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ARTICLE

An Improved One-Pot Multicomponent Strategy for the Preparation of Thiazoline, Thiazolidinone and Thiazolidinol Scaffolds

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A facile multicomponent synthesis of privileged medicinal scaffolds based thiazoline, thiazolidinone and thiazolidinol derivatives has been disclosed. The reaction employs the reaction of primary amine and carbon disulphide in microwave to generate symmetrical thiourea *in situ*. The subsequent addition of 3-bromo-1,1,1-trifluoropropan-2-one, affording the desire product in an efficient one-pot process.

Introduction

Multicomponent reactions (MCRs) are attractive progressively due to their improved efficiency, reduced waste, atom economy, simplicity and rapid access for the synthesis of biologically active compounds[1]. Multicomponent reactions are privileged over conventional multistep sequences owing to redeemable in the costs of reagents, solvents and other resources required for purification and isolation[2]. The greater occurrence of infectious diseases and multi-drug-resistant strains has become a major concern in medicinal area. Therefore, the development of new potential drugs to counteract the advancing resistance is one of the key issues and challenges for medicinal chemistry and related disciplines nowadays. The current scenario highlights the need for discovery and development of new drugs.

In view of the fact that heterocyclic compounds in general, thiazolines, thiazolidinone and thiazolidines exhibit a wide variety of biological activities, the search for new approaches toward the concluding entities with a greater degree of efficiency is of significant importance.

The remarkable physiological activities of thiazolines, thiazolidinone and thiazolidines inspired as target compounds in organic synthesis. The unsaturated 2-imino-1,3-thiazolines exhibit the great attention in pharmaceutical chemistry, due to its important biological activities such as antimicrobial, anti-inflammatory, antihistaminic, antihypertensive, hypnotic, anticonvulsant activity, applicability for the identification of human cells with positive myeloperoxidase reactivity and in agriculture as acaricides, insecticides, plant growth regulators[3,4], inhibits melanin production in a dose dependent manner thus acting as a skin whitening agent[5] **I** (KHG22394, Figure 1) and act as reversible inhibitor of p53 mediated apoptosis and p53 dependent gene transcription[6] **II** (Pft-α, Figure 1). Thiazolidine-4-onethione is a five-membered heterocyclic scaffold, also gain much attraction due to their wide range of applications in medicinal chemistry such as antidiabetic[7], anticancer[8], calcium-channel blocking[9,10] **V** (Figure 1), platelet activating factor (PAF) antagonistic[11], anti-HIV activities[12], hypnotic[13,14], antitubercular[15], cardiovascular[16] **III** (Figure 1) and cyclooxygenase (COX) inhibitory activities[17] **IV** (Figure 1). 2-Imino-1,3-thiazolidines are well recognised for their anti-inflammatory, anodyne, anti-Alzheimer activity, in agriculture as pesticides and protective properties against *γ*-radiation[18-20].

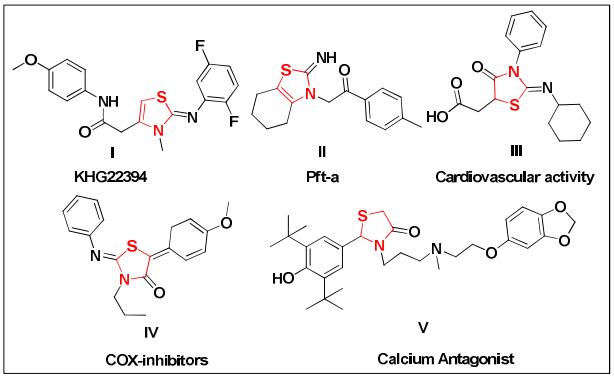

Fig.1. Some biological active scaffolds in relevance of thiazoline and thiazolidinone.

According to the literature, a number of strategies for the synthesis of and thiazolines, thiazolidinone and thiazolidines are known. A first approach toward the synthesis of 2-imino-1,3-thiazolines were published more than a century ago, encompasses with condensation reactions of α-haloketones with thiourea, in neutral or basic medium, or with ammonium thiocyanate also in aqueous

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media catalysed by diammonium hydrogen phosphate or DABCO[21]. In addition to 2-iminothiazolines, the condensation reaction of α-haloketones with thiourea under acidic conditions gave rise to variable amounts of aminothiazoles as side products.

