Article

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Facile Heterocyclic Synthesis and Antibacterial Activity of Substituted Isoxazol-5(4*H*)-ones

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An efficient, simple, and green procedure for the synthesis of isoxazol-5(4*H*)-one derivatives are described here through a convenient one-pot, three-component reaction at room temperature. The title compounds are isolated in high to excellent yields and after short reaction times, and are characterized by various spectroscopic methods such as IR, ^{1}H NMR, and ^{13}C NMR. The synthesized compounds **4a–c** and **4e–i** were tested for their in vitro activity against a panel of Gram-positive and Gram-negative bacteria, demonstrating their ability to inhibit microorganisms with a zone of inhibition ranging from 15 to 30 mm, minimum inhibitory concentration between 250 and 900 μg/mL, and minimum bacterial concentration between 700 and 1000 μg/mL.

Keywords: 3-Methyl-4-arylmethylene-isoxazol-5(4*H*)-ones; One-pot synthesis; Aqueous media; Lithium bromide; Antimicrobial activity.

INTRODUCTION

Heterocyclic compounds are of great importance to both medical and organic chemists, and their synthesis continues to represent a challenge from both academic and industrial perspectives.[1,2] Isoxazol-5(4*H*)-ones are important five-membered heterocycles characterized by a nitrogen–oxygen bond and are useful in the syntheses of various other heterocycles such as 1,3-oxazin-6-ones, pyrroles, imidazoles, tetrahydropyridines, pyridopyrimidines, and 2*H*-azirines.[3–8] Additionally, isoxazol-5(4*H*)-one derivatives have attracted much interest because of their significant pharmaceutical and therapeutic properties such as antibacterial, anticonvulsive, antifungal, and antidiabetic,[9–13] anti-androgenic, anticancer, and hypoglycemic.[2,9–12,14] Isoxazol-5(4*H*)-one derivatives are described as gamma-aminobutyric acid (GABA)-A receptors, potent inhibitors of PTP1B.[15,16] They act as inhibitors of the tumor necrosis factor-alpha.[17,18] It has been reported that 3,4-disubstituted isoxazol-5(4*H*)-one derivatives can be prepared using sodium sulfide in ethanol at room temperature[19] sodium acetate by visible light in aqueous ethanol[20] pyridine in H_2O under ultrasonic irradiation[21] and also KHP in H_2O at 50 °C.[22]

Carbon–carbon and carbon–heteroatom bond-forming reactions are the most important reactions in organic synthesis; these reactions are simple, fast, and efficient for chemical synthesis. They have considerable economic and ecological benefits.[23–26] Among the reactions, multicomponent reactions (MCR) are efficient methods for the synthesis of heterocyclic compounds, which have posed a real challenge in organic synthesis.[27–32] In the present work, we have developed a new multicomponent synthesis of arylmethylene-isoxazol-5(4*H*)-ones using lithium bromide as catalyst.

The use of lithium bromide as a mild Lewis acid to promote various organic transformations is well documented in the literature.[33–36] In particular, it has been found that lithium bromide efficiently catalyzes the Cannizzaro, Tichchenko, and Meerwein–Ponndorf–Verley reactions.[37]

In continuation of our work in catalysis, we here report a one-pot synthesis of 3-methyl-4-arylmethylene-isoxazol-5-(4*H*)-ones by a three-component reaction catalyzed by lithium bromide. This catalyst leads to

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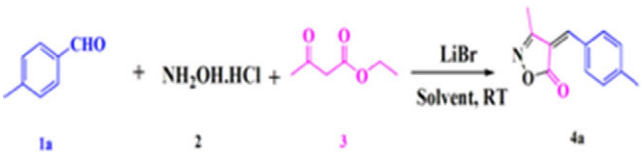
efficient yields (70–98%) using different aromatic aldehydes. Compared to previously published work,[22,38] this protocol has promising characteristics for the response of the reaction, such as a shorter reaction time, easy treatment, ease of separation of the pure product via simple filtration with high yields, and simplicity of the experimental procedure. This method is operationally simple and eco-friendly. In addition, some of the synthesized compounds were evaluated for their antimicrobial activity. Three of the compounds tested were highly promising because they showed very good antibacterial activity against all the three used strains.

