α,α- DIBROMOKETONES IN THE PREPARATION OF NEW HYDRAZINYL THIAZOLE DERIVATIVES

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Abstract

In medicative applications, succinimides are acknowledged heterocyclic compounds in drug invention which give rise to multiple remedially linked practices in pharmaceutical world. Both succinimide and thiosemicarbazide are vigorous intermediates for the fusion of pharmaceutic and biologically active matter and consequently these are utilized enormously in the discipline of medicinal chemistry. Various researchers and scientists have recognized and incorporated various derivatives of succinimide with numerous therapeutic belongings. Concurrently, SAR examination has been moderately acquired beside with a substantial concern of derivatives had been obtained for possible objective. In present paper, various derivatives of succinimide eventually be prepared by the analysis of succinimide with hydrazinecarbothioamide in ethanol under reflux condition and subsequently the resultant product was treated with various substituted α,α- dibromoketone by means of HTS (hantzsch thiazole synthesis) to coordinate further compounds and their structures were established by spectral studies and physical indications.

Paper Identification

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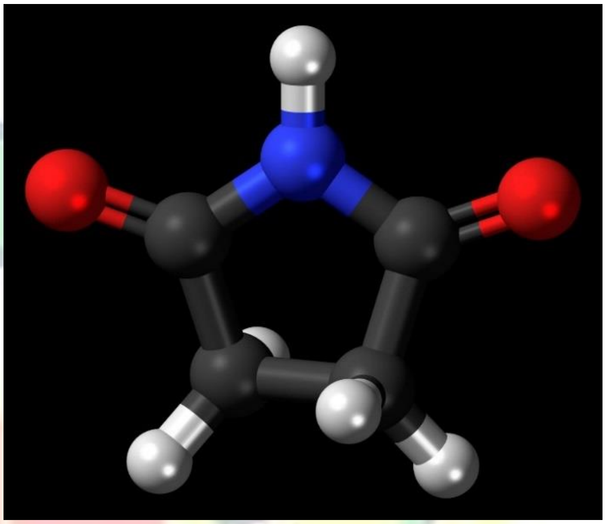
INTRODUCTION

A notable question of present-time drug invention is the composition of extremely well organized chemical reaction series that allow utmost structural complicacy and assortment with minimal integer of synthetic pathway to diagnose compounds with compulsive properties. Considerable attempts have been pointed on producing libraries of modest heterocyclic compounds due to their great advantages as curative agents and structural heterogeneity. Due to their diverse pharmacological interest, the derivatives of thiazoles have fascinated increasing recognition over the decade[1].

These have wide ranging applications for the cure of hypertension[2], allergies[3], inflammation[4], hypnotics[5], HIV infections[6], schizophrenia[7], anti-conconvalsant activity[8], pain[9], anti-inflammatory[10], analgesic[11-14], anti-fungal[15,16], anti-microbial[17,18]. Considering preceding benefits, we make an effort to prepare thiazolyl compounds by simple procedure which feasibly utilized in designing unfamiliar, effectual, particular and harmless anti-microbial agents. Although the synthetic utilization of α-halocarbonyl compounds in medicinal chemistry is familiar over a decade and they have been considerably beneficial for the construction of numerous heterocyclic structures but these contains several consequential handling issues due to high lachrymatory belongings correlated with them. Furthermore, α,α-dihalocarbonyl compounds are non- lachrymatory, excessive reactivity, effortlessly purification and comfortably prepared under mild conditions. So working with this reagent is very easy as compared to α-halocarbonyl compounds[19-29]. Thiazole is a familiar heterocyclic compounds with five membered ring arrangement and engage overwhelming biological significances[30-31]. Thiazoles were firstly reported by Hantzsch and Weber in 1887 and Bogert and associates made outstanding definition to diversify this area[32]. Eventually the physical and chemical of these compounds are equivalent to pyridine and pyrimidine. These compounds are chief segment of nucleus of penicillin and their derivatives exhibit anti-microbial (sulfazole), antiretroviral (ritonavir), antimalarial, antihistaminic, anticancer (tiazofurin) and photographic sensitizers. The derivatives of succinimide and thisemicarbazide are principal compounds and show remarkable pharmacological and medicative belongings. Succinimide is involved in various functional molecules and act as antitumor[33], cytostatic[34], muscle relaxant[35], hypotensive[36], nerve conduction blocking[37], bacteriostatic, anoretic, antitubercular, anticonvulsant and analgesic[38-40]. The present paper provides a description of the reactivity pattern and synthesis of some derivatives of succinimide. First of all we plan to define the procedure for the preparation of substituted succinimides and secondly we will discuss the general reactivity pattern of substituted succinimides with α,α-dibromoketones for the preparation of thiazoles.



