SYNTHESIS OF SOME NEW THIAZOLE DERIVATIVES WITH THE HELP OF HYDROXY(TOSYLOXY)IODOBENZENE

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Abstract

As we all know, succinimide and thiosemicarbazide are commercially available reagents. Firstly, we synthesised succinimide and thiosemicarbazide in the presence of ethanol. We synthesised it on stirring, but we did not get any product. Then we transfer the same reaction mixture on reflux conditions in the presence of the catalytic amount of glacial acetic acid, and we got a new synthesised of 2,2'(pyrrolidine-2,5-diylidine)bis(hydrazine-1-carbothioamide. The synthesised reactant was characterised by ^{1}H,^{13}C, and Mass spectroscopy. Further, the synthesised reactant was treated with substituted tosylates, and new and facile products of thiazoles were formed. The synthesised products were confirmed through spectral data. With the help of Hantzch, thiazole was treated with HTIB, and we got thiazoles. Further, we are interested in their biological activities, which give its pharmacological importance synthesis, the prepared hydrazine-1-carbothioamide derivatives.

Paper Identification

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Introduction:

As we all know, succinimide is commercially available in the market. Succinimide is an organic compound with a formula of $(CH_2)_2(Co_2)$ NH. It is a white crystalline solid used for various organic syntheses and in some industrial silver-plating processes. This white crystalline compound is classified as a cyclic imide. It was prepared through the thermal decomposition of ammonium succinate. Succinimides are used as anti-convulsant drugs such as ethosuximide, phensuximide and methsuximide. These compounds are used to form covalent bond proteins or peptides and plastics, which are beneficial in various assay techniques[1-4].

It is a dicarboximide called pyrrolidine, which an oxo group substitutes at positions 2 and 5. It is called pyrrolidinone and a dicarboxmide.

Along with anti-convulsant drugs, these compounds and their derivatives are also used as antiepileptic drugs, which were synthesised as modifications of the hydantoin-barbiturate heterocyclic ring[5]. These anti-convulsant drugs are used to treat absence seizures. Gabapentin is present in the class of medications called anti-convulsant, which helps treat seizures by decreasing abnormal excitement in the brain[6]. These medicines directly act on the Nervous system to reduce the number and severity of seizures. There are several anti-convulsant drugs for epilepsy diseases, such as Sodium Valproate, Carbamazepine, Lamatrigine, Levetiracetam, tropiramate etc. Several Hydantoin anti convulsants are Cerebyx, Dilantin, Dilantin 125, Ethotoin, Fosphenytoin, Peganone, Phenytek, Phenytoin, Sesquient.

These well-known Heterocyclic compounds in drug discovery produce diverse therapeutically related applications in pharmacological practices[7].

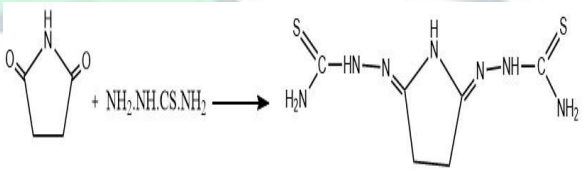
Succinimides and their substitutes are important compounds of many drugs and drug candidates. Cyclic imides and their derivatives contain an imide ring with a general formula -CO-N(R)-CO- so they are cross biological membranes in vivo[8]. Succinimides are part of many active molecules processing activities such as CNS depressant[9], analgesic[10], anti-tumour[11], and cytostatic[12]. It may be prepared by the thermal composition of ammonium succinate[13]. But it is commercially available in the market. It is used because of its easy availability, reactivity and cheap price.

