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A practical access to novel 2-amino-5-arylidene-1,3-thiazol-4(5*H*)-ones via sulfur/nitrogen displacement under solvent-free microwave irradiation

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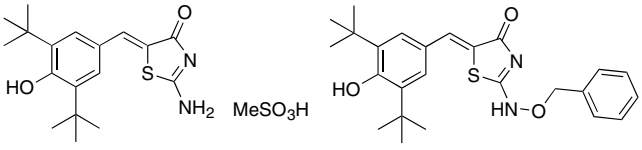
Abstract—A new effective approach to the synthesis of a small library of 2-amino-5-arylidene-1,3-thiazol-4(5*H*)-ones was reported using solvent-free reaction conditions under microwave irradiation. In the first step, rhodanines were subjected to Knoevenagel condensation with aryl aldimines according to a facile one-pot protocol. Then the (5*Z*)-5-arylidene rhodanine derivatives were transformed directly into the corresponding 2-amino-1,3-thiazol-4(5*H*)-ones by sulfur/nitrogen displacement reaction under microwaves with retention of configuration and good overall yields.

1. Introduction

The 2-amino-5-arylidene-1,3-thiazol-4(5*H*)-ones and their 5-arylidene rhodanine precursors 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, compounds containing 2-amino-5-arylidene-1,3-thiazol-4(5*H*)-one moiety are reported to have antiviral,[1] antimicrobial,[2] cardiotonic[3] and anti-inflammatory[4] effects. Among the anti-inflammatory agents, Darbufelone® mesilate[5] and PD-0167570 represented in Figure 1 are used as dual inhibitor[6] of cellular prostaglandin ($PGF_{2\alpha}$) and leukotriene production (LTB_4). Additionally, Darbufelone® is orally active in animal models of inflammation and arthritis,[7] and is nonulcerogenic at very high doses.



Darbufelone PD-067570

Figure 1. Biologically active 2-amino-1,3-thiazol-4(5*H*)-one lead compounds.

For the preparation of 2-amino-5-arylidene-1,3-thiazol-4(5*H*)-one derivatives, various routes and methods have been developed[8] from acyclic building blocks or by functionalization of the thiazolone core. In the second case, the thiazolone nucleus was prepared from acyclic or cyclic precursors. Most commonly, the Knoevenagel reaction[9] on rhodanine followed by the addition of amine[10] or after activation via thioether[6] constituted a practical route to 2-amino-5-arylidene-1,3-thiazol-4(5*H*)-ones. On the other hand, this sequence can be reversed by first condensing rhodanine with an amine and then reacting it with an aldehyde.[11]

The utility of microwave irradiation[12] (μw) to carry out organic reaction has now become a regular feature. The

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main benefits of performing the reaction under microwave conditions are the significant rate-enhancements and the higher product yields that can be observed. A key advantage of modern scientific microwave apparatus is the ability to control reaction conditions very specifically, monitoring temperature–pressure and reaction times. It is clear that the application of microwave technology to rapid synthesis of potential biological molecules is a useful tool for medicinal community, for whom reaction speed is of a great importance.[13] Here, we wish to disclose the development and implementation of a methodology allowing for the solventless synthesis of novel 2-amino-5-arylidene-1,3-thiazol-4(5*H*)-ones under microwave irradiation reaction conditions.

We have investigated the preparation of novel 2-amino-5-arylidene-1,3-thiazol-4(5*H*)-ones according to Scheme 1. In the first step, for the Koevenagel condensations from aryl aldehydes **2** and rhodanine derivatives **1**, there have been many methods employed in the literature. Many of these methods suffer from one or other limitations such as requiring harsh reaction conditions, low moderate yields, relatively long reaction time and 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,[14] tetrabutylammonium bromide in water,[15] sodium acetate in glacial acetic acid[16] or in ethanol[17] and piperidinium benzoate in toluene.[18] 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)[19] but without control of the reaction temperature.

