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Sufi An-Nur Abd Haris[1], Siti Sarah Shasuddin[1], Fazni Susila Abd Ghani[1], Najmah P.S Hassan[1], Mohd Tajudin Mohd Ali[1,2*]

[1] Faculty of Applied Sciences, Universiti Teknologi MARA, Shah Alam, Malaysia

[2]Institute of Sciences, Universiti Teknologi MARA, Shah Alam, Malaysia

*Corresponding author email: tajudinali@salam.uitm.edu.my

Abstract

This synthetic work reports a concise asymmetric synthesis of four (1*S*,2*S*)-hydroxy cyclohexene-1,2,3-triazole derivatives **6a-d** which will serve as an intermediate template for the synthesis of potentially anti tubercular (1*S*,5*S*)-γ-butyrolactone analogs. The synthesis of (1*S*,2*S*)-hydroxy cyclohexene-triazole was successfully achieved via epoxidation, epoxide ring opening, and click reaction. Epoxidation of 1,4-cyclohexadiene **1** gave epoxide **2**. The epoxide ring opening by Salen complex produced compound **4** with (1*S*,2*S*) stereocentres. The final click reaction step on compound **4** using alkynes **5a-5c** and 4-ethynylanisole **5d** afforded triazoles **6a-6d**.

Keywords: *anti tubercular, cis-butyrolactone, click reaction and triazole.*

1. Introduction

Triazole subunit is widely found in biologically active compounds. To give the disubstituted triazole, triazole subunit can be obtained by 'click chemistry'. The reaction take place between azide and alkyne to set the desired substituent by Huisgen 1,3 dipolar cycloaddition [1]. For example, a potential receptor, proliferator-activated receptor γ (PPAR-γ) against type II diabetes can be synthesized by using click chemistry protocol [2]. The regioselectivity of triazole can be control using different types of metal such as copper, ruthenium, nickel, indium, lithium and magnesium [3]. The ligand effect in the determination of regioselectivity is influenced by bond strength, polar and steric effects by which the orientation of radical addition is regulated [4].

A great deal of research has been performed on triazole and its derivatives, which has shown the pharmacological significance of this heterocyclic nucleus. Click chemistry is one of the potent reactions to carbon-heteroatomic-carbon bonds in aqueous environments with a wide range of chemical and biological applications in many fields [5]. For example, selective inhibitor

Mycobacterium tuberculosis tyrosine phosphate (mPTPB), a triazole was developed for treatment against human disease likes cancer, diabetes, obesity and inflammation [6]. As a result, the derivative-based combination salicylic acid library was designed to target the protein tyrosine phosphatase, PTP active site in the triazole scaffold in order to enhance the affinity and selectivity by finding SHP2, an inhibitor that are therapeutically potent for anti-cancer and anti-leukemia treatment[7].

Many structured methodologies have been constructed to modify the configuration of heterocyclic derivative [8]. In this synthesis, we would like to report (1*S*,2*S*)-hydroxycyclohexene-1,2,3-triazole derivatives through stereoselective epoxide opening of cyclohexene epoxide and click reaction.

2. Experimental / Computational details

2.1 Synthesis of 7-oxabicyclo[4.1.0]hept-3-ene (2)

To a stirred solution of 1,4-cyclohexadiene **1 (**3.38 g, 42.1 mmol) in dichloromethane (250 ml) at 0℃, was added with dipotassium phosphate (3.61 g, 20.7 mmol) and stirred for 10 minutes. Meta-chloroperoxybenzoic acid (10.2 g, 41.4 mmol) was added gradually with continue stirring until a white milk suspension was formed for 24 hours. The reaction mixture was filtered and the filtrate was washed with dichloromethane (50 ml), saturated sodium bicarbonate (50 ml), sodium sulfite (50 ml, 5%), water (50 ml) and brine (50 ml). The organic layers were dried with magnesium sulphate and the solvent was removed under reduced pressure. The crude epoxide was purified via vacumm distillation (20 mbar, 60-80℃) to afford the tittle of compound **2** as colourless liquid (3.8 g, 88%)[9][10].

