Synthesis of Sulfonyl 2-(prop-2-yn-1-ylthio) benzo[d]thiazole Derivatives

Mohammad A. Abbas
Department of Chemistry, College of Education, Al- Iraqia University, Baghdad-Iraq.
E mail: mohammed.alane@gmail.com.

Abstract

New series of benzothiazole-2-thiol (2-MBT) derivatives were synthesized and Structures of the synthesized compounds were established on the basis of ^{1}H NMR in DMSO- d^6 and FTIR in KBr spectral data. Acetylene derivatives were prepared by the reaction of 2-MBT with 3-bromo propyne in base medium (Nucleophilic Substitution reaction- S_N2) that gives (2-(prop-2-yn-1-ylthio) benzo[d]thiazole) 85% yield, these derivative was oxidized by using mixture of potassium dichromate and concentrated sulphuric acid in presence of glacial acetic acid as a solvent to give (2-(prop-2-yn-1-ylsulfonyl) benzo[d]thiazole) 72% yield.

Mannich reactions were done by using (2-(prop-2-yn-1-ylsulfonyl) benzo[d]thiazole), Para formaldehyde and various secondary amines in the presence of cuprous chloride as a catalyst and dioxane as a solvent to give different derivatives 44-68% yield, and we think these compounds may have biological activity.

Keywords: Benzothiazole-2-thiol, Acetylene, Mannich reaction's, Biological activity.

Introduction

Thiazole is a heterocyclic compound featuring both a nitrogen and sulfur atom as part of the aromatic five-membered ring Fig.(1-a). The applications of thiazoles were found in drug development for the treatment of allergies, hypertension, inflammation, schizophrenia, bacterial, HIV infections and hypnotics. Benzothiazoles, Benzothiazole-2-thiol as shown in Fig.(1-b) and Fig.(1-c) respectively have been widely explored for industrial applications since their discovery. However, the biological activity of this class of compounds deserves further investigation. The derivatives of these compounds have been studied and found to have various chemical and biological activities such as antipyretic [1], anti-inflammatory [2], antimicrobial [3], antitumor [4-6], antibacterial [7], Antioxidants [8], antimalarial [9], antiviral [10] and anticancer [11,12].

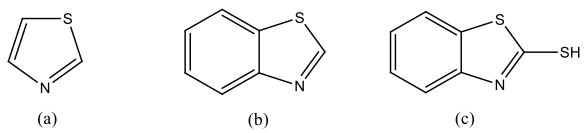


Fig.(1) Structure of Thiazole, Benzothiazole and Benzothiazole-2-thiol.

Experimental

1-Preparation of 2-(prop-2-yn-1-ylthio) benzo [d] thiazole (1).

(8.35g, 0.05mol) of benzothiazole-2-thiol was dissolved in (25mL) of dry tetrahydrofuran (nonpolar solvent) and (5.05g, 0.05mol) of triethylamine was added, the mixture was stirred for 45 min at room temperature, then (5.90g, 0.05mol) of 3-Bromo propyne was added drop wise, the mixture was warmed at (45^{0}C) for one hour under reflection condensation, the yield was Cooled, and (15ml) of Ammonium Chloride solution was added. The product was extracted by ether (2*25ml), and dried with $MgSO_4$. Then filtered, and the ether was evaporated and purified by petroleum ether to give Colorless crystals, Fig.(2).

The FTIR spectral data showed absorption at (2140cm^{-1}, υs: C≡C), (3300cm^{-1}, υs: ≡C-H),(660cm^{-1}, υs: C-S-C), (3080cm^{-1}, υs: C-H, Ar), (1400,1440,1465cm^{-1}, υs: C=C, Ar), (2930-2970cm^{-1}, υs: CH_2, aliphatic),(1645cm^{-1}, υs: C=N, stretching), *1H-NMR* spectra data showed signal at (δ=7.45, 2H, t, CH-(CH)$_2$-CH), Ar), (δ=8.00, 2H, d, C-(CH)$_2$-C, Ar,), (δ=4.25, 2H, d, S-CH_2-), (δ=3.30, 1H, t, ≡CH), mp = 47^{0}C.

2- Preparation of 2-(prop-2-yn-1-ylsulfonyl) benzo [d]thiazole (2).

