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Microwave assisted tandem reactions for the synthesis of 2-hydrazolyl-4-thiazolidinones

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Abstract

A tandem method for the synthesis of 2-hydrazolyl-4-thiazolidinones (**5**) from commercially available materials in a 3 component reaction has been developed. The reaction connects aldehydes, thiosemicarbazides and maleic anhydride, effectively assisted by microwave irradiation. The synthesis of a new type of compound, 2-hydrazolyl-5,5-diphenyl-4-thiazolidinone (**7**), obtained by treatment of thiosemicarbazone with benzil in basic media is also reported. HOMO/LUMO energies, orbital coefficients and charge distribution were used to explain the proposed reaction mechanism.

Keywords

2-hydrazolyl-4-thiazolidinones; 2-hydrazolyl-5; 5-diphenyl-4-thiazolidinones; microwave; tandem reactions

4-Thiazolidinones are an important group of heterocycles found in numerous natural products and pharmaceuticals.[1] In particular, 2-hydrazolyl-4-thiazolidinones (**5**) are a class of compounds that combine thiosemicarbazones with 4-thiazolidinones, two building blocks with interesting biological activities. For example, *Trypanosoma cruzi*,[2] *Plasmodium falciparum*3 and antitumor[4] activities have been described for thiosemicarbazones, and COX-2 inhibition, [5] anti-HIV,[6] and antibacterial[7] effects as well as human chondrocyte antidegenerative[8] properties have been found for 4-thiazolidinones. In addition, the combination of these two pharmacophores has been used to exhibit anti-*Toxoplanma Gondii*,[9a] antimicrobial,[9b] antiviral, [10] and antifungal properties.[11]

Among the reported methods for 2-hydrazolyl-4-thiazolidinone synthesis is a 2 step sequence: 1) a reaction between aldehydes (**1**) and thiosemicarbazides (**2**) to give thiosemicarbazones (**3**); 2) a thia-Michael addition of thiosemicarbazones (**3**) to maleic anhydride in dry PhMe and DMF at reflux to give the hydrazolyl-4-thiazolidinone (**5**) (Scheme 1).[9]

As a part of our search for new biologically active heterocyclic compounds, we focused on the possibility of optimizing this procedure by developing a tandem microwave-assisted reaction sequence.

Multi-step or cascade reactions can be defined as the combination of two or more reactions in a specific order that occur in one pot.[12] They are very attractive due to their ease of setup. In

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traditional single-step processes, the reaction and product isolation are carried out independently and repeatedly to synthesize the target compounds. The former process allows a minimization of waste, and, compared to stepwise reactions, the amount of solvent, reagents, adsorbents, and energy is extensibly decreased.[13]

The use of microwave ovens to perform organic synthesis has received a great deal of attention over the last 10 years. Several publications have shown that microwave irradiation can circumvent the need for prolonged heating,[14] and it is generally accepted that this source of energy minimizes side reactions and accelerates the rate of chemical reactions.[15]

Herein, we wish to report an efficient tandem procedure for the synthesis of 2-hydrazolyl-4-thiazolidinones under microwave conditions. Different solvents and various reaction equivalents were explored until we obtained good isolated yields of thiazolidinones (Scheme 2, Table 1). Microwave heating for the synthesis of thiazolidinone **5a** resulted in a significantly better yield compared to thermal conditions (75% vs 40%, entries 2 and 1, Table 1). Microwave irradiation also allowed for a faster conversion .

For tandem reactions, the best yields were obtained when a solvent mixture of PhMe/DMF (1:1) was used. Thiazolidinone **5a** was prepared in 68% yield (54% considering both reactions) using a stepwise sequence, and in 82% yield under tandem conditions (entries 3 and 4, Table 1). We found that a tandem sequence was more efficient than a stepwise conversion under microwave irradiation.

The optimal conditions for the microwave assisted tandem sequence were determined to be a mixture of PhMe/DMF (1:1) as a solvent, with catalytic p-TsOH and an excess of maleic anhydride (5 eq.) at 100–120 °C (Scheme 3).[16]

Under optimized microwave conditions, a range of aromatic and some aliphatic aldehydes were converted to the desired heterocycles (Table 2). Aromatic aldehydes provided good yields from 45 to 82%, at 120 °C after a 6–12 min reaction time, except for 2-thiophenecarboxaldehyde where the yield dropped to 33%, probably due to the formation of polymeric materials derived from the starting material (entries 1 to 8, Table 2). The reaction seems to be independent of electron withdrawing or electron donating substitutions in the aldehydes (entries 1 and 3, Table 2).

