-(Chloromethyl)-4-(2-hydroxy-3-methoxybenzylidene)isoxazol-5(4H)-one (4w) ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.85 (s, 3H, OCH_3), 4.88 (s, 2H, CH_2Cl), 6.87 (t, J = 8.1 Hz, 1H, Ar-H), 7.26 (d, J = 8.1 Hz, 1H, Ar-H), 8.34 (d, J = 8.2 Hz, 1H, Ar-H), 8.42 (s, 1H, H-vinyl), 10.45 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.4 (CH_2Cl), 56.3 (OCH_3), 113.3, 118.2, 118.7, 119.6, 123.4, 146.6, 147.8, 149.8, 161.4 (C=N), 167.5 (C=O).

3-(Chloromethyl)-4-((1-methyl-1H-pyrrol-2-yl)methylene)isoxazol-5(4H)-one (4aa) ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.92 (s, 3H, N-CH_3), 4.94 (s. 2H, CH_2Cl), 6.53-6.54 (m, 1H, Ar-H), 7.72 (t, J = 1.6 Hz, 1H, Ar-H), 7.78 (s, 1H, H-vinyl), 8.44 (dd, J = 1.6, 4.5 Hz, 1H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 34.8 (N-CH_3), 35.9 (CH_2Cl), 103.2, 113.7, 127.0, 130.1, 134.8, 138.5, 161.8 (C=N), 169.6 (C=O).

3-(Chloromethyl)-4-(3-(4(dimethylamino)phenyl)allylidene)isoxazol-5(4H)-one (4ab) ^{1}H NMR (500MHz, $CDCl_3$): δ 3.11 (s, 6H, $N(CH_3)_2$), 4.49 (s, 2H, CH_2Cl), 6.69 (d, J = 8.6 Hz, 2H, Ar-H), 7.34 (d, J = 3.5, 6.9 Hz, 1H, =CH), 7.55 (dd, J = 3.5, 6.7 Hz, 1H, =CH), 7.61 (d, J = 8.6 Hz, 2H, Ar-H), 8.90 (m, 1H, =CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 35.5 (CH_2Cl), 40.1 ($N(CH_3)_2$), 112.0, 118.1, 123.1, 132.3, 150.4, 153.3, 155.4, 159.2, 164.1 (C=N), 169.0 (C=O).

4-(4-(Methylthio)benzylidene)-3-propylisoxazol-5(4H)-one (4ac) ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01 (t, J = 7.2 Hz, 3H, $\underline{CH_3}CH_2CH_2$), 1.81 (sex, J = 7.5 Hz, 2H, $CH_3\underline{CH_2}CH_2$), 2.59 (s, 3H, SCH_3), 2.68 (t, J = 7.5 Hz, 2H, $CH_3CH_2\underline{CH_2}$), 7.45 (d, J = 8.7 Hz, 2H, Ar-H), 7.92 (s. 1H, H-vinyl), 8.42 (d, J = 8.7 Hz, 1H, Ar-H); ^{13}C NMR (125 MHz,$CDCl_3$): δ 13.9 ($\underline{CH_3}CH_2CH_2$), 14.5 (SCH_3), 19.8 ($CH_3CH_2\underline{CH_2}$), 27.6 ($CH_3CH_2\underline{CH_2}$), 112.2, 114.9, 116.2, 126.4, 131.4, 148.7, 166.3 (C=N), 169.1 (C=O).

(4-(Dimethylamino)phenyl)allylidene)-3-propylisoxazol-5(4H)-one (4ad) ^{1}H NMR(500 MHz, $CDCl_3$): δ 1.04 (t, J = 7.5 Hz, 3H, $\underline{CH_3}CH_2CH_2$), 1.74 (sex, J = 7.3 Hz, 2H, $CH_3\underline{CH_2}CH_2$), 2.55 (t, J = 7.3 Hz, 2H, $CH_3CH_2\underline{CH_2}$), 3.11 (s, 6H, $N(CH_3)_2$), 6.68 (d, J = 8.9 Hz, 2H, Ar-H), 7.22-7.27 (m, 1H, =CH), 7.46-7.51 (m, 1H, =CH), 7.56 (d, J = 8.9 Hz, 2H, Ar-H), 8.09-8.15 (m, 1H, =CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9 ($\underline{CH_3}CH_2CH_2$), 20.2 ($CH_3\underline{CH_2}CH_2$), 27.9 ($CH_3CH_2\underline{CH_2}$), 40.1 ($N(CH_3)_2$), 111.9, 118.2, 123.2, 131.2, 131.7, 148.5, 152.8, 153.3, 163.0 (C=N), 170.5 (C=O).