RESULTS AND DISCUSSION

3-Methyl-4-arylmethylene-isoxazol-5(4*H*)-one derivatives were synthesized from substituted aromatic aldehydes, mostly with electron-donating (ED) substituents. Mechanistic insights to the envisioned reaction suggested that high to medium polarity should be the primary factor contributing to the success of the reaction. We therefore decided to try lithium bromide, a cheap inorganic salt, as catalyst in water. The eventual success of the reaction in those conditions would clearly prove us right. On this basis, a one-pot reaction was performed using equimolar amounts of ethyl acetoacetate, hydroxylamine hydrochloride, and *p*-tolualdehyde in water, at room temperature (Scheme 1).

In a first set of optimization experiments, various amounts of LiBr were tried to study the influence of the catalyst upon the reaction behavior. As shown in Table 1, when the reaction was performed in the absence of the catalyst, the isoxazol-one product was obtained with a modest 49% yield (entry 1). When lithium bromide was used up to 5 mol%, the yield of **4a** increased from 49% to 90% (Table 1, entries 2–4). However, when the catalyst amount was further raised to 10 mol%, the yield of compound **4a** increased to 98% (Table 1, entry 5). A subsequent increase in the catalyst



Scheme 1. General operative conditions for the synthesis of arylmethylene-isoxazol-5(4*H*)-one derivatives.

Table 1. First set of optimization experiments: The effect of the catalyst amount on the synthesis of 4-(4-methyly-benzylidene)-3-methylisoxazol-5(4*H*)-one

Entry	Catalyst (mol%)	*T* (°C)	Time[1]	Yield (%)[2]
1	—	RT = 23	4 h	49
2	1	RT	2 h 30 min	60
3	2.5	RT	2 h 30 min	80
4	5	RT	2 h	90
5	10	RT	1 h 30 min	98
6	15	RT	1 h 30 min	98
7	20	RT	1 h 30 min	96
8	10	RT	2 h	98
9	10	RT	2 h 30 min	98
10	10	RT	5 h	98

[1] Progress of the reaction was monitored by TLC analysis.
[2] Isolated yield of product.

amount of up to 20% did not improve the yield, however (Table 1, entries 6–7). Consequently, 10 mol% of LiBr was selected as the preferred amount for further experiments.

In order to investigate the influence of the solvents, the model reaction between ethyl acetoacetate, hydroxylamine hydrochloride, and *p*-tolualdehyde was carried out in various solvents such as polar protic (EtOH, H_2O), polar aprotic (acetone, DMF, CH_2Cl_2), and also apolar (pentane, 1,4-dioxane) solvents. As shown in Table 2, the reaction proceeded well in ethanol (Table 2, entry 2) and water (Table 2, entry 1), whereas in the other solvents the yields varied from 30% to 92%. The general trend was that the yield improved upon increased solvent polarity, pure water

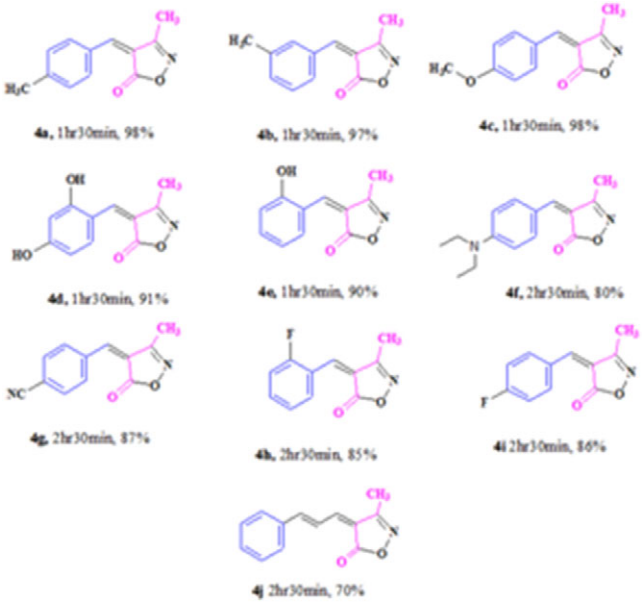
Table 2. Second set of optimization experiments: The synthesis of 4-(4-methyly-benzylidene)-3-methylisoxazol-5(4*H*)-one using various solvents