For aliphatic aldehydes, we found that the optimum temperature was 100 °C; otherwise polymerization products were obtained. Compounds **5j** and **5k** were thus isolated in 34% and 64% yield, respectively (entries 9 and 10, Table 2).

The reactivity of thiosemicarbazone **3g** with different Michael acceptors was also investigated. The reaction of thiosemicarbazone **3g** with methyl acrylate[17] or methyl cinnamate[18] did not produce the expected 6-membered 1,3-thiazin-4-one.

Furthermore, we explored the reaction of thiosemicarbazones **3e** and **3g** with benzil **9** as the electrophile. It is well known that ureas and thioureas react with benzil **9** to give 4-imidazolidinones through a benzilic acid rearrengenment.[19] Barbainte and coworkers reported recently the reaction of thiosemicarbazide (**2**) with benzil to give 1,2,4-triazin-3-thione. The formation of the 6-membered ring can be explained by the nucleophilic attack of both N_1 and N_4 in compound **2** to the benzil carbonyl groups.[20] Our results indicate that the reaction of thiosemicarbazone **3** with benzil **6** in KOH/DMSO under microwave conditions led to 2-hydrazolyl-5,5-diphenyl-4-thiazolidinones **10e**, and **10g** in 45% and 22% yield, respectively (Scheme 4).[21] This heterocycle was previously unknown and was fully characterized. The HMBC experiment revealed a cross-peak between the N-H proton and the carbonyl carbon at C_4, thus confirming the regiochemistry of the reaction.

With the goal of rationalize how this reaction proceeded, we undertook a frontier orbital analysis using the semi-empirical parametrization PM3.[22] Table 3 shows HOMO/LUMO energies, coefficients and charge distributions calculated for model compounds. The HOMO/LUMO energy gap is small and it would seem that the reaction with thiosemicarbazone and benzil is kinetically favored and frontier orbital control, and not charge control, should govern the process.

The proposed mechanism for the formation of 2-hydrazolyl-5,5-diphenyl-4-thiazolidinone **7** is depicted in Scheme 5. Based on HOMO/LUMO energies and orbital coefficients, the first step should be the nucleophilic attack of S to C_1, one of the two carbonyl groups present in benzil, to form the tetrahedral intermediate **8**. This intermediate proceeds by nucleophilic attack of N to C_2 to give intermediate **9**, in similar fashion to imidazoline formation.[23]

According to our results, the diol **9** undergoes a phenyl group migration, from C_1 to C_2, where the largest LUMO coefficient is located (entry 3, Table 3), which is in agreement with the observed regiochemistry, pathway a. Even though intermediate **10** was proposed by Butler and coworkers as the most favorable for phenyl group migration in the synthesis of imidazolines, in our case intermediate **10** would led to 5-thiazolidinone **11**, which was never isolated.

In summary, in this investigation we explored the microwave-mediated tandem reactions of aldehydes, thiosemicarbazones and maleic anhydrides to produce 2-hydrazolyl-4-thiazolidinones, with yields ranging from 33 to 82%. The advantages in the use of this methodology are shorter time reactions, higher yields, and a minimization of synthetic operations, solvent use, and waste generation.

When we investigated the scope of the tandem synthesis for hydrazolyl-4-thiazolidinones **5**, we were able to demonstrate that the process is general for aromatic and aliphatic aldehydes; however, the use of different types of Michael acceptors has not yet been accomplished. As an important part of this work, we also present the synthesis of 2-hydrazoyl-5,5-diphenyl-4-thiazolidinone **7**, a new class of 4-thiazolidinones. We propose a mechanism for the heterocycle formation based on a benzilic acid rearrangement promoted by thiosemicarbazone.

