

A SIMPLE ROUTE FOR SYNTHESIS OF NEW TRIAZOLE DERIVATIVES VIA REACTION BETWEEN ARYLGLYOXALS, ACETYLACETONE AND SODIUM AZIDE

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Abstract – A fast and green way to preparation of a new series of triazole derivatives is reported using the three-component reaction between arylglyoxals, acetylacetone and sodium azide in water as solvent.

INTRODUCTION

1,2,3-Triazoles are important heterocyclic scaffolds of interesting chemical and biological applications and are present as the key substructure in therapeutically active compounds such as antimicrobials, anti-HIV agents and kinase inhibitors.¹⁻⁴ In that respect, the development of new methods for their synthesis have gained special importance in triazole chemistry. 1,3-Dipolar cycloaddition of azides to carbon-carbon multiple bonds is a common method to obtain 1,2,3-triazoles.⁵⁻¹⁰

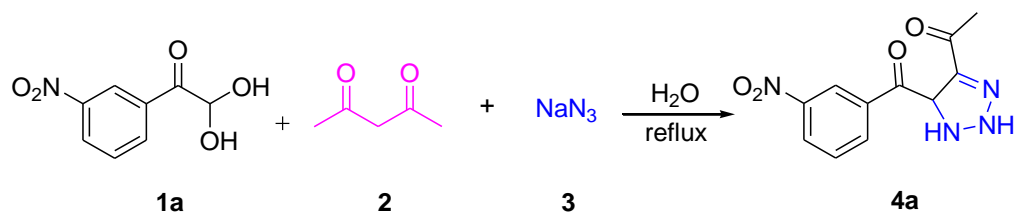
An important criterion of green chemistry is replacing hazardous organic solvents with environmentally favorable solvents. Water is the most desirable solvent in the green context and many successful examples of reactions in an aqueous medium are known.¹¹⁻¹⁴

Arylglyoxals with a carbonyl group adjacent to the aldehyde functionality, are reactive and versatile species which have been widely used for the synthesis of different heterocyclic and carbocyclic compounds.¹⁵⁻¹⁷ Recently we focused our attention on the application of multi-component reactions of arylglyoxals for synthesis of different carbocyclic and heterocyclic organic compounds.¹⁸⁻²⁰ In continuation of these works, we report here a simple method for synthesis of some new 1,2,3-triazole derivatives by a three-component reaction between arylglyoxals, acetylacetone and sodium azides in water as solvent.

RESULTS AND DISCUSSION

In order to investigate the reaction of arylglyoxals, acetylacetone and sodium azide, at first we studied the reaction between 3-nitrophenylglyoxal monohydrate **1a**, acetylacetone and sodium azide in water as

solvent (Scheme 1). A mixture of 3-nitrophenylglyoxal monohydrate and acetylacetone was stirred in water at 100 °C for 20 min. After cooling the reaction mixture to room temperature, sodium azide was added. The reaction mixture became quickly light-red and TLC of the reaction mixture showed the presence of only one product. After extracting the mixture with dichloromethane and evaporating the solvent a solid was obtained which was washed with diethyl ether to afford triazole derivative **4a** in 90% yield. Then the synthesis of **4a** was examined in different solvents (H₂O, EtOH, MeOH, THF, MeCN, CH₂Cl₂). The results are shown in Table 1. First, we tested the reaction in water at 25 °C under air atmosphere for 48 h, but no product was isolated (Table 1, entry 1). Stirring the reaction mixture in EtOH for 5 h at 25 °C, afforded the product **4a** in 56% yield (Table 1, entry 2). Using H₂O: EtOH (1:1) as a solvent at 25 °C lead to the desired product **4a** in 68% yield after 2 h, but refluxing the mixture for 20 min gave the product **4a** in 88% yield (Table 1, entries 3-4). The best result was obtained when water was used as solvent at 100 °C and compound **4a** was isolated after 20 min in 90% yield (Table 2, entry 5). Boiling ethanol and methanol were also effective, but the yields were lower than when the reaction was performed in boiling water (Table 2, entries 6-7). Aprotic solvents such as dichloromethane, acetonitrile and THF were not effective and only low yields of **4a** were obtained (Table 1, entries 8-10).



