

Synthesis and characterization of some novel 4-furyl substituted 3-imidazoline 3-oxides

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Abstract

Novel 4-furyl substituted 3-imidazoline 3-oxides were synthesized by the reaction of 2-bromo-1-(2-furanyl)ethanone oxime with aromatic amines and aldehydes, including formaldehyde, using one pot procedures involving the reactions of in situ formed α -amino oximes with aldehydes and also by one pot procedures involving the reactions of in situ formed imines with α -halo oximes.

Keywords: Furan, 3-imidazoline 3-oxide

Introduction

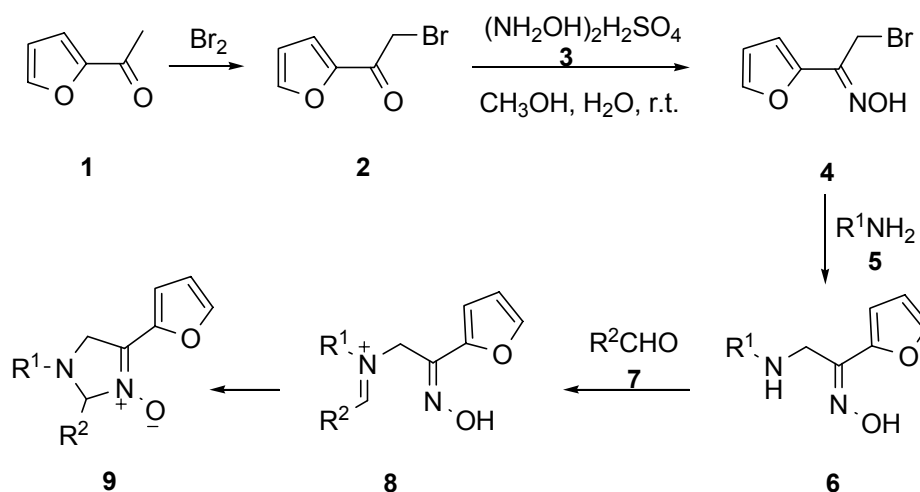
Cyclic nitrones, which are heterocyclic compounds containing an azomethine *N*-oxide group, have a wide range of synthetic potentialities.¹ This is due to the fact that, as in the case of heterocyclic *N*-oxides², the *N*-oxide oxygen atom activates them with respect to electrophilic, nucleophilic and radical reagents. In addition, the ability of the nitrones to undergo 1,3- and 1,4-cycloaddition reactions makes it possible to use them in the synthesis of various heterocyclic systems, including natural compounds.^{3,4}

In the literature, some papers have been found about the substituted 3-imidazoline 3-oxides containing phenyl, methyl, methoxy, amino, nitro, nitroso, hydroxy groups as substituents at different positions.⁵ The synthesis of 1,4-diaryl and 1,2,4-triaryl imidazoline 3-oxides containing a phenyl ring as aryl groups have been reported^{6a-d} and these *N*-oxides have been used as dipoles in [3+2] cycloaddition reactions with various dipolarophiles to obtain biologically important isoxazolidine and isoxazoline rings.^{7a-f}

There is no data about the 4-furyl substituted 3-imidazoline 3-oxides in the literature. In the present work, a series of novel 4-furyl substituted 3-imidazoline 3-oxides have been synthesized and will be used as dipoles in [3+2] cycloaddition reactions in forthcoming studies because of the importance of the furan ring. Furan, as one of the representative five-membered heterocycles, is found in many naturally occurring compounds.⁸ Besides this, oxidation of furan rings gives useful intermediates for the synthesis of new compounds.^{9,10}

Results and Discussion

Monobromination of acetyl furan **1** produces 2-bromo-1-(2-furanyl)ethanone **2**¹¹ (Scheme 1). Then, its reaction with hydroxylamine sulfate **3** yields 2-bromo-1-(2-furanyl)ethanone oxime **4**¹². Substitution reaction of 2-bromo-1-(2-furanyl)ethanone oxime **4** with an aromatic amine **5** gives amino oxime **6** and the condensation reaction of amino oxime **6** with an aldehyde **7** affords an imino oxime **8**. Cyclization reaction of this imino oxime **8** yields 4-furyl substituted 3-imidazoline 3-oxides **9** in a similar way as in literature.^{6c} The overall synthetic pathway is shown in Scheme 1 and the results are summarized in Table 1.