To (10.25g, 0.05mol) of 2-(prop-2-yn-1-ylthio) benzo [d] thiazole in (25ml) of glacial acetic acid as a solvent, potassium dichromate (2.0g, 35ml as Solution) with (20ml of concentrated sulfuric acid) were added drop wise slowly under controlled temperature between (0-5^{0}C) for 15 min. Then the temperature was increased slowly to (30^{0}C) and the mixture was stirred for 90 min. The yield was added to (200ml) cold water, and the precipitate appeared. Then separated by filtration, the precipitate was purified by ethanol: water (1:2) solution, to give white crystals, Fig.(2).

The FTIR spectral data showed absorption at (1150, 1350cm^{-1}, υs: SO_2 symmetric, asymmetric), (3080cm^{-1}, υs: C-H, Ar), (1400, 1430,1475cm^{-1}, υs: C=C, Ar), (2140cm^{-1}, υs: C≡C), (3280cm^{-1}, υs: ≡C-H), (2930 - 2970cm^{-1} υs: CH_2, aliphatic), (1655cm^{-1} υs: C=N, stretching), *^{1}H-NMR* spectra data showed signal at (δ=7.45, 2H, t, CH-$(CH)_2$-CH, Ar), (δ=8.00, 2H, d, C-$(CH)_2$-C, Ar), (δ = 6.10, 2H, d, SO_2-CH_2-), (δ=3.35, 1H, t, ≡CH), mp = 114^{0}C.

3- General procedure for Mannich reaction.

Compound (3) synthesized according to a literature method, To (11.85g, 0.05mol) 2-(prop-2-yn-1-ylsulfonyl) benzo[d] thiazole in (20ml) of Dioxane as solvent, with Para formaldehyde and little of cuprous chloride as catalyst, (0.05mol) of secondary amine was added drop wise, the reaction mixture was stirred for two hours under reflection condensation. The yield was separated by filtration. Filtered solutions were added to (150ml) cold water, and the precipitate appeared. Then separated by filtration, the precipitate was purified by a deferent solution, to give different crystals, Fig.(2).

Compound (3a): 4-(benzo [d] thiazol-2-ylsulfonyl) -N, N-*dibenzyl* but-2-yn-1-amine.

The FTIR spectral data showed absorption at (2920-2900cm^{-1}, υs: CH_2, aliphatic), (3055cm^{-1} υs: CH, Ar), (1450, 1490 cm^{-1}, υs: C=C, Ar), (2140 cm^{-1}, υs: C≡C), (1150, 1350 cm^{-1}, υs: SO_2, symmetric, asymmetric), (1655cm^{-1}, υs: C=N, stretching), *^{1}H-NMR* spectra data showed signal at (δ=7.45, 2H, t, CH-$(CH)_2$-CH, Ar), (δ=8.00, 2H, d, C-$(CH)_2$-C, Ar), (δ=6.10, 2H, d, SO_2-CH_2-), (δ=4.35, 2H, s, ≡C -CH_2), (δ=3 .70, 4H, s, N - $(CH_2)_2$ -$(ph)_2$), (δ=7.35-7.45, 10 H, m, $(ph)_2$), mp = 190^{0}C.

Compound (3b): 2-((4-(*piperidin*-1-yl) but-2-yn-1-yl) Sulfonyl) benzo[d]thiazole.

The FTIR spectral data showed absorption at, (1400, 1440,1465cm^{-1}, υs: C=C, Ar), (1150 cm^{-1}, 1350cm^{-1}, υs: SO_2 symmetric, asymmetric), (2800 -2850cm^{-1}, υs: CH_2, piperidin ring), (υs: 3080cm^{-1}, C-H, Ar), (1400, 1440, 1465cm^{-1}, υs: C=C, Ar), (2140cm^{-1}, υs: C≡C), (2850-2900 cm^{-1}, υs: CH_2, aliphatic), (1655 cm^{-1}, υs: C=N, stretching), *^{1}H-NMR* spectra data showed signal at (δ=7.45, 2H, t, CH-$(CH)_2$-CH, Ar), (δ=8.00, 2H, d, CH-$(CH)_2$-CH, Ar), (δ=6.10, 2H, d, SO_2-CH_2-), (δ=4.30, 2H, s, ≡C -CH_2), (δ=2.30, 4H, t, N- $(CH_2)_2$, piperidin), (δ=1.55, 6H, m, CH_2-CH_2 -CH_2, piperidin), mp=144^{0}C.

Compound (3c): 2-((4-(*pyrrolidin*-1-yl) but-2-yn-1-yl) Sulfonyl) benzo[d]thiazole.