Scheme 1

Table 1. Optimization of conditions for synthesis of triazole **4a**

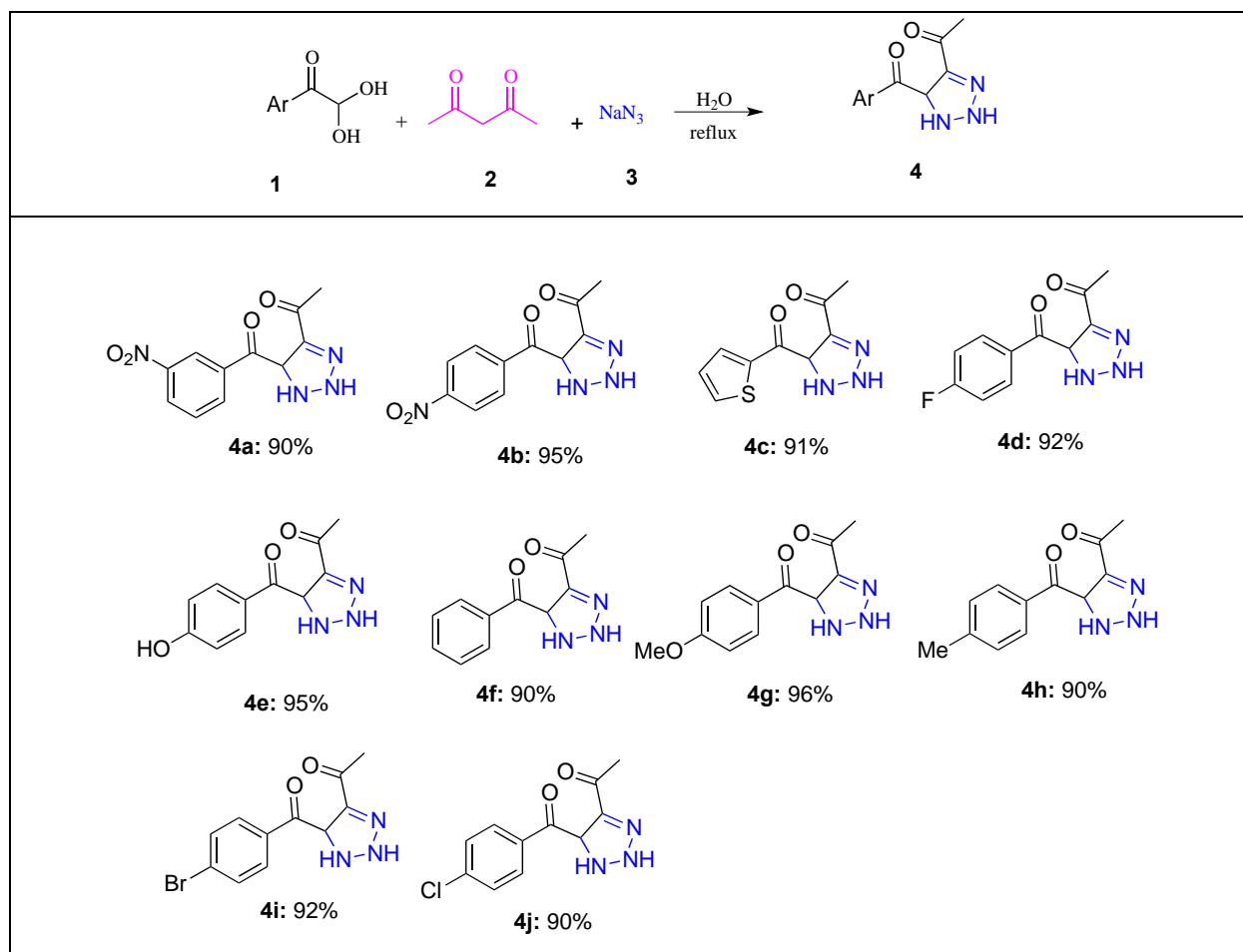
Entry	Solvents	T(°C)	Time	Yield(%)
1	H ₂ O	25 °C	48 h	-
2	EtOH	25°C	5 h	56
3	H ₂ O: EtOH(1:1)	25 °C	2 h	68
4	H ₂ O: EtOH(1:1)	reflux	20 min	88
5	H ₂ O	reflux	20 min	90
6	EtOH	reflux	15 min	87
7	MeOH	reflux	2 h	68
8	CH ₂ Cl ₂	25 °C	12 h	-
9	MeCN	reflux	8 h	-
10	THF	reflux	5 h	trace

To define the scope and generality of the method, a series of substituted arylglyoxals were examined (Table 2). Results showed when the reaction is carried out with different electron-poor and electron-rich arylglyoxal derivatives the desired triazole derivative **4a-j** were obtained in good yields.

