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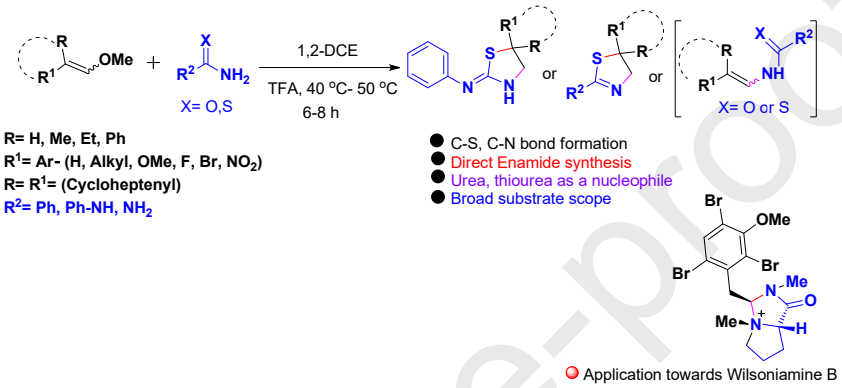

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Acid mediated synthesis of thiazolines, thiazoles and enamide derivatives from methyl enol ethers: application towards synthesis of wilsoniamine B

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ABSTRACT

An efficient metal-free synthesis of thiazolines, dihydrothiazole and enureas or thioureas from methyl enol ether with urea or thiourea derivatives in the presence of TFA (trifluoroacetic acid) are reported here. This synthetic protocol involves the formation of two bonds, C-N as well as C-S, in one step for the synthesis of thiazoline derivatives, dihydrothiazoles and a direct C-N bond for the synthesis of enamides with good to excellent yields. Further, this method was employed for the synthesis of wilsoniamine B alkaloid.

Introduction:-

Thiazoline derivatives which contain a nitrogen-sulfur (N-S) bond are known to have promising anti-HIV, antibacterial, antiviral, anticancer, antifungal activities[1,2] and expanded applications in peptide synthesis.[3] 2-Aminothiazoline moiety is an important pharmacophore among nitrogen and sulfur-containing heterocycles with wide spectrum of pharmaceutical agents such as cefotaxime,[4a] meloxicam,[4b] nitazoxanide with novel potent antiprotozoal agent, and compound showcasing herbicidal activity[4c] (Figure 1). Thus, N-S containing bonds are functionally and biologically important.

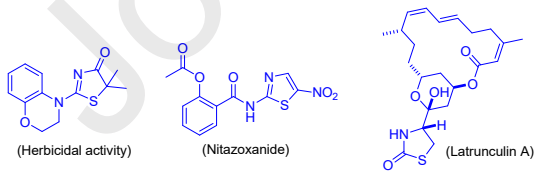
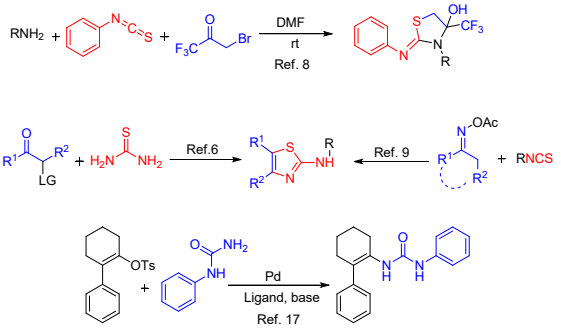


Figure 1. Biologically important natural products and drugs.