4-((1-Methyl-1H-pyrrol-2-yl)methylene)-3-propylisoxazol-5(4H)-one (4ae) ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.98 (t, J =7.2 Hz, 3H, $\underline{CH_3}CH_2CH_2$), 1.68 (sex, J = 7.4, 2H, $CH_3\underline{CH_2}CH_2$), 2.67 (t, J = 7.3, 2H, $CH_3CH_2\underline{CH_2}$), 3.91 (s, 3H, N-CH_3), 6.45 (dd, J = 1.6, 2.4 Hz, 1H, Ar-H), 7.51 (s, 1H, H-vinyl), 7.58 (t, J = 1.7 Hz, 1H, Ar-H), 8.38 (dd, J = 1.6 Hz, 1H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.2 ($\underline{CH_3}CH_2CH_2$), 19.9 ($CH_3\underline{CH_2}CH_2$), 27.4 ($CH_3CH_2\underline{CH_2}$), 34.7 (N-CH_3), 106.5, 112.7, 125.8, 129.7, 133.7, 164.8 (C=N), 170.0 (C=N).

3. Results and Discussion

This The propylamine-functionalized cellulose (Cell-Pr-NH_2, **C**) was synthesized based on the literature [71]. Briefly, microcrystalline cellulose (**A**, 10 g) and $AlCl_3{\cdot}6H_2O$ (10 g) in water (100 mL)

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was stirred at RT for 12 h. The mixture was the filtered, the residue was exposed to ammonia, washed with water, and dried in vacuum to produce the Cell-alumina (Cell-Al_2O_3) composite (**B**). Cell-Al_2O_3 composite (**B,** 10.0 g) and (3-aminopropyl)- trimethoxysilane (6.98 mL, 40.0 mmol) were mixed at refluxing toluene for 24 h. After cooling, the mixture was filtered off and washed with toluene. Finally, drying at RT in vacuum led to the formation of the Cell-Pr-NH_2 (**C**) (Figure 2). The X-ray diffraction (XRD) pattern of the Cell-Pr-NH_2 (**C**) is shown in Figure 3. The three peaks at 2θ = 15.5º, 22.5º and 34.5º, which are related to crystallographic planes (101), (002), and (040) are due to microcrystalline cellulose [72]. These peaks are also observed in the XRD pattern of other cellulose source containing NH_2 functional group [73]. Other peaks at 2θ = 16.7º and 21.5º can be attributed to other parts of the catalyst (probably, incorporation of amino groups on the cellulose surface.) (Figure 3). Of course, the peak located at 2θ = 16.4º is also found in microcrystalline cellulose [75].

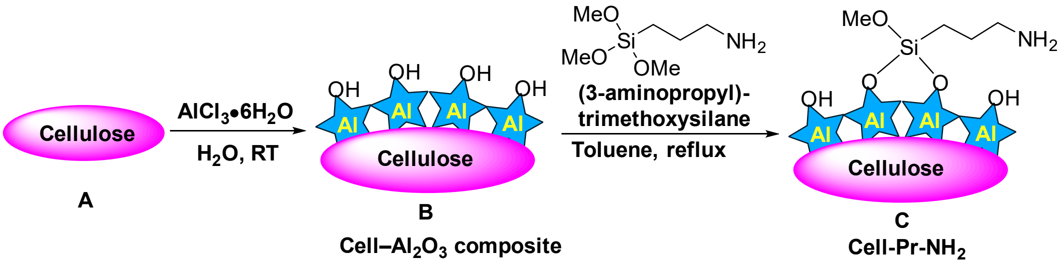


Figure 2. Preparation of cellulose propylamine (Cell-Pr-NH_2) (**C**).

