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Microwave Assisted Three Component Reaction Conditions to Obtain New Thiazolidinones with Different Heterocyclic Skeletons †

Fernando J. Lorenzo, Romina A. Ocampo * and Sandra D. Mandolesi *

Departamento de Química, Instituto de Química del Sur (INQUISUR-CONICET), Universidad Nacional del Sur, Avenida Alem 1253, 8000 Bahía Blanca, Argentina; fernando.lorenzo@uns.edu.ar

* Correspondence: rocampo@uns.edu.ar (R.A.O.); sdmando@criba.edu.ar (S.D.M.)

† Presented at the 23rd International Electronic Conference on Synthetic Organic Chemistry, 15 November–15 December 2019; Available online: https://ecsoc-23.sciforum.net/.

Published: 14 November 2019

Abstract: We present here a new proposal for the "one pot" generation of new 4-thiazolidinones (**9a–e**) through a multicomponent reaction under microwave irradiation conditions, using aromatic and heteroaromatic amines (**8a–e**), absolute ethanol as a "*green*" solvent and modifying the aldehyde group in the glycosidic residue, synthesized from D-mannitol. The study is focused in the variation of the irradiation times and the concentration of thioglycolic acid in order to study the possibility of controlling the structure and/or stereochemistry of the products formed in the reaction. Thiazolidinones **9a–d** were obtained with a 69–82% The generation of the corresponding reaction products were monitored by TLC and CG-MS, taking reaction aliquots. The conditions reaction proved to be chemoselective depending on the excess of acid and irradiation times.

Keywords: 4-thiazolidinones; green chemistry; multicomponent reactions

1. Introduction

Since the last decades, carbohydrates are no longer considered as simple supporting structures to become important compounds in specific biological activities as well as the advantages of their presence in larger macromolecular structures (low toxicity, low environmental impact, immunogenicity, high functionality and asymmetric sites). Therefore, a new discipline named *glycobiology* have been developed that is responsible for the study of the biological processes in which carbohydrates are involved [1]. On the other side, heterocyclic compounds containing nitrogen and sulphur like tiazepines and 4-thiazolidinones play an important role in synthetic organic and bioorganic chemistry because of their versatility in the preparation of targets molecules with potential biological interest. Tiazepine moiety exhibits important pharmacological properties as antiarrhythmic, antispasmodic, analgesic, anticancer, anti-inflammatory, antidepressive, antidiabetic and antioxidant [2]. Regarding 4-thiazolidinones, many pharmaceutical analogs have the N-C-S bond system in their basic structures and because of this, they are very interesting for studying the hypnotic [3], anticancer [4], antioxidant [5], anti-inflammatory [6], and anti-HIV effects, among others [7].

Taking into account that multicomponent reactions (MCRs) is an important synthetic tool [8], we believe that, indeed, the synthesis of new heterocyclic derivatives structurally modified by the presence of a carbohydrate fragment is a wonderful strategy to improve the solubility of the drug and/or decrease its toxicity and immunogenicity starting from a renewable resource of high functionality [9]. Given these facts and based on the versatile bioactivities of the above mentioned structures, we believe that the integration of heteroaromatic amines with carbohydrate scaffold segment through multicomponent reactions free from solvent and microwave assisted, might result a very good way to obtain excellent new drug candidates with unknown or enhanced bioactivities.

We have previously study the optimal microwave conditions for the synthetic strategy for the preparation of 4-thiazolidinones (**5**) starting from 2,3:4,5-di-O-isopropylidene-β-D-arabino-hexos-2-ulo-2,6-pyranose (**1a**), mercaptoacetic acid (**2**) and different aromatic and heteroaromatic amines (**3**), under 300 W and 120 °C without solvent (Figure 1) [10]. Depending on the substrate structure, two different type of products could be possible: benzothiazepines (**4**) and 4-thiazolidinones (**5**). Under these reaction conditions, only two diastereoisomers corresponding to 1,3-thiazolidin-4-ones in excellent yields (82–97%) were obtained. Diastereomeric relation in each case was determined by ^{1}H-NMR and GC-MS spectra. Recrystallization from absolute ethanol allowed us to purify one of the diastereoisomer and the characterization of the product was performed by ^{1}H-, ^{13}C, DEPT- HSQC-NOESY.2D y 1D selective NOESY-RMN