R_f = 0.23 (Hexane : Ethyl Acetate 9:1).^{1}H NMR-Spectra (400 Hz, $CDCl_3$): δ (ppm) 5.27-5.32 (s, 2H, C*H*=C*H*), 2.38-2.46 (d, 2H, CH_2, *J* = 17.6), 2.05-2.08 (CH_2), 2.51-2.57 (d, 2H, C*H*, *J* =17.6). ^{13}C NMR-Spectra (100 Hz, $CDCl_3$): δ (ppm) 121.2 (C=C), 50.8 (*C*O), 24.8 (CH-CH), ν_{max} (chloroform)/(cm^{-1}) 2995, 1665, 1432, 1214, 737.

2.2 Formation of (1*S*,6*S*)-6-azidocyclohex-3-enol (4)

To a stirred solution of *meso*-epoxide **2** (3 g, 31.2 mmol) in dry diethyl ether (4 ml) was mixed with Salen complex catalyst **3** (0.44 g, 0.63 mmol) and stirred for 15 minutes. Trimethylsilylazide (3.77 ml, 32.8 mmol) was put together gradually into the reaction mixture and stirred for 46 hours under room temperature. The solvent was removed under reduced pressure (389 mbar, 40℃) to afford yellow crude compound **4**. By using column chromatography on silica gel (Petroleum ether: Ethyl acetate, 9:1), the compound was refined to give compound **4** in 0.84 g with 68% yield.

R_f = 0.41 (Hexane : Ethyl Acetate 9:1).^{1}H NMR-Spectra (400 Hz, $CDCl_3$): δ (ppm) 5.6-5.7 (s,1H, C*H*), 3.5-3.7 (m,1H, C*H*, *J* =12.0), 2.5-2.6 (m, 2H, C*H*), 2.1-2.3 (m, 2H, C*H*, *J* =44.0), 2.0-2.1 (s,1H, C*H*). ^{13}C NMR-Spectra (100 Hz, $CDCl_3$): δ (ppm) 124.0 (C=C), 77.2 (*C*O), 64.0 (*C*-N), 34.0 (CH_2), 31.0 (CH_2), 2.0 (CH_3). ν_{max} (chloroform)/ (cm^{-1}) 3343, 2958, 2906, 1655, 1252, 1108, 668.

2.3(1*S*,6*S*)-6-(4-(aminomethyl)-1H-1,2,3-triazol-1-yl)cyclohex-3-enol (6a)

To a stirred solution of azide **4** (0.03 g, 0.23 mmol) in dry toluene (4 ml) was added iodocopper triethyl phosphite complex, $CuI[P(OEt)_3]$ (0.437 g, 0.31 mmol) into the mixture and stirred continuously for 15 minutes. Propargylamine **5a** (3.77 ml, 0.56 mmol) was added gradually and stirred for the next 24 hours under room temperature. Under reduced pressure (400 mbar, 40℃), the solvent was taken out to afford light yellow crude triazole **6a**. The product was purified by using column chromatography on silica gel (Petroleum ether: Ethyl acetate, 9:1) to afford the tittle compound **6a** (0.17 g, 17%). The same steps were repeated when using different types of alkynes **5b-5c** and 4-ethynylanisole **5d** to give various products of triazoles **6b- 6d**.

(1*S*,6*S*)-6-(4-(aminomethyl)-1H-1,2,3-triazol-1-yl)cyclohex-3-enol (6a)

R_f = 0.54 (Hexane : Ethyl Acetate 7:3).^{1}H NMR-Spectra (400 Hz, $CDCl_3$): δ (ppm) 7.21–7.28 (m, 1H, C*H*=C), 5.65-5.75 (s, 2H, C*H*=C*H*), 4.23-4.41 (m, 1H, C*H*O), 4.04-4.14 (m, 1H, C*H*N) , 2.76-2.93 (m, 1H, CH_2), 2.49-2.71 (m, 2H, CH_2), 2.33-3.35 (s, 2H, CH_2OH), 2.24-2.29 (m, 1H, CH_2). ^{13}C NMR-Spectra (100 Hz, $CDCl_3$): δ (ppm) 129.1 (C=C), 128.3 (CH=CH), 125.4 (CH=CH), 123.9

(*C*H=C), 66.8 (*C*HO), 63.8 (*C*HN), 34.5 (*C*H_2), 31.9 (*C*H_2), 29.7 (*C*H_2OH).). ν_{max} (chloroform)/ (cm^{-1}) 3418, 2925, 1651, 1441, 1025, 826, 765. MS [Cl,NH_3]: m/z (%) 194.0 [M^+].