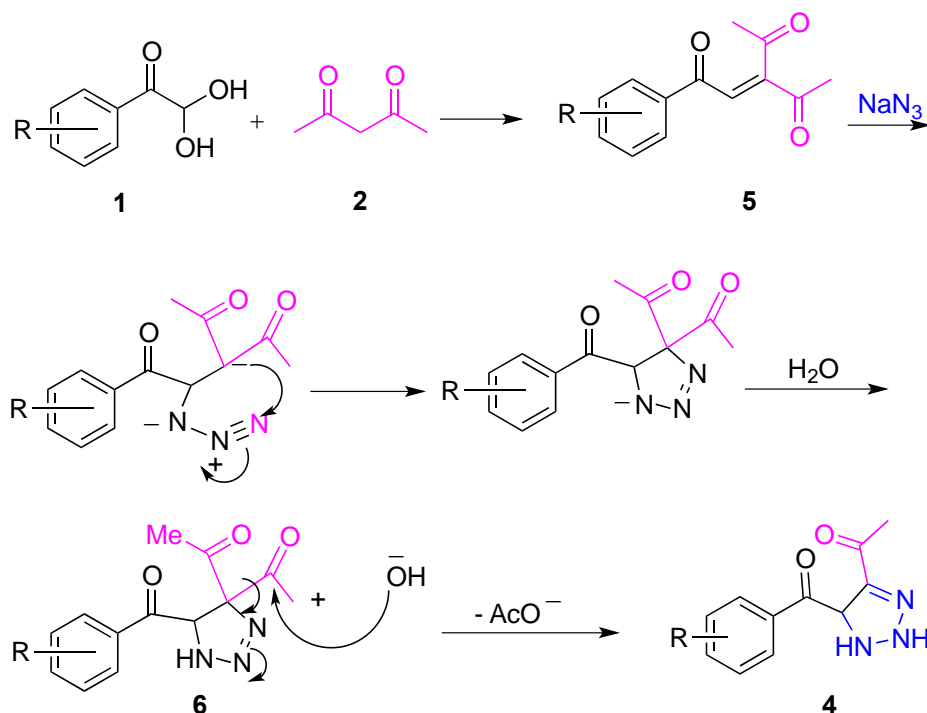
Compounds **4a-j** are all new and their structures were deduced from their elemental analyses and spectral data. The analytical data and the NMR spectra of compounds **4** showed the removal of an acetyl group from the three-component adduct of arylglyoxal, acetylacetone and azide anion. The ^1H NMR spectrum of compound **4a** exhibited single signals for methyl and aliphatic CH proton at 2.59 and 6.46 ppm respectively. Two NH protons resonated at 6.45 and 9.42 ppm as two broad signals which disappeared after addition of a few drops D_2O to CDCl_3 solution of **4a**. The aromatic protons resonated between 7.67 and 8.73 ppm. The ^{13}C NMR spectrum of **4a** showed the signals related to CH_3 and aliphatic CH carbons at 25.11 and 92.88 ppm. Other carbons resonated as 9 distinct signals in agreement with the proposed structure.

We also studied the reaction of β -ketoesters, such as ethyl acetoacetate, instead of acetylacetone, with arylglyoxals and sodium azide, but no product could be isolated from the reaction mixture.

Table 2. Synthesis of triazole derivatives under optimized conditions



A suggested mechanism for formation of triazoles **4** is showed in Scheme 2. At first, the Knoevenagel condensation of arylglyoxal with acetylacetone afforded enone intermediate **5**. In the following, the 1,3-dipolar cycloaddition of NaN_3 with enone **5** leads to triazole intermediate **6**. Intermediate **6** may be attacked by the hydroxide anion on the carbonyl of acetyl group, leading to product **4** after losing of an acetate anion.