Scheme 1

Cyclizations were carried out in ethanol at room temperature. In the ^1H NMR spectrum of nitrone **9a**, CH_3 protons belonging to a tolyl group gave a singlet at δ 2.20. CH_2 protons at C-4 and C-5 appeared as triplets at δ 4.65 and 5.25, respectively. Protons of the tolyl group show two doublets at δ 6.44 and 7.07. On the other hand, furyl group protons appeared as a doublet of doublets at δ 6.58; a singlet at δ 7.48 and a doublet at δ 7.79.

In the ^1H NMR spectrum of 2-arylsubstituted nitrone **9b**, CH_3 protons belonging to the tolyl group gave a singlet at δ 2.15. CH_2 protons at C-5 gave a doublet of doublets at δ 4.73 and 5.05, the CH proton between two nitrogen atoms at C-2 appeared as a doublet of doublets at δ 6.06. Protons of the tolyl group show two doublets at δ 6.43 and 6.95. On the other hand, furyl group protons appeared as a doublet of doublets at δ 6.54 and two doublets at δ 7.47 and 7.71, respectively. Protons of phenyl group appeared as multiplets at δ 7.30-7.37 and 7.51-7.57.

Table 1. 1,2-Diaryl-4-(2-furyl)-3-imidazoline-3-oxides (**9a-h**)

R ¹	R ²	Yield of (9a-h) from 4 (%)		Mp (°C)
		Method A	Method B	
9a 4-MeC ₆ H ₄	H	20	50	194-198
9b 4-MeC ₆ H ₄	Ph	30	30	195-200
9c 4-MeC ₆ H ₄	4-MePh	58	55	164-166
9d 4-MeC ₆ H ₄	4-MeOPh	56	59	208-212
9e 4-MeOC ₆ H ₄	H	20	40	182-184
9f 4-MeOC ₆ H ₄	4-MePh	32	-	192-196
9g Ph	4-MePh	49	50	178-182
9h Ph	4-MeOPh	49	53	166-168

Conclusions

In summary, some novel 4-furyl substituted 3-imidazoline 3-oxides were synthesized. The methods that were used in this study are easy and short to synthesize potentially biologically active compounds. It has been thought that these new compounds can have some biological activities because of the imidazoline and furan moieties presented in their structures. Also, these novel 4-furyl substituted 3-imidazoline 3-oxides will be used as dipoles in [3+2] cycloaddition reactions in forthcoming studies.

Experimental Section

General Procedures. Melting points were recorded on Stuart Scientific SMP 1 instrument. IR spectra were recorded on Jasco FT-IR spectrometer, NMR spectra were recorded on Bruker DPX-400 High Performance Digital FT-NMR and on Varian Mercury 400 MHz FT-NMR spectrometer (Varian Inc., Palo Alto, CA, USA). The Mass spectra were taken on a Waters ZQ micromass LC-MS spectrometer (Waters Corporation, Milford, MA, USA) by using ESI (+) method. Elemental analyses were performed on LECO 932 CHNS (Leco-932, St. Joseph, MI, USA) instrument and were within ± 0.4 % of the theoretical values; they were performed at Scientific and Technical Research Council of Turkey, Test and Analyses Laboratory, Ankara and Central Laboratory of Pharmacy Faculty of Ankara University, Turkey.

