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A facile synthesis of novel 3-(aryl/alkyl-2-ylmethyl)-2-thioxothiazolidin-4-ones using microwave heating

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ABSTRACT

(*Z*)-5-(2-(1*H*-Indol-3-yl)-2-oxoethylidene)-3-(aryl/alkyl-2-ylmethyl)-2-thioxothiazolidin-4-ones (**7a–w**) have been synthesized by the Knoevenagel condensation reaction of 3-(aryl/alkyl-2-ylmethyl)-2-thioxothiazolidin-4-ones (**3a–d**) with suitably substituted 2-(1*H*-indol-3-yl)2-oxoacetaldehydes (**6a–g**) under microwave conditions. The thioxothiazolidin-4-ones were prepared from the corresponding aryl/alkyl amines (**1a–d**) and di-(carboxymethyl)-trithiocarbonyl (**2**). The aldehydes (**6a–g**) were synthesized from the corresponding acid chlorides (**5a–g**) using $HsnBu_3$.

Introduction

5-Benzylidene-3-phenyl-2-thioxothiazolidine-4-ones (rhodanine derivatives) represent privileged scaffolds in drug discovery. A survey of recent papers dealing with the pharmacological properties of such compounds reveals that they display a wide range of activities. For example 2-aryl-5-(4-oxo-3-phenethyl-2-thioxothiazolidinylidene methyl)furans (**A**) with molecular weight ≈500 Da exhibit anti-HIV-1 activity[1] as seen in Fig. 1. In a later study, the same group found that 5-((arylfuran/1*H*-pyrrol-2-yl)-methylene)-2-thioxo-3-(3-(trifluromethyl)phenyl)-thiazolidin-4-ones (**B**) exhibited a high potency against infection by laboratory-adapted and primary HIV-1 strains with EC_{50} at low nanomolar levels and inhibiting HIV-1-mediated cell–cell fusion and the trans membrane subunit gp41 six-helix bundle formation.[2] Various 5-substituted rhodanine derivatives have been shown to prevent mildew formation[3] and to exhibit antifungicidal[4] and antipesticidal[5] activities. The 5-benzylidine-3-phenyl-2-thioxo-thiazolidin-4-one core has been shown to inhibit the Jun NH_2-terminal kinase (Jnk) stimulatory phosphatetase-1 (JSP-1).[6] In addition, rhodanine-based molecules have become the popular small-molecule inhibitors of numerous targets such as HCV NS3 protease,[7a] aldose reductase,[7b,c] β-lactamase,[7d] UDP-*N*-acetylmuramate/L-alanine UDP-*N*-acetylmuramate/L-alanine ligage,[7e] antidiabetic agent,[7f] Cathepsin D,[7g] and histidine decarboxylase.[7h]

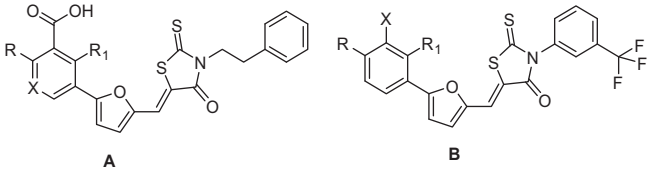

Figure 1. Competitive inhibitor of HIV-1 and JSP-1.

The use of microwave irradiation in the synthesis of small biomolecules is growing in importance.[8] The major benefits of performing reactions under microwave condition are: significant rate enhancements and higher product yields as compared to reactions which run under conventional heating. A key advantage of modern, scientific microwave apparatus is their ability to control reaction conditions precisely, by monitoring temperature/pressure, and reaction times. Since quick reaction times for the synthesis of potentially active biological molecules is crucial to the medicinal community, the use of microwave technology has grown rapidly.[9]

For the past few years, our group has also been preparing and evaluating biologically important compounds using microwave heating.[10] For example, we recently prepared several 5-(2-(1*H*-indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-ones in 89–96% yields using microwave radiation for 10 min at 90 °C. Several of these compounds possessed strong neuroprotecting activity against Alzheimer and Parkinson diseases.[10a]