Murru *et al*.[22] reported the one pot reaction of 1,1/-(ethane-1,2-diyl) dipyridinium bistribromide (EDPBT), as a brominating agent, enolizable ketones and disubstituted thioureas. Several alternative methods have been developed, which include use of catalyst such as copper, $TiCl_4$[23-30] and other condensation as well as cycloaddition reactions. Recently, one-pot, three-component reaction of aromatic α-bromoketones, primary amines and phenyl isothiocyanate have been reported for the synthesis of thiazol-2-imines using catalytic amount of triethylamine[31].

The general methods for the synthesis of 2-iminothiazolidin-4-ones includes the cyclization of thiourea with α-halocarboxylic acids, acyl halides, carboxylic esters or the condensation reaction of the appropriate amine, aldehyde and mercapto acids[32-39]. Recently thiazolidinone derivatives have been prepared by using $CuFe_2O_4$ magnetic nanoparticles as a catalyst[40].

Various reports are available for the synthesis of 2-iminothiazolidines, which involves the acid mediated or in the presence of triphenylphosphine and diethyl azodicarboxylate, intramolecular cyclization of *N*-(2-hydroxyethyl) thiourea[41], 2-Imino-1,3-thiazolidines have also been prepared from treatment of aziridines with thiocyanuric acid, reaction of 2-vinylaziridine with phenyl isothiocyanate, condensation of α- halo ketones with thioureas, etc[42-44].

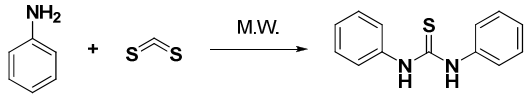
As per the literature reviews, most of the methods uses thiourea or substituted thiourea as a substrates, while in reports of one pot synthesis they require the use catalysts or base and harsh reaction conditions, whereas in aqueous medium obtained the less yield. To improve on these limitations, it is important to investigate regarding improved strategies for the synthesis of thiazoline, thiazolidinone and thiazolidinol derivatives.

Previously, we successfully used *N*,*N*-dimethylformamide (DMF) as a reaction medium and phenylisothiocyanate as substrate to accomplish the synthesis 2-imino-4-(trifluoromethyl)thiazolidin-4-ol derivatives[45]. As our on-going efforts in exploring the new route for heterocyclic synthesis and their biological evaluation[46], herein we report an efficient, one pot synthesis of thiazolidinol, thiazolidinone and thiazoline derivatives using carbon disulphide (CS_2) as substrate under microwave irradiation.

Results and discussion

In order to optimization the reaction condition, we have selected the synthesis of (*Z*)-*N*-(3,4-diphenylthiazol-2(3H)-ylidene)aniline (**4a**) as a model reaction (Table 3, entry a). Initially, the reaction of aniline (1 mmol), Carbon disulphide (1mmol) and 2-bromo-1-phenylethanone (1mmol) was performed in DMF at room temperature but there is no progress of reaction. Later on conventional heating at 90 ^{0}C in DMF for 2 hrs we observed fewer yields (40%) with some side products. Subsequently, in order to improve the reaction efficiency, we carried out the reaction under microwave irradiation and varied the molar ratios of the reactants, when a ratio of 2:1:1 (1:CS_2:3, Scheme 1) was used, the product was isolated in the highest yield in shorter time. The cause for no reaction at room temperature and fewer yield on conventional heating, may be the more time require for formation of thiourea. Most of the literature reports on thiourea notify more time for thiourea formation. So we selected microwave method for the reaction. To further increase the productivity of the reaction, independently, we studied the synthesis of thiourea in various conditions. We attempt the reaction of aniline (2mmol) and carbon disulphide (1mmol) under microwave irradiation in various solvent systems (Table 1). Among the various solvent, reaction proceeds smoothly in *N*,*N*-dimethylformamide (DMF) to give the corresponding thiourea in 98 % yield (Table 1, Entry 2). Further, optimization of reaction condition for thiourea synthesis, we performed the same reaction in *N*,*N*-dimethylformamide (DMF) solvent at various conditions. Surprisingly, under microwave condition we observed good yield (98%) of corresponding thiourea (Table 2, Entry 3). Indication of time required for the thiourea preparation has constituted the focus of our investigations regarding improved strategies for further synthesis. Microwave condition and *N*,*N*-dimethylformamide (DMF) seemed to be the best choice.

