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Baker's yeast promoted green synthesis of functionalized imidazoles using multicomponent reaction of guanidine

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Abstract: In this research new derivatives of imidazoles were prepared using multicomponent reactions of primary amines, isocyanates, diethyl oxalate and guanidine in water at room temperature in the presence of baker's yeast as catalyst in good yields. The short time of reaction, high yields of product and easy separation of them are some advantages of this procedure. Another work in this research is investigation of antioxidant property of some synthesized compounds by diphenyl-picrylhydrazine (DPPH) radical trapping experiment. Presently, bacteria that are not destroyed with drug have generated many problems in the performance of much transferable disease. For this reason, discovering appropriate and new procedures for the dealing with these pathogens are important and recent study has focused on the investigation of the antibacterial effects on the prepared compounds.

Keywords: Primary amines, Imidazole, Isothiocyanate and Diethyl oxalate.

Introduction

Five membered heterocycles with a nitrogen atom, such as pyrroles and imidazoles, are important building blocks in a wide number of biologically active compounds [1-6]. Among them, pyrroles are heterocycles of great importance because of their frequent presence in natural products similar to heme, chlorophyll, vitamin B_{12}, and various cytochrome enzymes [7]. Some recently isolated pyrrole-containing marine natural products have been found to display significant cytotoxicity and function as multidrug resistance (MDR) reversal agents [8]. Many of these biologically active compounds function as chemotherapeutic agents.

Also, the imidazole system can be found in numerous medically relevant compounds, such as the fungicide Ketoconazole [9] and its family members, the benzodiazepine antagonist Flumazenil [10], the antineoplastic drug Dacarbazine [11], the antibiotic Metronidazole [12], the antiulcerative agent Cimetidine [13], the antihyperthyroid drug Methimazole [14], the rohormone Thyroliberin [15], the muscarinic receptor agonist Pilocarpine [16] and the hypnotic agent Etomidate [17]. The use of biocatalysis in organic synthesis has been increasing day by day because of its various advantages. It catalyzes the transformations under mild conditions, with specificities and without side reactions [18]. Among the biocatalysts used in organic synthesis baker's yeast [19] is the most popular due to its easy

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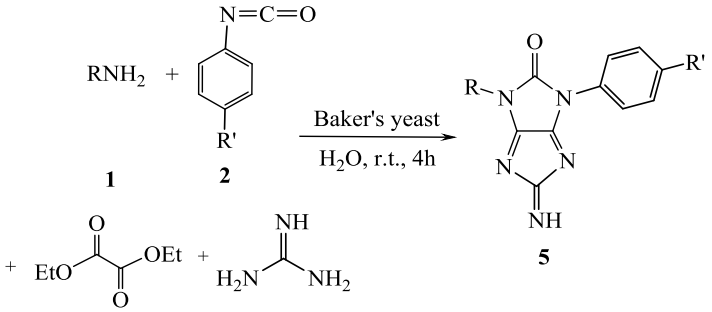
availability, ease of handling, and versatile nature to catalyze a wide range of organic transformations via reduction of variety of carbonyl compounds, oxidation of thioethers to sulfoxides, reduction of C=C bond and some of the cyclocondensation reactions [20]. Our research group reported the synthesis of a series of imidazoles using the reaction of primary amines with isocyanates, diethyl oxalate and guanidine in the presence of baker's yeast as catalyst in water at room temperature with excellent yields (Scheme **1**).

Results and discussion

Four component reactions between primary amine **1**, arylisocyanate **2**, diethyl oxalate **3** and guanidine **4** at room temperature in water produce 1*H*-imidazole derivatives **5** in the presence of baker's yeast in excellent yields (Scheme **1**).