With these promising results, we have extended our research on biologically active rhodanines for the design and preparation

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Table 1
Screening of solvents, reaction time, and temperature

Solvent	Condition	Time (min)	Yield%
No solvent	1:1; **3a**/**6a**, 80 °C	10	40
No solvent	1:1.2; **3a**/**6a**, 80 °C	10	41
No solvent	1:1.2; **3a**/**6a**, 90 °C	15–20	45–50
Ethanol	1:1; **3a**/**6a**, 80 °C	15	68
Ethanol	1:1; **3a**/**6a**, 90 °C	15	90
Ethanol	1:1.2; **3a**/**6a**, 90 °C	15	98
Acetonitrile	1:1.2; **3a**/**6a**, 90 °C	15	75
DMF	1:1.2; **3a**/**6a**, 90 °C	15	49
Water	1:1.2; **3a**/**6a**, 90 °C	15	Trace
Toluene	1:1.2; **3a**/**6a**, 90 °C	15	Trace
Isopropanol	1:1.2; **3a**/**6a**, 90 °C	15	45
THF	1:1.2; **3a**/**6a**, 90 °C	15	38
n-Butanol	1:1.2; **3a**/**6a**, 90 °C	15	30
DME	1:1.2; **3a**/**6a**, 90 °C	15	Trace
Sulfolane	1:1.2; **3a**/**6a**, 90 °C	15	Trace
NMP	1:1.2; **3a**/**6a**, 90 °C	15	Trace
Dimethylsulfone	1:1.2; **3a**/**6a**, 90 °C	15	Trace
Acetone	1:1.2; **3a**/**6a**, 90 °C	15	30

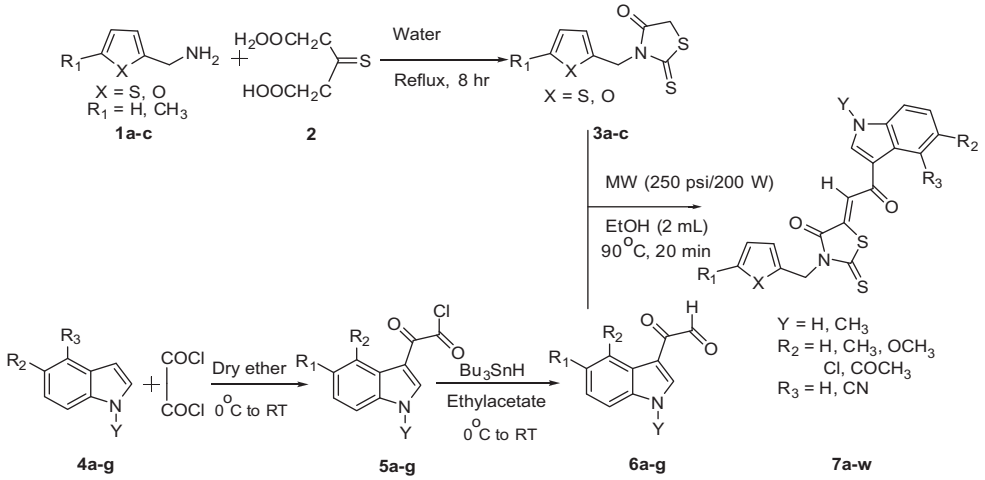
of novel (*Z*)-5-(2-(1*H*-indol-3-yl)-2-oxoethylidene)-3-(alkyl/aryl-2-ylmethyl)rhodanines and report the results herein. We have focused our attention on introducing side-chain linkers attached to *N*-atom of the rhodanine core and substituting the benzene ring with thiophene, furan, and tetrahydrofuran moieties with the hopes of developing rhodanine compounds possessing inhibitory properties against HIV-1 and neuroprotecting ability in the low micro-molar range. We should mention that there is a plethora of literature precedence for Knoevenagel condensation with aryl aldehydes or rhodanine derivatives however, most of the methods suffer from one or other limitations such as requiring harsh reaction conditions, low moderate yields, relatively long reaction time, and a cumbersome experimental process. Among these reported methods, the Knoevenagel reaction has been performed in the presence of a catalyst with various solvents: piperidine in ethanol,[11] tetrabutylammonium bromide in water,[12] sodium acetate in glacial acetic acid,[13] or ethanol[14] and piperidinium benzoate in toluene.[15] The use of microwave irradiation has also been employed with solid inorganic support (Al_2O_3 or KSF) in a domestic microwave oven (multimode cavity)[16] with a complete lack of control of the reaction temperature.[13]