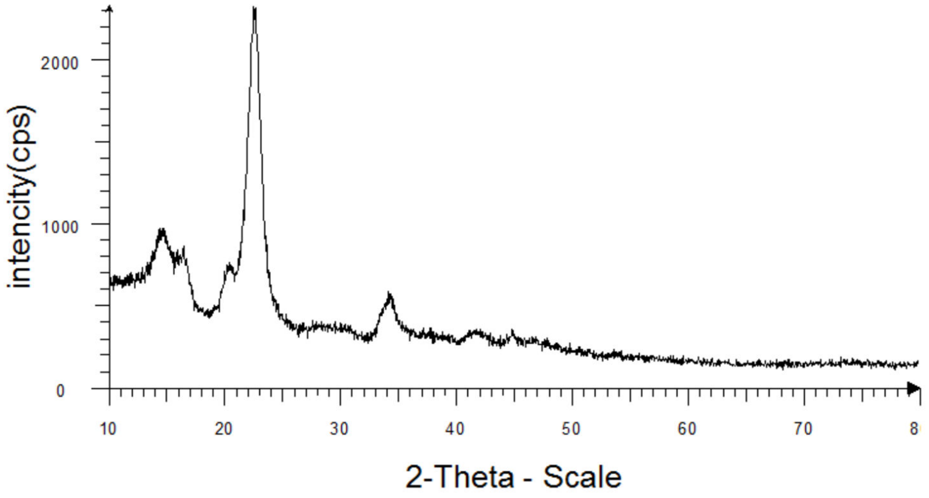


Figure 3. XRD pattern of aminopropyl cellulose Cell-Pr-NH_2 (**C**).

The field emission scanning electron microscopy image (FE-SEM) indicates the rough structure of cellulose and the presence of new parts. In parts of the micrographs, nano-sized spots can be seen (Figure 4, left), which size is approximately 28 to 36 nm.

The one-pot, three-component reaction of ethyl acetoacetate (**1a**), hydroxylamine hydrochloride (**2**), and vanillin was first designated for investigation with the aim of achieve the best conditions for carrying out the reaction. The experimental results of these studies are listed in Table 1. When the reaction was carried out without a catalyst in water at room temperature (RT), a yellow solid product was obtained after 40 min with a yield of 50% (Table 1, Entry 1). Continuation of the reaction did not change the efficiency appreciably. After purification, measuring the melting point (214-216 ºC; Lit.[52] 215-217 ºC), and recording the ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra, it was determined that the compound formed is the expected heterocycle, *i.e.*, 4-(4-hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (**4l**). The ^1H NMR spectrum of this compound exhibited the peaks of CH_3, OCH_3, H-vinyl, OH as four characteristic singlet signals at δ 2.28, 3.89, 7.90, and 10.81 ppm, respectively. Furthermore, two doublet peaks at δ 6.98 (*J* = 8.4 Hz) and 8.56 ppm, as well as a doublet of doublets peak at δ 7.93 ppm were assigned to three protons of benzene ring. The ^{1}H NMR decoupled spectrum of **4l** showed 12 distinct signals in agreement with the desired product. The characteristic signals of CH_3, OCH_3, C=N, and C=O carbons were observed at δ 11.9, 55.8, 162.9, and 169.6 ppm, respectively. Six carbons of the benzene ring, one carbon of the vinyl group, and the 4-position of the isoxazolone ring appeared in the expected regions (114.1-154.4 ppm). After observing this favorable result, we decided to continue the experiments in order to find the best reaction conditions. In this context, important parameters such as the amount of catalyst, the type of solvent, and reaction temperature were investigated. The reactions were performed under aqueous conditions at RT. Various amounts of cell-Pr-NH_2 (**C**) as the catalyst (2-14 mg) were loaded into the reaction mixture in water solvent. It was found that using 14 mg of cell-Pr-NH_2 (**C**) led to the best results in terms of reaction time (25 min) and isolated reaction yield (97%) (Table 1, Entry 8). Due to this excellent result, other catalyst loading values were not checked and 14 mg of cell-Pr-NH_2 (**C**) as the catalyst was used to check other parameters. After testing various catalyst loading in water at RT, some solvents available in our laboratory were investigated. Solvents including ethanol (EtOH), acetone (CH_3COCH_3), chloroform ($CHCl_3$), dimethylformamide (DMF), *n*-hexane, and a mixture of EtOH-H_2O (1:1, *v*: *v*) were screened at room temperature (Table 1, Entries 9-14). It was observed that these solvents did not have a significant and acceptable effect on the reaction times or yields. In some solvents such as $CHCl_3$ and DMF, small amount of the product **4l** was seen (checked with the help of TLC analysis) and the reactants remained almost intact (Table 1, Entries 11 and 12). When the reaction was carried out in the solvent-free conditions and using the optimal amount of catalyst at RT, no favorable results were obtained (Table 1, Entry 15). The search for checking the temperature parameter led us to explore other temperatures in addition to the room temperature. The reaction was investigated at different temperatures in water solvent and using the optimal amount of the catalyst. Two results are given in the optimization table (Table 1, Entries 16 and 17). No significant results were obtained in all these studies. With all this controversy, it can be concluded that the best conditions for carrying out the reaction are water as a solvent for reaction, 14 mg of cell-Pr-NH_2 (**C**) as the catalyst, and RT (Table 1, Entry 8).