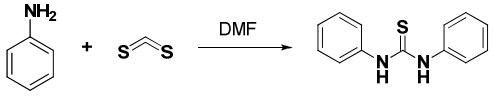
Table 1. Solvent effect on the reaction of aniline and carbon disulphide



Entry	Solvent	Ratio of solvents	Yield(%)[a]
1	THF	–	95
2	DMF	–	98
3	Acetone	–	97
4	DMF : H_2O	2:1	97
5	DMF : H_2O	1:1	94
6	DMF : H_2O	1:2	92
7	Water	–	89
8	Neat	–	85

The reaction was performed with 2mmol of aniline, 1mmol of CS_2, [a]Isolated yield

Table 2. Reaction condition effect on synthesis of substituted thiourea



Entry	Conditions	Time	Yield (%)
1	RT	4 hr	79
2	70 ^{0}C	1 hr	87
3	MW- 100 ^{0}C	7 min	98

The reaction performed with 2mmol of aniline and 1mmol of CS_2 in DMF solvent. [a] Isolated yield.

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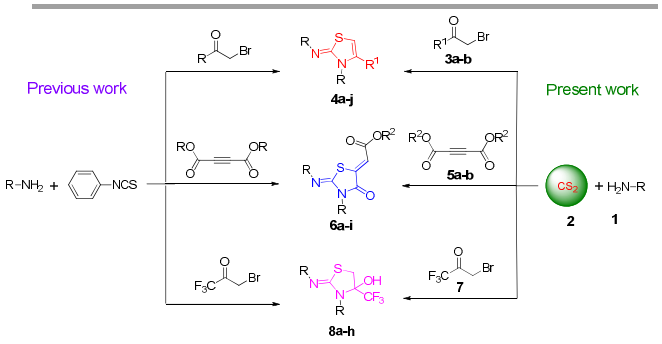
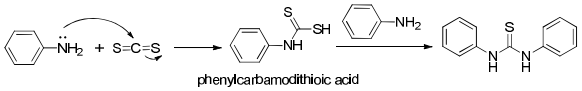
The possible mechanism for thiourea formation is outlined in scheme 2. The reaction may proceed *via* formation of phenylcarbamodithioic acid.



Scheme 1. Comparison of previous work with our strategy.

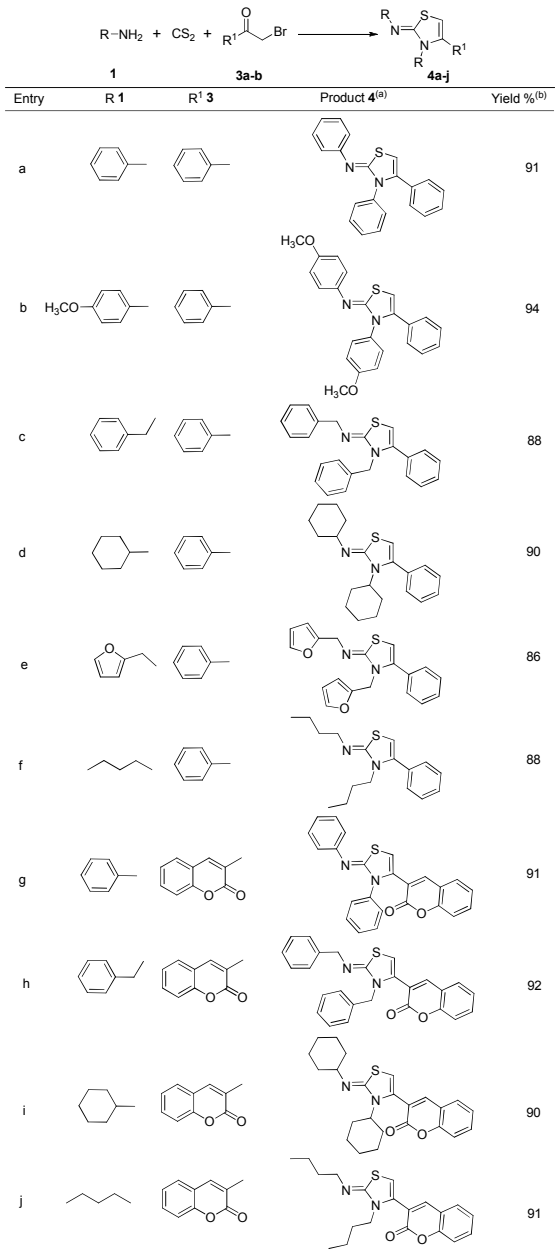


Scheme 2. Plausible mechanism of thiourea formation.