Entry	Solvent	Time	Yield (%)[1]
1	H_2O	1 h 30 min	98
2	EtOH	1 h 30 min	80
3	Acetone	1 h 30 min	30
4	1,4-Dioxane	1 h 30 min	45
5	Pentane	1 h 30 min	44
6	CH_2Cl_2	1 h 30 min	60
7	DMF	1 h 30 min	65
8	EtOH–H_2O 1:1	1 h 30 min	86
9	EtOH–H_2O 1:2	1 h 30 min	92

[1] Isolated yield of product.

offering the best results. This second set of experiments clearly demonstrated that medium polarity is in fact the major parameter leading to the success of the reaction.

A three-component one-pot procedure (3-MCR) was developed to assemble the isoxazol-one nucleus from commercially available materials. This new methodology affords the desired products in high yields. The compounds could be obtained in crystalline form of almost analytical quality from the reaction mixture and without the use of chromatography. The results of these reactions are regressed in Scheme 2. It was observed that aromatic aldehydes containing ED groups participate in the reaction, giving products in excellent yields. In addition, reaction with unsaturated aldehydes such as cinnamaldehyde was carried out, which resulted in product formation with high yield (**4j**). What was surprising, yet very satisfying, was the case of aromatic aldehydes with electron-withdrawing groups (EWGs), such as 4-CN (**4g**), which led to the corresponding isoxazol-5(4*H*)-ones derivatives still in good yields (85–88%). To our knowledge, no other method has been able to generate this type of yield in the case of EWGs under simple and inexpensive conditions. Some authors have in fact described the use of EWGs but could obtain only traces of the desired compounds.[20,22]



Scheme 2. Synthesis of isoxazol-5(4*H*)-one derivatives **4a–j** using various aldehydes.

Finally, we looked at the recovery and recycling impact of the reaction medium, since all synthesized compounds were crystalline in nature. Hence, after performing its synthesis on a 12.4 g scale (0.1 mol), compound **4g** was filtered off (85% yield), and the obtained filtrate was directly reused in the synthesis of another 12.4 g batch. The operative conditions were maintained identical to the previous ones, thus allowing for the isolation of compound **4g** with 83% yield in the second run. Once again, the filtrate was reused a third time, still using the same conditions and amounts, resulting in another 85% yield. We therefore believe that these operative conditions can be very practical and of great interest for industrial use, owing to the possibility of medium recycling.

Determination of antibacterial activity

The in vitro antibacterial activity evaluation of our compounds was carried out by the cup-plate agar diffusion method,[39,40] based on the recommendations of the National Clinical Committee Laboratory Standards (NCCLS). The strains of pathogenic bacteria used are responsible for foodborne illness (G+ *Clostridium perfringens* [CECT 486]/G−: *Escherichia coli* [CECT 515], *Enterococcus faecium* [DSM 20477]) and are classified according to the inhibitory diameter. Gentamicin (CN 120) and ampicillin (AM 50) were used as standard drugs for comparing antibacterial activity. The Mueller–Hinton sterilized agar medium was poured into Petri dishes and allowed to solidify. On the surface of the medium, microbial suspensions were spread, and cavities were hollowed out using a glass cylinder of 6 mm diameter (presterilized) and a micropipette. Fifty microliters of each of the synthesized compounds (with a final concentration of 1000 μg/mL) was placed serially in the cavities to diffuse, with dimethyl sulfoxide (DMSO) as the solvent for all compounds and as control. These Petri dishes were incubated at 37 °C for 24 h. The inhibition zone was observed around the cavities after incubation and measured.

