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Asymmetric synthesis of *(1S,2S)*-hydroxy cyclohexene-1,2,3-triazole derivatives

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ABSTRACT

In this study, four (*1S*,*2S*)-hydroxycyclohexene-triazoles were synthezeid from 1,4-cyclohexadiene via epoxidation, epoxide ring-opening, and click reactions. The epoxidation of 1,4-cyclohexadiene yielded the monoepoxide cyclohexene. Subsequent epoxide ring-opening of epoxide catalyzed by the Salen complex produced (*1S*,*6S*)-6-azidocyclohex-3-enol. These four (*1S*,*2S*)-hydroxycyclohexene-triazoles were synthesized via a final click reaction of (*1S*,*6S*)-6-azidocyclohex-3-enol with four different alkynes, i.e., propargyl amine, 2-propyn-1-ol, propargyl bromide, and 1-ethylanisole.

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1. INTRODUCTION

Triazole subunit is widely found in many biologically active compounds with important pharmacological implications. The heterocyclic triazole or disubstituted triazole could be synthesized using a 'click' reaction, in which compounds with azide functionalities and chemical compounds bearing alkyne group would react in the presence of catalytic metal iodide, such as copper iodide, to give the Huisgen 1,3 dipolar cycloaddition product (Totobenazara and Burke, 2015). For example, the potential proliferator-activated receptor γ (PPAR-γ) against type II diabetes could be synthesized using the click chemistry protocol (Zhang et al., 2009; Matin et al., 2009). The regioselectivity of triazole could be controlled using different types of metals, such as copper, ruthenium, nickel, indium, lithium, and magnesium (Kim. et al., 2020). The ligand effect in the determination of regioselectivity or efficiency is, in turn, influenced by the formation of polynuclear copper acetylides and the binding of Cu(I)-ligand (Hein and Fokin, 2010).

The 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 (Kharb et al., 2011). For example, the selective inhibitor tyrosine phosphate (mPTPB) from *Mycobacterium tuberculosis* is a triazole developed for the treatment of human diseases, such as cancer, diabetes, obesity, and inflammation (Thirumurugan et al., 2013). As a result, the derivative-based products of triazoles in combination with salicylic acid were designed to target the mPTPB, i.e., the PTP

active site in triazole scaffold, to enhance affinity and selectivity by finding SHP2, which is an inhibitor that could potentially be used in anti-cancer and anti-leukaemia treatments (Zhang et al., 2010).

In this study, four (*1S,2S*)-hydroxycyclohexene-1,2,3-triazole derivatives were synthesized via modifying the configuration of heterocyclic derivatives. Specifically, (*1S,2S*)-hydroxycyclohexene-1,2,3-triazole derivatives were synthesized from 1,4-cyclohexadiene through epoxidation and followed by stereoselective epoxide opening of cyclohexene epoxide and click reactions. These synthesized triazoles might have anti-tubercular activities.

2. MATERIALS AND METHODS

2.1 Materials

Salen complex catalyst was purchased from Sigma Aldrich. TLCs (Merck, Malaysia) and preparative thin-layer chromatography were performed on silica gel GF/UV 254 (Merck, Malaysia), and the chromatograms were performed on silica gel (100-200 mesh) from Merck, Malaysia visualized under UV light (Perkin Elmer, Waltham, MA) at 254 nm and 365 nm. All solvents were of reagent grade and, when necessary, were purified and dried by standard methods. Organic solutions were dried over anhydrous magnesium sulphate (Merck, Malaysia) or sodium sulphate (Merck, Malaysia).

2.2 Instrument

Infrared (IR) spectra were recorded on a Thermo Nicolet Impact 6700 (Perkin Elmer, Waltham, MA) instrument (KBr pellet). Proton NMR spectra were recorded with a Bruker Ultra Shield 300 MHz spectrometer at 300 K (Perkin Elmer, Waltham, MA), using trimethylsilyl TMS as an internal standard. Chemical shifts were expressed in parts per million (ppm). Coupling constants were in hertz (Hz). The spin multiplicities were indicated by the symbols s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), and br (broad). MS spectra were recorded on an Agilent GC-7890A MS 5975 and Agilent LCMS QTof 6520 (Agilent, Santa Clara, CA). The concentration of solutions after reaction and extraction involved the use of a rotary evaporator operating at a reduced pressure of about 20 Torr.

