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Novel domino reactions for the efficient synthesis of 5,6-dihydro-1,4,2-oxathiazines

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ABSTRACT

A facile efficient synthesis of novel 3-aryl-5,6-dihydro-1,4,2-oxathiazin-6-ols from the reaction of (*E*)-*N*-hydroxyarylimidoyl chlorides and 1,4-dithiane-2,5-diol in the presence of triethylamine is described. This transformation presumably proceeds via in situ generation of 2-mercaptoacetaldehyde and nitrile oxide and their concomitant [3+3] annulation.

Low molecular weight heterocycles are among the most prevalent pharmacophores.[1] In particular, heterocycles comprising nitrogen, oxygen, and sulfur atoms in one ring are undoubtedly of great importance in view of their biological applications. Among these, the oxathiazine and its derivatives have been used for a long time in agricultural and biological applications. They act as nematicides,[2] herbicides, fungicides, plant desiccants and defoliants,[3] antifouling agents,[4] and wood preservatives.[5] Bethoxazine (Bethoguard™, Fig. 1) is a broad spectrum industrial microbicide introduced by Janssen Pharmaceutica.[6] Oxathiazines also serve as crop protection agents and crop growth regulators,[7] anticancer, antiinfectious, antigastric acid secretion, antiosteoporosic and anti-inflammatory agents,[8] estrone sulfatase inhibitors,[9] and in the treatment of hyperglycemia.[10] Oxathiazine derivatives also serve as key intermediates for the synthesis of thiadiazoles[11] and β-lactam analogues[12] as well as artificial sweetener.[13]

Despite the above biological importance of 1,4,2-oxathiazines, investigation on their assembly is scarce.[6c,d] This led us to report in this Letter a two-component domino reaction for the facile synthesis of 3-aryl-5,6-dihydro-1,4,2-oxathiazin-6-ols, whose retrosynthetic analysis (Scheme 1) points to simple readily accessible starting materials, viz. (*E*)-4-bromo-*N*-hydroxybenzimidoyl chloride and 1,4-dithiane-2,5-diol.

It is pertinent to note that 2-mercaptoacetaldehyde endowed with both electrophilic and nucleophilic reaction centers, generated from 1,4-dithiane-2,5-diol in the presence of base, has the versatility to combine with reactants possessing both nucleophilic and electrophilic centers and hence has been used in the synthesis of important heterocycles such as thiophenes,[14] dihydrothiophene carbaldehyde,[15] tetrahydrothiophenes,[16] thiacytidine,[17] 1,4-dithiin,[18] thienopyrimidine,[19] and penicillin analogues.[20] This study forms a part of our research embarked recently on the synthesis

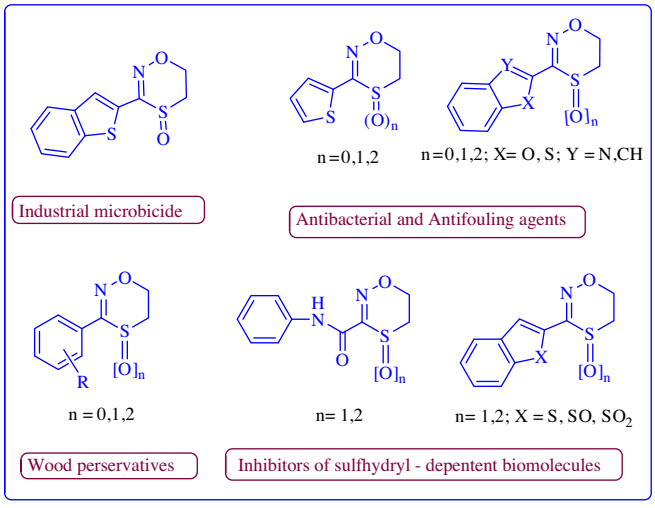

Figure 1. Selected examples of biologically active 5,6-dihydro-1,4,2-oxathiazine derivatives.