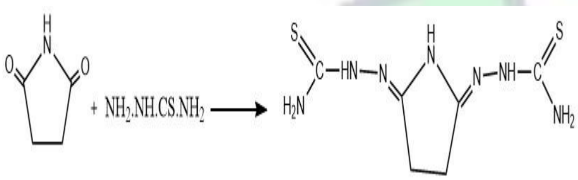
Structure of succinimide

RESULT AND DISCUSSION

Synthesis of 2,2’(pyrrolidine-2,5-diylidene)bis(hydrazine-1-carbothioamide)

Firstly a calculated amount of succinimide **(1a)** and hydrazinecarbothioamide **(1b)** was stirred in the presence of ethanol as a solvent at normal temperature but we did not find any successful completion of the reaction. Then for the production of desired product, the same reaction mixture was refluxed in ethanol by adding few drops of glacial acetic acid as a stimulant for 9-10 hours on water bath. Frequently the successful completion of the reaction was examined by analytical thin layer chromatography (TLC) and finally after continuous heating the off white coloured crystalline solid product was obtained cleansed with water four to five times and then for further purification the synthesized product was recrystallized with ethanol and dried . The pure crystalline product 2,2’(pyrrolidine-2,5-diylidene)bis(hydrazine-1-

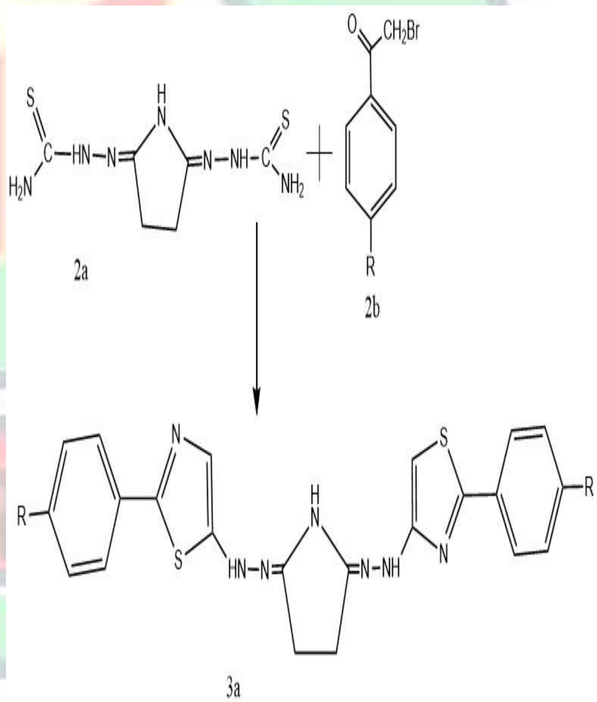
carbothioamide) **(2a)** was obtained with melting point 64-65˙c. The composition of synthesized compound **(2a)** was predicted on the basis of spectral information [1]HNMR, IR and elemental-evaluation. The IR data shows stretching frequencies of (C=N) at 1620 and (N-H) at 3460. The proton NMR display signals at δ 2.45(s,2H,CH), 5.16(s, imidiyl-H), 7.57(s, NH_2), 11.19(s,NH).