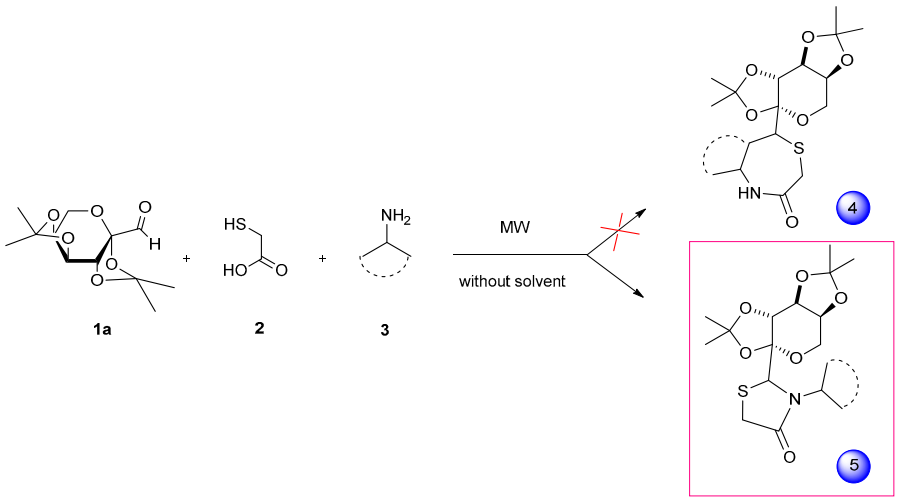


Figure 1. Optimal microwave conditions for the chemoselective reaction.

2. Results and Discussion

Considering the results mentioned above, in the present work we study the variation of the glycosidic residue, now with a mannitol derivative. This strategy would seem promising, because new different asymmetric centers in this molecule could have new or more amplifying effect on the biological activity due to the action mechanisms at the molecular level, which implies a specific interaction between the chiral ligand and the activity center.

In the first place, (R)-2,3-O-isopropiliden-D-glyceraldehyde (**7**) was synthetized. The reaction of D-mannitol with acetone and $ZnCl_2$ gave from 1,2:5,6-di-O-isopropiliden-D-mannitol (**6**) followed by oxidative cleavage with $NaIO_4$ in silica gel (Figure 2).

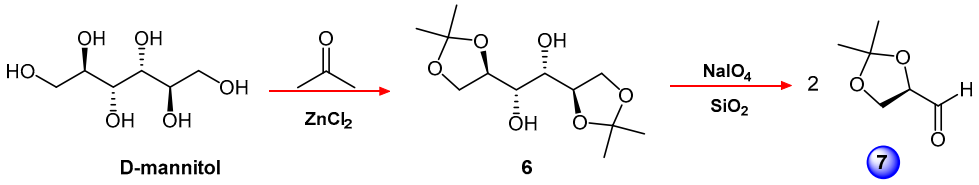


Figure 2. Synthesis of (R)-2,3-O-isopropiliden-D-glyceraldehyde (**7**).

Then, in order to find suitable and efficient new microwave-assisted conditions, a control multicomponent reaction to obtain 3-(benzo[d]thiazol-2-yl)-2-[(R)-2,2-dimethyl-1,3-dioxolan-4-yl]thiazolidin-4-one (**9**) starting from **7** and aminobenzothiazole (**8**) as model substrates with mercaptoacetic acid (**2**) was tested (Figure 3).