The antibacterial activity of the various compounds was examined against the selected bacterial strains (*E. coli* [CECT 515], *C. perfringens* [CECT 486], and *E. faecium* [DSM 20477]) using the cup-plate agar diffusion method. The diameters of the inhibition zone were compared, and the results are grouped in the Table 3. Compounds **4**-F, **4**-CH_3, and **2**-OH showed a

very good antibacterial activity against all the tree used strains. They also showed better activity when compared with standard drug (CN120) and AM50. The rest of the compounds showed moderate to good antibacterial activity except **4**-$N(CH_3)_2$ which showed complete resistance to all the strains. The compound **4**-CN showed the same antibacterial activity against *E. coli* and *E. faecium*, whereas compound **2**-F and **4**-OMe were found to be effective against only one strain (*E. faecium* and *C. perfringens*, respectively).

The evaluation of the antibacterial activity of the various compounds tested against the three bacterial strains showed good antibacterial activity.

The minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) were determined in a liquid medium (Mueller–Hinton broth)[41] on compounds inhibiting the growth of one or more microorganisms tested in the medium diffusion method. The technique consists of inoculating the same amount of bacteria in a series of tubes filled with the tested compounds dissolved in DMSO and then diluted in Mueller–Hinton broth at concentrations ranging from 50 to 1000 μg/mL. After 24 h of incubation at 37 °C, the first tube in which no microbial growth is observed gives by definition the MIC in μg/mL. MBC was found out by taking samples in the tubes without visible growth, which were then seeded in an agar medium. After 24 h of incubation at 37 °C, the values of the MBC obtained are given in Table 4. Compound **4i** was found to have a broad antimicrobial spectrum with MIC of 250 μg/mL and MBC of 900 μg/mL.

Table 3. Antibacterial activity of isoxazol-ones (the inhibition zone is in mm)

Compounds	CECT 515	CECT 486	DSM 20477
4a	20	20	25
4g	15	(−) *R*	15
4c	(−) *R*	15	(−) *R*
4h	(−) *R*	(−) *R*	20
4i	30	20	25
4b	15	20	(−) *R*
4e	15	20	20
4f	(−) *R*	(−) *R*	(−) *R*
(CN120)	25	26	30
(AM50)	20	12	15

(−) *R*: resistance.

Table 4. MIC (μg/mL) and MBC (μg/mL) results of compounds

		CECT 515	CECT 486	DSM 20477
4a	MIC	700	250	500
	MBC	1000	700	900
4g	MIC	500	—	500
	MBC	900	—	900
4c	MIC	—	900	—
	MBC	—	500	—
4h	MIC	—	—	900
	MBC	—	—	500
4i	MIC	250	250	250
	MBC	900	900	900
4b	MIC	500	500	—
	MBC	900	900	—
4e	MIC	700	500	700
	MBC	1000	900	1000

MBC, minimum bactericidal concentration; MIC, minimum inhibitory concentration.

EXPERIMENTAL

A mixture of ethyl acetoacetate (10 mmol), hydroxylamine hydrochloride (10 mmol), aromatic aldehyde (10 mmol), and 10% of lithium bromide was stirred in water (5 mL) at room temperature. After the completion of the reaction (monitored by thin-layer chromatography [TLC]), the solid obtained was filtered off and washed with diethyl ether. The desired product was isolated in high yields in the essentially pure form.

*(Z)-4-(4-Methylbenzylidene)-3-methylisoxazol-5(4H)-one (**4a**).* Yield: 98%, m.p. 132–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_{ppm} 8.21–8.19 (2H, d, J = 8.00 Hz, $H_{aromatic}$); 7.3245 (1H, s, CH); 7.25–7.23 (2H, d, J = 8.00 Hz, $H_{aromatic}$); 2.37 (3H, s, CH_3); 2.21 (3H, s, CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ_{ppm} 168.22; 161.23; 149.98; 145.73; 134.15; 129.95; 129.89; 118.41; 22.06; 11.63 ppm. IR (neat/cm^{-1}): 1730.40; 1698.34; 1169.28.