2-Bromo-1-(2-furanyl)ethanone (2).¹¹ Under a nitrogen atmosphere, bromine (38 mmol) was added dropwise over a 30 min. period to an ice-cold solution of 3.303 g (30 mmol) of 2-acetylfuran **1** in 18 ml of dioxane-ether (1:2). The reaction mixture was warmed to ambient temperature and stirred for 12 h., then quenched with 20 ml of saturated aqueous ammonium

chloride. The organic extract was dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The residue was purified by column chromatography using hexane-ethyl acetate as eluent and the product **2** was obtained as a light yellow semisolid (3.97 g, 70%, mp: 28-32 °C).

2-Bromo-1-(2-furanyl)ethanone oxime (3).¹² 2-Bromo-1-(2-furanyl)ethanone **2** (16.5 mmol) was dissolved in minimum amount of methanol and hydroxylamine sulfate **3** (16.5 mmol) dissolved in minimum amount of water was added on it. Reaction mixture was stirred for one day under argon atmosphere. Methanol was then removed, and extraction was made with benzene. Organic phase was dried and solvent was evaporated. Crystallization from chloroform afforded oxime **4** (2.03 g, 60%).

1,2-Diaryl-4-(2-furyl)-3-imidazoline-3-oxides (9a-h). General procedure.^{6c} All 1,2-diaryl-4-(2-furyl)-3-imidazoline-3-oxides (**9a-h**) were synthesized according to two methods which are given below.

Method A

To a solution of aromatic amine **5** (5 mmol) in 10 ml ethanol 2-bromo-1-(2-furanyl)ethanone oxime **4** (2.5 mmol) was added and the resulting mixture was stirred for 20 min., then aromatic aldehyde **7** was added and the resulting mixture was stirred for 3 h. at room temperature. The formed precipitate was collected by filtration and recrystallized from ethanol.

Method B

To a solution of aniline derivative **5** (5 mmol) in 10 ml ethanol aromatic aldehyde **7** (5 mmol) was added and the resulting mixture was stirred for 20 min. 2-Bromo-1-(2-furanyl)ethanone oxime **4** (2.5 mmol) was then added and the mixture was stirred overnight at room temperature. The formed precipitate was collected by filtration and recrystallized from ethanol.

4-Furan-2-yl-1-*p*-tolyl-3-imidazoline 3-oxide (9a). IR (KBr) ν C=N 1574 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 2.20 (3H, s), 4.65 (2H, t, *J* = 4.3), 5.25 (2H, t, *J* = 4.3), 6.44 (2H, d, *J* = 8.4), 6.58 (1H, dd, *J* = 1.8, 3.6), 7.07 (2H, d, *J* = 8.3), 7.48 (1H, s), 7.79 (1H, d, *J* = 3.4). ¹³C NMR (100 MHz, CDCl₃) δ 20.4, 51.4, 111.8, 112.7, 115.3, 128.2, 130.3, 131.2, 142.1, 143.3, 144.1. ESI (+) *m/e* 243 (M+1, 100). Anal. calcd. for C₁₄H₁₄N₂O₂ · 0.1 HOH : C, 68.89; H, 5.86; N, 11.47. Found: C, 68.82; H, 5.79; N, 11.26.

4-Furan-2-yl-2-phenyl-1-*p*-tolyl-3-imidazoline 3-oxide (9b). IR (KBr) ν C=N 1572 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 2.15 (3H, s), 4.73 (1H, dd, *J* = 3.1, 14.8), 5.05 (1H, dd, *J* = 5.5, 14.8), 6.06 (1H, dd, *J* = 3.1, 5.5), 6.43 (2H, d, *J* = 8.4), 6.54 (1H, dd, *J* = 1.6, 3.3), 6.95 (2H, d, *J* = 8.4), 7.30-7.37 (3H, m), 7.47 (1H, d, *J* = 1.0), 7.51-7.57 (2H, m), 7.71 (1H, d, *J* = 3.5). ¹³C NMR (100 MHz, CDCl₃) δ 20.3, 51.1, 88.4, 112.6, 112.7, 115.2, 127.9, 128.2, 128.6, 128.9, 130.0, 130.1, 135.7, 141.9, 143.6, 144.0. ESI (+) *m/e* 319 (M+1, 100). Anal. calcd. for C₂₀H₁₈N₂O₂ · 0.1 HOH : C, 75.03; H, 5.73; N, 8.75. Found: C, 74.61; H, 5.99; N, 8.97.