Scheme 2

In summary, we report herein that the reaction between arylglyoxals with acetylacetone and sodium azide provides a facile and efficient route for the synthesis of some triazole derivatives in good yields. The advantages of the method are readily available starting materials, easy purification of products and green solvent.

EXPERIMENTAL

All chemicals and solvents were purchased from commercial sources and used without further purification. All of the utilized arylglyoxals were prepared by SeO_2 -oxidation of the related aryl methyl ketones on the basis of the reported procedure and used as their monohydrates.²¹ Melting points were determined on a Melt-Tem II melting point apparatus. IR spectra (KBr, Neat) were obtained on a Thermo Scientific, Nicolet iS10 Fourier transform IR spectrometer (Thermo Fisher Scientific, Waltham, MA). Peaks are reported in wave numbers (cm^{-1}). All of the NMR spectra were recorded on a Varian model

UNITYInova 500 MHz (^1H : 500 ^{13}C : 125) NMR spectrometer. Chemical shifts of ^1H and ^{13}C NMR are reported in parts per million (ppm) from tetramethylsilane (TMS) as an internal standard in CDCl_3 as a solvent.

Synthesis of 1,2,3-triazole derivatives 4 (General procedure). A mixture of acetylacetone (1 mmol) and arylglyoxal (1 mmol) in water (5 mL) was heated at 100 °C for 20 min. Then sodium azide (1 mmol) was added to the mixture at room temperature (20-25 °C); the resultant mixture was stirred at the same temperature for 5 min. Then aqueous layer was extracted with CH_2Cl_2 (2 \times 15 mL). The organic phase was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the solid residue was washed with Et_2O (15 mL) to afford the pure product.

1-[4-(3-Nitrobenzoyl)-3,4-dihydro-2H-1,2,3-triazol-5-yl]ethan-1-one (4a)

Yield 263 mg (92%), orange solid. mp 162-165 °C. IR spectrum, ν , cm^{-1} (KBr): 3417, 3270 (OH, NH), 1698 (C=O). ^1H NMR spectrum, δ , ppm (J , Hz): 2.59 (3H, s, CH_3), 6.45 (1H, bs, NH), 6.46 (1H, s, CH), 7.67 (1H, t, $^3J_{\text{HH}} = 7.9$, H Ar), 8.29-8.24 (1H, m, H Ar), 8.37 (1H, dd, $J_{\text{HH}} = 8.2, 2.3$, H Ar), 8.73 (1H, t, $^4J_{\text{HH}} = 2.3$, H Ar), 9.42 (H, bs, NH). ^{13}C NMR spectrum, δ , ppm (J , Hz): 25.11, 92.78, 122.14, 126.17, 129.70, 133.03, 140.71, 148.41, 152.21, 189.33, 195.16 (C=O). Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}_4$: C, 50.38; H, 3.84; N, 21.37. Found, %: C, 50.27; H, 3.71; N, 21.59.

1-[4-(4-Nitrobenzoyl)-3,4-dihydro-2H-1,2,3-triazol-5-yl]ethan-1-one (4b)

Yield 272 mg (95%), orange solid. mp 167-169 °C. IR spectrum, ν , cm^{-1} (KBr): 3416 (NH), 1708 (C=O). ^1H NMR spectrum, δ , ppm (J , Hz): 2.58 (3H, s, CH_3), 6.38 (1H, bs, NH), 6.45 (1H, s, CH), 8.07 (2H, d, $^3J_{\text{HH}} = 8.8$, H Ar), 8.32 (2H, d, $^3J_{\text{HH}} = 8.8$, H Ar), 9.45 (1H, s, NH). ^{13}C NMR spectrum, δ , ppm (J , Hz): 15.09, 93.33, 123.78, 128.26, 144.35, 149.61, 152.13, 189.97, 195.10. Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}_4$: C, 50.38; H, 3.84; N, 21.37. Found, %: C, 50.38; H, 3.74; N, 21.63.

1-[4-(Thiophen-2-yl)-3,4-dihydro-2H-1,2,3-triazol-5-yl]ethan-1-one (4c).

