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Ultrasonic synthesis, characterization of β-aminoketones by bismuth(III) triflate and determination of antigenotoxic properties

S Arda Ozturkcan[1], Kadir Turhan[1], Zuhal Turgut[1], Mehmet Karadayi[2] and Medine Gulluce[2]

Abstract

Direct-type catalytic Mannich reaction for the synthesis of β-aminoketones from cyclohexanone, substituted aromatic amines and aromatic or hetero-aromatic aldehydes has been applied in water with bismuth triflate under ultrasound. Good yields of the expected β-aminoketones were obtained from available substrates, at room temperature in 1–2 hours. This study was designed to evaluate the mutagenic and antimutagenic potential of synthesized β-aminoketones compounds using Ames/*Salmonella* and *Escherichia coli* WP2 bacterial reverse mutation assay systems.

Keywords

β-aminoketones, direct-type Mannich reaction, ultrasonic synthesis, bismuth(III) triflate, antigenotoxic properties

Introduction

Mannich reaction is an important carbon–carbon bond forming type in organic synthesis for the preparation of β-amino carbonyl compounds (Kobayashi and Ishitani, 1999). Attempts have been made in the past to improve methodologies based on two-step reactions, where the imine as electrophile is preformed and then reacted with nucleophiles such as enolates, enol ethers and enamines (Kobayashi et al., 2002). However, in most cases these protocols use hazardous organic solvents and suffer from long reaction time with low yields. Therefore, it is necessary to develop the modern versions of the reaction that could work under simple and mild conditions (Josephsohn et al., 2005).

The concept of modern innovations in synthetic chemistry has emerged as a major solution for the development of cleaner and more benign chemical processes (Hota et al., 2009). As part of this green concept, "water", "non-toxic catalyst" and "ultrasound" have become popular and received substantial interest. Water is one of the eco-friendly, ease of access, inexpensive solvent and can certainly be considered as the cleanest one available for chemists (Hong et al., 2009; Noei and Khosropour, 2009). Additionally, it often gives unique reactivity and selectivity that is difficult to attain with traditional organic solvents (Bhadra et al., 2008). Various methodologies and routes have been developed lately based on green chemistry or sonochemistry (Kantam et al., 2006). Recently, several laboratories disclosed significant advances regarding rare earth and lanthanide triflates as catalysts for direct-type Mannich reactions (Kobayashi et al., 1996, 1999). High catalytic activity, low toxicity, environmentally benign nature, moisture and air tolerance makes lanthanide triflates valuable catalysts. However, the high cost of these catalysts restricts their use. Bismuth compounds are of interest as lower toxicity and cheaper alternatives to the former ones (Ollevier and Nadeau, 2004, 2007; Ollevier et al., 2006). A few recent reports showed that organic molecules have

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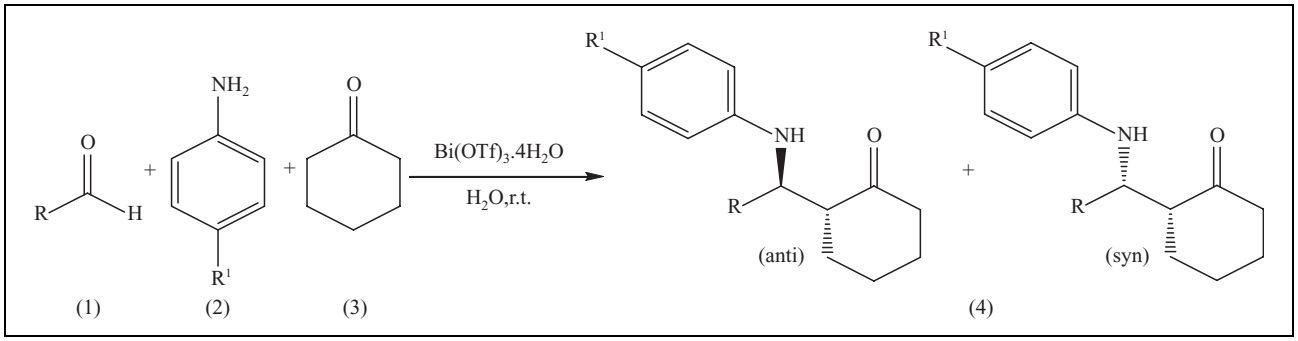


