Heterocyclic Letters
Vol. 11| No.4|515-520|August-October|2021
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

DESIGN AND SYNTHESIS OF A NEW DIAZOCINE-5,8-DIONE USING SOME CHEMICAL STRATEGIES

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ABSTRACT
Several diazocine analogs have been synthesized; however, some protocols use expensive reagents which are difficult to handle. The aim of this research was to synthesize a new diazocine-5,8-dione using some chemical strategies. Chemical structure of the compounds was confirmed using elemental analysis and NMR spectrum. In conclusion, in this research, is reported a facile synthesis of a new diazocine-5,8-dione which require no special conditions such as different pH and higher temperatures.

Keywords: Diazocine, dione, Copper(II).

INTRODUCTION
Heterocyclic compounds are very useful in the field of pharmacy and organic chemistry[i-iii]; in this way, several heterocyclic derivatives have been synthesized using different methods[iv-vi]. For example, the heteroarylation of an aromatic group from a diazo derivative an *N*-methylpirrole[vii]. Other study showed the Cooper-catalyzed borylation of some pyrrole derivatives in basic conditions[viii]. Besides, several trifluoromethyl, and fluoroalkyl-selenolated heterocyclics were prepared via intramolecular ring closures of alkyne derivatives in the presence of CF_3SeCl[ix]. Other report displays the preparation of heterocyclic which contain nitrogen in their chemical structure such as the azo- and diazocines; in this way, a diazocino [2,1-a]isoindol-one was synthesized from an isobenzofuranone and an aniline analog[x]. Additionally, a report showed the synthesis of dibenzo[b,f][1,5]diazocines via reaction of aminobenzophenone and diphenyl phosphate[xi]. Other studies, indicated the synthesis of a

diazocine-5-yl]arylglycinamide via an Ugi 4CC/Staudinger/aza-Wittig sequence[xii]. Recently, a diazocine-steroid derivative was prepared via reaction intramolecular of a carbaldehyde derivative in the presence of Copper(II)[xiii]. All these experimental data show methods which are available for synthesis of some azocine analogs; However, these protocols require expensive reagents and special conditions such as differences in the pH and higher temperatures; therefore, in this study, a new diazocine-5,8-dione derivative was synthesized using some chemical strategies.

EXPERIMENTAL

General methods

Starting materials were purchased from commercial suppliers (Sigma-Aldrich and AKos Consulting & Solutions). NMR spectra were recorded on a Varian VXR300/5 FT apparatus (300 MHz/$CDCl_3$) using tetramethylsilane as an internal standard. Electron Ionization mass spectrometry (EIMS) was recorder on a Finnigan PolarisQ ion trap mass spectrometer. Melting-point (m.p.) was determined on an electrothermal-900 model apparatus. The infrared spectrum (IR) was determined on a thermo-scientific iSOFT/IR device. Elemental analysis was determined using a PerkinElmer apparatus (Ser. II CHNS / 02400).

Chemical synthesis

3-(4,5-dinitro-imidazol-1-yl)prop-2-yn-1-amine (2)

In a round bottom flask (10 ml), 4,5-dinitro-1*H*-imidazole (100 mg, 0.63 mmol), Prop-2-ynylamine hydrochloride (60 mg, 0.65 mmol) and sodium hydroxide (20 mg, 0.50 mmol) in ethanol (5 ml) was stirring for 72 h at room temperature. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane (4:1) system; yielding 44% of product; m.p. 102-104 ^oC; IR (V_{max}, cm^{-1}) 3380, 3320, 2190 and 1536: ^1H NMR (300 MHz, $CDCl_3$-*d*) δ_H: ^1H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 2.00 (broad, 2H), 3.90 (m, 2H), 8.50 (s, 1H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 30.20, 57.60, 79.72, 135.92, 130.10, 165.40 ppm. EI-MS m/z: 211.03. Anal. Calcd. for $C_6H_5N_5O_4$. C, 34.13; H, 2.39; N, 33.17; O, 30.31. Found: C, 34.10; H, 2.37.