5	R	R'	Yield (%) of **5**
a	Bn	Me	87
b	4-$MeC_6H_4CH_2$	OMe	85
c	4-$MeOC_6H_4CH_2$	Me	90
d	*n*-Bu	NO_2	78
e	Et	OMe	80

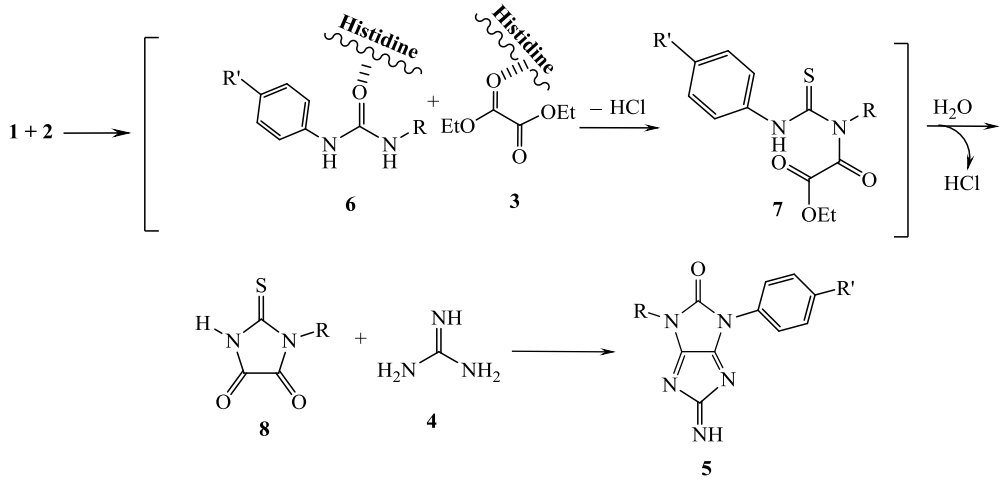
Scheme 1: Synthesis of compound **5** in the presence of baker's yeast

Table 1. Optimization conditions for preparation of 5**a**

Entry	Catalyst	Temp.(°C)	catalyst (g)	Time (h)	Yield%[a]
1	none	r.t.	-	12	-
2	none	100	-	8	-
3	none	120	-	8	-
4	baker's yeast	r.t.	0.5	4	87
5	baker's yeast	100	0.5	4	87
6	baker's yeast	r.t.	1.0	4	87
7	ZnO-NPs	r.t.	0.5	4	68
8	Fe_3O_4 MNPs	r.t.	0.5	4	58
9	Fe_3O_4/ZnO	r.t.	0.5	4	75
10	ZnO/CuO	r.t.	0.5	4	78

In all of organic compounds synthesis, the optimization of reaction condition is the important point. For achieving to this purpose, firstly, the reaction of benzyl amine **1a**, 4-methyl isocyanate **2a**, diethyl oxalate **3** and guanidine **4** was employed as a sample reaction to achieve the best conditions for

performing these reactions (Table 1). These reactions aren't performed without catalyst and for producing the products needed to catalyst. Thus, 0.5 g catalyst such as baker's yeast was added to the reaction mixture. After 4 h, 87% yield of 5a was generated (entry 4, Table 1). For more evaluation of the catalytic activity, some catalysts such as ZnO-NPs, ZnO/CuO-NPs, Fe_3O_4 MNPs and Fe3O4/ZnO-MNCs were investigated in sample reaction. Consequently, these results showed the baker's yeast is the best catalyst for this reaction. Then, the reaction was performed in the presence of 0.5 g of baker's yeast as catalyst. By increasing the amount of catalyst from 0.5 g to 1.0 g didn't observed any significant alter in the product yields. Also, by increasing the reaction temperature to 100 ^{o}C didn't see any considerable change in the yields of reaction (entry 2, Table 1). As a result, to discover the optimal catalyst loading, different amounts (0.5–1.0 g) of baker's yeast were utilized. The results exhibited that 0.5 of baker's yeast are sufficient for generate an excellent yield of **5a** (entry 4, Table 1).The structures of compounds **5** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data, and these data were showed in supporting information. For example, the ^{1}H NMR spectrum of **5a** exhibited one singlet for methyl protons at (δ 2.35) and one singlet for NCH_2 protons at (δ 5.14) along with signals for an aromatic moiety. Three resonances at 154.3 (C=O), 156.7 (C=O), and 183.6 (C=O) ppm were observed in the ^{13}C NMR spectrum of **5a**, which is attributed to the carbonyl and thionyl groups, further confirming the proposed structure. Although we have not established the mechanism of the reaction between the amines and aryisocyanate in the presence of baker's yeast in an experimental manner, a possible explanation is proposed in Scheme **2**. Compound **5** results from the initial addition of the amine **1** to isocyanate **2** and subsequent attack of the resulting reactive compound **6** on the diethyl oxalate **3** to yield intermediate **7**. Cyclization of the intermediate **7** by reaction with guanidin leads to compound **5**.



Scheme 2: Proposed mechanism for the synthesis of compound **5**.

Aantioxidant ability of synthesized spirooxadiazepines utilizing diphenyl-2-picrylhydrazyl (DPPH)

DPPH radical trapping examin is broadly utilized for the approval the power of synthezied compounds to get free radicals and its antioxidant property in foods and biological structures. In these valuation, antioxidant ability of prepared 1*H*-imidazole was proved by taking the hydrogen atom or one electron by DPPH radical.