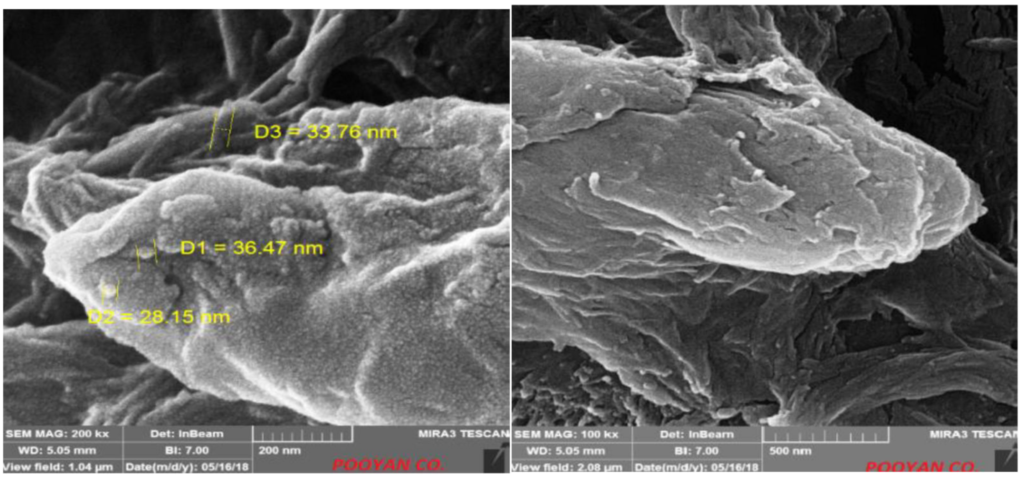
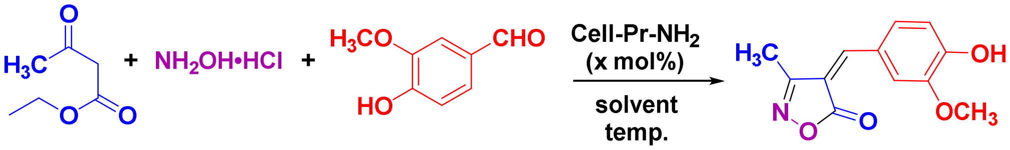


Figure 4. Field emission scanning electron microscopy (FESEM) micrographs of Cell-Pr-NH_2 (**C**).

After optimizing the reaction conditions, the substrate scope of the reaction was explored using ethyl acetoacetate (**1a**), hydroxylamine hydrochloride (**2**), and substituted benzaldehydes. Consequently, using 14 mg of cell-Pr-NH_2 (**C**) in H_2O at RT, the reaction between ethyl acetoacetate (**1a**), hydroxylamine hydrochloride (**2**), benzaldehyde/or structurally diverse substituted benzaldehydes produced a broad spectrum of arylideneisoxzol-5(4*H*)-ones (**4a**-**4n**). The results indicate that aryl aldehydes with the electron-donating groups participate better in this three-component reaction and produce the corresponding heterocyclic products in good to excellent yields (Table 2, Entries 1-14). When heteroaryl aldehydes such as thiophene-2-carboxaldehyde and *N*-methyl-2-