Figure 1. Ultrasonic synthesis of β-aminoketones.

been applied successfully as catalysts under aqueous medium or solvent-free conditions (Chen and Li, 2009; Kureshy et al., 2010; Xia and Lu, 2007). Sonochemistry as a green innovation powerful technique has attracted increasing interest in accelerated organic reactions (Tabatabaeian et al., 2008; Xu et al., 2007). This modern technique can be extremely efficient and is applicable to a wide variety of practical synthesis. Luche and coworkers have done many studies that provided the basis of sonochemistry (Ando et al., 2001; Cabello et al., 2003; Meciarova et al., 2001). The notable features of the ultrasound approach are enhanced reaction rates, formation of pure products in high yields and easier manipulation, and it is also considered as a processing aid in terms of energy conservation and waste minimization compared to traditional methods (Kumar et al., 2007; Sinha et al., 2007).

Aminoketone derivatives exhibit remarkable antitubercular, antifungal, antimalarial, antidiabetic, anti-inflammatory, and antitumor activities (Mhaske and Argade, 2006). A recent and significant study by Rai and coworkers has shown excellent antimicrobial activity of β-aminoketones comparable to that of the standard drug *Ceftriaxone* at same concentration (Sankappa Rai et al., 2010). Our study has researched the antigenotoxic properties of β-aminoketones against sodium azide (NaN_3) and N-methyl-N′-nitro-N-nitrosoguanidine (MNNG) genotoxicity. They are two well-known genetoxic agents widely affecting many organisms. NaN_3 is known as a powerful mutagen in several organisms including bacteria, plants and animals. Previous studies showed clearly that the mutagenicity of NaN_3 is mediated through the production of an organic metabolite of azide called L-azidoalanine (Sadiq and Owais, 2000). On the other hand, MNNG is a well-known carcinogen and is known to exert its mutagenic and lethal effects by methylation of DNA (Kumaresan et al., 1995). Previous studies have shown that O^6-methylguanine is one of its important products which is formed, which appears to be responsible for the mutagenic action (Eadie et al., 1984; Loveless, 1969).

Until now, there have been a lot of studies focused on NaN_3 and MNNG genotoxicity in order to determine the mechanisms and prevention perspectives, because of their hazardous potential. In this manner, combination of natural or synthetic compounds and effective genotoxicity test systems has a great importance and potential to develop preventative agents against mutagens and their negative effects (Gulluce et al., 2010).

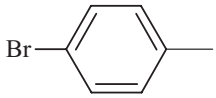
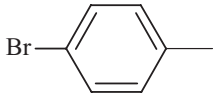
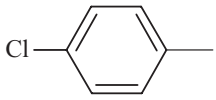
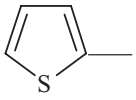
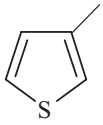
In this study, direct-type 3-component catalytic Mannich reaction using bismuth(III) triflate and water as the only solvent under ultrasound irradiation at room temperature is reported. In addition, the study was designed to evaluate the antimutagenic potential of five β-aminoketones compounds using Ames/*Salmonella* and *Escherichia coli* WP2 bacterial reverse mutation assay systems. To the best of our knowledge, only one report on determination of mutagenic/antimutagenic activities was published by our research group for two of these compounds with different bacteria system, and there is no report on three of them with any bacteria system (Ozturkcan et al., 2012a, 2012b).

Chemistry

A convenient procedure for the synthesis of β-aminoketones has been developed and applied in water with bismuth triflate under ultrasound (Figure 1).

The 3-component direct type Mannich reaction proceeded smoothly in short time (1-2 hours) in the presence of 5 mol % of $Bi(OTf)_3.4H_2O$ under ultrasound irradiation to give the corresponding products in high yields. The results were summarized in Table 1.