The FTIR spectral data showed absorption at (2700-2940cm^{-1}υs: CH_2, pyrrolidin ring), (3080 cm^{-1} , υs: C-H, Ar), (1400, 1440, 1465 cm^{-1}, υs: C=C, Ar), (2140 cm^{-1}, υs: C≡C), (1150 cm^{-1}, 1350 cm^{-1}, υs: SO_2 symmetric, asymmetric), (2850-2900 cm^{-1}, υs: CH_2, aliphatic.), (1655 cm^{-1}, υs: C=N, stretching), *^{1}H-NMR* spectra data showed signal at (δ=7.45, 2H, t, CH-$(CH)_2$-CH, Ar), (δ=8.00, 2H, d, CH-$(CH)_2$-CH, Ar), (δ= 6.10, 2H, d, SO_2-CH_2-), (δ=4.35, 2H, s, ≡C -CH_2), (δ=2.35 ,4H, t, N-$(CH_2)_2$), (δ=1.40, 4H, m, CH_2 -CH_2), mp=95^{0}C.

Compound (3d): 4-(4-(benzo[d]thiazol-2-ylsulfonyl) but -2-yn-1-yl) *morpholine*.

The FTIR spectral data showed absorption at (2750-2950cm^{-1}, υs: CH_2, morpholine), (1140 cm^{-1}, υs: C-O-C), (3080cm^{-1}, υs: C-H, Ar), (1400, 1440,1465cm^{-1}, υs: C=C, Ar), (2140cm^{-1}, υs C≡C), (1150cm^{-1}, 1350cm^{-1}, υs: SO_2 symmetric, asymmetric), (2850-2900 cm^{-1} υs: CH_2 aliphatic), (1655 cm-^{1}, υs, C=N, stretching), *^{1}H-NMR* spectra data showed signal at (δ=7.45, 2H, t, CH-$(CH)_2$-CH, Ar), (δ=8.00, 2H, d, CH-$(CH)_2$-CH, Ar), (δ=6.10, 2H, d, SO_2-CH_2-), (δ=4.35, 2H, s, ≡C -CH_2), (δ=2.40, 4H, t, N-$(CH_2)_2$), (δ=3.50, 4H, t, $(CH_2)_2$ -O), mp=135^{0}C.

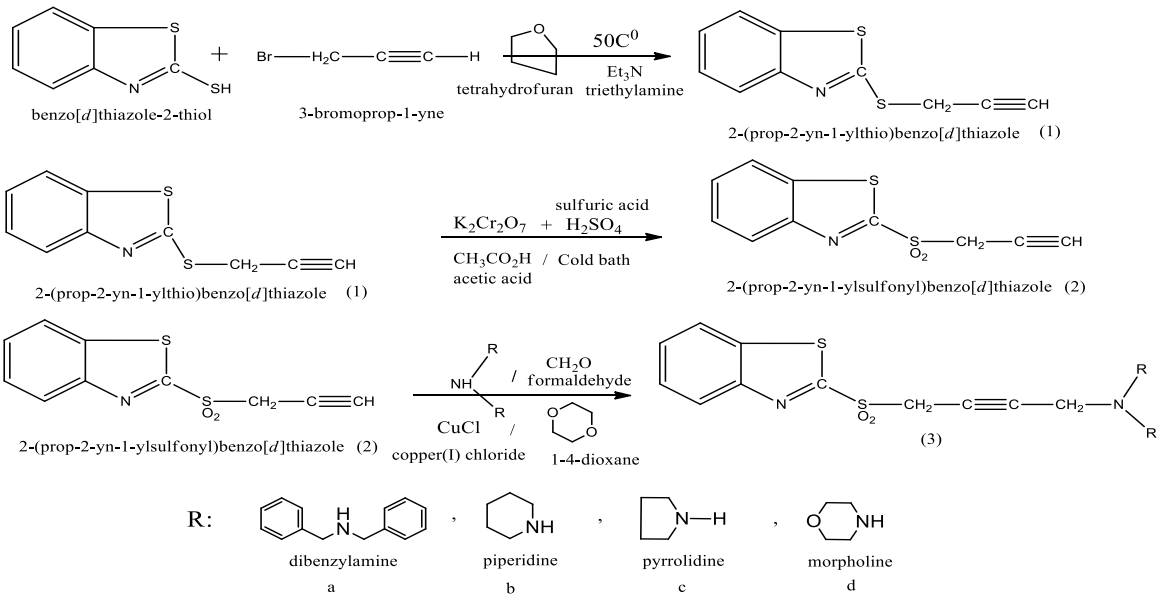


Fig.(2) Synthesis scheme of compounds.