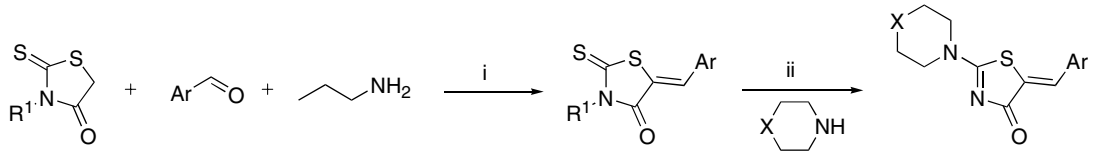
In this context, we decided to investigate the reactivity of commercial rhodanine **1a** (R = H) and readily available derivatives **1**(**b**,**c**) (**1b**: R = Me[20] and **1c**: R = Ph[21]) with a series of aryl aldehydes **2**(**a**–**i**) using solvent-free conditions under microwave irradiation. The microwave instrument (Synthewave® 402 reactor[22]) comprises a monomode (sometimes also called single-mode) microwave cavity that operates at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W. The reaction temperature in the microwave cavity was measured with an IR captor[23] (infrared thermometry) and the software algorithm regulates the microwave output power so that the preselected maximum temperature is maintained for the desired reaction/irradiation time.

Usually, the Knoevenagel reaction on rhodanine needs the presence of an organic base (CH_3CO_2Na[17] or piperidine[14]) and in order to be able to carry out this condensation in avoiding these conditions, we planned to employ aryl aldimines in place of aryl aldehydes. Using propylamine **3** as a volatile primary amine, we screened a range of reaction parameters in order to find the optimum conditions for one-pot tandem reaction. We were particularly interested in the effects of microwave irradiation time and various powers. During this study, the experiments revealed that the optimal reaction conditions were obtained after 30 min at 60 °C (power 70 W) with a stoichiometry of 1/1.2 of aryl aldehyde **2**/propylamine **3** to generate in situ the corresponding aryl aldimine followed immediately by the addition of 1 equiv of rhodanine **1**. The resulting reaction mixture was submitted again to microwave irradiation at 80 °C (with a power of 80 W) for 30 min. After the second irradiation period, the reaction vial was cooled rapidly to ambient temperature by compressed air (gas jet cooling) and the crude reaction mixture was washed with AcOEt or cooled EtOH. Having found suitable conditions for this one-pot tandem reaction (aldimine synthesis/Knoevenagel condensation), we proceeded to screen a range of different aryl aldehydes **1**(**a**–**i**), the results being shown in Table 1.

As can be seen from inspection of the data presented in Table 1, the 5-arylidene rhodanine derivatives **4**(**a**–**l**) were prepared in yields ranging from 65% to 85% with the same reaction time from various aryl aldehydes **1**(**a**–**i**) carrying a variety of electron-donating substituents (excepted for **1i**). The structures of compounds **4**(**a**–**l**) were substantiated by ^1H, ^{13}C NMR and HRMS analyses[24] and only the thermodynamically more stable *Z*-isomers were obtained.[25]

With the 5-arylidene rhodanine derivatives **4** in hand, we designed a strategy for the preparation of the targeted 2-amino-5-arylidene-1,3-thiazol-4(5*H*)-one **6**. Commonly, the synthesis of 2-amino-thiazol-4-one involves activation of the C=S bond of rhodanine derivative via the thioether intermediate that subsequently undergoes a thioalkyl/nitrogen displacement with a primary amine.[6b,26] Owing to the nature of the heteroatom (N, S) in the rhodanine moiety, the molecule presents a thione-thiol tautomerism[27] in homogeneous solution phase and reaction with an halogenoalcane gave the corresponding *S*-alkyl 1,3-thiazol-4(5*H*)-one together with *N*-alkyl rhodanine derivative as a side product.[28]