2-chloro-N-[3-(4,5-dinitro-imidazol-1-yl)prop-2-ynyl]acetamide (3)

In a round bottom flask (10 ml), compound **2** (130 mg, 0.62 mmol) chloroacetyl chloride (50 µl, 0.63 mmol) and triethylamine (80 µ l, 0.57 mmol) in 5 ml of ethanol was stirring for 72 h at room temperature. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane:water (4:2:1) system; yielding 56% of product; m.p. 116-1118 ^oC; IR (V_{max}, cm^{-1}) 3322, 1538, 2190 and 1630: ^1H NMR (300 MHz, $CDCl_3$-*d*) δ_H: ^1H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 4.20 (m, 2H), 4.34 (m, 2H), 6.80 (broad, 1H), 8.40 (s, 1H), ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 26.00, 43.44, 58.62, 82.84, 135.92, 139.12, 162.32, 165.42 ppm. EI-MS m/z: 287.00. Anal. Calcd. for $C_8H_6ClN_5O_5$. C, 33.41; H, 2.10; Cl, 12.33; N, 24.35; O, 27.81. Found: C, 33.40; H, 2.08.

N-[3-(2-methyl-4,5-dinitro-imidazol-1-yl)prop-2-ynyl]-3-phenyl-oxiran-2-amine (4)

In a round bottom flask (10 ml), compound **3** (200 mg, 0.70 mmol), benzaldehyde (100 µl, 0.98 mmol), sodium hydroxide (20 mg, 0.50 mmol) in 5 ml of ethanol was stirring for 72 h at room temperature. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane:water (4:2:1) system; yielding 65% of product; m.p. 132-134 ^0C; IR (V_{max}, cm^{-1}) 3322, 2192, 1536 and 1244: ^1H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 2.00 (broad. 1H), 3.80 (m, 2H), 4.00-4.10 (m, 2H), 7.16-7.26 (m, 5H), 8.50 (s, 1H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 34.44, 47.70, 57.00, 77.86, 80.12,

123.90, 128.24, 128.40, 135.92, 139.18, 140.84, 165.40 ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 34.44, 47.70, 57.00, 77.84, 80.12, 123.92, 128.22, 128.40, 135.98, 139.12, 140.80, 165.40 ppm. EI-MS m/z: 329.07. Anal. Calcd. for $C_{14}H_{11}N_5O_5$. C, 51.07; H, 3.37; N, 21.27; O, 24.30. Found: C, 51.04; H, 3.34.

1-[3-[(3-phenyloxiran-2-yl)amino]prop-1-ynyl]imidazole-4,5-diamine (5)

In a round bottom flask (10 ml), compound **4** (200 mg, 0.60 mmol), sodium cyanoborohydride (100 mg, 1.60 mmol), metallic zinc powder (50 mg) in 5 ml of ethanol was stirring for 72 h at room temperature. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane:water (4:2:1) system; yielding 76% of product; m.p. 162-164 ^{o}C; IR (V_{max}, cm^{-1}) 3382, 2190 and 1244: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 3.80 (m, 2H), 4.00-4.10 (m, 2H), 4.14 (broad, 5H), 7.00 (s, 1H), 7.16-7.26 (m, 5H) ppm. 34.44, 47.70, 57.70, 77.84, 86.34, 107.70, 123.92, 128.22, 128.40, 137.55, 140.44, 140.80 ppm. EI-MS m/z: 269.12. Anal. Calcd. for $C_{14}H_{15}N_5O$. C, 62.44; H, 5.61; N, 26.01; O, 5.94. Found: C, 62.42; H, 5.60.

3-[3-[(3-phenyloxiran-2-yl)amino]prop-1-ynyl]-4,6,7,9-tetrahydroimidazo[4,5-b][1,4] diazocine-5,8-dione (6)

In a round bottom flask (10 ml), compound **5** (200 mg, 0.74 mmol) succinic acid (100 mg 0.85 mmol) in 5 ml of methanol was stirring for 72 h at room temperature. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane:water (4:2:1) system; yielding 58% of product; m.p. 182-184 ^{0}C; IR (V_{max}, cm^{-1}) 3320, 2190, 1634 and 1242: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 2.00 (broad), 2.36 (m, 4H), 3.80 (m, 2H), 4.00-4.10 (m, 2H), 7.16-7.26 (m, 5H), 7.80 (s, 1H), 11.20 (broad, 1H), 11.30 (broad, 1H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 34.44, 34.96, 35.22, 47.70, 57.68, 77.86, 81.56, 106.40, 123.90, 128.24, 128.40, 139.12, 140.80, 140.84, 171.12, 172.62 ppm. EI-MS m/z: 351.13. Anal. Calcd. for $C_{18}H_{17}N_5O_3$. C, 61.53; H, 4.88; N, 19.93; O, 13.66. Found: C, 61.50; H, 4.86.