*(Z)-4-(3-Methylbenzylidene)-3-methylisoxazol-5(4H)-one (**4b**).* Yield: 97%; m.p. 141–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_{ppm} 8.13 (1H, br, $H_{aromatic}$); 8.05 (1H, s, CH); 7.32 (3H, br, Haromatic); 2.35 (3H, s, CH_3); 2.21 (3H, s, CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ_{ppm} 167.94; 161.19; 150.28; 138.83; 134.99; 134.41; 132.32; 131.04; 128.80; 119.35; 21.29; 11.64 ppm. IR (neat/cm^{-1}): 1728.36; 1693.32; 1165.36.

(Z)-4-(4-Methoxybenzylidene)-3-methylisoxazol-5(4H)-one (***4c***). Yield: 98%. m.p. 175–176 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ_{ppm} 8.38–8.36 (2H, d, J = 8.00 Hz, $H_{aromatic}$); 7.27 (1H, s, CH); 6.95–6.93 (2H, d, J = 8.00 Hz, $H_{aromatic}$); 3.85 (3H, s, OCH_3); 2.21 (3H, s, CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ_{ppm} 168.78;164.62; 161.29; 149.37; 136.97; 125.83; 116.33; 114.66; 55.71; 11.64 ppm. IR (neat/cm^{-1}) 1726.37; 1648.12; 1112.23.

(Z)-4-(2,4-Dihydroxybenzylidene)-3-methylisoxazol-5(4H)-one (***4d***). Yield: 91%, m.p. 233–234 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 11.15 (2H, s, OH); 9.00–8.98 (1H, d, J = 8.00 Hz, $H_{aromatic}$); 7.96 (1H, s, CH), 6.45–6.40 (3H, t, $H_{aromatic}$), 2.20 (3H, s, CH_3) ppm. ^{13}C NMR (400 MHz, DMSO-d_6): δ_{ppm} 169.90, 167.13, 163.61, 162.70, 144.42, 135.64, 113.52, 111.05, 109.52, 102.20, 11.66 ppm. IR (neat/cm^{-1}): 1719.36; 1673.36; 1055.36.

(Z)-4-(2-Hydroxybenzylidene)-3-methylisoxazol-5(4H)-one (***4e***). Yield: 90%, m.p. 203–204 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} 11.00 (1H, s, OH); 8.75–8.73(1H, d, J = 8.00 Hz, $H_{aromatic}$); 8.09 (1H, s, CH), 7.47–7.51 (1H, t, $H_{aromatic}$), 7.03–7.00 (1H, d, J = 12 Hz, $H_{aromatic}$), 6.95–6.91 (1H, t, $H_{aromatic}$), 2.26 (3H, s, CH_3) ppm, ^{13}C NMR (400 MHz, DMSO-d_6): δ_{ppm} 168.73, 162.59, 160.11, 145.45, 137.19, 132.78, 119.95, 119.56, 116.90, 116.60, 11.65 ppm. IR (neat/cm^{-1}): 1770.02; 1670.25; 1080.25.

4-(4-(Dimethylamino)benzylidene)-3-methylisoxazol-5(4H)-one (***4f***). Yield: 85%; m.p. 225–226 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_{ppm} 2.23 (s, 3H, CH_3); 3.15 (6H, s, $N(CH_3)_2$); 6.71–6.73 (2H, d, J = 8 Hz, $H_{aromatic}$); 7.21 (s, 1H, CH), 8.39–8.41 (2H, d, J = 8 Hz, $H_{aromatic}$) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ_{ppm} 170.25; 162.08; 154.71; 149.10; 127.02; 125.22; 124.71; 111.53; 40.05; 11.64 ppm; IR (neat/cm^{-1}): 1780.25, 1626.0.36; 1012.36.

