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One-pot synthesis of functionalized isoxazole-thiolane hybrids *via* Knoevenagel condensation and domino sulfa-1,6-Michael / intramolecular vinylogous Henry reactions†

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One-pot synthesis of highly functionalized tetrahydrothiophene (thiolane) derivatives conjugated with biologically useful isooxazole are reported *via* the Knoevenagel condensation followed by domino sulfa-1,6-Michael / intramolecular vinylogous Henry reactions of aldehydes, 1,4-Dithiane-2,5-diol and 3,5-dimethyl-4-nitroisoxazole. From the base and solvent screening, it was found that piperidine (30 mol%) and ethanol are best suitable conditions giving the desired products with >95% yields in 2-2.5 h overall reaction time.

Isoxazole moiety is present in natural molecules like AMPA,[1a] Ibotenic acid.[1b] The synthetic derivatives of isoxazole are known as inhibitors of Heat Shock Protein90 activity,[2a] initiators of neurogenesis,[2b] broad spectrum antibiotics,[2c] antiviral agents[2d] non-steroidal anti-inflammatory drugs[2e] and immunosuppressive agents.[2f] The tetrahydrothiophene is part of natural glucosidase inhibitor (salacinol),[3a] Cholecystokinin type-B receptor antagonist (tetronothiodin)[3b] and used for the development of HIV and hepatitis B inhibitors.[3c] The thiophene-isoxazole molecules also used for pulmonary hypertension (Sitasentan TBC 11251) and as phosphodiesterase 4B inhibitors.[4] Along with these, isoxazole can be used for the preparation of carboxylic acids[5] and thiophene is extensively used in medicinal and materials chemistry.[6]

Dimeric α-mercaptoacetaldehyde (1,4-Dithiane-2,5-diol, **1**) was used for the thiazole synthesis by Gewald and co-workers in 1966.[7] Later, Belleau (1984)[8a] and Spino (1995)[8b] groups used this molecule for the preparation of cyclic thia derivative via Michael type addition and intramolecular Aldol reactions which was further used for the diene generation. In 2006 Pollini and co-workers exploited the bifunctional nature of 1,4-Dithiane-2,5-diol (**1**) (-CHO as electrophile and –SH as nucleophile) for the tandem Michael–Henry or Michael–Michael reactions resulting in to 3,4-disubstituted tetrahydrothiophenes.[9a] Similar strategy was adopted by Southern[9b,c] and Ramström[9d] groups for the preparation of substituted nitro-thiophenes starting from β-nitrostyrenes.

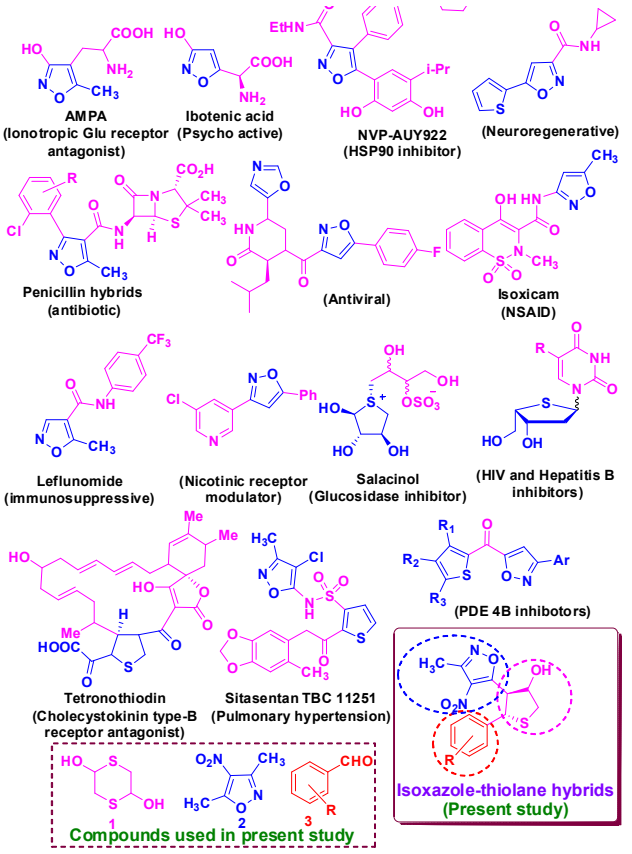

Figure-1. Different biologically active molecules with substituted isoxazole, tetrahydro thiophene and isoxazole-thiophene moieties and present investigation