We determined optimum microwave conditions by studying the reaction of 3-(thiophen-2-ylmethyl)-2-thioxo-thiazolidin-4-one **3a** with 2-(1*H*-indol-3-yl)-2-oxoacet-aldehyde (**6a**) using a series of solvents at different reaction times and temperatures. Previously, Knoevenagel condensation reactions have used organic base such as CH_3CO_2Na[14] or piperidene,[11] however our previous experience has shown 2,2,6,6-tetramethyl piperidine to be a superior base in these condensation reactions[10a] and thus was used in the optimizing experiments. As shown in Table 1, optimal microwave-assisted reaction conditions were obtained using a power of 200 W, a pressure of 250 psi, and a ratio of 1/1.2 rhodanine/aldehyde in the presence of a catalytic amount of 2,2,6,6-tetramethyl piperidine in 2 mL of ethanol.

Using these microwave optimal conditions, the synthesis of titled compounds (**7a–w**) by a microwave assisted Knoevenagel condensation of (**3a–c**) with suitably substituted 2-(1*H*-indol-3-yl)-2-oxoacetaldehydes (**6a–g**) was carried out (Scheme 1). The starting 3-(aryl/alkyl-2-ylmethyl)-2-thioxothiazolidin-4-one (**3a–d**) derivatives were prepared from the literature procedures[17a–c] which involved refluxing equimolar quantities of suitably substituted amines and di-(carboxymethyl)-trithiocarbonyls in the presence of 0.5 equiv of potassium carbonate. The 2-(1*H*-Indol-3-yl)2-oxoacetaldehydes (**6a–g**) were synthesized by treating corresponding acid chlorides with $HSnBu_3$..[18] The acid chlorides were prepared by the acylation of indole (or substituted indole) with oxalylchloride.[19]

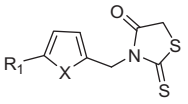
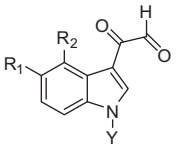
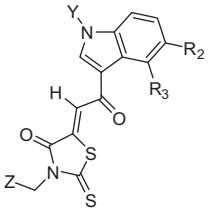
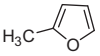
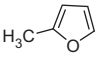
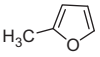
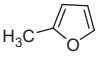
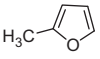
As shown in Table 2, the rhodanine derivatives (**7a–w**) were prepared in excellent yields ranging from 85% to 98% using aldehydes carrying either electron-donating and/or electron-withdrawing groups. On the other hand, yields of **7a–w** using conventional heating for 3 h at 90 °C were significantly lower, ranging from 43% to 80%. The solvent plays an important role in this MW assisted reaction. It is found that ethanol is the best solvent for these types of reaction, may be due to the stabilization of the final product through H-bonding. In addition the starting materials are also soluble in ethanol which makes it a better solvent than water, isopropanol or *n*-butanol. The products **7a–w** were isolated as stable *Z*-isomers which were confirmed by noting that vinyl proton shift in the ^{1}H NMR spectrum occurred around 8 Hz which is similar to those previously reported.[10a] The structures of compounds **7a–w** were further substantiated by, ^{13}C NMR, DEPT-135, HRMS, (see Supplementary data) and IR analyses. For example, IR(KBr) spectra of **7a–w** exhibited absorption bands due to the stretching vibrations of NH group of indole cycles (3200 cm^{-1} range) and displayed characteristic absorption bands of the C=S group (intense band at 1628–1610 cm^{-1} range) and two C=O groups (1720 cm^{-1} range).