pyrrolecarboxaldehyde were used, the cyclocondensation reaction proceeded well and the corresponding products (**4o** and **4p**) were obtained in high isolated yields and reasonable reaction times (Table 2, Entries 15 and 16). In addition, the scope of the substrate was further explored. In this context, ethyl 4-chloroacetoacetate (**1b**) was employed instead of ethyl acetoacetate (**1a**). A good result was obtained when benzaldehyde was used as precursor (Table 2, Entry 17). When the substituted benzaldehydes containing electron-donating functional groups including, OCH_3, CH_3, $N(CH_3)_2$, and OH in different positions at the aryl ring were used in this three-component catalytic reaction, the processes proceeded well and the corresponding 3-chloromethyl substituted isoxazole-5(4*H*)-ones (**4r**-**4y**) were obtained in good to excellent yields and in satisfactory reaction times (Table 2, Entries 18-25). We also tested two five-membered heteroaryl aldehydes, thiophene-2-carbaldehyde and 1-methyl-1*H*-pyrrole-2-carbaldehyde, in reaction with ethyl 4-chloroacetoacetate (**1b**) and hydroxylamine hydrochloride (**2**). Fortunately, the two desired heterocyclic products (**4z** and **4aa**) were synthesized with excellent isolated reaction yields (Table 2, Entries 26 and 27). Under the optimized reaction conditions as described in Table 1, Entry 8, the use of the α,β-unsaturated aldehyde containing a phenyl ring (4-(dimethylamino)cinnamaldehyde) was also fruitful and the desired heterocyclic product (**4ab**) was formed in excellent isolated yield of reaction and short reaction time (Table 2, Entry 28). Moreover, under optimal conditions, the attempt to use ethyl 3-oxohexanoate (**1c**) as a β-keto ester precursor was fruitful. In this regard, three heterocycles **4ac**-**4ae** were successfully synthesized and the target compounds were isolated with satisfactory yields along with rational reaction times (Table 2, Entries 29-31).

Table 1. Optimization of the reaction conditions.



1a (1 mmol) **2** (1 mmol) **vanillin** (1 mmol) **4l**

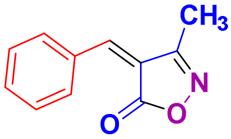
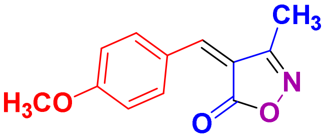
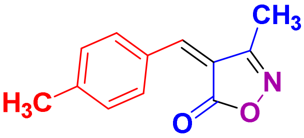
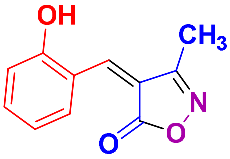
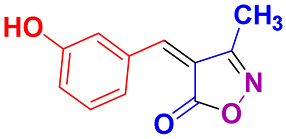
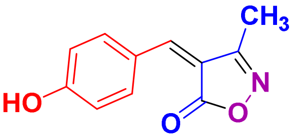
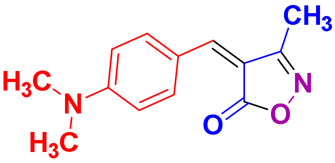
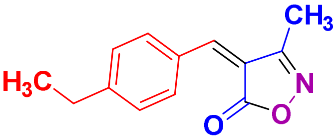
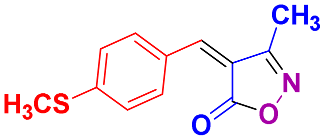
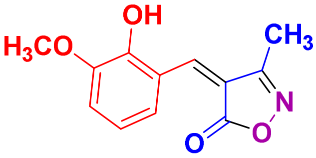
4-(4-Hydroxy-3-methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (4l)