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16. Typical procedure for thiazolidinone preparation (**5c**): To a stirred solution of *p*-*N*,*N*-dimethylamine benzaldehyde (300 mg, 2.0 mmol) in toluene (1 mL) and DMF (1 mL) were added thiosemicarbazide (220 mg, 2.4 mmol), *p*-toluene sulfonic acid (30 mg, 0,2 mmol,) and maleic anhydride (987 mg, 10.0 mmol). The reaction mixture was heated in a stirred microwave vial for 9 min at 120 °C (200 W), poured into water (30 mL) and extracted with ethyl acetate (3 ×30 mL). The combined organic layers were dried (Na_2SO_4) filtered and concentrated. The residue was finally recrystallized from methanol to give **5c** (527 mg, 82 % yield) as a yellow solid: mp 278–279 °C: ^{1}H NMR (400 MHz, D_2O/K_2CO_3) δ 2.42 (dd, J_2 = 11.7, J_3 = 16.2 Hz, 1 H), 2.93 (s, 6 H), 3.06 (dd, J_2 = 4.1, J_3= 16.2 Hz, 1 H), 4.22 (dd, J_1 = 4.1, J_2 = 11.7 Hz, 1 H), 6.88 (d, *J* = 9.0 Hz, 2 H), 7.61 (d, *J* = 9.0 Hz, 2 H), 8.20 (s, 1 H); ^{13}C NMR (100MHz, D_2O/K_2CO_3) δ 40.02, 41.90 (C_{endo}), 41.99 (C_{exo}), 49.90, 113.44, 122.80, 129.22, 152.83, 155.88, 161.05, 178.95 (C_{exo}), 179.37 (C_{endo}), 190.77 (COOH); HRMS calculated for $C_{14}H_{16}N_4O_3S$ [M^+-H]: 319.0865, found: 319.0859.
17. Under the following reaction conditions: methyl acrylate acid, **3h**, EtOH, μW, K_2CO_3, 120 °C, 15 min or EtOH, KOH, μW 120 °C, 15 min, no product was observed.
18. Under the following reaction conditions: methyl cinnamate, **3h**, PhMe, μW 120 °C, p-TosOH 19 min, no product was observed.
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21. To a stirred solution of 4-methoxybenzylidene thiosemicarbazone **3g** (177 mg, 0.91 mmol) in DMSO (1.5 mL) were added benzil (150 mg, 0.60 mmol) and KOH 1.2 M (0.3 mL, 0.36 mmol). The reaction mixture was heated in a microwave for 10 min at 120 °C (200 W) with stirring, poured into water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) filtered and concentrated. The residue was finally purified by chromatography on SiO_2 (AcOEt/Hexanes, 1:4) to give compound **10g** (80 mg, 22%) as a white solid: mp 192.5–193.1 °C; ^{1}H NMR (400MHz, $CDCl_3$) δ 3.85 (s, 3 H), 6.94 (d, *J* = 8.8 Hz, 2 H), 7.36–7.42 (m, 10 H), 7.81 (d, *J* = 8.8 Hz, 2 H), 9.08 (s, 1 H), 9.10 (s, 1 H_{NH}). ^{13}C NMR (100 MHz, $CDCl_3$) 55.41, 71.36, 114.25, 125.29, 127.01, 127.56, 128.69, 129.01, 130.64, 137.60, 162.91, 169.73, 180.14; HRMS calculated for $C_{14}H_{16}N_4O_3S$ [M^++Na]: 424.1081, found: 424.1090.
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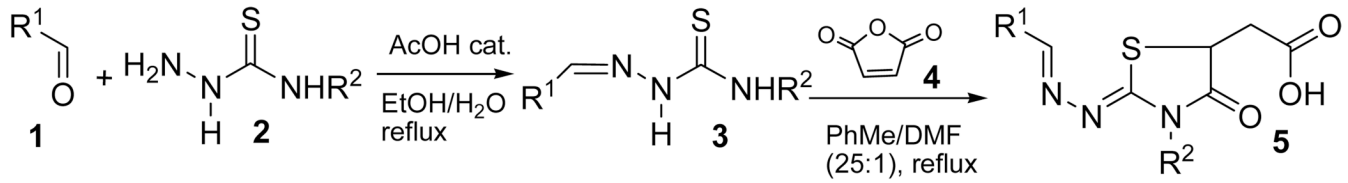
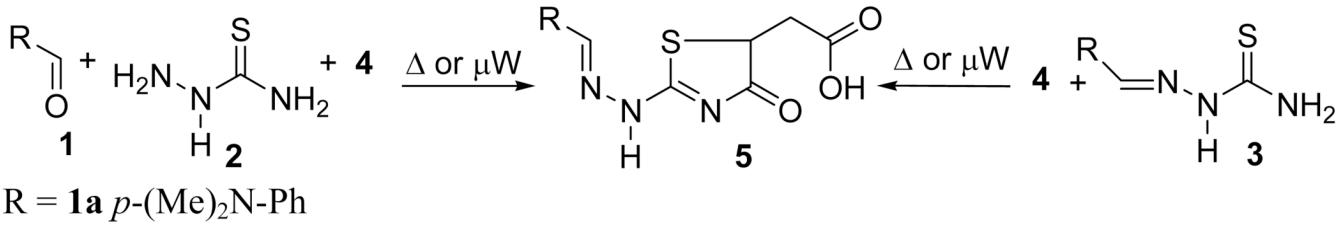
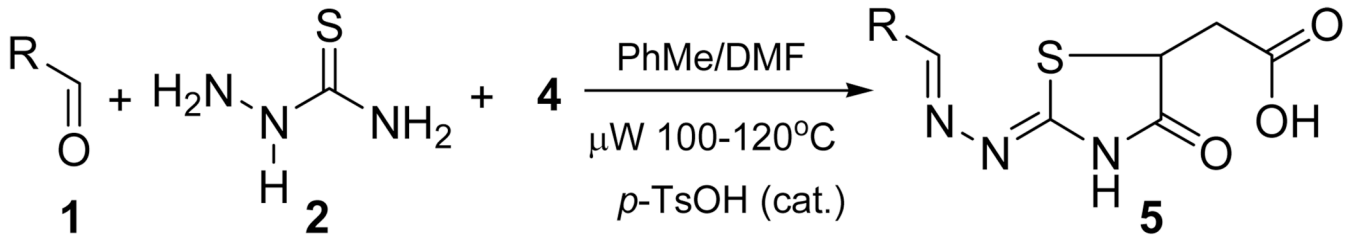