(Z)-4-((3-Methyl-5-oxoisoxazol-4(5H)-ylidene) methyl) benzonitrile (***4g***). Yield: 87%; m.p. 193–194 °C, ^{1}H NMR (400 MHz, DMSO-d_6):): δ_{ppm} 8.46–8.44 (2H, d, J = 8.00 Hz, $H_{aromatic}$); 8.06–8.04 (3H, t, CH + $H_{aromatic}$); 2.31 (3H, s, CH_3) ppm, ^{13}C NMR (400 MHz, DMSO-d_6):): δ_{ppm} 167.73; 162.53; 149.29; 136.56; 133.68; 132.92, 130.34, 122.35, 118.74, 115.09, 11.74 ppm. IR (neat/cm^{-1}): 1720.70; 1675.30; 1055.50; 2265.25.

(Z)-4-(4-Fluorobenzylidene)-3-methylisoxazol-5(4H)-one (***4h***). Yield: 86%; m.p. 139–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_{ppm} 8.38–8.35 (2H, m, $H_{aromatic}$); 7.33 (1H, s, CH); 7.14–7.10 (2H, m, $H_{aromatic}$); 2.23 (3H, s, CH_3) ppm, ^{13}C NMR (400 MHz, $CDCl_3$): δ_{ppm} 168.04; 167.23; 164.65; 161.10; 148.37; 136.77 (d, J = 36 Hz); 128.87 (d, J = 12 Hz); 119.17 (d, J = 8 Hz); 116.58; 116.36; 11.60 ppm. IR (neat/cm^{-1}): 1723.36; 1650.36; 1065.36.

(Z)-4-(2-Fluorobenzylidene)-3-methylisoxazol-5(4H)-one (***4i***). Yield: 85%; m.p. 159–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_{ppm} 8.22–8.19 (1H, d, J = 8.00 Hz, $H_{aromatic}$); 7.92–7.90 (1H, d, J = 12 Hz, $H_{aromatic}$); 7.45–7.39 (1H, m, $H_{aromatic}$); 7.32 (1H, s, CH); 7.24–7.19 (1H, m, $H_{aromatic}$); 2.24 (3H, s, CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ_{ppm} 167.50; 163.76; 161.30; 160.91; 148.11 (d, J = 12 Hz); 134.00 (d, J = 32 Hz); 130.54 (d, J = 32); 129.87 (d, J = 12 Hz); 121.02 (d, J = 84 Hz); 119.72 (d, J = 92 Hz); 11.59 ppm. IR (neat/cm^{-1}): 1731.15; 1640.98.

(Z)-3-Methyl-4-((E)-3-phenylallylidene)isoxazol-5(4H)-one (***4j***). Yield: 70%; m.p. 172–173 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_{ppm} 8.35–8.28 (dd, J = 12 Hz, 1H, CH), 7.66–7.64 (2H, m, CH□CH), 7.44–7.43 (3H, m, $H_{aromatic}$),; 7.32–8.26 (2H, m, $H_{aromatic}$); 2.25 (s, 3H, CH_3)ppm ^{13}C NMR (400 MHz, $CDCl_3$): δ_{ppm} 168.94; 159.78; 151.31; 147.45; 135.00; 131.53; 129.18; 128.93; 122.47; 117.99; 11.15 ppm. IR (neat/cm^{-1}): 1735.00; 1670.21.

CONCLUSIONS

In conclusion, we have developed a simple and green process to access substituted isoxazol-5(4*H*)-ones using lithium bromide as catalyst in water. A library of aromatic aldehydes was constructed under those conditions, which can be generalized for the synthesis of other substituted isoxazol-5(4*H*)-ones. The process is easy and can accommodate multi-gram scale syntheses, thus making it attractive for industrial use. The evaluation of the antibacterial activity of the various compounds tested against three bacterial strains showed good activity.

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SUPPORTING INFORMATION

Additional supporting information is available in the online version of this article.

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