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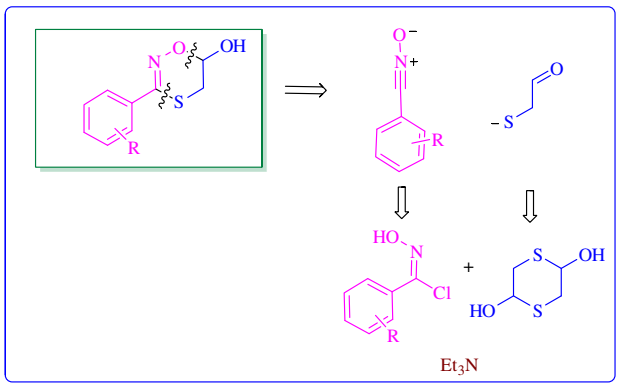


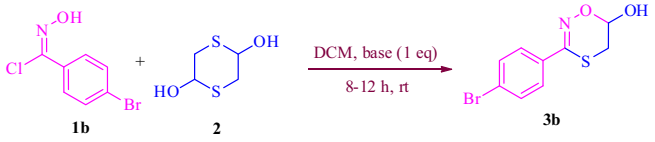
Scheme 1. Retrosynthesis of 5,6-dihydro-1,4,2-oxathiazines.

of biologically relevant heterocycles employing domino transformations.[21]

We started our study with the optimization of the model two-component reaction between (*E*)-4-bromo-*N*-hydroxybenzimidoyl chloride (1 mmol) and 1,4-dithiane-2,5-diol (0.5 mmol) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (1 equiv) in ethanol at room temperature for 10 h.

After standard work-up and purification of the reaction mixture via silica gel column chromatography, product **3b** was obtained in 52% yield (Table 1, Entry 1). Then we proceeded with the optimization of reaction conditions for maximizing the yield of the product. As shown in Table 1, various bases such as potassium carbonate, triethylamine, pyrrolidine, piperidine, pyridine, *N*,*N*-dimethylaminopyridine, and 1,4-diazabicyc-lo[2.2.2]octane were screened for their catalytic efficacy in the reaction. Among the above bases, triethylamine is found to be superior to other bases and the yield of the desired product could be increased to 65% in ethanol (Table 1, Entry 12) and 74% in dichloromethane (Table 1, Entry 10) under mild reaction conditions. Next, the model reaction was investigated in other solvents, such as *N*,*N*-dimethylformamide, methanol, water, and 1,4-dioxane (Table 1, Entries 10–16). From the data listed in Table 1, it is clear that triethylamine–dichloromethane pair is ideal for obtaining a maximum yield of **3b** (74%).

Table 1
Solvent and base-screen for the synthesis of **3b**[a]

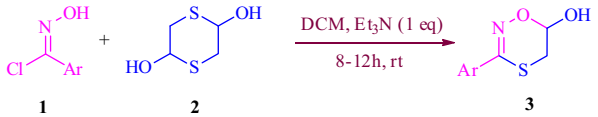


1b **2** **3b**

Entry	Base (1 equiv)	Solvent	Time (h)	Yield of **3b**[a] (%)
1	DBU	EtOH	10	52
2	DBU	DCM	12	58
3	DMAP	DCM	12	60
4	Pyridine	DCM	12	63
5	Piperidine	DCM	12	Trace
6	Pyrrolidine	DCM	12	Trace
7	L-Proline	DCM	10	—[b]
8	K_2CO_3	DCM	10	—[b]
9	Na_2CO_3	DCM	12	—[b]
10	Et_3N	DCM	8	74
11	Et_3N	MeOH	8	69
12	Et_3N	EtOH	8	65
13	Et_3N	DMF	9	68
14	Et_3N	CH_3CN	10	64
15	Et_3N	1,4-Dioxane	12	—[b]
16	Et_3N	Water	12	—[b]

[a] Isolated yield after purification.
[b] No reaction occurred.

Table 2
Synthesis of 3-aryl-5,6-dihydro-1,4,2-oxathiazin-6-ols **3**



1 **2** **3**

Entry	Compd	Ar	Time (h)	Yield of **3**[a] (%)
1	**3a**	4-ClC_6H_4	12	67
2	**3b**	4-BrC_6H_4	8	74
3	**3c**	4-PhC_6H_4	9	85
4	**3d**	4-MeC_6H_4	8	86
5	**3e**	4-EtC_6H_4	8	84
6	**3f**	4-$Pr^iC_6H_4$	8	88
7	**3g**	4-$^tBuC_6H_4$	8	87
8	**3h**	C_6H_5	8	82
9	**3i**	2-MeC_6H_4	10	74
10	**3j**	3-FC_6H_4	5	65[b]
11	**3k**	3-BrC_6H_4	12	69
12	**3l**	1-Naphthyl	9	81
13	**3m**	2-Naphthyl	10	80
14	**3n**	2-Thienyl	9	70
15	**3o**	2-Benzothienyl	10	72

[a] Isolated yield after purification.
[b] The reaction was performed with corresponding (*E*)-*N*-hydroxyarylimidoyl chloride and 1,4-dithiane-2,5-diol in the presence of Et_3N in CH_3CN at reflux.[24]