The synthesized compounds have two NH groups and because of having acidic hydrogen have antioxidant activity. The antioxidant activity of investigated compounds **5a-5d** has not much different from each other. The percentage of DPPH free radical trapping indicates the antioxidant degree of the synthesized 1*H*-imidazole **5a-5d**. In other words, the order of antioxidant ability of 1*H*-imidazole **5a-5d** is determined basis of the electron or hydrogen donating power of 1*H*-imidazole to the DPPH radical. When DPPH give one electron or hydrogen from antioxidant or a radical typs, its absorbtion was decreased from 517 nm. In this research, the ability of getting free radicals by 1*H*-imidazole **5a-5d** was compared with

BHT and TBHQ as standard syntheiszed antioxidant at different concentrations. In general, the order of antioxidant activity of some synthesized 1*H*-imidazole **5a-5d** is TBHQ≈BHT>**5a**>**5c**>**5b**>**5d** (Figure 1). Good difference relative to BHT and TBHQ existed in all concentrations of the new prepared spirooxadiazepines that are showed in Figure 1. In among investigated 1*H*-imidazole **5a** exhibited good activity for trapping of radical relative to BHT and TBHQ as standard antioxidant.

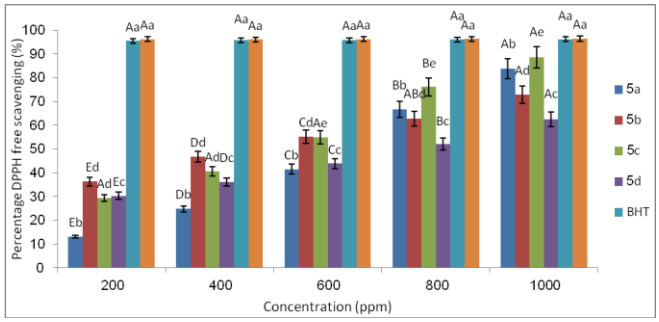


Figure 1. Radical scavenging activity (RSA) of **5a-d**

The Ferric ions (Fe^{3+}) reducing potential of synthesized imidazoles

The calculating reducing quantity of Fe^{3+}/ferricyanide to the Fe^{2+}/ ferrous at 700 nm is important factor for ferric ions (Fe^{3+}) reducing ability of some synthesized imidazoles such as **5a-5d** [36]. Among the investigated spirooxadiazepines **7c** was displayed good reducing ability than to BHT and TBHQ as standard antioxidants (Figure 2). The order of reducing activity of the investigated spirooxadiazepines is: TBHQ>BHT>**5a**>**5c**>**5b**>**5d**. The outcomes are displayed in Figure 2.

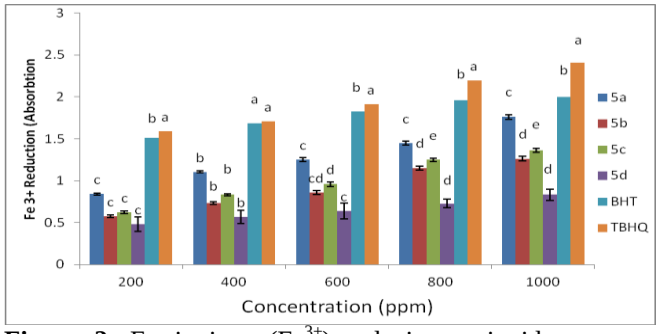


Figure 2. Ferric ions (Fe^{3+}) reducing antioxidant power (FRAP) of compounds **5a-5d**

Conclusion

In conclusion, we reported a novel method involving primary amines and isocyanate in the presence of diethyl oxalate and guanidin for the synthesis of 1*H*-imidazole derivatives in the presence of baker's yeast. The advantages of our work are that the reaction is performed in water without using a catalyst.

Experimental Section

General

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. ^{1}H, ^{13}C and ^{31}P NMR spectra were obtained with a Bruker FT-500 spectrometer in $CDCl_3$, and tetramethylsilane (TMS) was used as an internal standard or 85% H_3PO_4 as external standard. Mass spectra were recorded with a Finnigan Mat TSQ-70 spectrometer. Infrared (IR) spectra were acquired on a Nicolet Magna 550-FT spectrometer. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus. The results of elemental analyses (C, H, N) were within ±0.4 % of the calculated values. Acetylenic ester, phenacyl bromide or its derivatives and triphenylphosphine were obtained from Fluka and were used without further purification.