1a **1b** **2a**

SCHEME - 1

Systematically, we initiated our mechanism with the reaction of 2,2'(pyrrolidine-2,5-diylidene)bis(hydrazine-1-carbothioamide) **(2a)** with substituted α,α- dibromoketones **(2b)** and ethanol was used as a solvent on stirring for 7-8 hours at ambient temperature. Simultaneously, in the preliminary stage of reaction process the interactants were absolutely dispersible in the solvent. Frequently the successful completion of the reaction was examined by analytical thin layer chromatography (TLC) and ultimately after the achievement of reaction a dark brown powdered form solid 2-(4-chlorophenyl)-5-(2-(5-(2-(2-(4-chlorophenyl)thiazol-4-yl)hydrazineylidene) pyrrolidin-2-ylidene)hydrazineyl)thiazole **(3a)** was collected with 85% yield. Considerably the reaction was performed with multiple substituted α,α-dibromoketones **(3b-3g)** to prepare the corresponding derivatives of thiazoles. The composition of synthesized compound **(3a)** was predicted on the basis of spectral information [1]HNMR, IR and elemental-evaluation. The proton NMR display signals at δ 2.56(s, 2H, CH), 6.66-6.86(s, thiazolyl-H), 5.64(s, imidiyl-H), 7.45-8.34(m, 8H, Ar-H), 10.38(s, NH of succinimide). The data of [13]CNMR shows signal values at δ 28.4, 28.4,121.5, 128.7, 128.7, 128.7, 128.7, 129.8, 129.8, 129.8, 129.8 , 134.6, 134.6, 141.4, 141.4, 145.5, 147.8, 151.5, 153.5, 153.5, 169.7, 169.7 congruent with our supposition. By conducting thin layer chromatography of chemical mixture successively indicated the production of single derivative. Systematic workup of the product mixture eventually decontaminate the impure solid by washing with water three to four times and recrystallized with ethanol to achieve the thiazole compound in pure form. The compounds **3b-3g** is prepared by using same methodology and similar purification technique.



Where R = H, Cl, Br, NO_2, CH_3, F, OCH_3

SCHEME 2 - α, α-Dibromoketones reagent during preparation of various new hydrazineyl thiazole derivatives.

TABLE 1 Physical data of hydrazineyl thiazole derivatives

COMPOUND	MOLECULAR	MELTING POINT	YIELD %

	FORMULA	(˚c)	
3a	$C_{22}H_{17}ClN_7S_2$	167-168	85
3b	$C_{22}H_{17}BrN_7S_2$	183-184	78
3c	$C_{24}H_{23}N_7O_2S_2$	140-141	72
3d	$C_{24}H_{23}N_7S_2$	125-126	88
3e	$C_{22}H_{17}N_9O_4S_2$	178-179	91
3f	$C_{22}H_{19}N_7S_2$	154-155	82
3g	$C_{22}H_{17}F_2N_7S_2$	204-205	75

EXPERIMENTATION

The required α,α- dibromoketones were integrated on the explanation of publications methodology and identified on the basis of physical evidence like by contrasting their melting point[41] **(Boeykens, M.; Kimpe, N. D. Tetrahedron, 1994).** Succinimide, thiosemicarbazide, ethanol, different acetophenones, chloroform and bromine were used during synthesis were of analytical grade obtained from the commercialized manufacturer and utilized subsequently without extra purification. Frequently the successful completion of the reaction was examined by analytical thin layer chromatography (TLC) by making use of Aluminium Merck TLC silica gel plates .

Melting point was determined in unconcealed capillaries and were left uncorrected. IR characterization was registered on PerkinElmer spectrum IR version 10.6.2. The ^{1}HNMR and ^{13}CNMR was registered on Bruker Avance NEO 500 MHz NMR spectrometer SAIF, P.U. and DMSO was used as a solvent.

CHARACTERIZATION

2-(4-chlorophenyl)-5-(2-(5-(2-(2-(4-chlorophenyl)thiazol-4-yl)hydrazineylidene)pyrrolidin-2-ylidene)hydrazineyl)thiazole. (3a)

Pale yellow powder ; M.pt. 167-168˚c

IR (ν_{max}, KBr): 1617 (C=N), 3414 (N-H), 1089 (C-N).

^{1}H NMR (DMSO-d_6 500MHz): δ 2.56(s, 2H, CH), 6.66-6.86(s, thiazolyl-H), 5.64(s, imidiyl-H),7.45-8.34(m, 8H, Ar-H) 10.38(s, NH of succinimide).