Table 1. Direct type 3-component catalytic Mannich reaction under ultrasound.

Products	*R*	*R*	Time (h)	Yield (%)[a]	*Anti/Syn*[b]	m.p.(°C)[c]
4a		$-CH_3$	1	89	97:3	119.3–120.1
4b		$-CH_2CN$	1,5	77	69:31	114.3–115.9
4c		$-CH_3$	1	84	99:1	115.7–118.3
4d		$-CH_2CN$	2	73	94:6	122.2–125.3
4e		$-CH_3$	2	67	99:1	104.1–105.7

[a] Yield of product after either column chromatography or trituration.
[b] Anti/syn ratio of the purified product was determined by ^{1}H-NMR.
[c] Melting point are uncorrected.

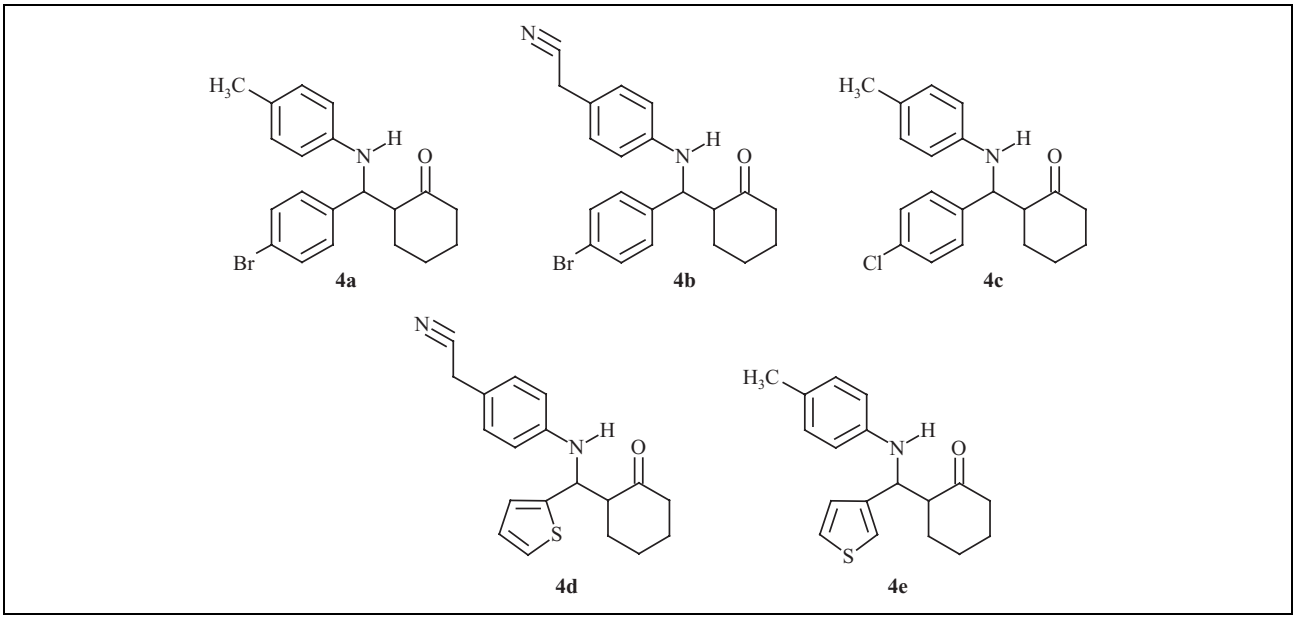


Figure 2. Investigated β-aminoketones.

After the purification processes, the structures of the obtained new compounds have been clarified by spectroscopic methods (Fourier-transform infrared [FT-IR], proton nuclear magnetic resonance [^{1}H-NMR], carbon 13 nuclear magnetic resonance [^{13}C-NMR], elemental analysis [EA] and mass

spectrometry [MS]) (Ozturkcan et al., 2012a). All compounds were summarized in Figure 2.