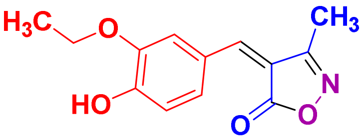
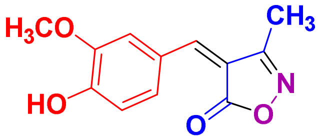
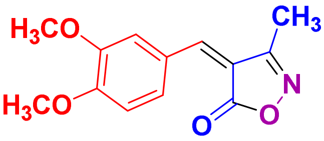
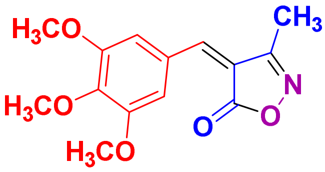
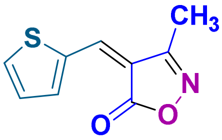
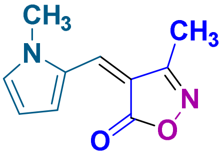
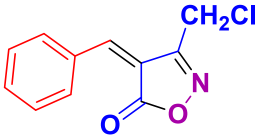
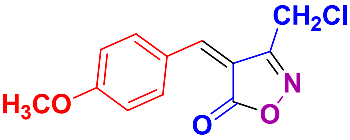
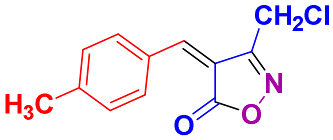
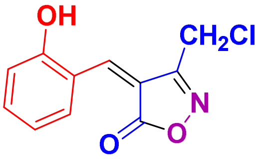
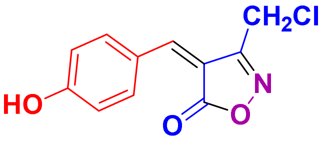
Entry	Solvent	Catalyst (mg)	Temp. (°C)	Time (min)	Isolated yields (%)
1	H_2O	-	RT	75	40
2	H_2O	2	RT	75	50
3	H_2O	4	RT	60	55
4	H_2O	6	RT	50	65
5	H_2O	8	RT	45	70
6	H_2O	10	RT	30	85
7	H_2O	12	RT	30	88
8[1]	**H_2O**	**14**	**RT**	**25**	**97**
9	EtOH	14	RT	45	65
10	CH_3COCH_3	14	RT	80	20
11	$CHCl_3$	14	RT	80	trace
12	DMF	14	RT	80	Trace
13	*n*-Hexane	14	RT	80	45
14	H_2O: EtOH (1:1)	14	RT	50	60
15	-	14	RT	80	35
16	H_2O	14	50	60	70
17	H_2O	14	Reflux	65	62

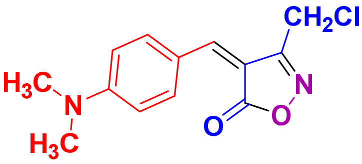
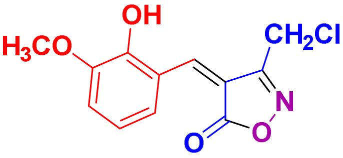
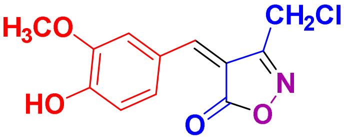
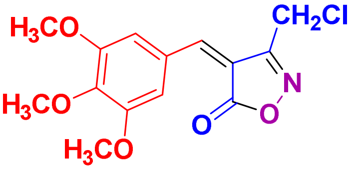
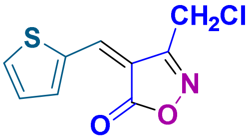
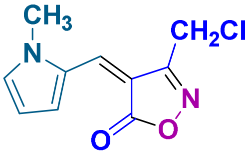
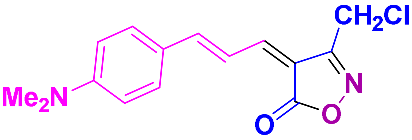
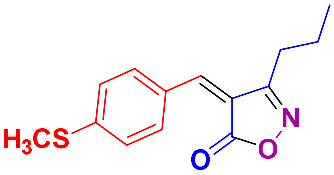
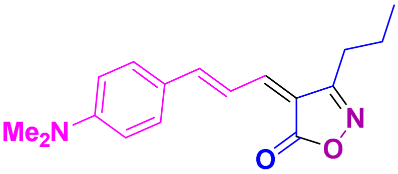
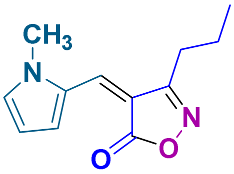
[1] Optimized Conditions.

Cellulose is partially soluble in ethanol [74]. Since the amount of catalyst containing cellulose is very small, it dissolves in ethanol during the washing process. The filtrate containing the catalyst can be reused in subsequent reactions. The catalyst was reused three times (25 min, 95%; 50 min, 85%; 65 min, 80).