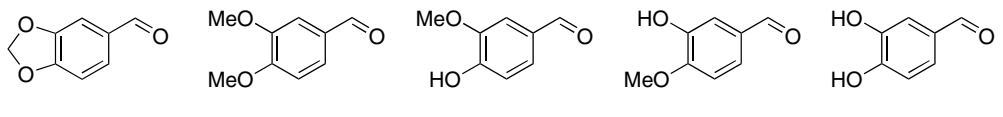
In order to be able to carry out such sulfur/nitrogen displacement in a faster and more efficient way—avoiding



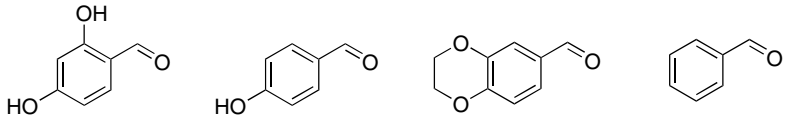
Scheme 1. Reagents and conditions: (i) **2** 1 equiv, **3** 1.2 equiv, 60 °C, 70 W, μw, 30 min (Synthewave® 402 reactor), then **1** 1 equiv, 80 °C, 80 W, μw, 30 min; (ii) **5** 1.2 equiv, 80 °C, 80 W, μw, 30–60 min.

Table 1. Results for the preparation of 5-arylidene rhodanine derivatives **4**(**a**–**l**) under solvent-free microwave irradiation

Product	R^1	Starting aldehyde **1**	Mp (°C)	Yield[a] (%)
4a	H	**1a**	246–250	65
4b	Me	**1a**	210–212	78
4c	C_6H_5	**1a**	202–204	79
4d	H	**1b**	232–234	76
4e	H	**1c**	222–224	84
4f	H	**1d**	220–222	85
4g	H	**1e**	210–212	82
4h	H	**1f**	230–232	80
4i	H	**1g**	240–242	75
4j	H	**1h**	250–252	70
4k	Me	**1i**	179–181	72
4l	C_6H_5	**1i**	196–198	81



1a **1b** **1c** **1d** **1e**



1f **1g** **1h** **1i**

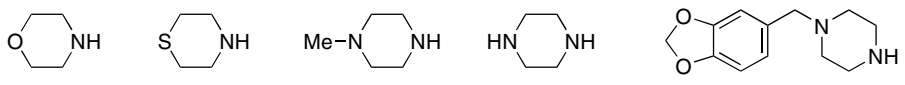
[a] Yield of isolated product.

the synthesis of the thioether intermediate—we continued to examine the influence of microwave irradiation on a neat mixture of 5-arylidene rhodanine **4** and amino reagent **5**. For this study, the polar cyclic secondary amines employed were, morpholine **5a**, thiomorpholine **5b**, 1-methylpiperazine **5c**, piperazine **5d** and 1-piperonylpiperazine **5e**. Reaction optimization for the preparation of compounds **6** consisted in varying the reaction temperature (70, 80, 90 and 100 °C), the power for microwave irradiation (70, 80 and 90 W), the reaction concentration (ratio **5**/**4** from 1.5 to 2) and the reaction time (from 10 to 60 min). After performing the test reaction, the experiments revealed that the optimal ratio **5**/**4** was obtained with 1.2 equiv of amino reagent **5** and for the other parameters, the results under microwave irradiation are presented in Table 2. It is noteworthy that for safety reasons, a 4-min. heating ramp was performed before the temperature was maintained at the selected maximum of 80 °C (power 80 W).

As seen from the results of Table 2, the reaction time is dependent upon the nature of the cyclic secondary

Table 2. Results for the preparation of 2-amino-5-arylidene-1,3-thiazol-4(5*H*)-one **6**(**a**–**i**) from 5-arylidene-rhodanine **4** and reagents **5**(**a**–**e**) by sulfur/nitrogen displacement under solvent-free microwave irradiation

Product	Starting reagents		Reaction time (min)	Yield[a] (%)	Overall yield[d] (%)
	4	**5**			
6a	**4a**	**5a**	20[b]	96	62
6b	**4a**	**5b**	30[b]	80	52
6c	**4a**	**5c**	60[b]	84	55
6d	**4d**	**5a**	25[b]	64	49
6e	**4e**	**5a**	20[b]	86	72
6f	**4a**	**5d**	60[b]	78	51
6g	**4f**	**5a**	20[b]	88	75
6h	**4a**	**5e**	30[c]	75	49
6i	**4d**	**5b**	35[b]	78	59