4-Furan-2-yl-1,2-di-*p*-tolyl-3-imidazoline 3-oxide (9c). IR (KBr) ν C=N 1570 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 2.23 (3H, s), 2.34 (3H, s), 4.79 (1H, dd, *J* = 3.2, 14.8), 5.11 (1H, dd, *J* = 5.6, 14.8), 6.09 (1H, dd, *J* = 3.2, 5.6), 6.51 (2H, d, *J* = 8.8), 6.606 (1H, dd, *J* = 1.6, 3.6), 7.03 (2H, d, *J* = 8.4), 7.21 (2H, d, *J* = 8.4), 7.48 (2H, d, *J* = 7.6), 7.55 (1H, d, *J* = 0.8), 7.78 (1H, d, *J* = 3.6). ¹³C

NMR (100 MHz, CDCl₃) δ 20.50, 21.53, 51.24, 88.51, 112.85, 115.25, 127.99, 128.25, 128.58, 129.86, 130.20, 132.97, 140.28, 142.22, 143.86, 144.10. ESI (+) m/e 333 (M+1, 100). Anal. calcd. for C₂₁H₂₀N₂O₂ · 1.2HOH : C, 71.28; H, 6.38; N, 7.91. Found: C, 71.34; H, 6.01; N, 7.52.

4-Furan-2-yl-2-(4-methoxyphenyl)-1-*p*-tolyl-3-imidazoline 3-oxide (9d). IR (KBr) ν C=N 1570 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 2.23 (3H, s), 3.79 (3H, s), 4.78 (1H, dd, *J* = 3.2, 14.8), 5.12 (1H, dd, *J* = 5.2, 14.8), 6.08 (1H, dd, *J* = 3.2, 5.2), 6.43 (2H, d, *J* = 8.2), 6.52 (2H, d, *J* = 8.8), 6.61 (1H, dd, *J* = 1.6, 3.6), 6.93 (2H, d, *J* = 8.8), 7.04 (2H, d, *J* = 8.0), 7.53 (1H, d, *J* = 8.4), 7.54 (2H, s), 7.78 (1H, d, *J* = 3.6). ¹³C NMR (100 MHz, CDCl₃) δ 20.53, 51.22, 55.56, 88.29, 112.88, 112.93, 114.61, 115.26, 127.90, 128.31, 128.48, 129.41, 130.21, 142.27, 143.86, 144.13, 161.20. ESI (+) m/e 349 (M+1, 100). Anal. calcd. for C₂₁H₂₀N₂O₃ · 0.01 HOH : C, 72.35; H, 5.78; N, 8.03. Found: C, 72.23; H, 5.63; N, 8.13.

4-Furan-2-yl-1-(4-methoxyphenyl)-3-imidazoline 3-oxide (9e). IR (KBr) ν C=N 1572 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 3.70 (3H, s), 4.63 (2H, t, *J* = 4.2), 5.20 (2H, t, *J* = 4.2), 6.45-6.51 (2H, m), 6.58 (1H, dd, *J* = 1.8, 3.6), 6.82-6.87 (2H, m), 7.48 (1H, s), 7.78 (1H, d, *J* = 3.4). ¹³C NMR (100 MHz, CDCl₃) δ 51.8, 55.8, 77.1, 112.7, 112.9, 115.3, 115.4, 131.3, 138.8, 143.3, 144.1, 153.0. ESI (+) m/e 259 (M+1, 100). Anal. calcd. for C₁₄H₁₄N₂O₃ · 0.33 HOH : C, 63.64; H, 5.59; N, 10.60. Found: C, 63.65; H, 5.54; N, 10.31.