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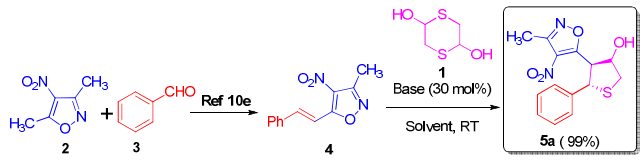
The bifunctionality of 1,4-Dithiane-2,5-diol (**1**) is very much exploited in combination with α,β-unsaturated carbonyl compounds and their derivatives. In this context, Tang et al, reported the domino thia-Michael/Aldol condensation reactions using proline-based organocatalyst with good enantioselectivity.[10a] After this report, many methods appeared in the literature for the construction of complex /spirocyclic molecules using chalcones derivatives (in presence of chiral squaramide as catalyst,[10b-d] and catalyst free conditions[10e,f]), oxindoles [(squaramide catalyst; *via* [3+2] annulation),[11a] N,N'-dioxide–nickel(II) complex,[11b]], and isoindigos.[11c] Along with these, recently cyclopropane derivatives[11d-f] N-substituted imides (*via* [3+2]-cycloaddition),[12a-c] azomethine imine (*via* [3+3]-cycloaddition),[13a] alkynols,[13b] hydroxylamines,[13c] and vinyl azides[13d] has also been used for the construction of thiolane rings.

3-methyl-4-nitro-5-styrylisoxazole (**2**) in which the two double bonds are in conjugation with Nitro group can be used as cinnamate equivalent. The 1,6-Michael addition of 3-methyl-4-nitro-5-styrylisoxazole is a well-known concept.[14] However, the formation of two new bonds with Michael addition followed by [2+3]-cyclo-addition is less explored in the literature.[15] Moreover, there are no reports with the formation of C-C, C-S bonds and [2+3]-annulation in intramolecular fashion (One-pot synthesis).

Considering the importance of isoxazole and thiophene moieties, growing applications of α-mercaptoacetaldehyde **4** and in continuation of our efforts of developing greener synthetic methods,[16] here in we report one-pot synthesis of functionalized isoxazole-thiolane hybrids. Towards this, the α-mercaptoacetaldehyde **4** was reacted with isoxazole derivative **3** in presence of DABCO (30 mol%) in water to give the isoxazole-thiolane hybrid **5** (with three consecutive sterogenic centres) in 90% yield (Scheme-1). After confirmation of the product (see ESI for spectral data), attempts were made to optimise the reaction conditions using different combinations of solvents and bases (organic and inorganic) and the best results are given in Table-1.

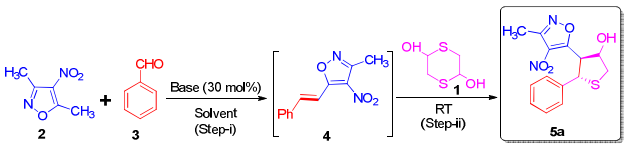


Scheme-1. Sulfa-1,6-Michael / intramolecular vinylogous (Henry) reactions of 1,4-dithiane-2,5-diol (**1**) and isoxazole based nitrostyrene (**4**)

S. No.	Solvent	Base (30 mol%)	Reaction time (h)	Isolated Yield (%)[a]
1	**Water**	**DABCO**	**10**	**90**
2	Acetonitrile	DABCO	24	70
3	**Chloroform**	**DABCO**	**5**	**99**
4	Dichloromethane	DABCO	24	60
5	Methanol	DABCO	24	85
6	Ethanol	DABCO	10	87
7	Dimethylsulfoxide	DABCO	24	70
8	N,N-Dimethylformamide	DABCO	24	65
9	Water	DBU	24	50
10	Chloroform	DBU	24	65
11	Dichloromethane	DBU	24	50
12	Methanol	DBU	24	60
13	Ethanol	DBU	24	65
14	Water	TEA	24	45
15	Chloroform	TEA	24	70
16	Dichloromethane	TEA	24	60
17	Methanol	TEA	24	75
18	Ethanol	TEA	10	80
19	Water	Piepridine	24	70
20	Chloroform	Piepridine	24	76
21	Dichloromethane	Piepridine	24	60
22	Methanol	Piepridine	5	85
23	**Ethanol**	**Piepridine**	**15 min**	**99**

Table-1. Optimization of reaction conditions for Sulfa-1,6-Michael/intramolecular vinylogous (Henry) reaction; *Reaction conditions:* [a]All the reactions were performed at 100 mg scale of isoxazole styrene derivative using 30 mol% of base