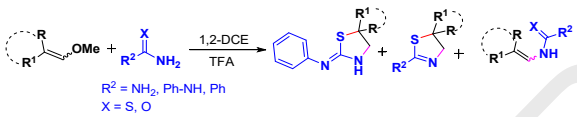
Due to their biological significance, syntheses of thiazoline containing scaffolds has been attractive goal.[5] For example, several strategies have been developed for the syntheses of such heterocycles containing derivatives and the most common methods are summarized in Scheme 1. Among them, compound with α-halo carbonyl and thiourea are the common methods utilized for synthesizing these derivatives.[6] An alternative method for the synthesis of 4-substituted 2-aminothiazole was reported by Zhang and co-worker from vinyl azides and potassium thiocyanates in the presence of Pd-catalyst.[7] An one-pot, three-component reaction for the syntheses of thiazolidin-4-ol derivatives,[8a] and one-pot synthesis of glycothiazolines from glycals have also been reported in the literature.[8b] Copper-catalyzed coupling reaction also established for the synthesis of 2-aminothiazole.[9] Enantiospecific synthesis of thiazolidine derivatives from inactivated chiral aziridines with isothiocyanates were also exploited in the literature.[10] Triflouromethylation of alkenes with thiourea from Togni reagent were used for the syntheses of thiazolines and thiazines by intramolecular C-S bond formation.[11] Recently, a radical pathway was employed for the syntheses of 2-aminothiazoles from active methylene compound and thiourea in the presence of TBHP/AIBN.[12] Cross-dehydrogenative coupling reaction was also used for the synthesis of iminothiazolines.[13] Similarly, enureas or thioureas (enamides) motifs are found in several biologically active molecules,[14a] and in important organic substrates.[14b] The conventional method involves their synthesis from the reaction of imine with isocyanates.[15] The reported drawback in these reactions is the toxicity of isocyanates and removal of water during the reactions. Other methods have also been developed for their synthesis, such as, carbolithilation of amines,[16] Pd-catalyzed C-N coupling reaction of alkenyl tosylates or mesylates with urea derivatives,[17] reaction of acylamino alcohols with Lawesson's reagent,[18] hydroalumination of ketenimines.[19] Although, syntheses of thiazoline core containing compounds have been known in the literature, to the best of our knowledge, there has

be t of dihydrothiazoles and unsaturated enamides from methyl enol ethers. Methyl enol ethers are good starting materials because they can act as both electrophile as well as nucleophile[20] and also easy to prepare. In continuation to our previous work, where enol ethers were used as a nucleophile, whereas in this work methyl enol ether acts as an electrophile. This method also provides an alternative to the existing methods where halogen containing compounds are generally required. Therefore, we report a metal free, acid-mediated method for the synthesis of thiazolines, enamides from enol ethers via C-S and C-N bond formation.



Scheme 1: Previous reports

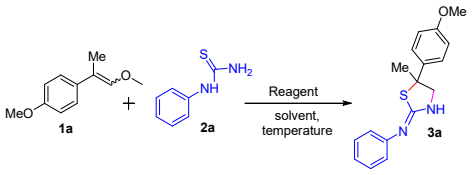
This work: Methyl enol ether as electrophile



Result and Discussion:

To investigate the reaction condition, we selected enol ether (**1a**) and N-phenyl thiourea (**2a**) as model substrates (Table 1). Optimization of the reaction condition was carried out by changing solvents, temperatures, and reagents. First, the reaction was conducted in CH_3NO_2 as solvent with Lewis acids like BF_3-OEt_2, $Bi(OTf)_3$ as catalysts but the reaction didn't work (Table 1, entry 1-2). So we changed various types of catalysts and solvents to check the feasibility of reaction and it was found that solvent plays an important role in the formation of the desired product (Table 1, entry 3-5). After observing product formation in chlorinated solvents like 1,2-DCE, and $CHCl_3$, we screened for a suitable catalyst to improve the yield. When reaction was carried out at room temperature in the presence of Bronsted acid like TfOH (0.5 equivalents), we observed 54% yield with longer reaction time (Table 1, entry 5). Similarly, when the reaction was performed by using $CHCl_3$ as a solvent yield has improved to 66% in 14 hours (entry 6). When trifluoroacetic acid (TFA) was used in 1,2-DCE as a solvent at room temperature, the reaction proceeded well with improvement of yield in longer reaction time (entry 7). After observing very good yield, we thought of increasing the catalyst to reduce the reaction time. When the catalyst was increased to 1.0 equivalent or 2.0 equivalent reaction time has reduced drastically with improvement in yield as well (entries 8-9). Triflic acid (TfOH) in dichloromethane (DCM) also gave the product in moderate yield (entry 10). In summary, the TFA as a reagent and 1,2-DCE at 40 °C for 8 h.