Table 2. Substrate scope of aldehydes and *β*-keto esters for the synthesis of isoxazole-5(4*H*)-ones (**4a-4ae**).[a]

Entry	Compounds structure	Time (min)/isolated yields (%)	Melting points (Lit. [ref.])
1	 **4a**	40/85	140-142 (141-143 [52])
2	 **4b**	35/94	176-178 (175-177 [52])
3	 **4c**	45/90	136-137 (134-136 [52])
4	 **4d**	30/85	200-202 (198-200 [52])
5	 **4e**	37/92	202-204 (201-203 [52])
6	 **4f**	40/94	211-212 (211-213 [52])
7	 **4g**	40/90	225-227 (226-228 [52])
8	 **4h**	55/85	87-89 (88-90 [24])
9	 **4i**	45/89	128-130 (128-130 [39])
10	 **4j**	35/93	218-220 (217-219 [52])

11	 **4k**	27/94	135-137 (135-138 [39])
12	 **4l**	25/97	213-214 (212-214 [52])
13	 **4m**	30/91	127-128 (126-128 [52])
14	 **4n**	40/92	170-172 (171-173 [52])
15	 **4o**	45/90	146-148 (145-147 [52])
16	 **4p**	40/96	212-214 (213-215 [28])
17	 **4q**	45/80	182-184 (181-183 [52])
18	 **4r**	38/92	176-178 (175-177 [52])
19	 **4s**	45/90	178-179 (177-178 [52])
20	 **4t**	30/85	198-200 (200-201 [52])
21	 **4u**	40/94	184-185 (184-186 [52])

22	 **4v**	40/91	179-181 (178-181 [52])
23	 **4w**	45/87	167-169 (166-168 [52])
24	 **4x**	25/96	144-146 (143-144 [52])
25	 **4y**	45/93	128-130 (128-130 [52])
26	 **4z**	45/88	137-138 (137-139 [52])
27	 **4aa**	50/92	82-84 (82-83 [28])
28	 **4ab**	35/92	212-215 (New)
29	 **4ac**	35/92	146-148 (145-148 [39])
30	 **4ad**	50/93	158-160 (New)
31	 **4ae**	50/89	145-148 (New)

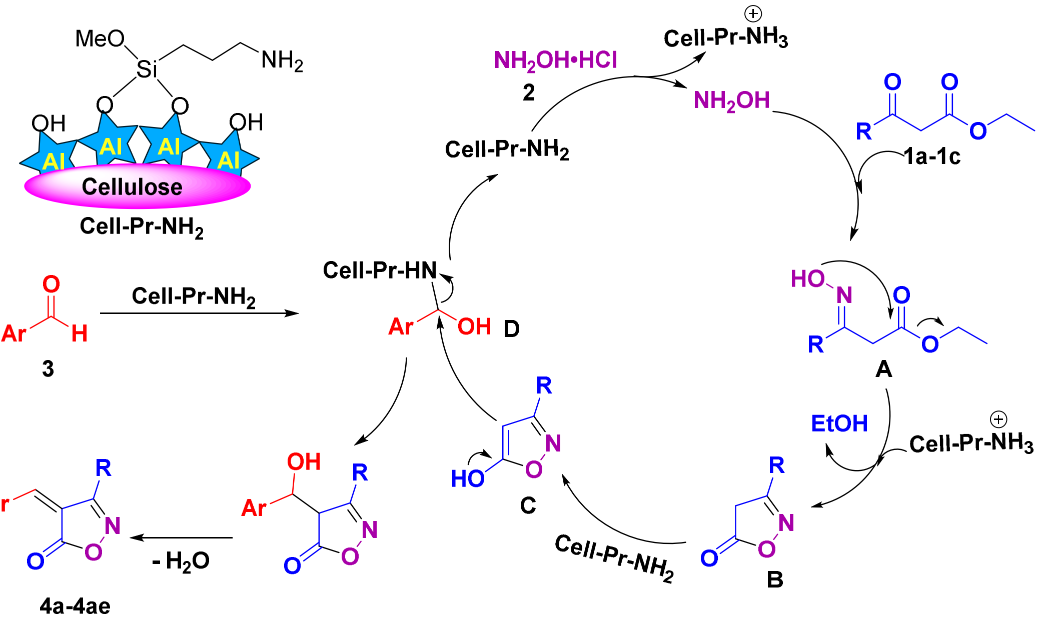
[a] The reactions were conducted by means of **1a-1c** (1 mmol), **2** (1 mmol), and aldehyde derivatives (**3**, 1 mmol) in H_2O (10 mL) in the presence of the catalyst (14 mg) at RT.