4-Furan-2-yl-1-(4-methoxyphenyl)-2-*p*-tolyl-3-imidazoline 3-oxide (9f). IR (KBr) ν C=N 1570 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 2.34 (3H, s), 3.72 (3H, s), 4.76 (1H, dd, *J* = 3.6, 15.2), 5.10 (1H, dd, *J* = 5.6, 15.2), 6.06 (1H, dd, *J* = 3.6, 5.6), 6.55 (2H, dd, *J* = 2.4, 7.2), 6.61 (1H, dd, *J* = 1.6, 3.6), 6.81 (2H, dd, *J* = 2.4, 6.8), 7.22 (2H, d, *J* = 8.0), 7.50 (2H, d, *J* = 8.4), 7.54 (1H, d, *J* = 1.6), 7.78 (1H, d, *J* = 3.6). ¹³C NMR (100 MHz, CDCl₃) δ 21.54, 51.57, 55.91, 88.81, 112.85, 113.90, 115.23, 115.31, 128.07, 128.66, 129.86, 133.02, 138.90, 140.32, 143.87, 144.10, 153.09. ESI (+) m/e 349 (M+1, 100). Anal. calcd. for C₂₁H₂₀N₂O₃ · 0.01HOH : C, 72.35; H, 5.78; N, 8.03. Found: C, 72.06; H, 5.66 N, 8.07.

4-Furan-2-yl-1-phenyl-2-*p*-tolyl-3-imidazoline 3-oxide (9g). IR (KBr) ν C=N 1570 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 2.27 (3H, s), 4.77 (1H, dd, *J* = 2.8, 14.8), 5.05 (1H, dd, *J* = 5.4, 14.8), 6.02-6.08 (1H, m), 6.51 (1H, d, *J* = 7.9), 6.75 (1H, t, *J* = 7.3), 7.10-7.20 (4H, m), 7.40 (2H, d, *J* = 8.0), 7.48 (1H, s), 7.71 (1H, d, *J* = 3.4). ¹³C NMR (100 MHz, CDCl₃) δ 21.3, 50.9, 88.2, 112.6, 112.7, 115.2, 118.8, 127.7, 128.3, 129.5, 129.7, 132.6, 140.2, 143.6, 144.0, 144.1. ESI (+) m/e 319 (M+1, 100). Anal. calcd. for C₂₀H₁₈N₂O₂ · 1.6C₂H₅OH : C, 71.07; H, 7.10; N, 7.14. Found: C, 70.90; H, 6.61 N, 6.98.

4-Furan-2-yl-2-(4-methoxyphenyl)-1-phenyl-3-imidazoline 3-oxide (9h). IR (KBr) ν C=N 1570 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 3.79 (3H, s), 4.83 (1H, dd, *J* = 3.2, 14.8), 5.12 (1H, dd, *J* = 5.6, 14.8), 6.11 (1H, dd, *J* = 3.2, 5.6), 6.604 (2H, d, *J* = 7.6), 6.606 (1H, s), 6.82 (1H, t, *J* = 7.6), 6.93 (2H, d, *J* = 8.8), 7.23 (2H, t, *J* = 8.0), 7.53 (2H, d, *J* = 8.8), 7.55 (1H, d, *J* = 1.6), 7.79 (1H, d, *J* = 3.6). ¹³C NMR (100 MHz, CDCl₃) δ 51.06, 55.55, 88.15, 112.88, 114.64, 115.31, 119.03, 127.74, 128.33, 129.37, 129.69, 143.79, 144.17, 144.36, 161.23. ESI (+) m/e 335 (M+1, 100). Anal. calcd. for C₂₀H₁₈N₂O₃ : C, 71.86; H, 5.39; N, 8.38. Found: C, 72.31; H, 4.62; N, 8.73.

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