(1*S*,6S)-6-((R)-5-(hydroxymethyl)-3H-pyrazol-3-yl)cyclohex-3-enol (6b)

R_f = 0.81 (Hexane : Ethyl Acetate 9:1).^{1}H NMR-Spectra (400 Hz, $CDCl_3$): δ (ppm) 7.14-7.32 (m, 2H, N*H*$_2$), 5.58-5.83 (m, 2H, C=C*H*), 4.23-4.03 (m, 2H, C-O*H*), 4.02-4.17 (m, 1H, C*H*N), 3.63-3.83 (m, 2H, C*H*$_2$NH), 2.09-2.91 (m, 4H, C*H*$_2$). ^{13}C NMR-Spectra (100 Hz, $CDCl_3$): δ (ppm) 129.0 (C=C, quart), 124.8 (CH=CH), 123.3 (CH=CH), 67.8 (*C*HO), 63.4 (*C*HN), 41.0 (*C*H_2), 30.8 (*C*H_2), 25.5 (*C*H_2OH). ν_{max} (chloroform)/ (cm^{-1}) 3351, 2926, 1667, 1460, 1383, 1216, 759. MS [Cl,NH_3]: m/z (%) 195.02 [M^+].

(1*S*,6*S*)-6-(4-(bromomethyl)-1H-1,2,3-triazol-1-yl)cyclohex-3-enol (6c)

R_f = 0.48 (Hexane : Ethyl Acetate 8:2). ^{1}H NMR-Spectra (400 Hz, $CDCl_3$): δ (ppm) 7.52-7.58 (m, 1H, C*H*=C), 5.03-5.34 (s, 2H, C*H*=C*H*), 4.27-4.36 (m, 1H, CHO*H*), 4.20-4.25 (d, *J* = 3.6 Hz, 2H, C*H*$_2$Br), 4.07-4.12 (m, 1H, C*H*N), 2.70-2.88 (m, 1H, C*H*$_2$), 2.21-2.40 (m, 2H, C*H*$_2$), 1.95-2.20 (m, 1H,C*H*$_2$). ^{13}C NMR-Spectra (400 Hz, $CDCl_3$): δ (ppm) 127.3 (CH=CH), 125.5 (CH=CH), 124.9 (CH=CH), 120.5 (CH=CH), 66.0 (*C*-OH), 62.7 (*C*HN), 34.5 (*C*H_2), 17.2 (*C*H_2Br). ν_{max} (chloroform)/ (cm^{-1}) 3020, 2400, 2110, 1215, 758, 669. MS [Cl,NH_3]: m/z (%) 279.11 $[M]^+$ + Na.

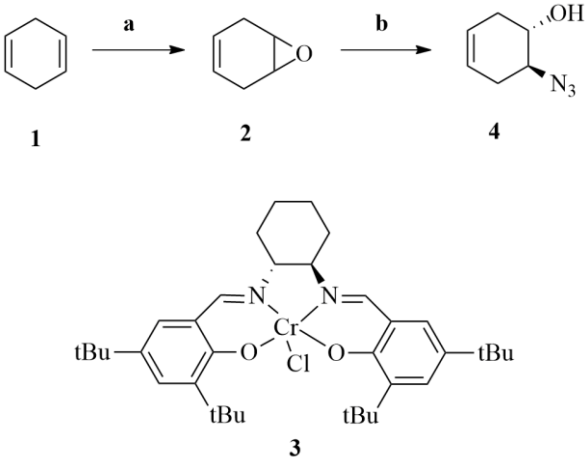
(1*S*,6*S*)-6-(4-methoxy-1H-1,2,3-triazol-1-yl)cyclohex-3-enol (6d)

R_f = 0.66 (Hexane : Ethyl Acetate 9:1).^{1}H NMR-Spectra (400 Hz, $CDCl_3$): δ (ppm) 7.44-7.51 (d, 1H, CH=CH), 5.65-5.78 (s, 2H, CH=CH), 4.43-4.57 (m, 1H, C*H*OH), 4.04-4.19 (m, 1H, C*H*N), 3.79-3.92 (s, 3H, OC*H*$_3$), 2.82-3.00 (m, 1H, C*H*$_2$), 2.61-2.71 (m, 2H, C*H*$_2$), 2.21-2.43 (m, 1H, C*H*$_2$). ^{13}C NMR-Spectra (100 Hz, $CDCl_3$): δ (ppm) 126.7 (C=C), 125.2 (CH=CH), 123.7 (CH=CH), 122.7 (CH=C), 69.1 (*C*-OH), 63.8 (*C*HN), 55.3 (O*C*H_3), 33.9 (*C*H_2), 31.6 (*C*H_2). ν_{max} (chloroform)/ (cm^{-1}) 3734, 1614, 1353, 1187, 746. MS [Cl,NH3]: m/z (%) 196.1 $[M]^+$ + H^+.