Pharmacology

Our initial study aimed to determine the mutagenic and antimutagenic potential of the various synthesized β-aminoketones against the genotoxic agents NaN_3 and MNNG. The mutant bacterial tester strains were NaN_3-sensitive *Salmonella typhimurium* TA1535 and MNNG-sensitive *Escherichia coli* WP2uvrA.

Materials and methods

Chemicals

All chemicals for synthesis were purchased from Merck, Fluka and Aldrich, and all were further purified by recrystallization or distillation using standard procedures. Moreover, direct acting mutagens NaN_3 and MNNG were obtained from Sigma-Aldrich (St. Louis, MO) and ABCR GmbH & Co. KG (Karlsruhe, Germany), respectively. Other solvents and pure chemicals including magnesium sulfate ($MgSO_4$), sodium ammonium phosphate ($Na_2NH_2PO_4$), D-glucose, L-histidine, D-biotin, sodium chloride (NaCl), L-histidine HCl, sodium phosphate dibasic (Na_2HPO_4), crystal violet, citric acid monohydrate, potassium phosphate dibasic (K_2HPO_4) and sodium phosphate monobasic (NaH_2PO_4) were also obtained from Difo (NJ), Fluka (Steinheim, Germany), Merck (Darmstadt, Germany) and Sigma.

Apparatus and analysis

Reactions were performed in an Intersonik ultrasound cleaner (model: MIN4) with a frequency of 25 kHz, an ultrasound output power of 100 W, a heating at 200 W. The temperature of the water bath can be controlled by an adjustable automatic constant temperature cooling circulatory system. Thin layer chromatography (TLC) was carried out on silica gel 60 F_{254} precoated plates and visualized with "Camag UV light" (254/366 nm). Column chromatography was performed on silica gel 60, 70–230 mesh. FT-IR spectra were recorded on a Philips PU 9714 ATR spectrophotometer and using "Perkin-Elmer Spectrum One" program. ^{1}H-NMR and ^{13}C-NMR (500 MHz) spectra were recorded on an "Inova 500" spectrometer using tetramethylsilane (TMS) as an internal standard in chloroform ($CDCl_3$) or dimethyl sulfoxide (DMSO). MS were obtained using "Finnigan Trace DSQ" instrument. Melting points were determined with Gallenkamp melting point apparatus and were uncorrected.

Ultrasound-assisted synthesis of β-aminoketones

To a solution of $Bi(OTf)_3.4H_2O$ (0.05 mmol) in 1 mL of water was added the aldehyde (1 mmol), aniline (1 mmol) and cyclohexanone (2 mmol). The reaction mixture was sonicated at room temperature in an ultrasound cleaner bath according to the time indicated in Table 1. The progress of the reaction was monitored by TLC and then stopped by the addition of ethyl acetate. The aqueous phase was extracted with ethyl acetate (3×10 mL). The organic phases were combined and washed with water (2 mL) and brine (2 mL) consecutively, dried over $MgSO_4$, and filtered. The solvents were removed under reduced pressure. The crude mixture was purified either by column chromatography (hexane/etoac) or by recrystallization in hexane, giving the diastereoisomeric mixture of β-aminoketone (Ozturkcan et al., 2012a) (Table 1 4a-e).

Bacterial strains

S. typhimurium TA1535 (ATCC® Number: 29629) strains were provided by The American Type Culture Collection–Bacteria Department of Georgetown University, Washington, and *E. coli* WP2*uvrA* (ATCC® Number: 49979) strain was provided by LGC standards Middlesex, UK. All strains were stored at −80°C. Working cultures were prepared by inoculating nutrient broth with the frozen cultures, followed by an overnight incubation at 37°C with gentle agitation (Oh et al., 2008).