Although, Thiosemicarbazide is also commercially available in the market. Its chemical formula is $NH_2NHCSNH_2$. It is a white powdered solid with no characteristic smell and is commonly related with thiourea having formula (NH_2CSNH_2) by the deletion of NH bond[14]. Most of the thiosemicarbazides are known because of their considerable use. Thiosemicarbazides are the predecessors to thiosemicarbazones and also precursors to many heterocycles[15]. Due to C=O and C=N groups is one of the main reason for the preparation of biologically active compounds like pyrazole, thiazole, thiadiazole, triazole, oxadiazole, triazine, thiadiazine. In the past 15 years, a rapid interest is increased in the chemistry of thiosemicarbazide taken as precursors[16].

HTIB is an industrially available reagent for the phenyliodination and oxytosyllation of a range of organic substrates. But a well-known literature procedure also prepares it. Sometimes, it is called Koser's Reagent. It was prepared from IBD and p-toluene sulphonic acid in acetonitrile. From all the I(III) reagents, HTIB was a very flexible reagent for the preparation of different heterocycles[17-20].

Result and Discussion:

Here, we started our work with the help of synthesised products of Succinimide and thiosemicarbazide. Firstly, it was prepared by stirring in the presence of ethanol, but we did not get any product. Then, we tried the same reaction mixture on reflux conditions in the presence of the catalytic amount of glacial acetic acid for 10-12 hours. A white-coloured solid so obtained was recrystallised with ethanol and washed with water for the pure product. The synthesised product was confirmed through its spectral data. The reaction mixture in **Scheme 1:** 2,2'(pyrollidine-2,5-diylidine)bis(hydrazine-1-carbothioamide) afforded a single product in a very good amount **3a.**

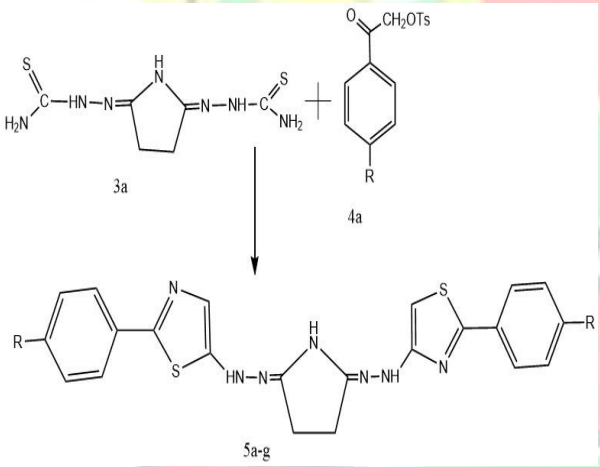


1a **2a** **3a**

Scheme 1

With the help of the synthesised product of 2,2'(pyrrolidine-2,5-diylidine)bis(hydrazine-1-carbothioamide), we prepared different 4-phenylthiazoles.

With the help of the synthesised compound of **3a** was mixed with substituted 1-(α-tosyloxy) acetophenones for the preparation of thiazoles. Firstly, the equimolar amount of **3a** and 1-(α-tosyloxy) acetophenones **4a** was stirred at room temperature, but we did not get any expected product. Then we transfer the same reaction mixture under heating conditions in the presence of the catalytic amount of pinch of potassium carbonate. The sticky mass was triturated with pet ether and then recrystallised with ethanol, and then washed with water to get a solid and pure product of 2-(p-tolyl)-5-(2-(5-(2-(2-(p-tolyl) thiazol-4-yl) hydrazineylidene) pyrrolidin-2-ylidene) hydrazineyl) thiazole. The reaction mixture in **Scheme 2:** 2-(p-tolyl)-5-(2-(5-(2-(2-(p-tolyl) thiazol-4-yl) hydrazineylidene) pyrrolidin-2-ylidene) hydrazineyl) thiazole gives a single product in good amount **5a**.