General procedure for preparation of compounds 4a-e.

To a mixture of primary amine **1** (2 mmol) and arylisocyanate **2** (2 mmol) was added diethyl oxalate **3** (2 mmol) and guanidine **4** at room temperature. The reaction mixture was then stirred for 4 h. After completion of the reaction [TLC (AcOEt/hexane, 1:4 v/v) monitoring], the reaction mixture was purified by flash column chromatography on silica gel (Merck 230–400 mesh) using *n*-hexane–EtOAc as eluent to afforded pure compounds **5**.

1-Benzyl-3-(4-methylphenyl)-2-thioxodihydro-1H-imidazole-4,5-dione (5a):

Yellow powder, m.p. 158-160°C, yield: 0.53g (85%), IR (KBr) (ν_{max}/cm^{-1}): 1764, 1735, 1666, 1441, 1340 cm^{-1}. ^{1}H NMR (500.1 Hz, $CDCl_3$): δ = 2.35 (3 H, s, Me), 5.14 (2 H, s, N-CH_2), 7.28 (1 H, d, ^{3}J = 7.2 Hz, CH), 7.32 (2 H, t, ^{3}J = 7.6 Hz, 2 CH), 7.38 (2 H, d, ^{3}J = 7.3 Hz, 2 CH), 7.41 (2 H, d, ^{3}J = 7.3 Hz, 2 CH), 7.52 (2 H, d, ^{3}J = 7.4 Hz, 2 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 22.4 (Me), 45.6 (N-CH_2), 117.5 (2 CH), 128.2 (CH), 129.0 (2 CH), 129.2 (2 CH), 132.4 (2 CH), 133.2 (C), 137.5 (C), 139.4 (C), 154.3 (C=O), 156.7 (C=O), 183.6 (C=S) ppm. MS: *m*/*z* (%) = 310 (M^{+}, 10), 219 (68), 91 (100), 77 (60). Anal. Calc. for

$C_{17}H_{14}N_2O_2S$ (310.37): C, 65.79; H, 4.55; N, 9.03. found: C, 65.83; H, 4.62; N, 9.14%.

1-(4-Methylbenzyl)-3-(4-methoxyphenyl)-2-thioxodihydro-1H-imidazole-4,5-dione (5b):

Pale yellow powder, m.p. 168-170°C, yield: 0.54g (80%), IR (KBr) (ν_{max}/cm^{-1}): 1759, 1748, 1667, 1443, 1347 cm^{-1}. ^{1}H NMR (500.1 Hz, $CDCl_3$): δ = 2.34 (3 H, s, Me), 5.12 (2 H, s, N-CH_2), 7.15 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.24 (2 H, d, ^3J = 7.5 Hz, 2 CH),7.34 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.42 (2 H, d, ^3J = 7.5 Hz, 2 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 22.5 (Me), 46.7 (N-CH_2), 55.3 (MeO), 114.6 (2 CH), 128.5 (2 CH), 129.4 (2 CH), 131.8 (C), 132.2 (2 CH), 136.4 (C), 139.3 (C), 155.2 (C=O), 155.8 (C=O), 160.4 (C), 180.4 (C=S) ppm. Anal. Calc. for $C_{18}H_{16}N_2O_3S$ (340.39): C, 63.51; H, 4.74; N, 8.23. found: C, 63.62; H, 4.83; N, 8.32%.

1-(4-Methoxybenzyl)-3-(4-methylphenyl)-2-thioxodihydro-1H-imidazole-4,5-dione (5c):

Yellow powder, m.p. 165-167°C, yield: 0.37g (87%), IR (KBr) (ν_{max}/cm^{-1}): 1764, 1735, 1670, 1445, 1340 cm^{-1}. ^{1}H NMR (500.1 Hz, $CDCl_3$): δ = 2.36 (3 H, s, Me), 5.15 (2 H, s, N-CH_2), 7.18 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.28 (2 H, d, ^3J = 7.9 Hz, 2 CH), 7.38 (2 H, d, ^3J = 7.9 Hz, 2 CH), 7.45 (2 H, d, ^3J = 7.6 Hz, 2 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 22.2 (Me), 47.3 (N-CH_2), 55.5 (MeO), 113.8 (2 CH), 128.8 (2 CH), 129.6 (2 CH), 132.3 (C), 132.8 (2 CH), 135.7 (C), 138.4 (C), 155.3 (C=O), 156.2 (C=O), 161.3 (C), 181.7 (C=S) ppm. Anal. Calc. for $C_{18}H_{16}N_2O_3S$ (340.39): C, 63.51; H, 4.74; N, 8.23. found: C, 63.65; H, 4.84; N, 8.30%.