With the above optimized reaction conditions in hand, we proceeded to investigate the synthesis of a series of 3-aryl-5,6-dihydro-1,4,2-oxathiazin-6-ols **3** (Table 2) employing differently substituted (*E*)-*N*-hydroxyarylimidoyl chlorides (1 mmol) and 1,4-dithiane-2,5-diol (0.5 mmol) in the presence of triethylamine (1 equiv) in dichloromethane at room temperature for 8–12 h.[23] After completion of the reaction (TLC), the solvent was removed under reduced pressure and the resulting crude product was purified by flash silica column chromatography using petroleum ether–ethyl acetate as eluent (4:1 v/v) to obtain a series of novel 3-aryl-5,6-dihydro-1,4,2-oxathiazin-6-ols **3a**–**o** in 65–88% yields (Table 2). As shown in Table 2, the (*E*)-*N*-hydroxyarylimidoylchlorides bearing moderately electron-releasing groups such as phenyl, naphthyl, heteroaryl, and alkyl gave better yields in shorter reaction time than that with mild electron-withdrawing groups. However, this transformation with **1** having either strong electron-releasing or electron-withdrawing groups such as 4-NO_2, 4-CF_3, 3-NO_2, 4-OMe, 4-$(Me)_2N$, and 3-OMe failed even at high temperature. The structure of 3-aryl-5,6-dihydro-1,4,2-oxathiazin-6-ols **3** was deduced from one- and two-dimensional NMR spectroscopic data as detailed for **3b** as a representative example (Fig. 2).

In the ^1H NMR spectrum of **3b**, the H-6 appears as a doublet of doublets at 5.64 ppm (J = 2.4, 0.9 Hz). The diastereotopic H-5 hydrogens appear as a doublet of doublets at 3.21 (J = 12.3, 3.6 Hz) and 3.35 ppm (J = 12.3, 2.2 Hz). These H-5 hydrogens show (i) a C,H-COSY correlation with the carbon signal at 29.1 ppm due to C-5 and (ii) a HMB correlation with C-6 at 85.3 ppm. The H-2′,6′ hydrogens appear as a multiplet at 7.57–7.60 ppm and show (i) a C,H-COSY correlation with the carbon signal at 127.6 ppm assigning it to C-2′,6′ and (ii) HMB correlations with C-3 and C-4′ at 150.0 and 125.1 ppm respectively. Similarly, the H-3′,5′ appearing as a multiplet at 7.51–7.55 ppm show a C,H-COSY correlation with the carbon signal at 131.8 ppm and a HMB correlation with C-1′ at 133.8 ppm. The hydroxyl proton gives a broad singlet at 3.95 ppm. The ^1H and ^{13}C chemical shifts of **3b** are depicted in Figure 2. The structure deduced from NMR spectroscopic data is also in accord with ESI-Mass spectra. Finally, the structure of the product **3d** has been unequivocally determined by X-ray structurallographic study (Fig. 3).[22]

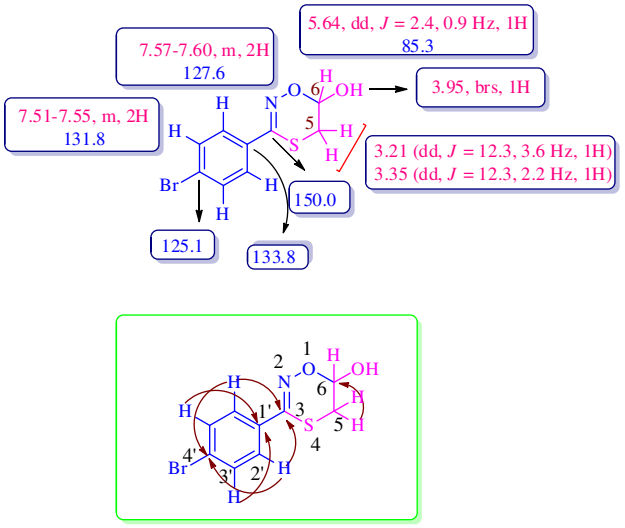
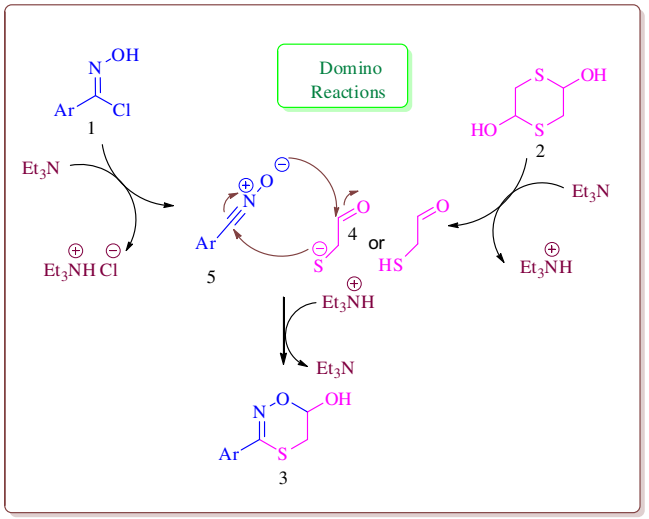


