

Multistep organic synthesis leading to the formation of triazinothiazoloquinoxalines involving cost effective reagents

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Abstract

A simple and efficient chemical method has been attempted for the synthesis of biologically and commercially important 2-aryl [-s-] triazino [1], [3], [5] thiazolo [6], [5-b] quinoxalin -4- thiones in moderate to excellent yields through cyclization reaction of o-phenylenediamino using readily available and fewer costly reagents viz. oxalic acid, PCl₅thiourea, aromatic aldehydes and ammonium thiocyanate at an ambient temperature.

Keywords: β-Lactamase; Brevity, 2; 3-Dichloroquinoxaline.

1. Introduction

At the moment, much emphasis is being laid on the drug design through conjunction, which is known as the systematic formulation of analogues of a prototype agent, in general toward structurally more complex products, which may be viewed as structures embodying, in a general specific way, certain or all the features of the prototype. In this type of drug design, the main principle involved is the 'principle of mixed moieties' i.e. a drug molecule is essentially made up with two or more pharmacophoric moieties embedded into a single molecule. Based on this principle a synthesis of 2-aryl [-s-] triazino [1], [3], [5]thiazolo [6], [5-b] quinoxalin -4- thiones (Scheme 1) has been undertaken. Thus, theazole nucleus constitute a major part of all available penicillin related antibiotics, which interfere with a critical series of proteases involved in bacterial cell wall construction [1].

It is though the production of one of a series of enzyme collectively known as β-lactamases [2]. Within the past decades; several pharmaceutical companies have developed drugs which act as β-lactamase inhibitors. The known mechanism of inhibition usually involves a nonreversible acylation of serine hydroxyl at an active site [3]. In addition a number of quinoxalinederivatives have been shown to pass a wide variety of pharmacological properties like antibacterial [4], antifungal [5], antituberculosis [6], antitumor [7], antiviral [8] and antiinflammatory [9]. Further s-triazines have been very well established as diuretics [10] and antiviral agents [11-14]. Several s-triazine compounds have been thoroughly examined in neoplastic diseases with promising results but despite the considerable efforts denoted to these compounds, they have not proven to have any clinical application [15], [16]

2. Results and discussion

Our initial effort was to carry out a cyclization reaction leading to the formation of quinazolines-2,3 (1H, 4H) dione (1a) with the interaction of O-phenylenediamine with oxalic acid dehydrate using 4N HCl and 10% NaOH solution. This compound existed in

tautomeric form (Quinoxaline - 2,3-diol 1b) which on fusion with PCl₅ afforded 2,3-dichloroquinoxaline (2). For the construction of thiazolo[5], [4-b] quinoxalin-2-amine (3), the protocol adopted was to allow the reaction of 2 with thiourea in absolute alcohol. This was a cyclization reaction, and the cyclized product (3) on reaction with aromatic aldehydes resulted in N-arylidene thiazolo [5], [4-6] quinoxalin - 2 - amines (4a-c). (Table 1) The target compounds (5a-e) (Table 2) designated as 2-aryl - s= triazino[1], [3], [5] - thiazolo [6], [5 -b] quinoxalin-4-thiones were prepared by refluxing a mixture of 4 with thiocyanate in dioxane solvent. All the synthesized compounds have been characterized by IR, ¹H NMR, [¹³C NMR mass and element analysis. The spectral and analytical data of new compounds (4a-e and 5a-e) are presented in experimental section. In conclusion, we have attempted the synthesis of target molecules involving three cyclization reaction using readily available and fewer costly reagents viz. oxalic acid, thiourea and ammonium thiocyanate. Thus considerable attempts have been made to use minimum catalyst and less-expensive solvents in the accomplishment of synthesis i.e. brevity and efficiency consideration have been maintained to a greater extent.

Table 1: Synthesis of N-Arylidene thiazolo [5], [4-B] Quinoxalin - 2 - Amines

Entry	Compound	R	Yield
1	4a	C ₆ H ₅	75
2	4b	4-OH C ₆ H ₄	70
3	4c	4-OCH ₃ C ₆ H ₄	70
4	4d	2-OH C ₆ H ₄	65
5	4e	4-OH 3-OCH ₃ C ₆ H ₃	60

Table 2: Synthesis of 2-Aryl [-S-] Triazino [1], [3], [5] Thiazolo [6], [5-B] Quinoxalin -4- Thiones

Entry	Compound	R	Yield
1	5a	C ₆ H ₅	70
2	5b	4-OH C ₆ H ₄	72
3	5c	4-OCH ₃ C ₆ H ₄	82
4	5d	2-OH C ₆ H ₄	70
5	5e	4-OH, 3-OCH ₃ C ₆ H ₃	65