Scheme 2

The reaction process for synthesising different 4-phenylthiazoles (**5b-g)** was prepared similarly. The expected products were obtained in all the cases, as shown in **Table 1**

Compound	**R**	**Molecular Weight**	**M. Pt.**	**Yield %**
5a	4-CH3C6H4	$C_{24}H_{23}N_7S_2$	123 - 124	88
5b	4-ClC6H4	$C_{22}H_{17}ClN_7S_2$	169 - 170	80
5c	4-OCH_3-C_6H_4	$C_{24}H_{23}N_7O_2S_2$	142 - 143	75
5d	4-FC_6H_4	$C_{22}H_{17}F_2N_7S_2$	200 - 201	82
5e	4-$NO_2C_6H_4$	$C_{22}H_{17}N_9O_4S_2$	180 - 181	86
5f	C_6H_4	$C_{22}H_{19}N_7S_2$	152 - 153	85
5g	4-BrC_6H_4	$C_{22}H_{17}BrN_7S_2$	185 - 186	70

Experimentation:

In an open capillary tube, melting points were taken, which were uncorrected. The IR data were taken using a Perkin Elmer Spectrum IR, Version 10.6.2. ^1H,^{13}C NMR were collected using a Bruker Avance Neo 500 MHz NMR Spectrometer SAIF, P.U. The chemical shifts were communicated in ppm units. The completion of the reaction was checked from time to time on ready-made TLC plates and was of Aluminium Merck silica gel plates. The solvents and Chemicals used for synthesis were Analytical grades. The synthetic substances were brought from business providers and utilised without recrystallisation.

We started our work with the synthesis of succinimide and thiosemicarbazide. A new product was obtained, which was confirmed through its spectral data. Firstly, the equimolar amount of succinimide and thiosemicarbazide was taken and stirred at room temperature in the presence of ethanol, but we did not get any product. Then, we tried the same reaction

mixture on heating conditions in the presence of the catalytic amount of glacial acetic acid. A new product of **3a** was obtained, which was further recrystallised with ethanol and washed with water to get a pure product.

Preparation of 1-(α-tosyloxy) acetophenone:

HTIB was mixed in a substituted amount of acetophenones in 40 ml DCM, and at a temperature of 50-60℃, the reaction mixture was left to stir. Initially, HTIB was Insoluble in DCM. Further, the reaction proceeded. It totally dissolved in the reaction mixture and became soluble in the reaction product. It takes 5-6 hours to complete the reaction. The gummy mass was so obtained. Iodobenzene was removed from the reaction mixture by triturating it with pet ether(60-80℃). The white-coloured solid was recrystallised with ethanol after being washed with water to produce the tosyloxy product[21].

Preparation of Thiazoles and its derivatives:

With the help of the synthesised compound of **3a** was mixed with substituted 1-(α-tosyloxy) acetophenones for the preparation of thiazoles. Firstly, the equimolar amount of **3a** and 1-(α-tosyloxy) acetophenones **4a** was stirred at room temperature, but we did not get any expected product. Then we transfer the same reaction mixture under heating conditions in the presence of the catalytic amount of pinch of potassium carbonate. The sticky mass was triturated with pet ether and then recrystallised with ethanol, and then washed with water to get a solid and pure product of 2-(p-tolyl)-5-(2-(5-(2-(2-(p-tolyl) thiazol-4-yl) hydrazineylidene) pyrrolidin-2-ylidene) hydrazineyl) thiazole. The reaction mixture in **Scheme 2:** 2-(p-tolyl)-5-(2-(5-(2-(2-(p-tolyl) thiazol-4-yl) hydrazineylidene) pyrrolidin-2-ylidene) hydrazineyl) thiazole gives a single product in good amount **5a**.

All the other compounds were prepared similarly as given above:

Spectral data of synthesised compound 2,2'(pyrrolidine-2,5-diylidine)bis(hydrazine-1-carbothioamide) **3a**

IR (v, cm^{-1} KBr): 1620 (C=N), 3460(N-H).

^{1}H-NMR (DMSO-d_6,500 MHz): 2.45(s,2H, CH),5.16(s,imidiyl,H), 7.57(s,NH_2), 11.19(s,NH).