This reaction is comparable to some other similar reactions in several aspects (Table 3). Albeit each of the methods revealed has its own merits but frequently suffers from some problems. This cyclocondensation process is comparable with some other similar chemical transformations in several aspects such as reaction yield, reaction time, type of reaction medium, amount of catalyst, and reaction temperature. From the efficiency point of view, it is superior to entries 1-4 and 7-13. From the aspect of the reaction medium, it is better than cases 11 and12 because no organic solvent was used. In comparison with methods 1-4 and 6-13, which are included in Table 3, the current reaction has been implemented in a shorter reaction time. It should also be noted that this reaction was carried out at RT, but when 2,2′-bpy (Table 3, Entry 4), [H_2-BiPyr][ClO_4]$_2$ (Table 3, Entry 5), 50 wt % aq. GAAS (Table 3, Entry 11), and PPTS (Table 3, Entry 13) were used as catalysts, harsh reaction conditions (70 °C and reflux) are needed.

Table 3. Comparison of various catalysts applied in synthesis of 4-(4-methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one (**4b**).

Entry	Catalyst (amount)/conditions	Time (min)	Yield (%)	Refs.
1	Silica-TLC grade (1 g)/H_2O, RT	1440	91	[11a]
2	Lipase (30 mg)/H_2O, RT	60-120	82	[25]
3	Guanidine hydrochloride (15 mol%)/H_2O, RT	70	88	[29]
4	2,2′-bpy (10 mg)/H_2O, reflux	70	80	[33]
5	[H_2-BiPyr][ClO_4]$_2$/H_2O, reflux	30	96	[33]
6	KHP (10 mol%)/H_2O, RT	45	95	[34]
7	Salicylic acid (15 mol%)/H_2O, RT	90	90	[37]
8[1]	Sulfanilic acid (20 mol%)/H_2O, RT	65	91	[38]
9	Succinic acid (10)/H_2O, RT	90	88	[50]
10	Eucalyptol (1 mL)/RT	180	84	[51]
11	50 wt % aq. GAAS (5 mL)/70 °C	45	92	[61]
12	$Na_2S{\cdot}9H_2O$ (5 mol%), EtOH, RT	90	88	[63]
13	PPTS (5 mol%)/H_2O, reflux	60	65	[64]
14	cell-Pr-NH_2 (14 mg)/H_2O, RT	35	94	[This work]

Although we did not carry out mechanistic investigations, but based on the literature [76], the mechanism drawn in Scheme 2 can be proposed for the reaction. The Cell-Pr-NH_2 catalyst helps the released hydroxylamine to initiate the oximation reaction and nucleophilic attack of the NH_2OH on the carbonyl carbon of the *β*-keto ester (**1a**-**1c**) leads to the formation of oxime intermediate **A**. Intermediate **A** was cyclized to generation 3-substituted-isoxazole-5(4*H*)-ones (**B**). In the presence of catalyst, In the presence of the catalyst, cyclic intermediates **B** are enolized to intermediates **C**. Finally, the Knoevenagel condensation reaction between enolized 3-substituted-isoxazole-5(4*H*)-ones (**C**) and activated aldehydes (**D**) leads to the formation of the corresponding heterocycles (**4a**-**4ae**) (Scheme 2).



Scheme 2. Synthesis of Plausible mechanism for the formation isoxazol-5(4*H*)-ones (**4a-4ae**).

4. Conclusions

In conclusion, this work introduces an efficient and green procedure to synthesize 3,4-disubstituted isoxzol-5(4*H*)-ones, heterocyclic compounds with potential biological activity, using commercially available starting materials. The reactions have been successfully implemented under aqueous conditions in the presence of Cell-Pr-NH_2 as the catalyst at RT. Employing this method for the synthesis of isoxazole-5(4*H*)-one heterocycles have advantages including ease of reaction implementation, simplicity of product purification, reasonable yields, acceptable reaction times, performing the reactions in non-organic solvents, as well as cheap, the availability and abundance of the reaction solvent.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: title; Table S1: title; Video S1: title.

Author Contributions: Conceptualization, H.K.; investigation, S.G.; data curation, S.G.; writing—original draft preparation, H.K; S.G.; writing—review and editing, H.K.; supervision, H.K.; project administration, H.K.; All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest.

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