3. Experimental

All the chemicals were used as received without any further purification. Melting points were determined in open capillaries using a Toshnial melting point apparatus and are uncorrected IR spectra in KBr were recorded on a Perkin-Elmer 157 Spectrophotometer (ν_{\max} in cm^{-1}), ^{13}C NMR and ^1H NMR spectra in CDCl_3 on a varian. A₆₀D instrument (300MHz) using TMS as internal Standard (Chemical shift in δ ppm). The FAB mass spectra was recorded on JEDL Sx 102/DA-600 mass spectrometer/Data system using Argon/Xenon (6KV, 10mA) as the FAB gas. The accelerating voltage was 10 KV, and the spectra were recorded at room temperature. m-Nitrobenzyl alcohol (NBA) was used as the matrix unless specified otherwise. The matrix peaks may have appeared at m/z 136, 137, 154, 289, 307 in the absence of any metal ions. Elemental analysis were performed on a Perkin-Elmer 240 CHN elemental analyzer. Homogeneities of the compounds were checked using silica gel coated TLC plates and Iodine vapour as visualizing agent.

(1). Quinoxaline-2,3-(1H, 4H) - dione (1)-

A mixture of o-phenylenediamine(100mmol), oxalic acid dihydrate (120mmol) and HCl (4N, 200ml) was heated to boiling for half an hour. The reaction mixture was cooled to room temperature. A solid separated out which was filtered off and dissolved in 10% NaOH solution. It was left overnight after placing animal charcoal to it. It was filtered off and the filtrate was acidified with concentrated HCl. The precipitate which was obtained in this manner was dried at 100°C and recrystallized from rectified Spirit m.p.>300°C[>300°C][17] yield 91%.

(2).2,3-dichloroquinoxaline (2)-

Quinoxalines-2,3-[1H,4H]-dione (50mmol) was fused with phosphorouspentachloride (PCl_5) (100mmol) for 2h. Subsequently, the molten mass was cooled to room temperature. Cold water (100ml) was added and gently heated. The solid materia was filtered off and dried in air. It was recrystallized from ethenol as white crystalline mass m.p.>300°C[>300°C][18] yield 80%

(3).Thiazolo [5], [4-b] quinoxalin - 2 - amine (3) -

A mixture of 2,3 - dichloroquinoxaline (20mmol) and thiourea (20mmol) in absolute ethanol (100ml) was heated under reflex for 2hr. The reaction mixture on cooling and neutralization with anhydrous potassium carbonate solution yielded the free base which on crystallization from dimethyl formamide (DMF) furnished light yellow crystalline mass m.p.>300°C[>300°C] [19] yield 65%

(4).General procedure for the synthesis of N-arylideneethiazolo [5], [4-b] quinoxalin-2-amines (4a-e) -

Thiazolo[5], [4-b] quinoxalin - 2 - amines (10 mmol) and an aromatic aldehydes (10mmol) in DMSO (100ml) were heated under reflux for 2h. Subsequently, Solvent was removed by distillation and the pasty mass was triturated with petroleum ether. It was washed with a solution of sodium carbonate (10%), Solidification occurred and the solid thus separated out was washed with cold water and dried under vacuum. It was recrystallized from diluted ethanol.

(5).N-Benzylidenethiazolo [5], [4-b] quinoxalin-2-amine (4a) -

Yellow coloured solid; m.p. 160°C; ν_{\max} (film, cm^{-1}): 3050, 1645, 1575, 1490, 1449, 1240, 1035; $^1\text{Hnmr}(\text{CDCl}_3)$; δ 6.70-7.40 (m, 9H, Ar -H), 8.50 (s, 1H, N=C-H), [13] $\text{Cnmr}(\text{CDCl}_3)$: δ 155.5, 141.5, 130.9, 128.7, 128.1, 127.4, 123.3, 117.5; MS m/z 290 (M^+); Anal. calcd for $\text{C}_{16}\text{H}_{10}\text{N}_4\text{S}$: C, 66.20; H, 3.44; N, 19.31. Found: C, 66.18; H, 3.46; N, 19.40

(6).N-4 Hydroxybenzylidenethiazolo [5], [4 - b] quinoxalin - 2 - amine (4b) -

Brown coloured solid; m.p, 231°C; ν_{\max} (film, cm^{-1}): 3605, 3045, 1642, 1570, 1495, 1445, 1235, 1195, 1032, 710; $^1\text{Hnmr}(\text{CDCl}_3)$; δ 6.85-7.76 (m, 8H, Ar -H), 8.54 (s, 1H, N=C-H),4.65 (s, 1H, Ar -OH); $^{13}\text{Cnmr}(\text{CDCl}_3)$: δ 153.6, 141.2, 137.5, 131.4, 125.7, 121.3, 117.5, 115.2; MS m/z 306 (M^+); Anal. calcd for $\text{C}_{16}\text{H}_{10}\text{N}_4\text{OS}$: C, 62.74; H, 3.26; N, 18.30. Found: C, 62.82; H, 3.14; N, 18.42.