The spectral data of prepared derivatives of thiazoles are given below:

2-(p-tolyl)-5-(2-(5-(2-(2-(p-tolyl) thiazol-4-yl) hydrazineylidene) pyrrolidin-2-ylidene) hydrazineyl) thiazole **5a**

IR (v, cm^{-1} KBr): 1635 (C=N), 3470 (N-H).

^{1}H-NMR (DMSO-d_6,500 MHz): 2.52(s, 3H, CH_3),2.53(s,2H, CH) 5.56(s,imidiyl-H),6.54-6.62(s, thiazolyl-H),7.31-7.75(m, 8H, Ar-H),10.56(s, NH).

^{13}CNMR(DMSOd_6,500MHZ):21.3,21.3,28.5,28.5,121.8,127.4,127.4,127.4,127.4,129.5,129.5,129.5,129.5,131.7,131.7,140.3,140.3,143.1,147.4,151.3,153.0,153.0,169.3,169.3

Elemental Analysis: Calculated for $C_{24}H_{23}N_7S_2$: C:60.76, H: 4.80, S:13.44. Found C: 66.66, H: 4.76, S:13.64.

Molecular wt.:473.62 m/z:473.15,474.15,475.14.

2-(4-chlorophenyl)-5-(2-(5-(2-(2-(4-chlorophenyl)thiazol-4-yl)hydrazineylidene)pyrolidin-2-ylidene)hydrazineyl)thiazole **5b**

IR (v, cm^{-1} KBr): 1615 (C=N), 3464 (N-H).

^{1}H-NMR (DMSO-d_6,500 MHz): 2.54(s, 2H, CH),6.64-6.84(s, thiazolyl-H), 5.62(s,imidiyl-H)7.43-8.32(m, 8H, Ar-H),10.36(s,NH).

^{13}CNMR(DMSOd_6,500MHZ):28.2,28.2,121.4,128.6,128.6,128.6,128.6,129.8,129.8,129.8,129.8,134.6,134.6,141.3,141.3,143.5,147.7,151.5,153.3,153.3,169.6,169.6.

Elemental Analysis: Calculated for $C_{22}H_{17}ClN_7S_2$ C: 51.36, H: 3.33, S:12.46. Found C:51.26, H:3.43, S:12.56.

Molecular wt.:514.45 m/z:513.04,515.03,514.04.

2-(4-methoxyphenyl)-5-(2-(5-(2-(2-(4-methoxyphenyl)thiazol-4-

yl)hydrazineylidene)pyrolidin-2-ylidene)hydrazineyl)thiazole **5c**

IR (v, cm^{-1} KBr): 1625 (C=N), 3480 (N-H).

^{1}H-NMR (DMSO-d_6,500 MHz):2.47 (s, 2H, CH),3.70(s, 3H, CH_3), 5.42(s,imidiyl,-H 6.45-6.52(s, thiazolyl-H),7.01-7.67(m, 8H, Ar-H),10.16(s, NH).

^{13}CNMR(DMSOd_6,500MHZ):28.3,28.3,55.2,55.2,114.2,114.2,114.2,114.2,121.3,128.1,128.1,128.1,128.1,135.1,135.1,143.3,147.8,151.6,153.2,153.2,160.9,160.9,169.7,169.7.

Elemental Analysis: Calculated for $C_{24}H_{23}N_7O_2S_2$: C:57.01, H:4.59, S:12.68. Found C:57.04, H: 4.46, S:12.58.

Molecular wt.:505.62 m/z:505.14,506.14,507.13.

2-(4-fluorophenyl)-5-(2-(5-(2-(2-(4-fluorophenyl)thiazol-4-yl)hydrazineylidene)pyrolidin-2-ylidene)hydrazineyl)thiazole **5d**

IR (v, cm^{-1} KBr): 1620(C=N), 3465 (N-H).

^{1}H-NMR (DMSO-d_6,500 MHz): 2.75(s, 2H, CH) 5.26(S,imidiyl,H),6.45-6.55(s, thiazolyl-H),7.13-7.57(m, 8H, Ar-H),10.64(s, NH).