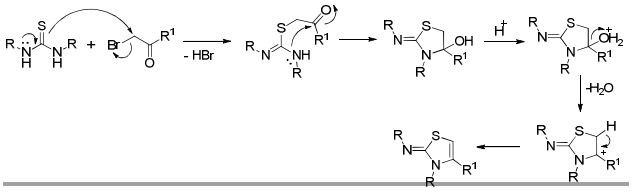
After the optimization, further studied the scope of substrate for this method, different amines subjected to the treatment with CS_2 under microwave irradiation, followed by addition of various bromo acylketones in *N*,*N*-dimethylformamide (DMF) and the results are summarized in Table 3. Remarkably, several primary amines, including aniline, benzylamine, furan-2-ylmethanamine, cyclohexalamine, substituted aniline, butylamine and 2-bromo-1-phenylethanone, 3-(2-bromoacetyl)-2H-chromen-2-one reacted with carbon disulphide affording the corresponding thiazoline derivatives in the form of HBr salt, later neutralized with saturated sodium bicarbonate and achieved desired thiazoline derivatives (**4a-j**) in good to excellent yields (Table 3, entries a-j). The plausible reaction mechanism of formation of product (**4a-j**) is summarized in scheme 3. The reaction proceeds *via* attack of thiocarbonyl group of thiourea on bromomethyl group of bromoacylketones followed by cyclization and dehydration process afforded the product **4a-j**.

During the synthesis of thiazolidinone derivatives, we try to optimize the reaction conditions. The reaction of primary amine (2 mmol) and carbon disulphide (1 mmol) was subjected to microwave irradiation for 5 min. After cooling to room temperature, DMF (3 ml) was added to the reaction mixture and then diethyl but-2-ynedioate (or) dimethyl but-2-ynedioate (1mmol) was added. The reaction mixture was stirred at room temperature for 10–15 min. The reaction proceeded smoothly affording the corresponding thiazolidinone derivatives (**6a-i**) in good to excellent yield (Table 4, entries a-i). Various amines, including substituted aniline, benzylamine, furfulamine, butylamine and diethyl but-2-ynedioate and dimethyl but-2-ynedioate reacted with carbon disulphide to give corresponding thiazolidinone derivatives (Table 4). This method efficiently employed not only for aliphatic and hetero aryl primary amines but also for aromatic primary amines. The proposed reaction mechanism for formation of thiazolidinone derivatives is outlined in scheme 4. The reaction proceed via is situ formation of thiourea followed by the attack of thiocarbonyl group of thiourea on acetylene fragment of diethyl but-2-ynedioate affording the product 6a-i.

Table 3. Synthesis of Thiazoline derivatives.



Reaction was performed with 2mmol of amine,1mmol CS_2 and 1mmol of phenacyl bromide.
[a] All products were characterized by ^1H and ^{13}C NMR, IR and mass spectroscopy.
[b] Yield refers to pure product after column chromatography



Scheme 3. Plausible reaction mechanism of Thiazoline derivatives.

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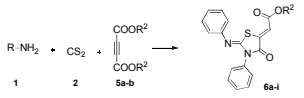
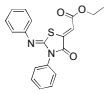
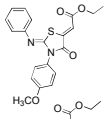
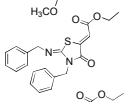
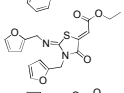
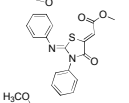
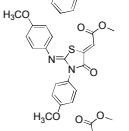
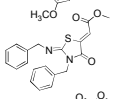
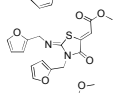
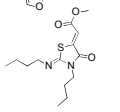
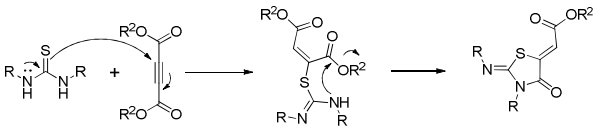
Table 4. Synthesis of thiazolidinone derivatives.



Entry	R 1	R² 2	Product 6[a]	Yield (%)[b]
a		C_2H_5		85
b		C_2H_5		84
c		C_2H_5		90
d		C_2H_5		83
e		CH_3		82
f		CH_3		89
g		CH_3		91
h		CH_3		85
i		CH_3		90

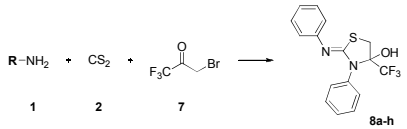
The reaction was perford with 2mmol of amine, 1mmol of CS_2 and 1mmol of diethyl but-2-ynedioate (or) dimethyl but-2-ynedioate
[a] Product was characterized by ^1H and ^{13}C NMR, IR and mass spectroscopy. [b] isolated yield after column chromatography

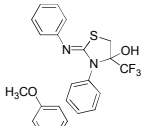
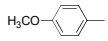
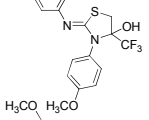
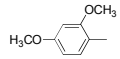
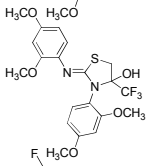
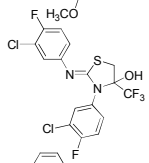
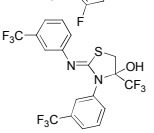
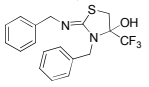
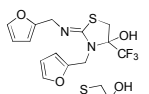
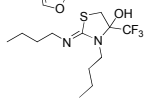


Scheme 4. Plausible reaction mechanism of thiazolidinone derivatives.