Viability assays and determination of test concentrations

The toxicity of test materials toward *S. typhimurium* 1535 and *E. coli* WP2*uvrA* strains was determined as described previously (Santana-Rios et al., 2001; Yu et al., 2001). These tests confirmed that there was normal growth of the background lawn, spontaneous colony numbers within the regular range, and no significant reduction in cell survival. Thus, for the concentrations and conditions reported here, no toxicity or other adverse effects were observed.

Mutagenicity and antimutagenicity tests

The bacterial mutagenicity and antimutagenicity assays were performed according to what has been described before (Mortelmans and Zeiger, 2000). The known

Table 2. The mutagenicity assay results of β-aminoketones for *E. coli* WP2*uvrA* and *S. typhimurium* TA1535 bacterial tester strains.

		Number of revertants			
		E. coli WP2*uvrA*		*S. typhimurium* TA1535	
Test items	Concentration (mM/plate)	Mean ± S.E.	Mut. %	Mean ± S.E.	Mut. %
4a	0.01	33.25 ± 1.33	–	25.50 ± 0.95	–
	0.1	34.50 ± 1.11	–	24.50 ± 1.02	–
	1	33.75 ± 1.55	–	25.00 ± 1.34	–
4b	0.01	16.00 ± 2.79	–	14.50 ± 1.74	–
	0.1	18.00 ± 1.67	–	12.00 ± 2.89	–
	1	14.25 ± 2.26	–	12.00 ± 2.64	–
4c	0.01	33.00 ± 1.36	–	26.50 ± 1.28	–
	0.1	35.75 ± 0.54	–	25.75 ± 1.07	–
	1	33.25 ± 0.91	–	24.50 ± 1.36	–
4d	0.01	11.00 ± 2.20	–	14.50 ± 2.28	–
	0.1	16.00 ± 1.71	–	17.50 ± 2.67	–
	1	12.00 ± 0.27	–	14.25 ± 1.94	–
4e	0.01	14.00 ± 2.19	–	17.50 ± 1.34	–
	0.1	16.25 ± 1.17	–	15.50 ± 1.10	–
	1	17.00 ± 1.35	–	16.00 ± 0.97	–
MNNG[a]	1	374.00 ± 03.62			
NaN_3[a]	1			482.00 ± 04.13	
DMSO[b] (μL/plate)	100	37.50 ± 1.39		29.75 ± 1.71	

MNNG: N-methyl-N′-nitro-N-nitrosoguanidine; *E. coli: Escherichia coli; S. typhimurium: Salmonella typhimurium*; NaN_3: sodium azide; DMSO: dimethyl sulfoxide.
[a] MNNG (1 μg/plate) and NaN_3 (1 μg/plate) were used as positive controls for *E. coli* WP2uvrA and *S. typhimurium* TA1535 strains, respectively.
[b] DMSO (dimethylsulfoxide; 100 μL/plate) was used as the negative control.

mutagens NaN_3 (in distilled water 1 μg/plate) for *S. typhimurium* TA1535 and MNNG (in DMSO 1 μg/plate) for *E. coli* WP2uvrA were used as positive controls, and DMSO was used as negative control in these studies.

In the mutagenicity test performed with TA1535 strain of *S. typhimurium*, 100 μL of the overnight bacterial culture, 50 μL test compounds at different concentrations (0.01, 0.1, and 1 μg/plate in 10% DMSO) and 500 μL phosphate buffer were added to 2 ml of the top agar containing 0.5 mM histidine/biotin. The mixture was poured onto minimal glucose plates. Histidine independent revertant colonies and viable cells were scored on plates after incubation at 37°C for 48 h.

In the antimutagenicity test performed with the same strains, 100 μL of the overnight bacterial culture, 50 μL mutagen, 50 μL test compounds at different concentrations, and 500 μL phosphate buffer were added to 2 mL of the top agar containing 0.5 mM histidine/biotin. The mixture was poured onto minimal glucose plates. Histidine independent revertant colonies and viable cells were scored on plates after incubation at 37°C for 48 h.