From the above studies, it is clear that the reaction is successful in chloroform + DABCO and ethanol + piperidine combinations (Table 1; **entries 3** and **23**). After optimization of the reaction conditions, one-pot synthesis of isoxazole-thiolane hybrid **5** was attempted starting from corresponding aldehyde. However, it was observed that the formation of styrene derivative in less yield [> 45% (in water and chloroform medium)]. Whereas, in ethanol + piperidine combination, the reaction went to completion yielding desired isoxazole-thiolane hybrid **5** in quantitative yield (with *in situ* formation of isoxazole-styrene as intermediate **3**) as shown in Scheme-2.



A : Step-i) DABCO (30 mol), $CHCl_3$, 65 °C, 5 h (**4** ; 50%); Step-ii) RT, 18-19 h (**5a** ; 45%)
B : Step-i) DABCO (30 mol), H_2O, 65 °C, 5 h (**4** ; 45%); Step-ii) RT, 18-19 h (**5a** ; 20%)
C : Step-i) Piperidine (30 mol%), Ethanol, 65 °C, 2 h (**4**); Step-ii) RT, 15 min (**5a** ; > 95% in two steps)

Scheme 2. One-pot Knoevenagel condensation followed by sulfa-1,6-Michael / direct vinylogous (Henry) reactions of 1,4-dithiane-2,5-diol (**1**) and isoxazole based nitrostyrene (**4**)

From the mechanism, we assume that the generation of isoxazole-styrene **3** is a result of Knoevenagel condensation which react with mercaptaldehyde **4** (in situ generated monomer) *via* sulfa-1,6-Michael/intramolecular vinylogous (Henry) reactions to give the desired cyclised product **5** (Figure 2).

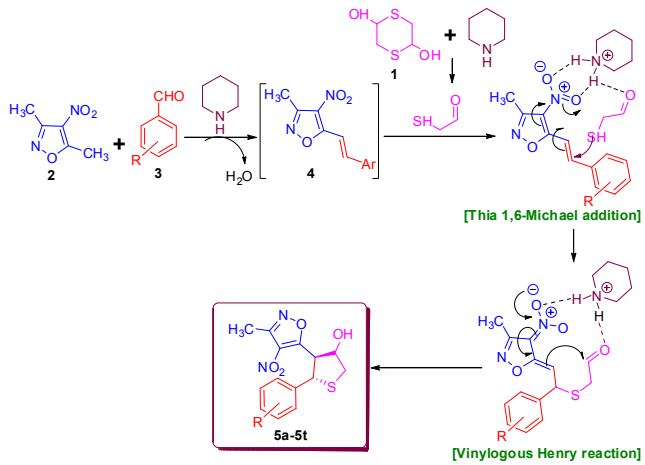


Figure-2. Plausible reaction mechanism for sulfa-1,6-Michael / direct vinylogous (Henry) reactions of 1,4-dithiane-2,5-diol (**1**) and isoxazole based nitrostyrene (**4**)

Subsequently, various aromatic (with electron donating and electron withdrawing groups) and heteroaromatic aldehydes were reacted (65°C, 2 h) with 3,5-dimethyl-4-nitroisoxazole (**1**) in presence of catalytic amount of piperidine (30 mol%) to give the functionalized nitrostyrene derivatives (in situ) which were then treated with α-mercaptoacetaldehyde **4** (RT, 5-15 min) to give the functionalized isoxazole-thiolane hybrids (**5b**-**5t**) in excellent yields (Figure-3). Though the yields are very good, the substrate dependent reactivity was observed for completion of the reaction. The substrates with electron withdrawing groups require shorter reaction times than the substrates with electron donating groups as summarized in Figure-3.