In conclusion we have designed and prepared several rhodadine derivatives (**7a–w**) by a microwave-assisted Knoevenagel reaction



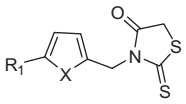
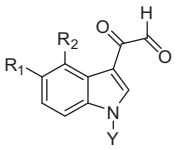
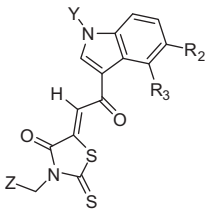
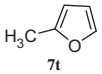
Scheme 1. Schematic representation for the syntheses of **7a–w**.

Table 2
Reaction of various indole based aldehydes with rhodanine derivatives

				Yield[a]	Yield[b]
1	R_1 = H, X = S	R_1 = R_2 = H, Y = H	Z =  **7a**	98	66
2	R_1 = H, X = S	R_1 = R_2 = H, Y = CH_3	Z =  **7b**	95	56
3	R_1 = H, X = S	R_1 = CH_3, R_2 = H, Y = H	Z =  **7c**	98	45
4	R_1 = H, X = S	R_1 = OCH_3, R_2 = H, Y = H	Z =  **7d**	95	48
5	R_1 = H, X = S	R_1 = Cl, R_2 = H, Y = = H	Z =  **7e**	90	44
6	R_1 = H, X = S	R_1 = $COCH_3$, R_2 = H, Y = H	Z =  **7f**	93	56
7	R_1 = H, X = S	R_1 = = H, R_2 = CN, Y = H	Z =  **7g**	85	43
8	R_1 = H, X = O	R_1 = R_2 = H, Y = H	Z =  **7h**	95	67
9	R_1 = H, X = O	R_1 = R_2 = H, Y = CH_3	Z =  **7i**	91	70
10	R_1 = H, X = O	R_1 = CH_3, R_2 = H, Y = H	Z =  **7j**	98	80
11	R_1 = H, X = O	R_1 = OCH_3, R_2 = H, Y = H	Z =  **7k**	96	80
12	R_1 = H, X = O	R_1 = Cl, R_2 = H, Y = H	Z =  **7l**	89	70
13	R_1 = H, X = O	R_1 = H, R_2 = CN, Y = H	Z =  **7m**	83	67
14	R_1 = H, X = O	R_1 = $COCH_3$, R_2 = H, Y = H	Z =  **7n**	98	55
15	R_1 = CH_3, X = O	R_1 = R_2 = H, Y = H	Z =  **7o**	92	60
16	R_1 = CH_3, X = O	R_1 = R_2 = H, Y = CH_3	Z =  **7p**	93	44
17	R_1 = CH_3, X = O	R_1 = CH_3, R_2 = H, Y = H	Z =  **7q**	97	80
18	R_1 = CH_3, X = O	R_1 = OCH_3, R_2 = H, Y = H	Z =  **7r**	96	61
19	R_1 = CH_3, X = O	R_1 = Cl, R_2 = H, Y = H	Z =  **7s**	81	51

(*continued on next page*)

Table 2 (*continued*)

				Yield[a]	Yield[b]
20	$R_1 = CH_3$, X = O	$R_1 = COCH_3$, R_2 = H, Y = H	Z =  **7t**	95	55
21	R_1 = H, X = O	$R_1 = R_2$ = H, Y = H	Z =  **7u**	93	79
22	R_1 = H, X = O	$R_1 = OCH_3$, R_2 = H, Y = H	Z =  **7v**	94	49
23	R_1 = H, X = O	$R_1 = COCH_3$, R_2 = H, Y = H	Z =  **7w**	89	60

[a] Isolated yield. All the compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS analyses.
[b] Conventional heating for 3 h at 90 °C.

in excellent yields using a reaction time of only 15 min at 90 °C. The mild workup conditions, good to excellent yields, and easily available substrates make this reaction an attractive method for the preparation of these biologically important molecules. We are currently investigating the synthesis of a number of other rhodanine based drug molecules by this method. Detailed biological activity studies (antibacterial, antifungal, anticancer, and neuroprotective kinase inhibitor activity) of these important compounds are being carried out. Preliminary results indicate that many of these compounds exhibit excellent neuroprotective properties. Their biological properties will be published in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.064.

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