5a **5b** **5c** **5d** **5e**

[a] Yield of isolated product.
[b] Reaction temperature: 80 °C (80 W obtained from Synthewave® 402 reactor).
[c] Reaction temperature: 100 °C (80 W).
[d] Yield of isolated product after Knoevenagel and S/N displacement reactions under microwave irradiations.

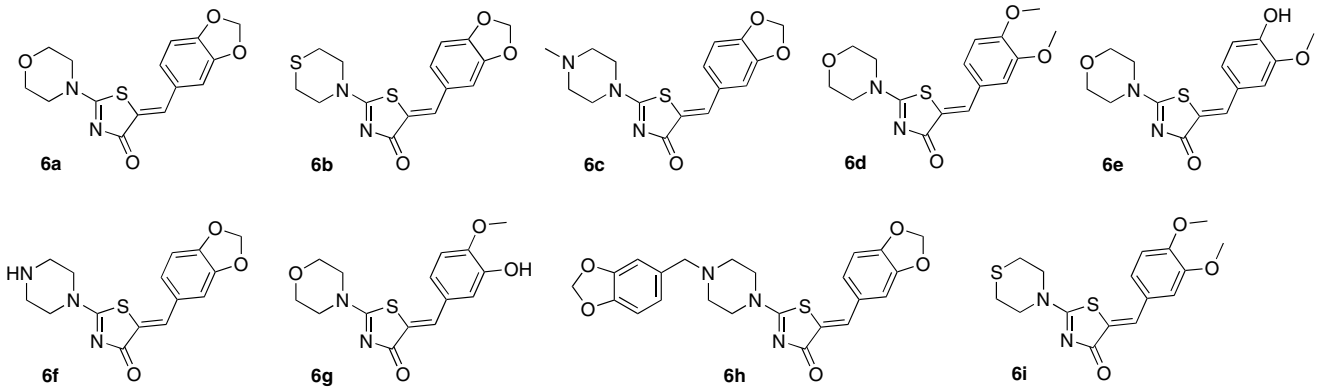


Figure 2. Small library of 2-amino-5-arylidene-1,3-thiazol-4(5*H*)-one **6**(**a**–**i**) obtained after sulfur/nitrogen displacement under solvent-free microwave irradiations.

amine **5**. For example, at 80 °C the use of morpholine **5a** requires a reaction of 20–25 min, 30–35 min for thiomorpholine **5b** and 60 min for reagents **5**(**c**,**d**), but with the 1-piperonylpiperazine **5e** it was necessary to heat at 100 °C (reaction time: 30 min). As illustrated in Figure 2, the versatility of the solvent-free sulfur/nitrogen displacement[29] reaction under microwave irradiation[30] was demonstrated through the preparation[31] of a small library of nine (5*Z*)-2-amino-5-arylidene-1,3-thiazol-4(5*H*)-one[32] **6**(**a**–**i**) in yields ranging from 64 to 96 and the overall yields from 49% to 75%.

2. Conclusion

In conclusion, new (5*Z*)-2-amino-5-arylidene-1,3-thiazol-4(5*H*)-ones bearing two diversity points have been developed according to a solvent-free microwave irradiation protocol. To our knowledge, this new approach has never been reported and may be a complement to those existing in the literature. This solvent-free practical access under microwave involves in the first step a one-pot tandem process (aldimine synthesis/Knoevenagel condensation) for the stereocontrolled obtention of 5-arylidene rhodanine derivatives followed by a sulfur/nitrogen displacement reaction for a straightforward preparation of 2-amino-5-arylidene-1,3-thiazol-4(5*H*)-ones with retention of configuration in good yields and high purity. Although a limited number of different and representative susbstituents on the 1,3-thiazol-4(5*H*)-one cores are represented here, it is obvious that a much larger diversity can be easily achieved. We are currently exploring the scope and the potential of this solvent-free microwave protocol for the synthesis of specific targets that will be more reliable for biological screening in a drug discovery program.