Figure 2. Selected ^{1}H and ^{13}C chemical shifts and HMBC correlations of **3b**.



Scheme 2. Probable domino mechanistic pathway leading to the formation of **3**.

In the present study, we also tried to synthesize biologically important 3-aryl-5,6-dihydro-1,4,2-oxathiazines from the corresponding 3-aryl-5,6-dihydro-1,4,2-oxathiazin-6-ols. Our efforts to (i) derivatize the hydroxyl group of 3-aryl-5,6-dihydro-1,4,2-oxathiazin-6-ols through tosylation/mesylation or substitution of the hydroxyl group by halogen by Appel reaction for further reduction and (ii) deoxygenate through Barton–Mc Combie deoxygenation did not fructify. Attempted deoxygenation of 3-aryl-5,6-dihydro-1,4,2-oxathiazin-6-ols using (i) $NaBH_4$ in acetic acid and (ii) $AlCl_3$ or Et_3SiH with $BF_3{\cdot}OEt_2/InCl_3/Cu(OTf)_2$ at −55 °C in dry dichloromethane also failed to afford the corresponding cyclic ethers.

A plausible mechanism for the formation of 3-aryl-5,6-dihydro-1,4,2-oxathiazin-6-ols is depicted in Scheme 2. Presumably, this transformation involves (i) the initial formation of the thiolate anion of 2-mercaptoacetaldehyde **4** from the reaction of 1,4-dithiane-2,5-diol **2** with base, (ii) generation of nitrile oxide **5** via dehydrochlorination of (*E*)-*N*-hydroxyarylimidoyl chloride **1** in the presence of triethylamine and (iii) [3+3] annulation of **4** and **5** affording product **3**. This mechanism also explains the failure to obtain the product with **1** bearing both powerful electron-releasing and the withdrawing substituents on the aryl ring. While strong electron-releasing groups could diminish the electrophilicity of the carbon of the nitrile oxide functionality, strong electron-withdrawing groups on the aryl ring could attenuate the nucleophilicity of the oxygen of the nitrile oxide, both of them forbid the reaction.

In this reaction, the mercaptoacetaldehyde and/or its anion generated from the 1,4-dithiane-2,5-diol could be involved in the annulation step. If the anion of mercaptoacetaldehyde reacts with the nitrile oxide, then for final protonation to give the product, the intermediate will abstract a proton from triethylammonium ion (Scheme 2). The fact that one mole of triethylamine is sufficient to catalyze the reaction discloses that deprotonation by triethylamine and reprotonation by triethylammonium ion could happen as equilibrium processes, which could facilitate the overall transformation even if one mole of triethylamine is used.

In conclusion, we have disclosed a facile, highly efficient synthesis of novel 3-aryl-5,6-dihydro-1,4,2-oxathiazin-6-ols in good yields via domino sequence of reactions from simple, readily available starting materials. This transformation occurs with the formation of a C—S and a C—O bond in a one pot operation.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.05.062.

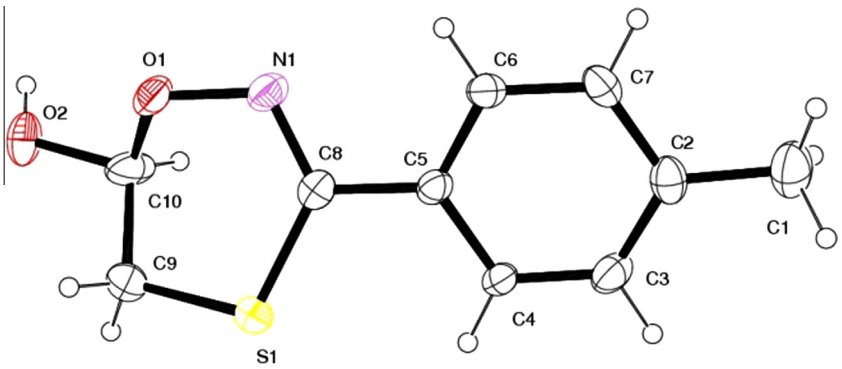

Figure 3. ORTEP diagram for **3d**.