The procedures of mutagenicity and antimutagenicity assays, which are described above for the *Salmonella* assay, are all applicable to the *E. coli* WP2 reverse mutation assay. The only difference in procedure is the addition of limited tryptophan (0.05 mM) instead of histidine to the top agar (Mortelmans and Riccio, 2000). The plate incorporation method was used to assess the results of mutagenicity and antimutagenicity assays (Maron and Ames, 1983).

For the mutagenicity assays, the mutagenic index was calculated for each concentration, which is the average number of revertants per plate divided by the average number of revertants per plate with the negative (solvent) control. A sample was considered mutagenic when a dose–response relationship and a two-fold increase were observed in the number of mutants with at least one concentration (Evandri et al., 2005; Santos et al., 2008).

For the antimutagenicity assays, the inhibition of mutagenicity was calculated using the following equation (M: number of revertants/plate induced by mutagen alone, S_0: number of spontaneous revertants and S_1: number of revertants/plate induced by the extract plus the mutagen):

Table 3. The antimutagenicity assay results of β-aminoketones for *E. coli* WP2uvrA and *S. typhimurium* TA1535 bacterial tester strains.

		Number of revertants			
		E. coli WP2uvrA		*S. typhimurium* TA1535	
Test Items	Concentration (mM/plate)	Mean ± S.E.	Inhib. %	Mean ± S.E.	Inhib.%
4a	0.01	227.75 ± 02.28	39.1[a]	297.75 ± 03.04	38.2[a]
	0.1	251.75 ± 03.76	32.7[a]	300.25 ± 02.81	37.7[a]
	1	334.00 ± 04.59	10.7	252.50 ± 04.22	47.6[a]
4b	0.01	278.25 ± 02.08	25.6[a]	376.00 ± 02.16	21.8
	0.1	299.00 ± 02.58	19.8	388.50 ± 01.79	19.4
	1	354.50 ± 01.47	5.2	451.75 ± 01.86	6.3
4c	0.01	211.75 ± 02.43	43.4[a]	283.00 ± 00.45	41.3[a]
	0.1	238.50 ± 00.84	36.2[a]	300.75 ± 03.15	37.6[a]
	1	254.75 ± 04.01	31.9[a]	361.50 ± 02.69	25.0[a]
4d	0.01	220.25 ± 02.95	41.1[a]	304.50 ± 03.21	36.8[a]
	0.1	221.50 ± 02.21	40.8[a]	299.25 ± 02.55	37.9[a]
	1	266.50 ± 03.76	28.7[a]	341.75 ± 02.96	29.1[a]
4e	0.01	188.75 ± 04.51	49.5[a]	251.50 ± 01.27	47.8[a]
	0.1	220.00 ± 01.84	41.2[a]	290.75 ± 02.19	39.7[a]
	1	221.75 ± 03.23	40.7[a]	289.75 ± 04.41	39.9[a]
MNNG[b]	1	374.00 ± 03.62			
NaN_3[b]	1			482.00 ± 4.13	
DMSO[c] (μL/plate)	100	37.50 ± 1.39		29.75 ± 1.71	

MNNG: N-methyl-N′-nitro-N-nitrosoguanidine; *E. coli: Escherichia coli; S. typhimurium: Salmonella typhimurium*; NaN_3: sodium azide; DMSO: dimethyl sulfoxide.

[a] $p < 0.05$.

[b] MNNG (1 μg/plate) and NaN_3 (1 μg/plate) were used as positive controls for *E. coli* WP2uvrA and *S. typhimurium* TA1535 strains, respectively.

[c] DMSO (100 μL/plate) was used as negative control.n

$$\% \text{ Inhibition} = [(M - S_1)/(M - S_0)] \times 100 \quad (1)$$

The results of the eq. (1), from 25% to 40% inhibition was defined as moderate antimutagenicity; from 40% or more inhibition as strong antimutagenicity and from 25% or less inhibition as no antimutagenicity (Evandri et al., 2005; Negi et al., 2003).