Yield 225 mg (91%), orange solid. mp 182-185 °C. IR spectrum, ν , cm^{-1} (KBr): 3416 (NH), 1708 (C=O). ^1H NMR spectrum, δ , ppm (J , Hz): 2.52 (3H, s, CH_3), 6.43 (1H, s, CH), 7.20 (1H, d, $^3J_{\text{HH}} = 5.0$, H Ar), 7.52 (1H, bs, NH), 7.87 (1H, d, $^3J_{\text{HH}} = 5.0$, H Ar), 8.00 (1H, d, $^3J_{\text{HH}} = 3.8$, H Ar), 8.99 (H, bs, NH). ^{13}C NMR spectrum, δ , ppm (J , Hz): 26.31, 92.70, 128.92, 130.62, 133.42, 146.96, 153.13, 184.31, 197.18 (C=O). Anal. Calcd for $\text{C}_9\text{H}_9\text{N}_3\text{O}_2\text{S}$: C, 48.42; H, 4.06; N, 18.82; S, 14.36. Found, %: C, 48.35; H, 4.13; N, 19.01; S, 14.25.

1-[4-(4-Fluorobenzoyl)-3,4-dihydro-2H-1,2,3-triazol-5-yl]ethan-1-one (4d).

Yield 238 mg (92%), yellow solid. mp 168-169 °C. IR spectrum, ν , cm^{-1} (KBr): 3416 (NH), 1709, 1621 (C=O). ^1H NMR spectrum, δ , ppm (J , Hz): 2.58 (3H, s, CH_3), 6.37 (1H, bs, NH), 6.45 (1H, s, NH), 8.07 (2H, d, $^3J_{\text{HH}} = 8.4$, H Ar), 8.33 (2H, d, $^3J_{\text{HH}} = 8.4$, H-Ar), 9.45 (1H, bs, NH). ^{13}C NMR spectrum, δ , ppm (J , Hz): 25.05, 93.33, 123.78, 128.24, 128.97, 144.35, 187.28, 189.97. Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{FN}_3\text{O}_2$: C, 56.17; H, 4.29; N, 17.86. Found, %: C, 56.09; H, 4.23; N, 17.84.

1-[4-(4-Hydroxybenzoyl)-3,4-dihydro-2H-1,2,3-triazol-5-yl]ethan-1-one (4e). Yield 244 mg (95%), orange solid. mp 192-195 °C. IR spectrum, ν , cm^{-1} (KBr): 3468, 3321(OH, NH), 1695 (C=O). ^1H NMR spectrum, δ , ppm (J , Hz): 2.06 (3H, s, CH_3), 5.98 (2H, bs, CH and NH), 6.39 (2H, d, $^3J_{\text{HH}} = 8.7$, H Ar), 7.36 (2H, d, $^3J_{\text{HH}} = 8.7$, H Ar), 8.69 (2H, bs, NH, OH). ^{13}C NMR spectrum, δ , ppm (J , Hz): 25.38, 93.33, 115.40, 129.53, 130.80, 151.38, 161.41, 190.64, 196.32 (C=O). Anal. Calcd for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_3$: C, 56.65; H, 4.75; N, 18.02. Found, %: C, 56.83; H, 4.55; N, 18.25.

1-[4-Benzoyl-3,4-dihydro-2H-1,2,3-triazol-5-yl]ethan-1-one (4f)

Yield 217 mg (90%), yellow solid. mp 160-163 °C. IR spectrum, ν , cm^{-1} (KBr): 3403 (NH), 1707, 1714 (C=O). ^1H NMR spectrum, δ , ppm (J , Hz): 2.73 (3H, s, CH_3), 5.93 (2H, bs, CH and NH), 7.58 (2H, t, $^3J_{\text{HH}} = 7.6$, H Ar), 7.71 (1H, t, $^3J_{\text{HH}} = 7.4$, H Ar), 8.02 (2H, d, $^3J_{\text{HH}} = 7.6$, H Ar), 8.24 (1H, s, NH). ^{13}C NMR spectrum, δ , ppm (J , Hz): 27.18, 55.45, 127.35, 128.14, 129.25, 133.70, 134.82, 148.50, 189.23, 192.54. Anal. Calcd for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_2$: C, 60.82; H, 5.10; N, 19.34. Found, %: C, 60.60; H, 5.03; N, 19.45.