(7).N-4 Methoxybenzylidenethiazolo [5], [4 - b] quinoxalin - 2 - amine (4c) -

Dark brown solid; m.p, 281-282°C; ν_{\max} (film, cm^{-1}): 3046, 1645, 1572, 1492, 1450, 1235, 1125, 1032; $^1\text{Hnmr}(\text{CDCl}_3)$; δ 6.65-7.67 (m, 8H, Ar -H), 8.61 (s, 1H, N=C-H),3.75 (s, 1H, Ar - OCH₃); $^{13}\text{Cnmr}(\text{CDCl}_3)$: δ 154.7, 140.8, 136.5, 133.2, 131.5, 127.4, 125.6, 117.2, 114.4, 39.1; MS m/z 320 (M^+); Anal. calcd for $\text{C}_{17}\text{H}_{12}\text{N}_4\text{OS}$: C, 63.75; H, 3.75; N, 17.50. Found: C, 63.54; H, 3.65; N, 17.62.

(8).N-2 Hydroxybenzylidenethiazolo [5,4-b] quinoxalin - 2 - amine (4d) -

Brown coloured solid; m.p.>300°C; ν_{\max} (film, cm^{-1}): 3608, 3055, 1645, 1572, 1492, 1450, 1238, 1190, 1036, 720; $^1\text{Hnmr}(\text{CDCl}_3)$; δ 6.80-7.72 (m, 8H, Ar -H), 8.50 (s, 1H, N=C-H),4.62 (s, 1H, Ar -OH); $^{13}\text{Cnmr}(\text{CDCl}_3)$: δ 168.5,145.2, 141.5, 139.5, 137.1, 131.7, 127.5, 125.4, 121.2, 119.0, 115.6, 112.5; MS m/z 306 (M^+); Anal. calcd for $\text{C}_{16}\text{H}_{10}\text{N}_4\text{OS}$: C, 62.74; H, 3.26; N, 18.30. Found: C, 62.70; H, 3.14; N, 18.42.

(9). N-4- Hydroxy-3-methoxy benzylidenethiazolo[5,4-b] quinoxalin (4e) -

Brown coloured solid; m.p.>300°C; ν_{\max} (film, cm^{-1}): 3605, 3045, 1642, 1570, 1496, 1440, 1230, 1195, 1120, 1032, 760; $^1\text{Hnmr}(\text{CDCl}_3)$; δ 6.50-7.62 (m, 7H, Ar -H), 8.48 (s, 1H, N=C-H),4.60 (s, 1H, Ar - OH) 3.70 (s, 3H, Ar-OCH₃); $^{13}\text{Cnmr}(\text{CDCl}_3)$: δ 166.4, 145.5, 141.4, 139.1, 135.4, 131.7, 129.2, 125.4, 121.4, 117.6,116.2, 115.2, 111.9; MS m/z 336 (M^+); Anal. calcd for $\text{C}_{17}\text{H}_{12}\text{N}_4\text{O}_2\text{S}$: C, 60.71; H, 3.57; N, 16.66. Found: C, 60.62; H, 3.68; N, 16.68.

(10). General procedure for the Synthesis of 2-aryl-s-triazino[1], [3], [5]-thiazolo [6], [5-b] quinoxalin - 4 - thiones (5a-e) -

N-arylideneethiazolo[5], [4-b] quinoxalin - 2 - amine (4) (8mmol) and ammonium thiocyanate (5mmol) were dissolved in dioxane (15ml) by warming slowly and stirring. The resultant solution are stirred for half an hour at room temperature and subsequently heated under reflux for 5h under anhydrous conditions solvent uses removed by distillation and the solid thus obtained was washed successively with cold water. It was dried in vacuo and recrystallized from ethanol.

(11).2-Phenyl-S-triazino [1], [3], [5] - thiazolo [6,5-b] quinoxalin - 4 - thione (5a) -

Pale yellow solid; m.p.>300°C; ν_{\max} (film, cm^{-1}): 3320, 3025, 2565, 1625, 1125,; $^1\text{Hnmr}(\text{CDCl}_3)$; δ 7.15-7.91 (m, 9H, Ar -H), 5.45 (brs, 1H, S=C-NH), 5.95 (s, 1H, S- H); $^{13}\text{Cnmr}(\text{CDCl}_3)$: δ 175.5, 164.6, 147.6, 143.5, 139.7, 131.6, 127.4, 121.1,117.6, 115.2; MS m/z 349 (M^+); Anal. calcd for $\text{C}_{17}\text{H}_{11}\text{N}_5\text{S}_2$: C, 58.45; H, 3.15; N, 20.05. Found: C, 58.35; H, 3.16; N, 20.08.