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

Dipotassium phosphate (3.61 g, 20.7 mmol) was added to a stirred solution of 1,4-cyclohexadiene **1** (3.38 g, 42.1 mmol) in dichloromethane (250 mL) at 0°C and stirred for 10 minutes. Then *m*-chloroperoxybenzoic acid (10.2 g, 41.4 mmol) was added gradually into the reaction mixture with stirring for 24 hours. The 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 vacuum distillation (20 mbar, 60-80°C) to give a colorless liquid compound **2** (3.8 g, 88%).

R_f = 0.23 (hexane:ethyl acetate 9:1).^{1}H NMR (400 Hz, $CDCl_3$): δ 5.27-5.32 (s, 2H), 3.73 (s, 2H), 2.51-2.57 (d, 2H, C*H*, *J* =17.6), 2.38-2.46 (d, 2H, *J* = 17.4). ^{13}C NMR (100 Hz, $CDCl_3$): δ 121.2, 50.8, 24.8. IR (film): $\tilde{\nu}$ = 2995, 1665, 1432, 1214, 737 cm^{-1}.

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

Salen complex catalyst **3** (0.44 g, 0.63 mmol) was added to a stirred solution of *meso*-epoxide **2** (3 g, 31.2 mmol) in dry diethyl ether (4 mL) and stirred for 15 minutes. Then, trimethylsilylazide (3.77 mL, 32.8 mmol) was gradually added into the reaction mixture and stirred for 46 hours at room temperature. The solvent was removed under reduced pressure (389 mbar, 40°C) to give the yellow crude compound, which was purified using the column chromatography on silica gel with the mobile phase petroleum ether: ethyl acetate (9:1) to give the compound **4** in 2.83 g with 68% yield.

R_f = 0.41 (hexane: ethyl acetate 9:1).^{1}H NMR (400 Hz, $CDCl_3$): δ 5.6-5.7 (s,1H), 3.5-3.7 (m,1H, *J* =12.0), 2.5-2.6 (m, 2H), 2.1-2.3 (m, 2H, *J* =44.0), 2.0-2.1 (s,1H). ^{13}C NMR (100 Hz, $CDCl_3$): δ 124.0, 77.2, 64.0, 34.0, 31.0, 2.0. IR (film): $\tilde{\nu}$ = 3343, 2958, 2906, 1655, 1252, 1108, 668 cm^{-1}. MS-ESI (Cl, NH_3): calculated for [$C_6H_9N_3O$]: 139.0746, MS [Cl,NH_3]: m/z (%) 140.14 [M + H$^+$].

2.5 General procedure for Click reaction

2.5.1 (*1S,6S*)-6-(4-(aminomethyl)-1H-1,2,3-triazol-1-yl)cyclohex-3-enol (5a-5d)

Iodocopper triethyl phosphite complex, CuI[P(OEt)$_3$] (0.437 g, 0.31 mmol), was added to a stirred solution of azide **4** (0.03 g, 0.23 mmol) in dry toluene (4 mL) with continuous stir for 15 minutes. Then, propargylamine (3.77 mL, 0.56 mmol)/ 2-propyn-1-ol/ propargyl bromide/ ethynylanisone was gradually added into the reaction mixture and stirred for the next 24 hours under room temperature. Under reduced pressure (400 mbar, 40°C), the solvent was taken out to yield the light yellow crude triazole, which was then purified using the column chromatography on silica gel with the mobile phase petroleum ether: ethyl acetate (9:1) to give the compound **5a** (0.01 g, 17%). Similar steps were repeated for the synthesis of the remaining three triazoles **5b**-**5d** (18-29%).

2.5.2 (*1S,6S*)-6-(4-(aminomethyl)-1H-1,2,3-triazol-1-yl)cyclohex-3-enol (5a)

As described in the general procedure. R_f = 0.54 (hexane: ethyl acetate 7:3).^{1}H NMR (400 Hz, $CDCl_3$): δ 7.21-7.28 (m, 1H), 5.65-5.75 (s, 2H), 4.23-4.41 (m, 1H), 4.04-4.14 (m, 1H), 2.76-2.93 (m, 1H), 2.49-2.71 (m, 2H), 2.33-3.35 (s, 2H), 2.24-2.29 (m, 1H). ^{13}C NMR (100 Hz, $CDCl_3$): δ 129.1, 128.3, 125.4, 123.9, 66.8, 63.8, 34.5, 31.9, 29.7. IR (film): $\tilde{\nu}$ = 3418, 2925, 1651, 1441, 1025, 826, 765 cm^{-1}. MS-ESI (Cl, NH_3): calculated for [$C_9H_{14}N_4O$]: 194.1168, MS [Cl,NH_3]: *m/z* (%) 194.04 [M$^+$].