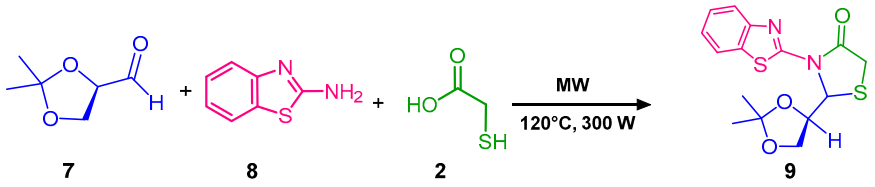
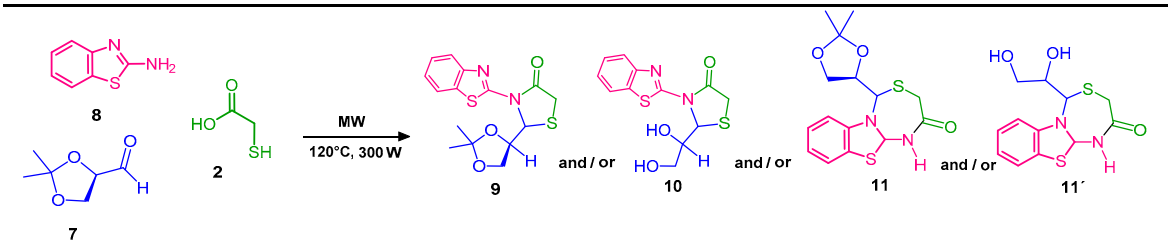


Figure 3. Control multicomponent reaction.

With the aim of study the possibility in control structure and/or stereochemistry of the products obtained in the reaction, irradiation times (periods of 5, 10 and 30 min), mercaptoacetic acid concentration (1, 4 and 10 equivalents) and the absence or presence of EtOH were varied. The monitoring of the reaction was made by TLC and CG-MS.

When the reaction was performed not only thiazolidinone **9** was not the only product obtained. As can be seen from the results shown in Table 1, type products **10**, **11** and **11′** were obtained too.

Table 1. Control microwave MCRs between aminobenzothiazole (**8**), aldehyde **7** and mercaptoacetic acid (**2**).



Entry	EtOH (eq)	7:8 (eq)	Mercapto Acetic Acid (eq)	Intervals of Irradiation (min)	Total Irradiation Time (min)	Product/s (% yield) [a]	d.r. [b]
1	1	1:1	10	10	30	**11** (95%)	---
2	1	1:1	10	30	60	**11** (80%) + **11′** (7%)	---
3	1	1:1	1	10	30	**9** (75%)	32:68
4	1	1:1	1	30	60	**10** (79%)	37:63
5	---	1:1	1	10	30	**9** (69%)	41:59

[a] Determined by CG-MS analysis of crude reaction through a standard curve generated from isolated pure product; [b] Diastereomeric relation (d.r.) was determined by CG-MS y 1H-NMR.

The excess of mercaptoacetic acid (10 eq.) strongly promotes that the protonated form of aminobenzothiazole [11,12] reacts via the nucleophilic endocyclic nitrogen to give **11** as the only product after 30 min of total irradiation every 10 min of interval steps (95%, entry 1). The same excess of acid media but doubling the irradiation total time (60 min) with only two step intervals of 30 min, cause that **11** suffered the opening of the dioxolane ring, so **11′** was detected too (entry 2). When 1 eq of mercapto acetic acid was used, but maintaining long irradiation times of 60 min with only two intervals, unprotected thiazolidinone **10** was observed as the only product (79 %, entry 4). These observations would suggest that the most influencing variable for the opening of the acetal is the irradiation time of 1 h, which is probably too long and the dioxolane ring was opened to give the corresponding diol. Only under the reaction conditions selected for entries **3** and **5** it was possible to generate 3-(benzo[d]thiazol-2-yl)-2-[(R)-2,2-dimethyl-1,3-dioxolan-4-yl] thiazolidin-4-one (**9**), with or without absolute ethanol as solvent. Because the presence on solvent improved the yield and the diastereomeric relation (75%, 32:68), conditions set in entry **3** were selected to carry out all the MCRs with the other aromatic and heteroaromatic amines.