Table-1. Optimization conditions[a,b]



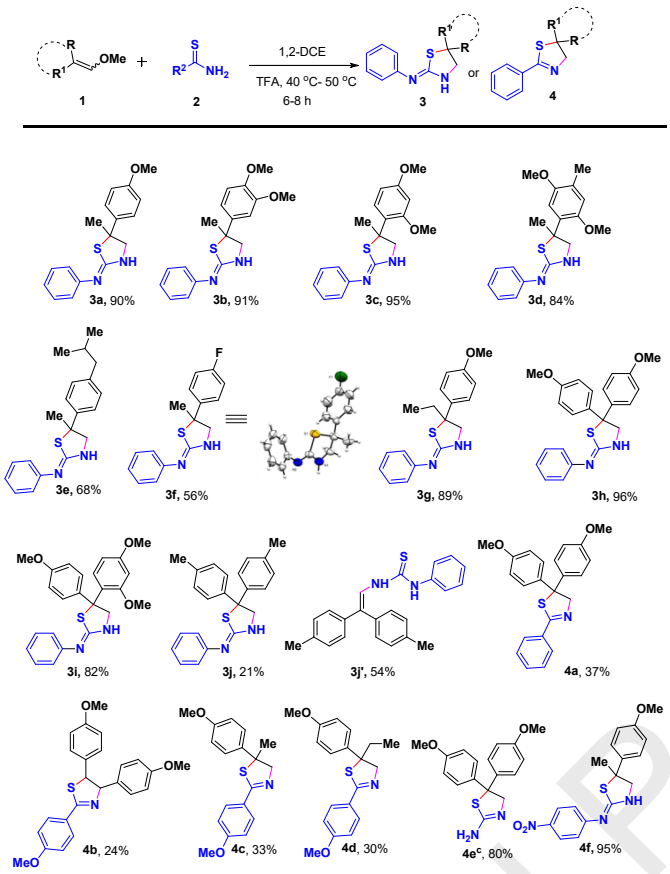
entry	Reagent (equiv.)	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	BF_3-OEt_2 (1.0)	CH_3NO_2	rt	24	ND
2	$Bi(OTf)_3$ (0.5)	CH_3NO_2	rt	24	ND
3	$FeCl_3$ (0.2)	Toluene	rt	24	ND
4	$MeSO_3H$ (0.5)	CH_3CN	rt- reflux	12	ND
5	TfOH (0.5)	1,2-DCE	rt	24	54
6	TfOH (0.5)	$CHCl_3$	40	14	66
7	TFA (0.5)	1,2-DCE	rt	23	88
8	TFA (1)	1.2-DCE	40	18	90
9	**TFA (2)**	**1,2-DCE**	**40**	**8**	**90**
10	TfOH (1.5)	DCM	rt	8	37

[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.4 mmol), 1,2-DCE (4 ml). [b]Isolated yields. ND = Not detected.

Under the optimized condition, the substrate scope of the reaction were studied using a series of enol ethers with respect to different thiourea or thiobenzamide derivatives (Table 2). As shown in Table 2, different substituted enol ethers were converted into corresponding thiazolines and thiazole derivatives in good to excellent yield. First, the effect of the substituent on enol ethers were explored. Substrate with electron-donating group like –OMe, at different positions on aromatic ring of enol ethers (**1a-1d**) were screened under the optimum condition with respect to **2a**, affording the corresponding desired product in good yields (**3a-3d**, Table 2). Similarly, alkyl substituent derived enol ether **1e** reacted well with compound **2a** to afford compound **3e** in 68% yield. Enol ether (**1f**) having fluoro substituent also gave the product as expected in fair yield with 56% (**3f**), which was further confirmed with single crystal X-ray analysis (Table 2). Enol ether **1g** (R=ethyl and R^1=aryl) also converted into the product (**3g**) with very well in 89% yield. Further, benzophenone derived enol ethers (**1h-1i**) with electron-donating substituent

were nd (**3h**, **3i**). While in the case of enol ether with **1j**, both cyclization (**3j**) and enthiourea (**3j'**) products were observed in 21% and 54% yields respectively.