1-[4-(4-Methoxybenzoyl)-3,4-dihydro-2H-1,2,3-triazol-5-yl]ethan-1-one (4g)

Yield 260 mg (96%), yellow solid. mp 166-169 °C. IR spectrum, ν , cm^{-1} (KBr): 3443 (NH), 1682, 1890 (C=O). ^1H NMR spectrum, δ , ppm (J , Hz): 2.72 (3H, s, CH_3), 3.92 (3H, s, OCH_3), 5.86 (2H, bs, CH and NH), 7.02 (2H, d, $^3J_{\text{HH}} = 8.6$, H Ar), 7.99 (2H, d, $^3J_{\text{HH}} = 8.6$, H Ar), 8.23 (1H, s, NH). ^{13}C NMR spectrum, δ , ppm (J , Hz): 27.23, 55.15, 55.67, 114.46, 126.59, 127.44, 130.57, 148.40, 164.81, 187.58, 192.61. Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_3$: C, 58.29; H, 5.30; N, 16.99. Found, %: C, 68.11; H, 5.32; N, 16.95.

1-[4-(4-Methylbenzoyl)-3,4-dihydro-2H-1,2,3-triazol-5-yl]ethan-1-one (4h)

Yield 230 mg (90%), yellow solid. mp 188-191 °C. IR spectrum, ν , cm^{-1} (KBr): 3451 (NH), 1701, 1679 (C=O). ^1H NMR spectrum, δ , ppm (J , Hz): 2.47 (3H, s, CH_3), 2.73 (3H, s, CH_3), 5.89 (2H, bs, CH and NH), 7.36 (2H, d, $^3J_{\text{HH}} = 7.9$, H Ar), 7.91 (2H, d, $^3J_{\text{HH}} = 7.9$, H Ar), 8.24 (1H, s, NH). ^{13}C NMR spectrum, δ , ppm (J , Hz): 21.35, 27.25, 92.43, 103.23, 125.82, 128.56, 129.17, 137.78, 139.98, 189.23, 192.54. Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_2$: C, 62.33; H, 5.67; N, 18.17. Found, %: C, 62.58; H, 5.56; N, 18.22.

1-[4-(4-Bromobenzoyl)-3,4-dihydro-2H-1,2,3-triazol-5-yl]ethan-1-one (4i).

Yield 294 mg (92%), yellow solid. mp 190-193 °C. IR spectrum, ν , cm^{-1} (KBr): 3444 (NH), 1692 (C=O). ^1H NMR spectrum, δ , ppm (J , Hz): 2.73 (3H, s, CH_3), 5.89 (2H, bs, CH and NH), 7.72 (2H, d, $^3J_{\text{HH}} = 8.5$, H Ar), 7.88 (2H, d, $^3J_{\text{HH}} = 8.5$, H Ar), 8.23 (1H, s, NH). ^{13}C NMR spectrum, δ , ppm (J , Hz): 27.25, 55.36, 127.36, 129.55, 130.40, 132.31, 132.68, 148.52, 188.43, 192.59. Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{BrN}_3\text{O}_2$: C, 44.62; H, 3.40; N, 14.19. Found, %: C, 44.73; H, 3.33; N, 14.24.

1-[4-(4-Chlorobenzoyl)-3,4-dihydro-2H-1,2,3-triazol-5-yl]ethan-1-one (4j)

Yield 246 mg (90%), yellow solid. mp 184-187 °C. IR spectrum, ν , cm^{-1} (KBr): 3369 (NH), 1688, 1622 (C=O). ^1H NMR spectrum, δ , ppm (J , Hz): 2.72 (3H, s, CH_3), 5.89 (2H, bs, CH and NH), 7.55 (2H, d, $^3J_{\text{HH}} = 8.2$, H Ar), 7.96 (2H, d, $^3J_{\text{HH}} = 8.2$, H Ar), 8.23 (1H, s, NH). ^{13}C NMR spectrum, δ , ppm (J , Hz): 27.22, 55.37, 126.58, 127.36, 129.52, 129.57, 129.67, 129.89, 195.19, 202.81. Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{ClN}_3\text{O}_2$: C, 52.50; H, 4.01; N, 16.70. Found, %: C, 52.78; H, 3.99; N, 16.81.

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