Scheme 1.
Stepwise 2-hydrazolyl-4-thiazolidinone synthesis under conventional conditions.

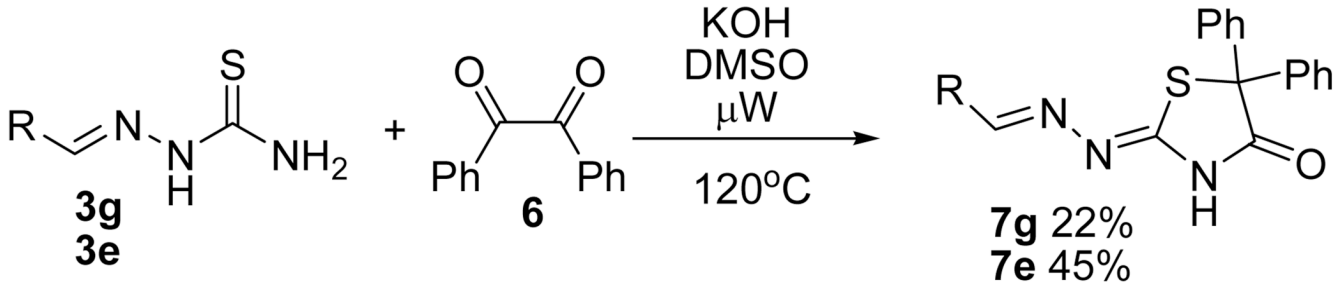


R = **1a** *p*-$(Me)_2$N-Ph

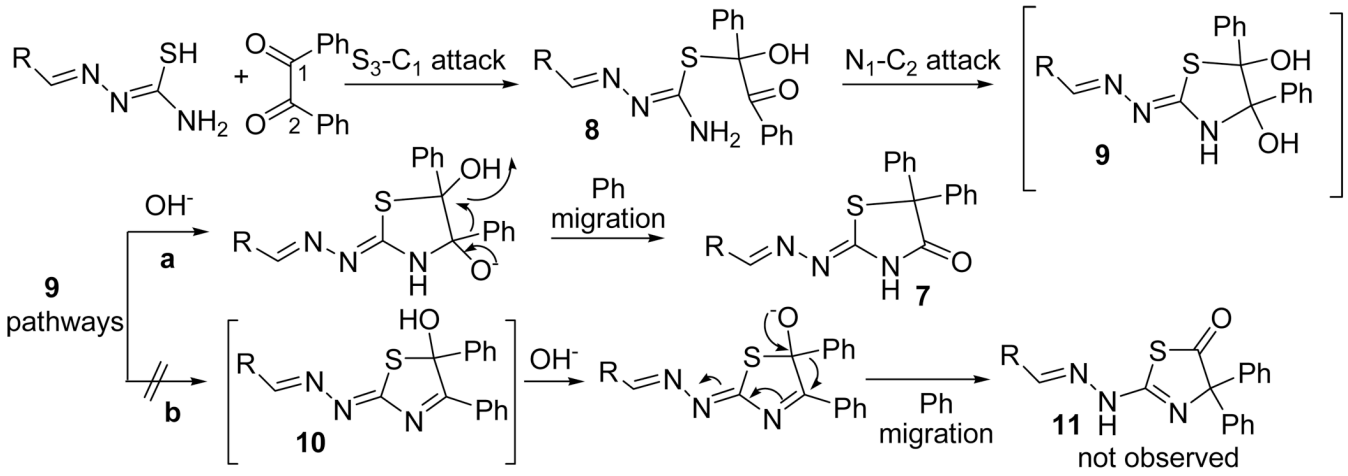
Scheme 2.
Tandem and stepwise reactions for the synthesis of 2-hydrazolyl-4-thiazolidinone.