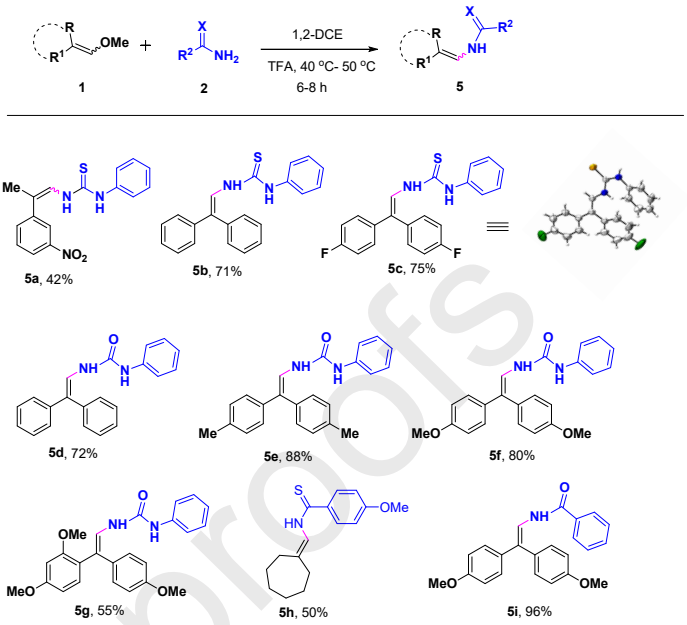
Table-2. Scope of Enol ethers and Thioureas[a,b]



[a]Reaction conditions: **1** (0.4 mmol), **2** (0.4 mmol), 1,2-DCE (4 ml), TFA (2.0 equiv), for 6-8 h. [b]Isolated yields after silica gel column chromatography. [c]Reaction was carriedout at 60 °C.

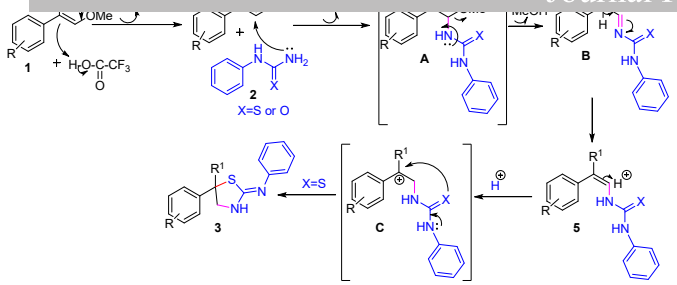
In order to broaden the scope of this reaction, dihydrothiazoles were also prepared by using simple benzothioamide derivatives (**2b**, **2c**, **2d**, Table 2) with enol ethers. When compound **1h** reacted with benzothioamide **2b**, a new product dihydrothiazole (**4a**) formation was observed in moderate yield. Surprisingly, when **1h** was reacted with compound **2c**, a new product (**4b**) formation was achieved with aryl group migration in low yield. The characteristic aryl attached C-H proton in ^{1}H nmr appeared at 5.66 (d, J = 6.6 Hz, 1H), 4.82 (d, J = 6.6 Hz, 1H) while the C-H attached carbon in ^{13}C appeared at δ 88.6 and 62.6. These values are in agreement with the core structure containing 2,4-diaryl thiazoline reported by Couture group.[21] To check whether migration will occur in acetophenone derived enol ethers or not, compound **1a** and **1g** were treated similarly with compound **2c**, but we ended up with simple dihydrothiazole derivatives (**4c** and **4d**) without migration of any group in 33% and 30% yields respectively. Simple thiourea **2d** also reacted well with enol ether **1h** to give the product (**4e**) in 80% yield. To our delight electron-withdrawing substituted thiourea derivative having –NO_2 afforded the product in excellent yield (**4f**).

Table-3: Direct Synthesis of Enureas or thioureas (Enamides).



[a]Reaction conditions: **1** (0.4 mmol), **2** (0.4 mmol), 1,2-DCE (4 ml), TFA (2.0 equiv), for 6-12 h at 40-50 °C. [b]Isolated yields after silica gel column chromatography.

After successfully synthesizing thiazolines and thiazoles, we moved to synthesize enamide derivatives directly from enol ethers because it serves as important building block in many natural products[22] as well as polymer synthesis. Different enol ethers having donating as well as withdrawing substituents were treated with urea, thiourea or benzamide derivatives for its synthesis (Table 3). Enol ether **1k** with –NO_2 substituent when treated with compound **2a**, gave the enamide derivatives as E/Z mixture in moderate yield (**5a**, Table 3). Compound **2a** also reacted well with benzophenone derived enol ethers **1l** and **1m** having substituent like (-H, -F) and gave the products **5b**, **5c** in 71% and 75% yields respectively and compound **5c** was further determined by single crystal X-ray structure (Table 3). N-phenyl urea (**2f**) derivative also gave the enamide derivatives (**5d-5g**) in good to moderate yields. Even cyclic aliphatic enol ether **1n** also reacted with compound **2c** and gave the product in 50% yield (**5h**). Simple benzamide **2g** derivative also underwent reaction with enol ether **1h** and delivered the product **5i** in 96% yield. Under similar reaction condition, compound **5c** and **5d** were further reacted to check the feasibility of cyclization, however, we didn't observe any cyclized products after 24 h (starting material recovered). The substrate scope in Table 2 and Table 3 indicates that the electron-rich enol ethers gave only cyclized product with thiourea (thiazoline derivatives), whereas urea derivative gave only enamide derivatives.