After setting the primary reaction conditions previously mentioned, we carried out the multi-component reaction of starting from **7** as the carbonyl substrate and mercaptoacetic acid (**2**) with aniline (**8a**), 3-amino-5-methylpyrazole (**8b**) 2-aminothiazole (**8c**) and aminobenzothiazole (**8d**), in order to obtain the new 4-thiazolidinones **9a–d** (including the product from aminobenzothiazole as

diastereomeric mixtures fused with bioactive heterocyclic skeletons and substituted by a carbohydrate moiety (Figure 4). The results are summarized in Table 2.

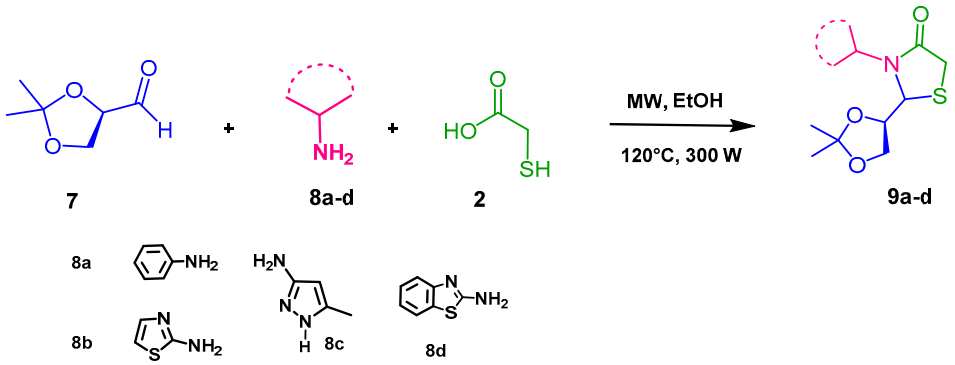
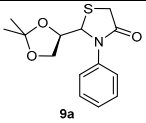
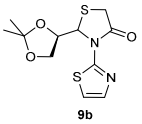
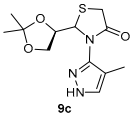
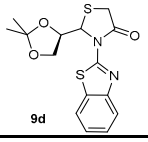


Figure 4. Synthesis of new 4-thiazolidinones **9a–d**.

Under the preset reaction conditions obtained from Table 1, the MCRs studied gave only the thiazolidinones **9a–d**. All the products were obtained in good to very good yields (69–82%) and the diastereomeric relations were acceptable for thiazolidinones **9a** and **9b** (entries **1** and **2**, 85:15 and 78:22 respectively) but regular for compounds **9c** and **9d** (entries **3** and **4**, 63:37 and 68:32 respectively). It is important to observe that no unprotected (10) and/or type **11** or **11′** products were detected. It could be assume that may be the excess of mercaptoacetic acid and long irradiation times (60 min) with few intervals (2 every 30 min) were probably responsible for the formation of them. One of the goals that we could achieve in these studies was that after cooling the crude reaction in the refrigerator for approximately one day, one of the stereoisomer precipitate and could be separated without further purification from the crude reaction after centrifugation. With this technique, no chromatography was needed.

Table 2. Diastereomeric relations (d.r.) and yields of synthetized thiazolidinones **10a–d**.

Entry	Product	Yield (%) [a]	d.r. [b]
1	 **9a**	**82**	**85:15**
2	 **9b**	**69**	**78:22**
3	 **9c**	**73**	**63:37**
4	 **9d**	**75**	**68:32**

[a] Yield of diastereomers from the crude mixture determined by CG-MS analysis; [b] Ratio of diastereomers determined by ^{1}H-RMN.

3. Conclusions

In summary, microwave-assisted MCRs between a carbohydrate moiety derived from mannitol (**7**), four aromatic and hetero aromatic amines (**8a–d**) and mercaptoacetic acid (**2**) with absolute ethanol, has proven to be stereoselective, inexpensive and sustainable way to generate substituted 4-thiazolidinones **9a–d** with a protected carbohydrate moiety. One of the most important facts of this method is that the reaction is chemoselective depending on the reactions conditions used for the

synthesis. The products obtained with excess of mercaptoacetic acid (**10**, **11** and **11'**) are very interesting too, especially regarding the possibility of generate thiazolidinones with OH groups in the case of 10, that would make them more soluble in aqueous media. This last consideration is important in the study of biological behavior. The reaction is easy to perform using economical starting materials and generates products in very good yields. The one-pot microwave-assisted conditions and subsequent purification by precipitation-centrifugation, proved to be a simple method, in terms of atom economy, energy consumption and time required, to make this new synthetic strategy highly attractive and promising for the access to pure and interesting stereoisomeric macromolecules. Further studies will be focused on the investigation of the potential biological activity of the new compounds reported here.