Results and Discussion

3.1.1 Synthesis of a nitro-amino derivative

Several nitro-amino analogs have been synthesized using some reagents such as dimethyl sulfoxide/KOH[xiv], nitric acid[xv], water/HCl[xvi], and others. In this investigation, 3-(4,5-dinitro-imidazol-1-yl)prop-2-yn-1-amine (**2**) was prepared from 4,5-dinitro-1*H*-imidazole and Prop-2-ynylamine in basic conditions (Figure 1). The ^{1}H NMR spectrum from **2** showed several bands at 2.00 ppm for amino group; at 3.90 ppm for methylene bound to both alkyne and amino groups; at 8.50 ppm for imidazole ring. ^{13}C NMR spectra display chemical shifts at 30.20 for methylene linked to both alkyne and amino groups; at 57.60-79.72 ppm for alkyne group; at 135.92-165.40 ppm for imidazole ring. Besides, the mass spectrum from **2** showed a molecular ion (m/z) 211.03.

3.1.2 Preparation of a chloroamide derivative

In the literature several methods for synthesis of chloroamide analogs have been reported; these protocols involved some reagents such as trichloroisocyanuric Acid[xvii], N-chlorobenzotriazole[xviii], chloroacetyl chloride[xix-xxi]. In this study, a chloroamide analog (compound **3**) was prepared via reaction of **2** with chloroacetyl chloride using triethylamine as catalyst. The ^{1}H NMR spectrum from **3** showed several bands at 4.20 ppm for methylene bound to both chloride and amide groups; at 4.34 ppm for methylene linked to both amide and alkyne groups; at 6.80 ppm for amide group; at 8.40 ppm for imidazole ring. ^{13}C NMR spectra display chemical shifts at 26.00 ppm for methylene linked to both amide and alkyne groups; at 43.44

ppm for methylene bound to both chloride and amide groups; at 58.62-82.44 for alkyne group; at 135.92-139.12 and 165.42 ppm for imidazole ring; at 162.35 ppm for amide group. In addition, the mass spectrum from **3** showed a molecular ion (m/z) 287.00.

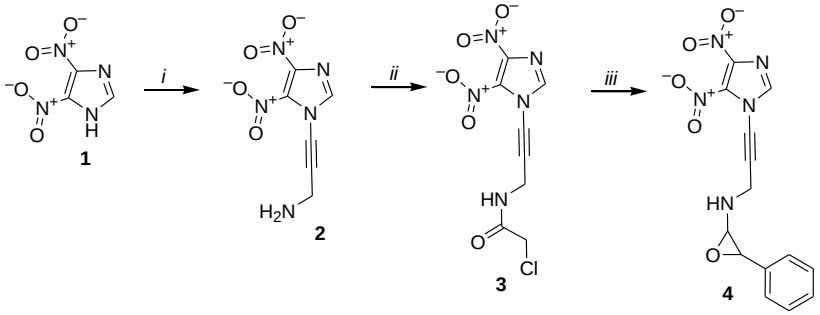

Figure 1. Synthesis of N-[3-(2-methyl-4,5-dinitro-imidazol-1-yl)prop-2-ynyl]-3-phenyl-oxiran-2-amine (**4**). *Reagents and Conditions. i* = Prop-2-ynylamine hydrochloride, NaOH, EtOH, 72 h rt; *ii* = chloroacetyl chloride, triethylamine, 72, rt *iii* = benzaldehyde, NaOH, EtOH, 72 h, rt.
rt = room temperature.

3.1.3 Synthesis of an epoxide analog

Several methods have been used to preparation of epoxide derivatives which involve some reagents such as chlorophyll[xxii], ethyl bromoacetate[xxiii], m-chloroperoxybenzoic acid[xxiv], potassium hydroxide[xxv], dimethyldioxiran[xxvi]. In this research, an epoxide derivative (compound **4**) was synthesized via reaction of **3** with benzaldehyde in basic medium to form **4**. The ^{1}H NMR spectrum from **4** showed several bands at 2.00 ppm for amide group; at 3.80 ppm for methylene bound to both alkyne and amino groups; at 4.00-4.10 ppm for oxirane ring; at 7.16-7.26 ppm for phenyl group; at 8.30 ppm for imidazole ring, ^{13}C NMR spectra display chemical shifts at 34.44 ppm for methylene linked to both alkyne and amino groups; at 47.70 and 77.84 ppm for oxirane ring; at 57.00 and 80.12 ppm for alkyne group; at 123.92-128.40 and 140.80 ppm for phenyl group; at 135.98-139.12 and 165.40 ppm for imidazole ring. Additionally, the mass spectrum from **4** showed a molecular ion (m/z) 329.07.