Scheme 3.
Optimized tandem reaction for 2-hydrazolyl-4-thiazolidinone synthesis.



Scheme 4.
Synthesis of 2-hydrazolyl-5,5-diphenyl-4-thiazolidinone.



Scheme 5.
Proposed mechanism for 2-hydrazolyl-5,5-diphenyl-4-thiazolidinone (**10**) formation.

Table 1

Comparison of stepwise and tandem reactions using regular thermal and microwave heating.

Entry	Reagents	Conditions	Solvent	Additive	Product, Yield (%)[a]
1	**3a** (1 eq.), **4** (1.2 eq.)	Δ, reflux, 12 h.	PhMe	p-TsOH (0.1 eq.)	**5c** (40)
2	**3a** (1 eq.), **4** (1.2 eq.)	μW, 120 °C, 6 min	PhMe	p-TsOH (0.1 eq.)	**5c** (72)
3	**3a** (1eq.), **4** (5 eq.)	μW,120 °C, 6 min.	PhMe/DMF	p-TsOH (0.1 eq.)	**5b** (68)
4	**1a** (1eq.), **2** (1.2eq.), **4** (5eq.)	μW,120 °C, 6 min.	PhMe/DMF	p-TsOH (0.1 eq.)	**5b** (82)

[a]Isolated yields after purification.

[a] Isolated yields after purification.

Table 2

Optimized tandem reaction for 2-hydrazolyl-4-thiazolidinone synthesis under microwave irradiation conditions.

Entry	Compound RCHO	Temperature, time	Product (Yield)[a]	Mp °C
1	**1a** *p*-N(Me)$_2$-Ph	120 °C, 6 min	**5a** (82%)	278–279 dec.
2	**1b** *p*-OBut-Ph	120 °C, 6 min	**5b** (63%)	249–250
3	**1c** *p*-NO$_2$-Ph	120 °C, 12 min	**5c** (61%)	270–271 dec.
4	**1d** *o*-F-Ph	120 °C, 12 min	**5d** (57%)	272–273
5	**1e** *p*-Cl-Ph	120 °C, 12 min	**5e** (70%)	273–274
6	**1f** Ph	120 °C, 6 min	**5f** (45%)	242–243
7	**1g** *p*-OMePh	120 °C, 9 min	**5g** (61%)	262–263
8	**1h** 2-thiophenyl	120 °C, 5 min	**5h** (33%)	255–256
9	**1i** CH(Me)$_2$	100 °C, 12 min	**5i** (34%)	229–230
10	**1j** CH$_2$CH$_2$Ph	100 °C, 6 min	**5j** (64%)	199–200

[a] Isolated yields after purification.

Table 3

Electronic parameters for selected model compounds and intermediates.

Entry	Compound	Energy (eV)		Coefficients (%)[a]		Charge
		HOMO	LUMO	HOMO	LUMO	
1	**3g**	−8.77	−1.05	S 44.3	-	S −0.32
				N 13.6	-	N 0.09
2	**6**	−10.01	−0.61		C_1 25.5	C_1 0.29
					C_2 25.5	C_2 0.29
3	**9**	−8.69	−0.38		C_2 17.0	C_2 0.09
					C_1 0.2	C_1 0.12

[a] Coefficients were calculated as $(\Sigma c_i^2) \times 100$.