^{13}C NMR (DMSO-d_6 500MHz): δ 28.4, 28.4,121.5, 128.7, 128.7, 128.7, 128.7, 129.8, 129.8, 129.8, 129.8 , 134.6, 134.6, 141.4, 141.4, 145.5, 147.8, 151.5, 153.5, 153.5, 169.7, 169.7.

Anal. Calculated for **$C_{22}H_{17}ClN_7S_2$** : C: 51.37, H: 3.35, S: 12.48. Found C: 51.28, H: 3.45, S: 12.58.

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

2-(4-bromophenyl)-5-(2-(5-(2-(2-(4-bromophenyl)thiazol-4-yl)hydrazineylidene)pyrrolidin-2-ylidene)hydrazineyl)thiazole. (3b)

Dark yellow powder ; M.pt. 183-184˚c

IR (ν_{max}, KBr): 1625 (C=N), 3420 (N-H), 1082 (C-N).

^{1}H NMR (DMSO-d_6 500MHz): δ 2.67(s, 2H, CH), 6.78-6.85(s, thiazolyl-H), 5.72(s, imidiyl-H),7.42-8.35(m, 8H, Ar-H) 10.42(s, NH of succinimide).

^{13}C NMR (DMSO-d_6 500MHz): δ 26.5, 26.5, 125.5, 126.9, 126.9, 126.9, 126.9, 125.7, 125.7, 125.7, 125.7 , 136.6, 136.6, 145.5, 145.5, 147.5, 149.8, 153.3, 157.5, 157.5, 170.8, 170.8.

Anal. Calculated for **$C_{22}H_{17}BrN_7S_2$** :C: 53.36, H: 3.37, S: 12.49. Found C: 52.25, H: 3.48, S: 12.59.

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

2-(4-methoxyphenyl)-5-(2-(5-(2-(2-(4-methoxyphenyl)thiazol-4-yl)hydrazineylidene)pyrrolidin-2-ylidene)hydrazineyl)thiazole. (3c)

Coffee brown powder ; M.pt. 140-141

IR (ν_{max}, KBr): 1630 (C=N), 3423 (N-H), 1180 (C-N).

^{1}H NMR (DMSO-d_6 500MHz): δ 2.45(s, 2H, CH), 3.72 (s, 3H, CH_3), 5.44(s, imidiyl-H),6.47-8.55(s, thiazolyl-H), 7.03- 7.68(m, 8H, Ar-H) 10.18 (s, NH of succinimide).

^{13}C NMR (DMSO-d_6 500MHz): δ 26.5, 26.5, 125.5, 126.9, 126.9, 126.9, 126.9, 125.7, 125.7, 125.7, 125.7 , 136.6, 136.6, 145.5, 145.5, 147.5, 149.8, 153.3, 157.5, 157.5, 170.8, 170.8.

Anal. Calculated for $\mathbf{C_{24}H_{23}N_7O_2S_2}$: C: 57.03, H: 4.57, S: 12.69. Found C: 57.06, H: 4.48, S: 12.58.

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

2-(p-tolyl)-5-(2-(5-(2-(2-(p-tolyl)hydrazineylidene)pyrrolidin-2-ylidene)hydrazineyl)thiazole. (3d)

Bronze brown colour powder ; M.pt. 125-126

IR (ν_{max}, KBr): 1645 (C=N), 3452 (N-H), 1156 (C-N).

^{1}H NMR (DMSO-d$_6$ 500MHz): δ 2.54(s, 3H, CH_3), 2.54(s, 2H, CH), 6.56-6.63(s, thiazolyl-H), 7.33-7.77(m, 8H, Ar-H), 5.58(s, imidiyl-H), 10.58(s, NH of succinimide).

^{13}C NMR (DMSO-d$_6$ 500MHz): δ 21.5, 21.5, 28.6, 28.6, 121.9, 127.6, 127.6, 127.6, 127.6, 129.7, 129.7, 129.7, 129.7, 131.9, 131.9, 140.5, 140.5, 143.3, 147.6, 151.5, 153.2, 153.2, 169.5, 169.5.

Anal. Calculated for $\mathbf{C_{24}H_{23}N_7S_2}$: C: 60.78, H: 4.82, S:13.47 Found C: 66.68, H: 4.78, S: 13.66.