2.5.3 (*1S,6S*)-6-((R)-5-(hydroxymethyl)-3H-pyrazol-3-yl)cyclohex-3-enol (5b)

As described in the general procedure. R_f = 0.81 (hexane: ethyl acetate 9:1).^{1}H NMR (400 Hz, $CDCl_3$): δ 7.14-7.32 (m, 2H), 5.58-5.83 (m, 2H), 4.23-4.03 (m, 2H), 4.02-4.17 (m, 1H), 3.63-3.83 (m, 2H), 2.09-2.91 (m, 4H). ^{13}C NMR (100 Hz, $CDCl_3$): δ 129.0, 124.8, 123.3, 67.8, 63.4, 41.0, 30.8, 25.5. IR (film): $\tilde{\nu}$ = 3351, 2926, 1667, 1460, 1383,

1216, 759 cm^{-1}. MS-ESI (Cl, NH_3): calculated for [$C_9H_{13}N_3O_2$]: 195.2184, *m/z* (%) 195.02 [M^+].

2.5.4 (*1S,6S*)-6-(4-(bromomethyl)-1H-1,2,3-triazol-1-yl)cyclohex-3-enol (5c)

As described in the general procedure. R_f = 0.48 (hexane: ethyl acetate 8:2). ^{1}H NMR (400 Hz, $CDCl_3$): δ 7.52-7.58 (m, 1H), 5.03-5.34 (s, 2H), 4.27-4.36 (m, 1H), 4.20-4.25 (d, *J* = 3.6 Hz, 2H), 4.07-4.12 (m, 1H), 2.70-2.88 (m, 1H), 2.21-2.40 (m, 2H), 1.95-2.20 (m, 1H). ^{13}C NMR (400 Hz, $CDCl_3$): δ 127.3, 125.5, 124.9, 120.5, 66.0, 62.7, 34.5, 17.2. IR (film): $\tilde{\nu}$ = 3020, 2400, 2110, 1215, 758, 669 cm^{-1}. MS-ESI (Cl, NH_3): calculated for [$C_9H_{12}BrN_3O$]: 257.0164, *m/z* (%) 280.11 [M + Na]$^+$.

2.5.5 (*1S,6S*)-6-(4-methoxy-1H-1,2,3-triazol-1-yl) cyclohex-3-enol (5d)

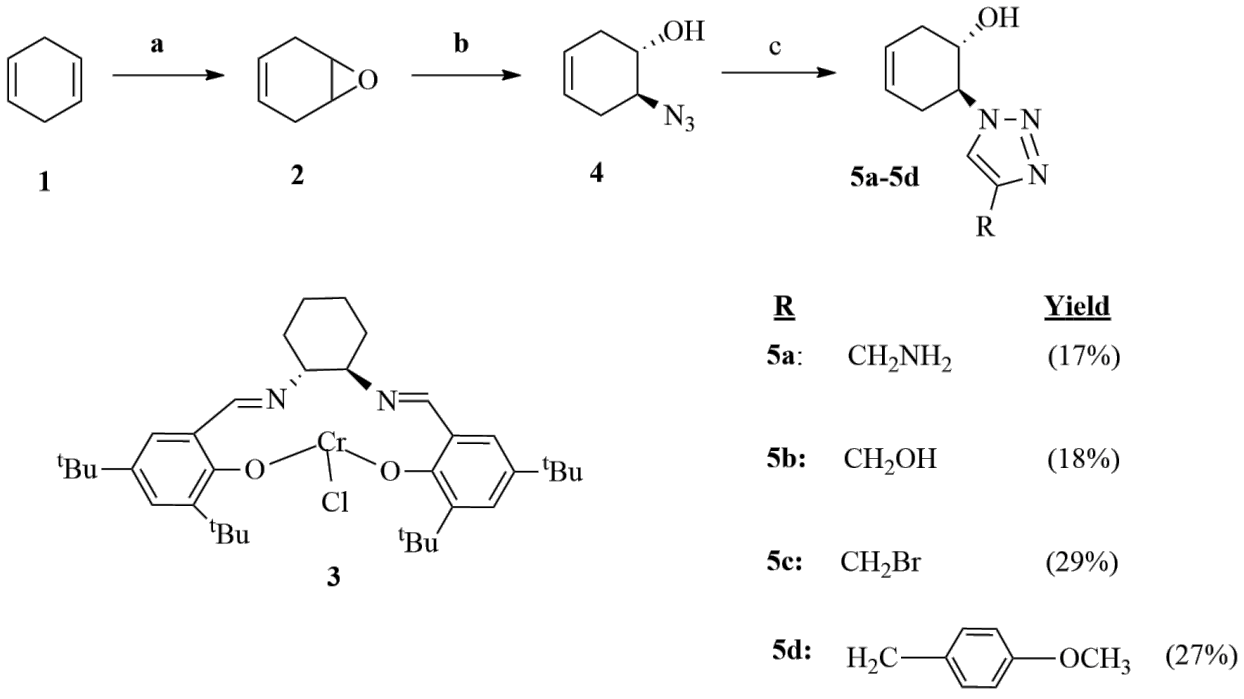
As described in the general procedure. R_f = 0.66 (hexane : ethyl acetate 9:1).^{1}H NMR (400 Hz, $CDCl_3$): δ 7.44-7.51 (d, 1H), 5.65-5.78 (s, 2H), 4.43-4.57 (m, 1H), 4.04-4.19 (m, 1H), 3.79-3.92 (s, 3H), 2.82-3.00 (m, 1H), 2.61-2.71 (m, 2H), 2.21-2.43 (m, 1H). ^{13}C NMR (100 Hz, $CDCl_3$): δ 126.7, 125.2, 123.7, 122.7, 69.1, 63.8, 55.3, 33.9, 31.6. IR (film): $\tilde{\nu}$ = 3734, 1614, 1353, 1187, 746 cm^{-1}. MS-ESI (Cl, NH_3): calculated for [$C_{16}H_{19}N_3O_2$]: 285.1477: *m/z* (%) 286.15 [M + H]$^+$.