4. Materials and Methods

4.1. General Information

Mass spectra were obtained with a GC/MS instrument (HP5-MS capillary column, 30 m/0.25 mm/0.25 mm) equipped with 5972 mass selective detector operating at 70 eV (EI). Microwave reactions were performed with a microwave oven (CEM Discover®) with a continuous focused microwave power delivery system in a pressure glass vessel (10 mL) sealed with a septum under magnetic stirring. The reaction mixture temperature was monitored using a calibrated infrared temperature control under the reaction vessel, and control of the pressure was performed with a pressure sensor connected to the septum of the vessel. Thin layer chromatography was performed on Merck precoated silica gel 60 F254 plates and visualization was accomplished with UV light and/or 5% ethanol solution of phosphomolibdic acid. Mass spectra were obtained with a GC/MS instrument (HP5-MS capillary column, 30 m/0.25 mm/0.25 mm) equipped with 5972 mass selective detector operating at 70 eV (EI). NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker ARX 300 Multinuclear instrument (300.1 MHz for 1H and 75.5 MHz for 13C) at 23 °C.

4.2. Synthesis of (R)-2,3-O-isopropiliden-D-glyceraldehyde (**7**)

A round bottomed flask containing zinc chloride (40 g, 293 mmol) was heated in open flame to melt the zinc chloride and remove any residual water. The flask was capped with a calcium chloride drying tube and cooled to room temperature. Anhydrous acetone (400 mL) was added to the reaction flask, stoppered and swirled to dissolve the solid. After the solution has cooled toroom temperature, D-mannitol (20 g, 110 mmol) was quickly added, the flask stoppered and the mixture stirred to a clear solution (5 h). The reaction mixture was poured onto a suspension of potassium carbonate (45 g) in water (45 mL), vigorously stirred, filtered and the zinc carbonate washed with acetone (50 mL). The filtrate was concentrated with a flow of compressed air to removeacetone and most of the residual water. The white solid was dissolved in diethylether (60 mL) and transferred to a separating funnel. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers was dried with anhydrous magnesium sulphate, filtered and washed with diethyl ether (20 mL). The solvent was removed under vacuum at room temperature to give a white slurry. Hexane (100 mL) was added to the slurry and stirred for 20 min. The mixture was kept in the freezer at −10 °C for 1 h and in the refrigerator at 8 °C for a further 1 h. The mixture was filtered under vacuum and the solid washed with 100 mL of cold hexane. The combined white solids of **6** were left in the desiccator under vacuum for 2 h to give a white solid (25 g, 87% yield). For the synthesis of **7**, an aqueous solution of 1, 24 g of $NaIO_4$ in 2.46 mL of water heated at 70 °C was prepared. When the solution is homogenous, 4.92 g of silica-gel 60 (230–400 mesh) was added. The mixture was vigorously stirred for 30 min, cool to room temperature and the 33 mL of CH_2Cl_2 were poured. In another flask, a solution of 1, 17 g of 6 in 22, 33 mL of CH_2Cl_2 was prepared. To this preparation, the previous silica/$NaIO_4$ solution was added, stirring during 30 min. The progress of the reaction was monitored by TLC. Once finished, the solids were filtrated and the solvent was eliminated by reduced pressure. Product **7** was obtained as an oil (0.85 g, 75% yield) [13].