Results and Discussion

Compound 2-(prop-2-yn-1-ylthio) benzo [d] thiazole was prepared by (S_N2 mechanism), (2-MBT) is the Nucleophilic that substitutes bromine in 3-bromo propyne (primary alkyl halide), Et_3N helped in the appearance of the negative charge at the sulfur atom in which case the reaction can be easier. The melting point to 2-MBT=177^0C is reduced to 47^0C because the dimer formation to (2-MBT) is crashed. The mechanism of reaction is shown in Fig.(3).

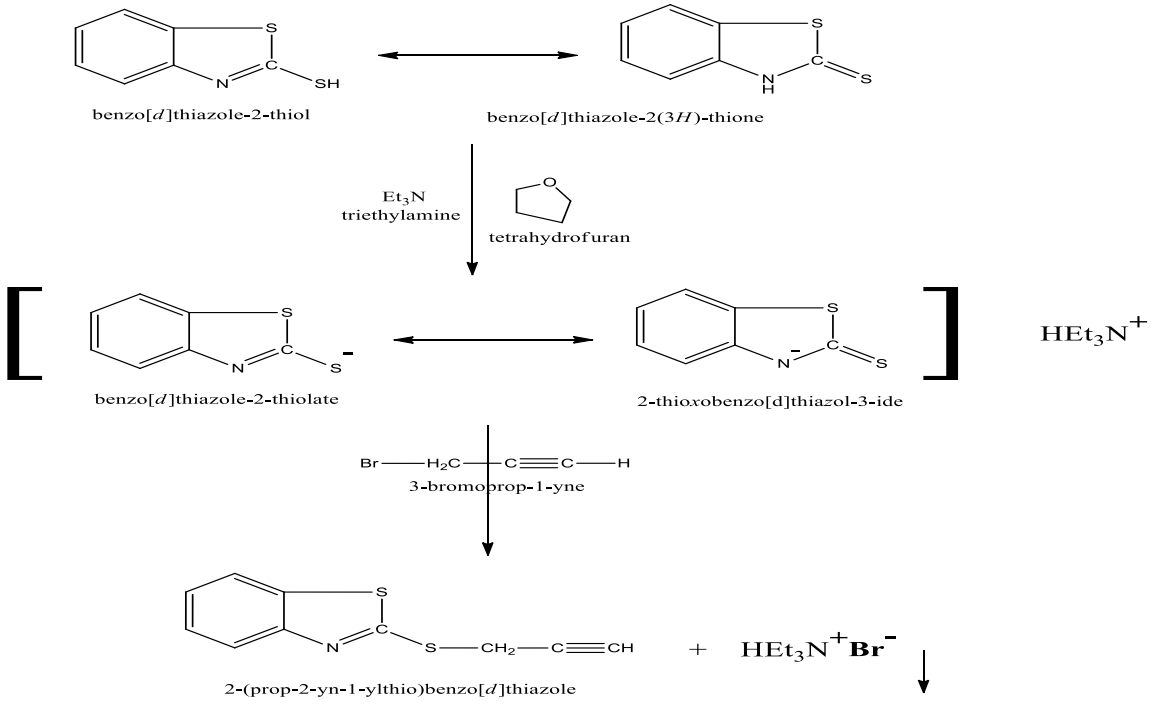


Fig.(3) The mechanism of reaction.

Compound 2-(prop-2-yn-1-ylsulfonyl) benzo [d] thiazole, in The FTIR spectral data showed absorption at (1150cm^{-1}, 1350cm^{-1}, υs: SO_2 symmetric, asymmetric), ^{1}H-NMR spectra data showed signal at (δ=6.10, 2H, d, SO_2-CH_2-) this signal of (2H) shifted to low field by the effect of SO_2 group, this improved the oxidation which occurred at the external sulfur atom.

Mannich reaction was prepared by condensation reaction between 2-(prop-2-yn-1-ylsulfonyl) benzo [d]thiazole and Para formaldehyde with different secondary amine, in presence of cupric chloride, the mechanism of Mannich reaction is shown in Fig.(4)