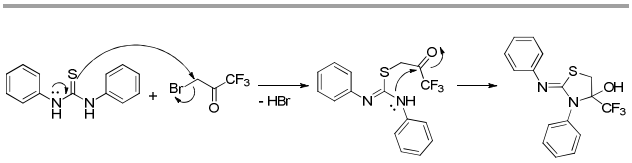
In case of thiazolidinol derivative synthesis, the reaction of primary amine and carbon disulphide performed under optimized microwave condition, followed by dropwise addition of 3-bromo-1,1,1-trifluoropropan-2-one in DMF at room temperature, giving the product good to excellent yield (Table 5, entries 8a-h). Scope of the reaction was investigated for various primary amines including benzylamine, furfulamine, butylamine and substituted anilines. In case of thiazoline product, after cyclization tertiary hydroxyl group in the intermediate undergoes dehydration process. But during the formation of thiazolidinol product, dehydration process was not taking place. This might be due to the electron withdrawing effect of trifluoromethyl group on same carbon. The proposed reaction mechanism of formation thiazolidinol derivatives is summerized in scheme 5. The reaction proceed via thiourea formation followed by the attack of thiocarbonyl group of thiourea on bromomethyl group of 1,1,1-trifluoropropan-2-one to give product 8a-h.

Table 5. Synthesis of thiazolidinol derivatives.



Entry	R	Product 8[a]	Yield (%)[b]
a			90
b			95
c			91
d			80
e			78
f			95
g			92
h			94

Reaction was performed with 2mmol of amine,1mmol CS_2 and 1mmol of 3-bromo-1,1,1-trifluoropropan-2-one. [a] All products were characterized by ^1H and ^{13}C NMR, IR and mass spectroscopy. [b] Yield refers to pure product after column chromatography



Scheme 5. Pausible reaction mechanism of thiazolidinol derivatives.

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All the products were characterized by IR spectroscopy, ^{1}Hand ^{13}C NMR spectroscopy, and mass spectrometry. The structure of **4j** (Table 3, entry h) was confirmed by X-ray crystallography as shown in fig. 2. (CCDC 1410087)[47]. The X-ray structure shows, compound 4j has crystallized in the form of a HBr salt, so we neutralized with saturated sodium bicarbonate to obtained the thiazoline derivatives.

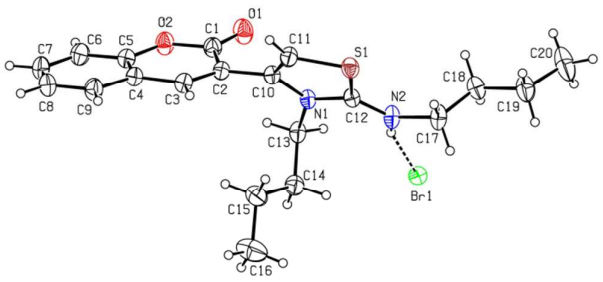

Fig. 2. ORTEP molecular diagram of **4j**

Conclusions

In summary, we have developed a novel, one pot, and versatile method for the synthesis of thiazoline, thiazolidinone and thiazolidinol derivatives via three component reaction of primary amine, carbon disulphide and various bromo acylketones or diethyl but-2-ynedioate (or) dimethyl but-2-ynedioate using microwave technology. The reaction used readily available, inexpensive and harmless precursors. The procedure is extremely useful in synthetic and medicinal chemistry as it provides the desired products in single step process in excellent to good yield.

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47 The supplementary crystallographic data (CIF file) and the respective ORTEP diagram for this compound have been provided in supporting information.

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Graphical Abstract

An Improved One-Pot Multicomponent Strategy for the Preparation of Thiazoline, Thiazolidinone and Thiazolidinol Scaffolds

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A simple three component protocol towards the synthesis of a Thiazoline, Thiazolidinone and Thiazolidinol Scaffolds have been designed and conveniently synthesized with good yield.