4.3. Microwave Reactions

All microwave reactions were carried out following the same procedure: A mixture of (R)-2,3-O-isopropiliden-D-glyceraldehyde (**7**, 0.390 g, 3 mmol), mercaptoacetic acid (**2**, 0.21 mL, 3 mmol), 0.2 mL (3 mmol) of EtOH and different aromatic and heteroaromatic amines (**9a–d**, 3.3 mmol) were heated in the microwave apparatus at 300 W and 120 °C. The reaction was monitored by TLC every 10 min and was left 30 min as total reaction time. The crude product was analyzed by CG-MS and ^{1}H-NMR and was subjected to a digestion procedure in absolute ethanol followed by centrifugation, which allowed isolating one of the diastereoisomers (**10a–d**) in each case. The structure of the pure diastereomer was determined by ^{1}H, ^{13}C and DEPT NMR spectroscopy. These stereoisomers were be subjected to future activity assays.

2-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-phenylthiazolidin-4-one (**10a**): 1H NMR (300 MHz, DMSO-d_6) δ 7.55–7.05 (m, 5H), 5.28 (d, *J* = 7.1 Hz, 1H), 4.75 (c, *J* = 7.0 Hz, 1H), 3.76 (dd, *J* = 11.5, 7.1 Hz, 2H), 3.63 (dd, *J* =11.5, 7.1 Hz 2H), 1.18 (s, 3H), 1.13 (s, 3H). 13C NMR (75 MHz, DMSO-d_6) δ 172.24, 136.41, 129.33, 126.42, 125.39, 109.75, 74.12, 68.61, 66.29, 32.62, 25.73.

2-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-(thiazol-2-yl)thiazolidin-4-one (**10b**): 1H NMR (300 MHz, DMSO-d_6) δ 8.09 (d, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 5.90 (d, *J* = 7.0 Hz, 1H), 4.85 (c, *J* = 7.0 Hz, 1H), 3.87 (dd, *J* = 11.5, 7.1 Hz, 2H), 3.52 (dd, *J* = 11.5, 7.1 Hz, 2H), 1.38 (s, 3H), 1.33 (s, 3H). 13C NMR (75 MHz, DMSO-d_6) δ 173.05, 154.76, 134.47, 112.73, 109.64, 74.24, 68.87, 68.46, 33.40, 26.09, 25, 28.

2-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-(4-methyl-1H-pyrazol-3-yl)thiazolidin-4-one (**10c**): 1H NMR (300 MHz, DMSO-d_6) δ 12.53 (s, 1H), 7.18 (s, 1H), 5.10 (d, *J* = 7.1 Hz, 1H), 4.71 (c, *J* = 7.0 Hz, 1H), 3.96 (dd, *J* = 11.5, 7.1 Hz, 2H), 3.73 (dd, *J* =11.5, 7.1 Hz, 2H), 3.42 (s, 3H), 1.20 (s, 3H), 1.15 (s, 3H). 13C NMR (75 MHz, DMSO-d_6) δ 175.87, 141.61, 136.33, 109.64, 107.01, 74.24, 68.46, 66.25, 33.40, 25.80, 25.12, 12.84.

3-(benzo[d]thiazol-2-yl)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)thiazolidin-4-one (**10d**): 1H NMR (300 MHz, DMSO-d_6) δ 7.65–6.98 (m, 4H), 5.35 (d, *J* = 7.0 Hz, 1H), 4.49 (c, *J* = 7.1 Hz, 1H), 4.01 (dd, *J* = 11.4, 7.0 Hz, 2H), 3.75 (dd, *J* = 11.5, 7.2 Hz, 2H), 1.21 (s, 3H), 1.19 (s, 3H). 13C NMR (75 MHz, DMSO-d_6) δ 170.92, 166.87, 153.26, 131.37, 125.87, 122.27, 121.26, 118.22, 81,80, 79.57, 67,83, 38.88, 38.61, 38.32.

Funding: This research was funded by CONICET (Buenos Aires, Argentina) and UNS (PGI 24/Q102, Universidad Nacional del Sur, Bahía Blanca, Argentina). A fellowship from Consejo Interuniversitario Nacional (CIN, Argentina) to FJL is acknowledged.

Conflicts of Interest: The authors declare no conflict of interest.

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