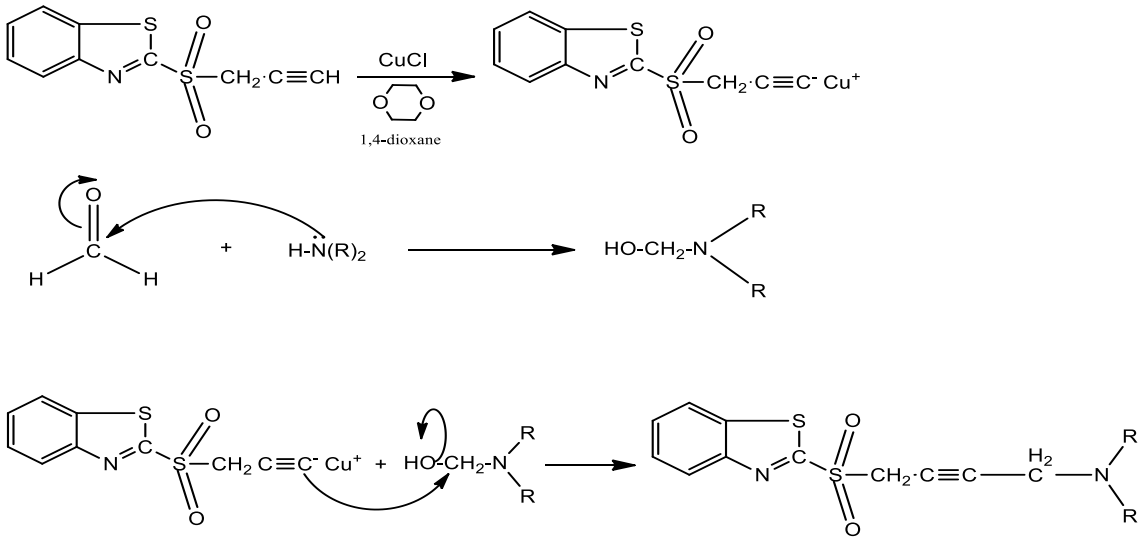
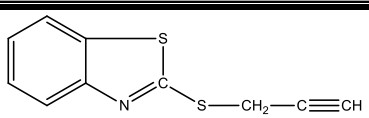
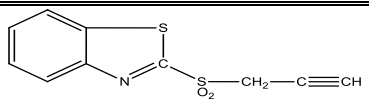
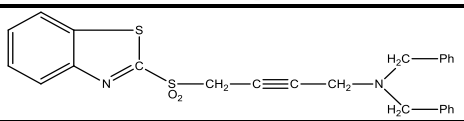
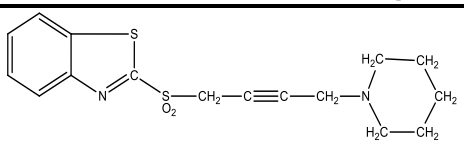
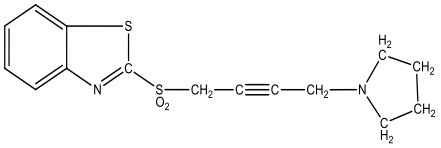
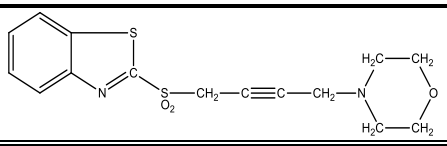


Fig.(4) The mechanism of Mannich reaction.

Table (1)
Physical properties of the prepared compounds.

Compound No.	*Compounds structure*	*mp.^{0}C*	*Yield %*	*Re-crystallization solvent*	*color*
1		**47**	**85%**	**Petroleum ether**	**Colorless**
2		**114**	**72%**	**Ethanol: water**	**white**
3a		**190**	**68**	**ethanol**	**Light brawn**
3b		**144**	**65**	**Ethanol: water**	**Light brawn**
3c		**95**	**52**	**Acetone: water**	**brawn**
3d		**135**	**44**	**Ethanol: water**	**yellow**

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الخلاصة

تم تحضير سلسة من المشتقات الاستلينية الجديدة للمركب (2-MBT)، البيانات الطيفية للمركبات المحضرة تم تشخيصها باستخدام الرنين النووي المغناطيسي والاشعة تحت الحمراء.

المشتق الاستليني 2-(prop-2-yn-1-ylthio[d] thiazole) حضر بتفاعل استبدال نيكلوفيلي بين (2-MBT) والمركب 3-bromo propyne بوجود triethylamine كوسط قاعدي للتفاعل، وباستخدام مذيب لا قطبي THF، هذا المشتق اكسد باستخدام مزيج من ثنائي كرومات البوتاسيوم وحامض الكبريتيك المركز بوجود حامض الخليك الثلجي كمذيب ووسط للتفاعل، ليعطي المركب 2-(prop-2-yn-1-ylsulfonyl) benzo[d]thiazole

اجري تفاعل مانخ بتكاثف المشتق الاستليني المؤكسد مع البارفورمالديهايد وبعض الامينات الثانوية. نتائج التحضير أعطت سلسله جديدة من المشتقات يتوقع ان تكون لها فعالية بيولوجية.