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

2-(4-nitrophenyl)-5-(2-(5-(2-(2-(4-nitrophenyl)thiazol-4-yl)hydrazineylidene)pyrrolidin-2-ylidene)hydrazineyl)thiazole. (3e)

Light brown powder ; M.pt. 178-179

IR (ν_{max}, KBr): 1648 (C=N), 3458 (N-H), 1142 (C-N).

^{1}H NMR (DMSO-d$_6$ 500MHz): δ 2.54(s, 2H, CH), 6.57-6.77(s, thiazolyl-H), 7.87-8.06(m, 8H, Ar-H), 5.64(s, imidiyl-H), 10.35(s, NH of succinimide).

^{13}C NMR (DMSO-d$_6$ 500MHz): δ 28.3, 28.3, 28.6, 28.6, 121.4, 121.4, 121.4, 121.4, 121.4, 128.6, 128.6, 128.6, 128.6, 143.5, 147.3, 150.7, 150.7, 151.5, 153.2, 153.2, 165.6, 165.6, 169.8, 169.8.

Anal. Calculated for $\mathbf{C_{22}H_{17}N_9O_4S_2}$: C: 49.36, H: 3.25, S:11.97 Found C: 49.45, H: 3.12, S: 11.75.

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

2-(phenyl)-5-(2-(5-(2-(2-phenylthiazol-4-yl)hydrazineylidene)pyrrolidin-2-ylidene)hydrazineyl)thiazole. (3f)

Almond colour powder ; M.pt. 154-155

IR (ν_{max}, KBr): 1655 (C=N), 3440 (N-H), 1156 (C-N).

^{1}H NMR (DMSO-d$_6$ 500MHz): δ 2.76(s, 2H, CH), 2.54(s, 2H, CH), 6.28-6.66(s, thiazolyl-H), 7.39-8.34(m, 10H, Ar-H), 5.38(s, imidiyl-H), 10.78(s, NH of succinimide).

^{13}C NMR (DMSO-d$_6$ 500MHz): δ 25.3, 25.3, 22.8, 22.8, 125.6, 125.6, 125.6, 125.6, 125.6, 124.8, 124.8, 124.8, 124.8, 145.7, 145.7, 153.9, 154.7, 154.7, 158.6, 158.6, 162.8, 162.8, 166.4, 166.4.

Anal. Calculated for $\mathbf{C_{22}H_{19}N_7S_2}$: C: 59.33, H: 4.35, S:14.42 Found C: 59.15, H: 4.8, S: 14.32.

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

2-(4-fluorophenyl)-5-(2-(5-(2-(2-(4-fluorophenyl)thiazol-4-yl)hydrazineylidene)pyrrolidin-2-ylidene)hydrazineyl)thiazole. (3g)

Dark brown powder; M.pt. 204-205

IR (ν_{max}, KBr): 1661 (C=N), 3456 (N-H), 1163 (C-N).

^{1}H NMR (DMSO-d$_6$ 500MHz): δ 2.77(s, 2H, CH), 6.46-6.53(s, thiazolyl-H), 7.15-7.59(m, 8H, Ar-H), 5.28(s, imidiyl-H), 10.67(s, NH of succinimide).

^{13}C NMR (DMSO-d$_6$ 500MHz): δ 28.3, 28.3, 116.3, 116.3, 116.3, 116.3, 121.5, 129.5, 129.5, 129.5, 129.5, 138.5, 138.5, 143.4, 147.9, 151.3, 153.5, 153.5, 162.4, 162.4, 169.6, 169.6.

Anal. Calculated for $\mathbf{C_{22}H_{17}F_2N_7S_2}$: C: 54.89, H: 3.58, S: 13.35. Found C: 54.80, H: 3.66, S: 13.35.

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

CONCLUSION

The current research provide excellent perspective for the formation of thiazolyl derivatives **3** due to accessible preparation of α,α- dibromoketones under convenient conditions. Thus, it cannot be denied that the methodology employed for this attempt is outstanding considering the reaction concerns uncomplicated analysis under suitable environment. This investigation explained the physiological comparison of α,α- dibromoketones with α-monobromoketones in current study.

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