Acknowledgements

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23. Temperature measured by an IR captor: Prolabo, French Patent 622 410, 14669 Fr, 1991.
24. *Selected spectral data of* (*5Z*)-*5*-(*1,3-benzodioxol-5-ylmethylene*)-*2-thioxo-1,3-thiazolidin-4-one* (**4a**): Yield = 65% from AcOEt. Yellow needles, mp = 246–250 °C. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ: 6.13 (s, 2H, OCH_2O); 7.11 (m, 3H, $J = 8.7$ Hz, H-2, H-3, H-6, Ar); 7.54 (s, 1H, =C*H*); 13.74 (br s, 1H, N*H*). ^{13}C NMR (300 MHz, $(CD_3)_2SO$) δ: 102.1 (OCH_2O); 109.2 (C-2′, Ar); 109.4 (C-5′, Ar); 122.8 (*C*=CH, C-5); 126.6 (C-6′, Ar); 127.1 (C-1′, Ar); 131.8 (=*C*H); 148.2 (C-4′, Ar); 149.6 (C-3′, Ar); 169.3 (C-4, *C*=O); 195.3 (C-2, *C*=S). HRMS, *m/z*: 264.9864 found (calculated for $C_{11}H_7NO_3S_2$, M^+ requires 264.9867).
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28. Reaction in solution phase between commercial rhodanine and benzyl bromide afforded a ratio of 4:1 for sulfur/nitrogen alkylation, see Ref. 8.
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30. *General procedure for the synthesis of 2-amino-5-arylidene-1,3-thiazol-4*(*5H*)*-one* **6** *under solvent-free microwave irradiation*: In a cylindrical quartz reactor (Ø = 1.8 cm) was placed a mixture of compound **4** (10 mmoles) and cyclic amine **5** (12 mmoles). The reactor was then introduced into a Synthewave® 402 Prolabo microwave reactor. The stirred mixture was irradiated (after a ramp of 4 min from 20 to 80 °C) at 80 °C (Power level: 30%, 90 W) with appropriate reaction time (from 20 to 60 min). After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and ethanol (20 mL) was added in the cylindrical quartz reactor. The resulting insoluble product **6** was filtered and dried under high *vacuum* for 2 h.
31. **CAUTION**: Owing to elimination of hydrogen sulfide during the sulfur/nitrogen displacement reaction, the experiments in the microwave reactor were realized under ventilated extractor hood.
32. *Selected spectral data for* (*5Z*)-*5*-(*1,3-benzodioxol-5-ylmethylene*)-*2-morpholin-4-yl-1,3-thiazol-4*(*5H*)*-one* (**6a**): Yield = 96% from EtOH. Yellow needles, mp = 250–252 °C. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ: 3.73 (m, 4H, CH_2N); 3.90 (m, 2H, CH_2O); 6.10 (s, 2H, CH_2O); 7.04 (d, 1H, $J = 8.1$ Hz, H-6′, Ar); 7.15 (d, 1H, $J = 8$ Hz, H-5′, Ar); 7.17 (d, 1H, $J = 7.9$ Hz, H-6′, Ar); 7.58 (s, 1H, =C*H*). ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ: 66.06 (CH_2N); 74.40 (CH_2O); 102.2 (CH_2O); 109.1 (C-2′, Ar); 109.4 (C-5′, Ar); 113.9 (*C*=CH, C-4); 125.1 (C-6′, Ar); 126.9 (C-1′, Ar); 130.6 (=*C*H); 148.6 (C-4′, Ar); 149.2 (C-3′, Ar); 174.9 (C-5, C=O). HRMS, *m/z*: 318.0688 found (calculated for $C_{15}H_{14}N_2O_4S$, M^+ requires 318.0674).