^{13}CNMR(DMSOd_6,500MHZ):28.1,28.1,116.3,116.3,116.3,116.3,121.3,129.3,129.3,129.3,129.3,138.2,138.2,143.4,147.8,151.0,153.3,153.3,162.3,162.3,169.4,169.4.

Elemental Analysis: Calculated for$C_{22}H_{17}F_2N_7S_2$: C:54.87, H:3.56, S:13.32. Found C:54.78, H:3.65, S:13.32.

Molecular wt.:481.10 m/z:481.10,482.10,483.09.

2-(4-nitrophenyl)-5-(2-(5-(2-(2-(4-nitrophenyl)thiazol-4-yl)hydrazineylidene)pyrolidin-2-ylidene)hydrazineyl)thiazole **5e**

IR (v, cm^{-1} KBr): 1605 (C=N), 3470 (N-H).

^{1}H-NMR (DMSO-d_6,500 MHz): 2.47(s, 2H, CH),5.62(s,imidiyl,H),6.54-6.74(s, thiazolyl-H),7.89-8.03(m, 8H, Ar-H),10.34(s, NH).

^{13}CNMR(DMSOd_6,500MHZ):28.1,28.1,121.2,121.2,121.2,121.2,121.4,128.8,128.8,128.8,128.8,143.3,147.1,150.6,150.6,151.4,153.0,153.0,165.5,165.5,169.6,169.6.

Elemental Analysis: Calculated for $C_{22}H_{17}N_9O_4S_2$: C:49.34, H:3.20, S:11.97. Found C:49.43, H:3.10, S:11.79.

Molecular wt.:535.56 m/z:535.08,536.09,535.08.

2-phenyl)-5-(2-(5-(2-(2-phenylthiazol-4-yl)hydrazineylidene)pyrolidin-2-ylidene)hydrazineyl)thiazole **5f**

IR (v, cm^{-1} KBr): 1610(C=N), 3474 (N-H).

^{1}H-NMR (DMSO-d_6,500 MHz): 2.74(s, 2H, CH),5.36(s,imidiyl,H),6.26-6.64(s, thiazolyl-H),7.35-8.30(m, 10H, Ar-H),10.76(s, NH).

^{13}CNMR(DMSOd_6,500MHZ):28.1,28.1,121.2,128.3,128.3,129.4,129.4,129.4,129.4,130.4,130.4,130.4,130.4,143.5,143.6,143.6,147.1,151.1,153.4,153.4,169.5,169.5.

Elemental Analysis: Calculated for $C_{22}H_{19}N_7S_2$: C:59.31, H:4.30, S:14.39. Found C:59.13, H:4.10, S:14.29.

Molecular wt.:445.56 m/z:445.11,446.12,446.11.

2-(4-bromophenyl)-5-(2-(5-(2-(2-(4-bromophenyl)thiazol-4-yl)hydrazineylidene)pyrolidin-2-ylidene)hydrazineyl)thiazole **5g**

IR (v, cm^{-1} KBr): 1630(C=N),3410(NH).

^{1}H-NMR (DMSO-d_6,500 MHz): 2.35(s, 2H, CH),4.90(s,imidiyl,H)6.62-6.76(s, thiazolyl-H),7.76-7.86(m, 8H, Ar-H),10.16(s, NH).

^{13}CNMR(DMSOd_6,500MHZ):28.1,28.1,121.3,123.4,123.4,129.3,129.3,129.3,129.3,132.4,132.4,132.4,132.4,142.5,142.5,143.4,147.1,153.4,153.4,169.6,169.6.

Elemental Analysis: Calculated for$C_{22}H_{17}BrN_7S_2$: C:43.80, H:2.84, S:10.63. Found C:43.70, H:2.48, S:10.36

Molecular wt.:603.36 m/z:602.93,600.94,604.93.

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