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22. Crystallographic data for the derivative **3d** in this manuscript have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number **CCDC** 980915 Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
23. *General procedure for the synthesis of 3-aryl-5,6-dihydro-1,4,2-oxathiazin-6-ols at ambient temperature (**3a–i**, **3k–o**).* A mixture of (*E*)-*N*-hydroxyarylimidoyl chloride (1 mmol), 1,4-dithiane-2,5-diol (0.5 mmol) and triethylamine (1 mmol) in dichloromethane (6 ml) was stirred for 10–12 h under room temperature. After completion of the reaction (TLC), the solvent was removed under reduced pressure and the resultant crude product was purified by flash silica column chromatography using petroleum ether–ethyl acetate as eluent (4:1 v/v).
24. *General procedure for the synthesis 5,6-dihydro-1,4,2-oxathiazin-6-ols under heating (**3j**).* A mixture of (*E*)-*N*-hydroxyarylimidoyl chloride (1 mmol), 1,4-dithiane-2,5-diol (0.5 mmol), and triethylamine (1 mmol) in acetonitrile (5 ml) was heated to reflux for 3 h at 100 °C. After completion of the reaction (TLC), the solvent was removed under reduced pressure and the resultant crude product was purified by flash silica column chromatography using petroleum ether–ethyl acetate as eluent (4:1 v/v). Characterization data for a representative compounds **3a–c** are given below. *3-(4-Chlorophenyl)-5,6-dihydro-1,4,2-oxathiazin-6-ol (**3a**):* white solid. Yield: 67%; mp = 104–105 °C; (300 MHz, $CDCl_3$) δ_H: 3.22 (dd, *J* = 12.3, 3.6 Hz, 1H), 3.34 (dd, *J* = 12.4, 1.9 Hz, 1H), 5.64–5.65 (m, 1H), 7.38 (d, *J* = 8.7 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR(75 MHz, $CDCl_3$) δ_c: 29.1, 85.1, 127.4, 128.8, 133.3, 136.8, 149.8; ESI-MS: *m/z*. Calcd: 229.00; Found: 230.00 (M^+); Anal. Calcd for $C_9H_8ClNO_2S$: C, 47.06; H, 3.51; N, 6.10. Found C, 47.18; H, 3.44; N, 6.18. *3-(4-Bromophenyl)-5,6-dihydro-1,4,2-oxathiazin-6-ol (**3b**):* white solid. Yield: 74%; mp = 173–174 °C; ^1H NMR(300 MHz, $CDCl_3$) δ_H: 3.21 (dd, *J* = 12.3, 3.6 Hz, 1H), 3.35 (dd, *J* = 12.3, 2.2 Hz, 1H), 3.95 (br s, 1H), 5.64 (dd, 3.3, 2.4 Hz, 1H), 7.52–7.55 (m, 2H), 7.57–7.60 (m, 2H); ^{13}C NMR(75 MHz, $CDCl_3$) δ_c: 29.1, 85.3, 125.1, 127.6, 131.8, 133.8, 150.0; ESI-MS: *m/z*. Calcd: 272.95; Found: 273.98 (M^+), 275.98 (M+3); Anal. Calcd for $C_9H_8BrNO_2S$: C, 39.43; H, 2.94; N, 5.11. Found C, 39.30; H, 2.88; N, 5.21. *3-(Biphenyl-4-yl)-5,6-dihydro-1,4,2-oxathiazin-6-ol (**3c**):* white solid. Yield: 85%; mp = 165–166 °C; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 3.24 (dd, *J* = 12.6, 3.6 Hz, 1H), 3.39 (dd, *J* = 12.4, 2.2 Hz, 1H), 3.58 (d, *J* = 4.5 Hz, 1H), 5.66 (br s, 1H), 7.37–7.40 (m, 1H), 7.43–7.49 (m, 2H), 7.60–7.68 (m, 4H), 7.78–7.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c: 29.3, 85.5, 126.6, 127.1, 127.2, 127.8, 128.8, 133.7, 140.1, 143.4, 150.6; ESI-MS: *m/z*. Calcd: 271.07; Found: 272.08 (M^+); Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16. Found C, 66.52; H, 4.70; N, 5.10.