3. RESULTS AND DISCUSSION

The synthesis of four triazoles, **5a**-**5d**, began with the preparation of *meso*-cyclohexane epoxide **2**, from 1,4-cylohexadiene **1**. Epoxidation of 1,4-cylohexadiene using meta-chloroperoxybenzoic acid (*m*-CPBA) gave a high yield of *meso*-cyclohexane epoxide (88%) (Ali et al., 2017a; Ali et al., 2017b). The epoxide ring opening of *meso*-cyclohexane **2** was then opened via the treatment with $TMSN_3$ in the presence of Salen complex catalyst to produce (*1S,6S*)-6-azidocyclohex-3-enol **4** with 68% yield and 85% enantiomeric excess (Scheme 1) (Ali et al., 2013; Ali et al., 2021).

The Salen catalyst acted as a difunctional complex by lowering the LUMO, thereby controlling the attacking trajectory side of the nucleophile (Chiong and Paraan, 2019). The chromium-azide coordinated had been rationalized by Jacobsen also afford trans-azido silyl ether, which would also drive the corresponding racemic in this process (Martinez et al., 1995). The functional groups of all synthesized compounds were characterized using carbon and proton NMR spectroscopy analysis, FT-IR, and mass spectroscopy.

In the subsequent click reaction, the azide (*1S,6S*) -6-azidocyclohex-3-enol **4** underwent 1,3-dipolar cycloaddition for the synthesis of triazoles with their corresponding alkynes, which were propargyl amine, 2-propyn-1-ol, propargyl bromide, and 1-ethylanisole. The reaction took place in the presence of the copper catalyst, iodocopper triethyl phosphite complex (CuI[P(OEt)$_3$]) to form the desired heteroatom rings, hydroxy cyclohexene-1,2,3-triazoles for four triazoles **5a**-**5d** with 17-29% yield. The CuI[P(OEt)$_3$] catalyst was reactive towards the additions of the conjugate.



Scheme 1. *Reagent and conditions*: (a) *meta*-chloroperbenzoic acid (*m*-CPBA), dipotassium hydrogen phosphate (K_2HPO_4), dichloromethane (DCM), 0°C-rt, 24h, 88%, (b) (*R,R*)-Salen complex **3**, trimethylsilyl azide ($TMSN_3$), diethyl ether (Et_2O), room temperature (rt), 46 h, 68%, (c) propargyl amine /2-propyn-1-ol / propargyl bromide / 4-ethynylanisole, CuI[P(OEt)$_3$], toluene, room temperature (rt), 24 h, 17- 29%

4. CONCLUSION

In this study, we reported the synthesis of derivatives of (*1S,2S*)-hydroxy cyclohexene-1,2,3-triazoles through an epoxidation reaction, in which the Salen complex catalyzed the epoxide ring-opening and click reaction.

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