3.1.4 Reduction of nitro group

Several compounds have been used as reducing reagents; for example, ruthenium bis(pyrazolyl) borate/$NaBH_4$[xxvii], Pd/C[xxviii], Ni/hydrazinium monoformate[xxix], $LiAlH_4$[xxx]. In this way, **4** reacted with $NaBH_4$ to form the compound **5** (Figure 2). The ^{1}H NMR spectrum from **5** showed several bands at 3.80 ppm for methylene linked to both alkyne and amino groups; at 4.00-4.10 ppm for oxirane ring; at 4.14 ppm for amino groups; at 7.00 ppm for imidazole ring; at 7.16-7.26 ppm for phenyl group. ^{13}C NMR spectra display chemical shifts at 34.44 ppm for methylene linked to both alkyne and amino groups; at 47.70 and 77.84 ppm for oxirane ring; at 57.00 and 86.34 ppm for alkyne group; at 107.70 and 137.55-140.44 ppm for imidazole ring; at 123.92-128.40 and 140.80 ppm for phenyl group. Besides, the mass spectrum from **5** showed a molecular ion (m/z) 269.12.

3.1.5 Amidation reaction

Several methods have used for preparation of amide derivatives which involves some reagents such as iodosuccinimide[xxxi], thioacid[xxxii], ruthenium[xxxiii], α-hydroxycarboxilic acid[xxxiv] and others. In this investigation, an amide derivative was prepared (compound **6**) from **5** and succinic acid in the presence of a carbodiimide derivative. The ^{1}H NMR spectrum from **6** showed several bands at 2.00 ppm for amino group; at 2.36 ppm for methylene groups of 1,4,6,7-Tetrahydro-[1,4]diazocine-5,8-dione ring; at 3.80 ppm for methylene group linked to

both amino and alkyne groups; at 4.00-4.10 ppm for oxirane ring; at 7.80 ppm for imidazole ring; at 7.16-7.26 ppm for phenyl group; at 11.20-11.30 for amide groups. ^{13}C NMR spectra display chemical shifts at 34.44 ppm for methylene linked to both alkyne and amino groups; at 34.96-35.22 and 106.40 ppm for 1,4,6,7-Tetrahydro-[1,4]diazocine-5,8-dione ring; at 47.70 and 77.86 ppm for oxirane ring; at 57.68 and 81.56 ppm for alkyne group; at 139.12-140.80 ppm for imidazole ring; at 123.90-128.40 and 140.84 ppm for phenyl group; at 171.12-172.62 ppm for amide groups. Finally, the mass spectrum from **6** showed a molecular ion (m/z) 351.13.

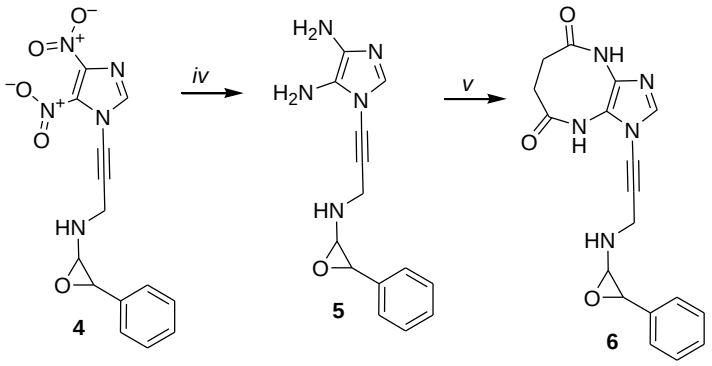

Figure 2. 3-[3-[(3-phenyloxiran-2-yl)amino]prop-1-ynyl]-4,6,7,9-tetrahydroimidazo[4,5-b][1,4]diazocine-5,8-dione (**6**). *Reagents and Conditions. iv* = sodium cyanoborohydride, metallic zinc powde, EtOH, 72 h, rt;
v = succinic acid, *N*,*N´*-dicyclohexylcarbodiimide, MeOH 72 h rt.
rt = room temperature.

CONCLUSIONS

In this research is reported a facile synthesis of a new diazocine-5,8-dione derivative using several chemical strategies; it is important to mention that the reagents used in this method are easy to handle and do not require specific conditions. In addtion, it is worth mentioning that analyzing the chemical structure of this compound, it could be interesting to evaluate their biological activity in some biological model.

ACKNOWLEDGEMENTS

None

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Received on October 7, 2021.