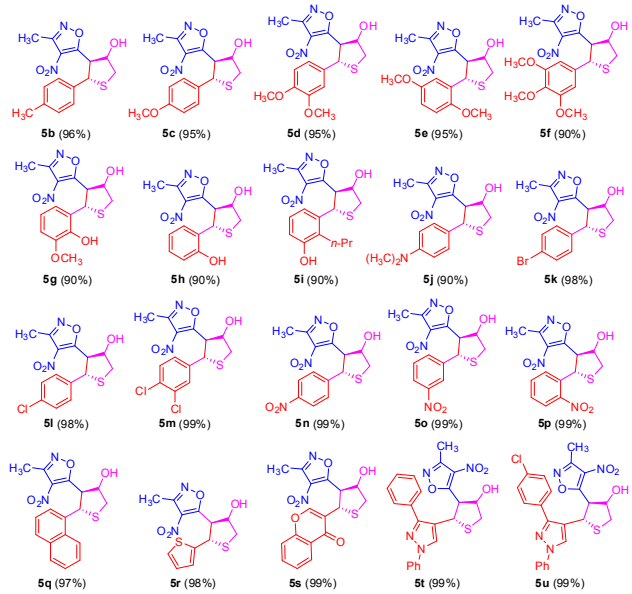


Figure-3. Different isoxazole-thiolane hybrids (**5b**-**5t**)

Towards establishing the stereochemistry of the resulting products, the X-ray crystallographic data was obtained for the compound **5k** as shown below (Figure 4; for the experimental details see ESI). The ORTEP diagram (CCDC 1426687) indicating that the protons on C1 and C4 are positioned in *anti*-configuration.

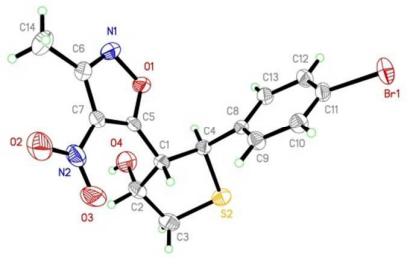
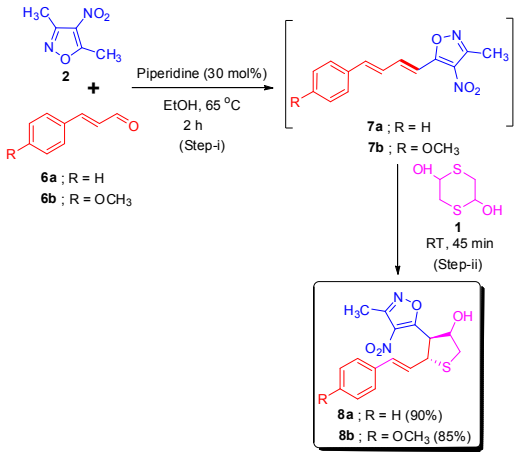
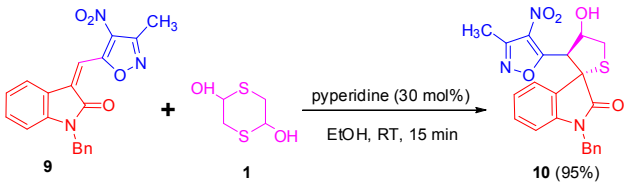


Figure-4. ORTEP diagram of compound **5k**; A view of AY15, showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are represented by circles of arbitrary radii.

After successful demonstration of one-pot synthesis of isoxazole-thiolane hybrids, focus was shifted towards the preparation of more complex derivatives. Thus, the nitrobutadienes (**7a**-**7b**) (in situ) and oxindole-based isoxazole nitrostyrene (**9**)[12c] were prepared using vinylogous Henry reaction followed by mesylation-elimination and reacted with α-mercaptoacetaldehyde **4** under optimized conditions to give functionalized isoxazole-thiolane hybrids (**8a**-**8b** and **10**) in good yields (Schemes 3 and 4).

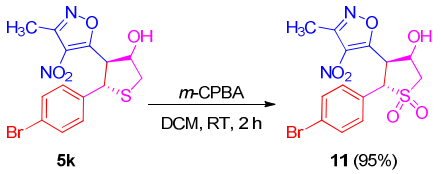


Scheme-3. One-pot Knoevenagel condensation followed by sulfa-1,6-Michael / direct vinylogous (Henry) reactions of 1,4-dithiane-2,5-diol (**1**) and isoxazole based nitrostyrene (**7a**-**7b**)



Scheme-4. Synthesis of spiro ixindole based isoxazole-thiolane hybrid (**10**)

Later, compound (**5k**) was used for further functionalization using *m*-CPBA in dichloromethane to give the sulfone **11** in 95% yield (Scheme 5).



Scheme-5. Functionalization of compound **5k** to sulfone **11**

In conclusion, we have demonstrated an efficient method for one-pot synthesis of functionalized isoxazole-thiolane hybrids under mild conditions with very good yields. The derivatives reported here can be used for biological applications. Also, aromatization followed by hydrolysis of isoxazole will give trisubstituted thiophene derivatives with carboxylic acids which can act as anchoring group for potential applications as materials.

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