^{1}H NMR and ^{13}C NMR Spectra was accounted on 400 Hz where chemical shifts are reported in δ (ppm) by using solvent $CDCl_3$ (7.26 ppm) as internal standard by using JEOL JNM-ECZS NMR Spectrometer. The spectra is analyzed by first order, the coupling constant (*J*) that been used in Hertz (Hz) [11]. IR Spectroscopy was used to determine the different functional groups which have the different characteristic absorption frequencies (cm^{-1}) by using Perkin Elmer FT-IR 1600 Spectrometer. Agilent Technologies 5890 Series II gas chromatography equipped with HP 5971 mass spectrometer detector and a 30m x 250μm x 0.25μm of HP 5-MS capillary column was used to determine the mass spectroscopy.

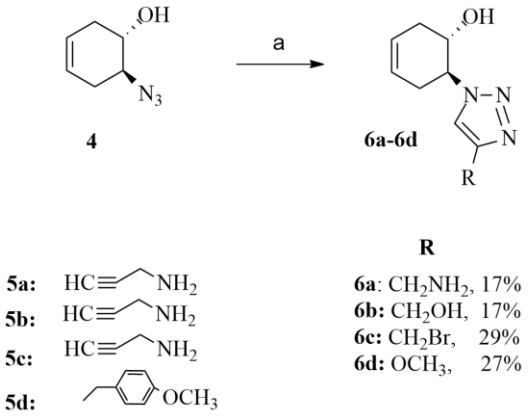
3. Results and Discussion

The synthesis of triazoles **6a-6d** begun with the preparation of epoxide **2** from 1,4-cylohexadiene **1**. Epoxidation of 1,4-cylohexadiene **1** using *m*-CPBA gave meso-cyclohexane epoxide **2** in high yield (88%). Epoxide rings are useful reagents that can be opened by further reaction to form stereospecific alcohols. As shown in Scheme 1, the ring opening of epoxide **2** by the treatment with $TMSN_3$ in the present of Salen complex catalyst **3** to give hydroxy azido cyclohexane **4** in 68% yield and 85% enantiomeric excess. Salen catalyst complex acted as difunctional complex by lowering the LUMO and control the attacking trajectory side of the nucleophile [12]. The chromium-azide coordinated is rationalized by Jacobsen which afforded trans-azido silyl ether product [13]. All the compounds are comfirmed by using carbon and proton NMR, FTIR and Mass Spectroscopy.



Scheme 1. *Reagent and conditions*: (a) *m*-CPBA, K_2HPO_4, DCM, 0℃-rt, 24h, 88%. (b) (*R*,*R*)-Salen complex, $TMSN_3$, Et_2O, rt, 46 h, 68%.

The next step in the synthesis was to effect the key click reaction on compound **4**. The azide **4** underwent 1,3-dipolar cycloaddition with their corresponding alkynes **5a-5c** and 1-ethylanisole **5d**. The reaction took place under the presence of copper catalyst CuI[P(OEt)$_3$] to form the desired heteroatom rings, hydroxy cyclohexene-1,2,3-triazoles **6a-6d** in 17-29% which shown in Scheme 2. Iodocopper triethyl phosphite complex, CuI[P(OEt)$_3$] is reactive towards on conjugate additions. The use of phosphine complexes generally will improve the reactivity of active copper, and the more EDG (electron donating electron) attached on phosphine, the more reactive the copper that promote a ligand acceleration [14].



Scheme 2. *Reagent and conditions:* (a) propargyl amine **5a**/2-propyn-1-ol **5b**/propargyl bromide **5c**/4-ethynylanisole **5d**, CuI[P(OEt)$_3$], toluene, rt, 24 h, 17- 29%.

4. Summary

In this study, we reported the synthesis of derivatives of (1*S*,2*S*)-hydroxy cyclohexene-1,2,3-triazoles. This synthesis was conveniently achieved in three steps that employed epoxidation, Salen complex catalyst coordinated for epoxide ring opening and click reaction.

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