(12). (4-hydroxyphenyl)-S-triazino[1], [3], [5]-thiazolo[6], [5-b] quinoxalin-4-thione (5b)-

Dark Brown solid; m.p.>250-251°C; ν_{\max} (film, cm^{-1}):3610, 3325, 3050, 2562, 1635, 1350, 1165,; $^1\text{Hnmr}(\text{CDCl}_3)$; δ 7.25-7.95 (m, 8H, Ar -H), 5.05 (s, 1H, Ar-OH), 5.40 (brs, 1H, S=C-NH), 5.95 (s, 1H, S- H); $^{13}\text{Cnmr}(\text{CDCl}_3)$: δ 164.6, 157.6, 149.6, 143.5, 141.4, 139.7, 134.6, 129.6, 127.3, 124.2, 118.4, 115.5, 111.1; MS m/z 365 (M^+); Anal. calcd for $\text{C}_{17}\text{H}_{11}\text{N}_5\text{OS}_2$: C, 55.89; H, 3.01; N, 20.05. Found: C, 55.90; H, 3.03; N, 19.20.

(13).2-(4-methoxyphenyl)-S-triazino [1], [3], [5]-thiazolo[6], [5-b]quinoxalin-4-thione(5c) -

Brown solid; m.p.265°C; ν_{\max} (film, cm^{-1}):3365, 3050, 2560, 1630, 1128, 1125; $^1\text{Hnmr}(\text{CDCl}_3)$; δ 6.95-7.67 (m, 8H, Ar -H), 3.75 (s, 3H, Ar-OCH₃), 5.35 (brs, 1H, S=C-NH), 5.87 (s, 1H, S- H); $^{13}\text{Cnmr}(\text{CDCl}_3)$: δ 172.4, 165.4, 147.6, 144.5, 142.4, 139.1, 131.6, 129.7, 127.3, 121.4, 117.1, 41.2; MS m/z 384 (M^+); Anal. calcd for $\text{C}_{18}\text{H}_{13}\text{N}_5\text{OS}_2$: C, 56.25; H, 3.38; N, 18.22. Found: C, 56.10; H, 3.28; N, 18.26.

(14).2-(2-hydroxyphenyl)-S-triazino[1], [3], [5]-thiazolo[6], [5-b]quinoxalin-4-thione(5d) -

Brown solid; m.p.245-246°C; ν_{\max} (film, cm^{-1}):3610, 3325, 3045, 2570, 1645, 1120; $^1\text{Hnmr}(\text{CDCl}_3)$; δ 6.720-7.95 (m, 8H, Ar -H), 4.95 (s, 1H, Ar-OH), 5.45 (brs, 1H, S=C-NH), 5.77 (s, 1H, S- H); $^{13}\text{Cnmr}(\text{CDCl}_3)$: δ 167.5, 143.6, 141.4, 135.5, 131.5, 128.6, 121.2,

116.8, 111.5; MS m/z 365 (M^+); Anal. calcd for $C_{17}H_{11}N_5O_2S_2$: C, 55.89; H, 3.01; N, 19.17, Found: C, 55.70; H, 2.99; N, 19.15. (15)-2-(4-hydroxy-3-methoxyphenyl)-S-triazino[1, 3], [5]-thiazolo[6], [5-b]quinoxalin-4-thione(5e) - Brown solid; m.p.>300°C; v_{max} (film, cm^{-1}):3615, 3320, 3055, 3025, 2575, 1647, 1125; $^1Hnmr(CDCl_3)$; δ 6.90-7.85 (m, 7H, Ar - H), 4.95 (s, 1H, Ar-OH), 3.65 (s, 3H, Ar-OCH₃), 5.35 (brs, 1H, S=C-NH), 6.10 (s, 1H, S-H); $^{13}Cnmr(CDCl_3)$: δ 165.6, 145.5, 141.4, 139.6, 131.5, 129.8,127.1, 120.2, 117.6, 115.7, 111.5.; MS m/z 395 (M^+); Anal. calcd for $C_{17}H_{13}N_5O_2S_2$: C, 54.68; H, 3.29; N, 17.72, Found: C, 55.2; H, 3.18; N, 17.70.

4. Conclusion

In conclusion, we have attempted the synthesis of target molecules involving three cyclization reaction using readily available and fewer costly reagents viz. oxalic acid, thiourea and ammonium thiocyanate. Thus considerable attempts have been made to use minimum catalyst and less-expensive solvents in the accomplishment of synthesis. i.e. brevity and efficiency consideration have been maintained to a greater extent. An effective drug design from a biologically active prototype, whether approached through disjunction or conjunction or both, normally aims at modifying collectively all the moiety attributes that are essential capacities of a drug eliminated to a great extent which otherwise would have reduced its specificity of action, or interference with the primary type of action sought.

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Scheme I