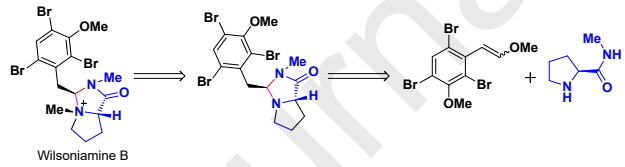


Scheme 2. Plausible Mechanism for Direct Synthesis of Enamides and Thiazolines

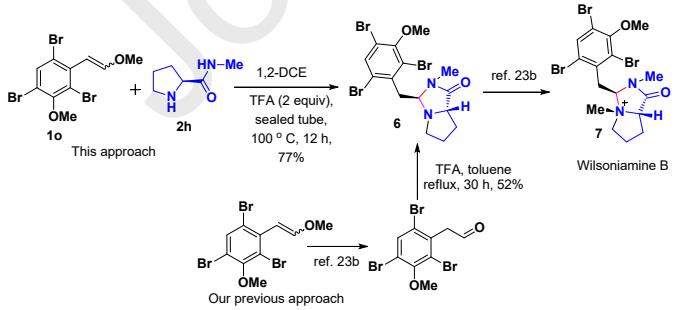
On the basis of observation from the substrate scope of the reaction, a possible mechanism for direct synthesis of thiazoline derivatives, enamide derivatives is shown in Scheme 2. First, compound **1** will be protonated in the presence of trifluoroacetic acid and further attack of nitrogen nucleophile of compound **2** at the α-position of enol ether would take place to give the intermediate (**A**), which may undergo -MeOH elimination to furnish the compound **5**, after tautomerization from intermediate **B**. Next, the protonation of an alkene moiety may occur to give benzylic carbocation intermediate **C**, and then intramolecular nucleophilic attack of sulfur atom to the carbocation center will take place to give thiazoline derivatives **3**.

From the substrate scope for the synthesis of enamide derivatives which indicates nitrogen source as a nucleophile, we further testified the utility of this methodology towards the synthesis of alkaloid wilsoniamine B[23a] from enol ether **1o**. Wilsoniamine B possesses a unique hyxahydro-1H-pyrrolo[1,2-c]imidazole-1-one ring system and was isolated from the bryozoan species.

Retrosynthesis:



Synthetic approach:



Scheme 3. Synthetic Application

Previously, our group also reported its synthesis[23b] from brominated homologated aldehyde with (*S*)-N-methylpyrrolidine-2-carboxamide (**2h**). However, we envisaged that compound **1o** of wilsoniamine B and the results were depicted in Scheme 3. When the enol ether **1o** was reacted with compound **2h** in the presence of trifluoroacetic acid in a sealed tube, resulted compound **6** in 77% yield. Further, wilsoniamine B (**7**) can be achieved by employing the known protocol for methyl quaternization of compound **6**.[23b]

CONCLUSION:

In conclusion, we have disclosed a new strategy for the synthesis of thiazoline, dihydrothiazole using urea or thiourea derivatives as nucleophile with methyl enol ethers in good to excellent yields. This method also involves metal free direct synthesis of enureas or thioureas (enamides) derivatives. Further, the applicability of this methodology was illustrated by synthesizing wilsoniamine B marine natural product. This protocol also provides an alternative route for the construction of quaternary center.

Acknowledgments

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☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Graphical Highlights

- Acid mediated synthesis of thiazolines and enamide derivatives from methyl enol ethers.
- Enol ethers acts as an electrophile.
- C-N and C-S bond formation was achieved.
- Application towards wilsoniamine B alkaloid.