1-butyl-3-(4-nitrophenyl))-2-thioxodihydro-1H-imidazole-4,5-dione (5d):

Yellow powder, mp: 137-139 °C, yield: 0.46g (75 %). IR (KBr) (ν_{max}/cm^{-1}): 1764, 1742, 1675, 1443, 1348 cm^{-1}. ^{1}H NMR (500.1 Hz, $CDCl_3$): δ = 1.12 (3 H, t, ^3J = 7.4 Hz, CH_3), 1.38 (2 H, m, CH_2), 1.52 (2 H, m, CH_2), 4.58 (2 H, s, N-CH_2), 7.76 (2 H, d, ^3J = 7.8 Hz, 2 CH), 8.37 (2 H, d, ^3J = 7.8 Hz, 2 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 13.4 (CH_3), 19.4 (CH_2), 28.4 (CH_2), 43.7 (N-CH_2), 118.7 (2 CH), 128.5 (2 CH), 140.2 (C), 142.3 (C), 155.2 (C=O), 155.4 (C=O), 178.6 (C=S) ppm. Anal. Calc. for $C_{13}H_{13}N_3O_4S$ (307.33): C, 50.81; H, 4.26; N, 13.67. found: C, 50.92; H, 4.36; N, 13.72%.

1-ethyl-3-(4-methoxyphenyl))-2-thioxodihydro-1H-imidazole-4,5-dione (5e):

Yellow powder, m.p. 140-142 °C, yield: 0.39g (75 %), IR (KBr) (ν_{max}/cm^{-1}): 1765, 1742, 1665, 1487, 1345 cm^{-1}. ^{1}H NMR (500.1 Hz, $CDCl_3$): δ = 1.28 (3 H, t, ^3J = 7.3 Hz, CH_3), 3.85 (3 H, s, MeO), 3.87 (2 H, q, ^3J = 7.4 Hz, NCH_2), 7.24 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.35 (2 H, d, ^3J = 7.6 Hz, 2 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 13.4 (CH_3), 36.7 (NCH2), 55.6 (MeO), 113.4 (2 CH), 132.4 (2 CH), 133.7 (C), 153.7 (C=O), 155.6 (C=O), 159.4 (C), 182.5 (C=S) ppm. Anal. Calc. for $C_{12}H_{12}N_2O_3S$ (264.30): C, 54.30; H, 4.58; N, 10.60. found: C, 54.42; H, 4.63; N, 10.70%.

Study of imidazole antioxidant activity utilizing DPPH radical trapping test

The DPPH radical scavenging experiment was utilized for investigation of some generated imidazole derivatives ability such as **5a-5d** like the method reported by Shimada et. al. [34]. For obtaining to this object, various concentrations (200–1000 ppm) of imidazoles **5a-5d** were added to equal volume of DPPH methanolic solution (1 mmol/L). The mixture was stirred for 30 min at environmental temperature and putted in a dark room after this time and the absorbance of mixture was recorded at 517 nm. The imidazoles **5a-5d** was replaced with standard type of methanol (3 mL). In this procedure, Butylated hydroxytoluene (BHT) and 2-tertbutylhydroquinone (TBHQ) are standard antioxidants. The percentage of inhibition for the radical of DPPH calculated by utilizing Yen and Duh [35] formula.

Study of reducing ability for synthesized imidazoles

The ability of iron (III) reducing by the imidazoles **5a-5d** was investigated utilizing Yildirim et al. method [36]. For this object, the samples (1 mL), potassium ferricyanide ($K_3Fe(CN)_6$; 2.5 mL, 10g/L) and buffer of phosphate (2.5 mL, 0.2 mol/L, pH 6.6) were combined together and maintained for 30 min at 50 ^{o}C. Then, trichloroacetic acid (2.5 mL, 10% w/v) was added to the previous solution and centrifuged for 10 min. Finally, the supernatant (2.5 mL), distilled water (2.5 mL) and $FeCl_3$ (0.5 mL, 1 g/L) mixed together and the absorbance of samples was measured at 700 nm. The higher absorbance of sample show higher reducing power of it. For accuracy of calculating, each measuring was carried out in three times. One way study of variance (ANOVA) that was used for data analyzing of compounds is running the SPSS software version 18.0 that proved difference of samples and control. Duncan multiple range experiments was employed for separation mean with the importance quantity of 95% ($P < 0.05$).

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