Statistical analysis

The results are presented as the average and standard error of three experiments with duplicate plates/dose experiment. The data were further analyzed for statistical significance using analysis of variance (ANOVA), and the difference among means was compared by high-range statistical domain using Tukey's test. A level of probability <0.05 was taken as indicating statistical significance (Ozbek et al., 2008).

Results and discussion

Various substituted aromatic or heteroaromatic aldehydes, substituted aromatic amines and cyclohexanone afforded various β-aminoketones in good yields (67%–89%), short time (1–2 h) and with antiselectivity at room temperature.

The anti- and syn- isomers were identified by the coupling constant of the vicinal protons of NH and CH (which is adjacent to NH) in their ^{1}H-NMR spectra. All of the coupling constants for anti-isomers are greater than that for syn-isomers in these types of systems. The ratio of anti- and syn- isomers was determined by the relative areas for NH in ^{1}H-NMR spectra after purification. For example, integration of these signals for 4a, comparing the anti-diastereomer at d 5.81 d (J = 8.29 Hz) to the syn-diastereomer at d 5.67 (d, J = 7.69 Hz), gave a 97:3 ratio. All of the products had high antiselectivity.

The prominent advantages of the proposed method are simple conditions, easy workup, low toxicity, shorter reaction time, antiselectivity and higher yields compared to traditional methods.

To investigate mutagenic and antimutagenic properties of various synthetic substances is a very important strategy owing to their large-scale usefulness in

medicine (Agar et al., 2010; Avunduk et al., 2008; Gulluce et al., 2010).

According to the mutagenicity assay results, as shown in Table 2, the test compounds do not have mutagenic potential for *S. typhimurium* TA1535 and *E. coli* WP2uvrA at tested concentrations.

The possible antimutagenic potential of test materials was examined against NaN_3 and MNNG in *S. typhimurium* TA1535 and *E. coli* WP2uvrA, respectively. The results were evaluated using standard plate incorporation method and summarized in Table 3, showing the antimutagenic activities of test materials, which were tested at three different concentrations (0.01, 0.1, and 1 mM/plate).

In the antimutagenicity assays performed with *E. coli* WP2uvrA strain, all of test compounds exhibited antimutagenic activity at various test concentrations between 0.01 and 1 mM/plate except 1 mM/plate of 4a, 0.1, and 1 mM/plate of 4b (Table 2). The inhibition rates of these substances were between 25.6% (4b—0.01 mM/plate) and 49.5% (4e—1 mM/plate).

Besides, all of test compounds also showed antimutagenic activity on *S. typhimurium* TA1535 at all tested concentrations, except 0.01, 0.1 and 1 mM/plate of 4b (Table 3). The inhibition rates of these substances were between 25.0% (4c—1 mM/plate) and 47.8% (4e—0.01 mM/plate).

Conclusions

The coupling reactions of cyclohexanone, various substituted aromatic amines and aromatic or heteroaromatic aldehydes were performed well under ultrasonic irradiation with bismuth(III) triflate in water at room temperature. In addition to the good yields and antiselectivity it provides, the versatility, convenience of operation, low cost, and environmental friendliness of this method, making it a green, rapid, highly efficient and practical one in preparing β-aminoketone derivatives.

The results obtained from the mutagenicity assays showed that all tested materials (4a-e) did not have mutagenic activity in *S. typhimurium* TA1535 and *E. coli* WP2uvrA strains at all tested concentrations.

In the antimutagenicity assays, it was shown that all tested materials (4a-e except 4b) have antimutagenic activity in *E. coli* WP2uvrA and *S. typhimurium* TA1535 strains at various tested concentrations including 0.01, 0.1 and 1 mM/plate. The mutagens used to determine the antimutagenic activity of the tested substances in this study were NaN_3 for TA1535 and MNNG for WP2uvrA.

In conclusion, all substances, which were investigated in the present study, can be considered genotoxically safe at the tested concentrations and some of them provided important antimutagenic properties. These activities are valuable toward an extension of the use of these drugs as new phytotherapeutic or preservative ingredients, besides their consolidated ethnomedical use.

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