Synthesis of novel 4-thiazolidinone derivatives via one-pot three-component reaction of maleimide, thiosemicarbazide, and Meldrum’s acid

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ABSTRACT
The synthesis of novel thiazolidinone derivatives via the three-component reaction has been developed involving the reaction of thiosemicarbazide with maleimide and Meldrum’s acid in a single pot. Optimization of reaction conditions was studied with different solvents and quantities of raw materials. The optimum results were obtained when the reaction was carried out in the ratio (2:2:1 mmol) of maleimide, thiosemicarbazide, and Meldrum’s acid, in the presence of two drops of triethylamine in ethanol. The products were formed with good yields with a significant decrease in reaction time. The structures of thiazolidinones were elucidated by 1H, 13C NMR, FT-IR spectroscopy, HRMS, and X-ray diffraction.

GRAPHICAL ABSTRACT

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Maleimide; Meldrum’s acid; multicomponent; thiazolidinone

Introduction
For several years, research work has focused on the synthesis of heterocyclic molecules containing nitrogen, sulfur, and oxygen atoms, as these compounds exhibit a broad spectrum of biological activities. Among them, 4-thiazolidinone derivatives, which are

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found in many drugs due to their antimicrobial,[2–5] anti-HIV,[6] anti-inflammatory,[7,8] anti-mycobacterial,[9] anti-convulsant,[10,11] anti-histaminic,[12] anti-cancer,[13–18] and antifungal activities (Fig. 1).[19–21] Some commercially available drugs containing a thiazolidinone nucleus, such as Ciglitazone and pioglitazone, are able to improve insulin sensitization and glucose metabolism in the treatment of type II diabetes as shown in Figure 2.[22–24]

A literature survey revealed that many different protocols have been developed in a way that allows the synthesis of 4-thiazolidinone skeletons, and several reactants or heterocyclic compounds were used as raw materials for the preparation of the 4-thiazolidinone fraction,[25,26] such as aldehyde, an amine or thiosemicarbazide, and mercaptoacetic acid or halogenoester.[27,28] This classic method still constitutes a valid strategy for the introduction of chemical diversity around the 4-thiazolidinone.[29]

In our research group, bioactive derivatives of 4-thiazolidinone were synthesized in a two-step process.[30–33] In the first step, the intermediate thiosemicarbazone was prepared from a thiosemicarbazide precursor, in the presence of multifunctional reagents, such as alpha tetralone[30] and dehydroacetic acid.[31–33] In the second step, the previously isolated thiosemicarbazone reacted with electrophilic substrates, in the presence of strong acids, to yield thiazolidinone derivatives. However, these reported methods still have some limits, such as the need for costly catalysts or extended heating. We, therefore, envisaged to synthesize an original series of 4-thiazolidinones using the one-pot process.

This work extends our previous research on the development of new approaches for the synthesis of 4-thiazolidinones. Here we report an efficient and simple method for the preparation of these molecules from the one-pot three-component reaction.

Multicomponent reactions (MCR) are one-pot processes, which always hold great importance in the repertoire of sustainable synthetic tools, because of their high

Figure 1. Structures of some pharmacologically important 4-thiazolidinones.
efficiency, atom economy, productivity, and easy execution.\textsuperscript{[34–36]} This type of reaction facilitates the synthesis of libraries of molecules and is therefore very attractive for the implementation of high-throughput screening systems,\textsuperscript{[37,38]} an environmentally friendly procedure that allows to rapidly obtain a high molecular diversity, in a single step.\textsuperscript{[39–41]}

In a one-pot process, a new series of functionalized thiazolidinones \textit{4} were synthesized from thiosemicarbazide \textit{1a–c} with substituted maleimide \textit{2a–d} and Meldrum’s acid \textit{3}. The latter reagent has been widely used in organic synthesis, particularly for the formation of C–C multiple bonds,\textsuperscript{[42–45]} due to its steric rigidity and its tendency to give, as a by-product, acetone which is easy to eliminate.

\subsection*{Results and discussion}

A mixture of thiosemicarbazide \textit{1a–c}, maleimide \textit{2a–d}, and Meldrum’s acid \textit{3}, in a 1:1:1 molar ratio, was reacted under refluxing ethanol solution, in the presence of two drops of triethylamine. After filtration and ethanol wash (Scheme 1), thiazolidinone derivatives \textit{4a–h} were isolated with lower yields, ranging from 15 to 37\% (Table 1).

To find the optimal conditions, we studied the synthesis of compounds \textit{4a–h} from the condensation of thiosemicarbazide \textit{1a–c}, maleimide \textit{2a–d}, and Meldrum’s acid \textit{3} under various reaction conditions (Table 1).

The optimization of the reaction conditions, including the reaction solvent, and the equivalents of starting materials was investigated. Firstly, we examined the influence of solvent on this reaction. When the reactions were carried out in ethanol or chloroform under the same reflux conditions and for the same duration, the products formed practically in the same yields. On the other hand, increasing the reaction time in ethanol under reflux conditions did not improve the yield for all compounds.

Finally, we observed that the amounts of starting materials also have an important influence on the reaction. A larger amount of \textit{1a–c}, \textit{2a–d}, and Meldrum’s acid \textit{3} (for example, 1:1.2:1.2 mmol) in ethanol under reflux resulted in moderate yields, between 25 and 41\% and shorter times were observed for all compounds. When the reaction was
carried out with 1a–c, 2a–d, and Meldrum’s acid 3 in the ratio of 2:2:1 mmol, the products formed in good yields (38–52%) with a significant decrease in reaction time (1–1.5 h). This series of experiments reveal that the optimal results were obtained when the reaction of thiosemicarbazide 1 (2.0 mmol) was conducted with maleimide derivatives 2 (2.0 mmol), Meldrum’s acid 3 (1.0 mmol), and two drops of triethylamine in ethanol under reflux conditions. Under these optimized conditions, the yield of 4a for example reached 52%.

The structure of compounds 4a–h was established by IR analysis, $^1$H NMR, $^{13}$C NMR, 2D NMR spectroscopy, and X-ray diffraction on a single crystal.

The IR spectra showed absorption bands around 1650–1700 and 1300–1350 cm$^{-1}$, corresponding, respectively to the C=O and N–C–S groups of the thiazolidinone ring.

Table 1. Optimization of the reaction conditions.

| Entry | mmol of 1a-c: 2a-d: 3 | $R^1$ | $R^2$ | Product | Time (h) | Yield (%) |
|-------|------------------------|-------|-------|---------|----------|-----------|
| 1     | 1:1:1                  | H     | H     | 4a      | 6        | 25        |
| 2     | 1:1:1                  | H     | CH$_3$| 4b      | 5        | 20        |
| 3     | 1:1:1                  | H     | C$_6$H$_5$| 4c      | 7        | 21        |
| 4     | 1:1:1                  | C$_6$H$_5$| H     | 4d      | 8        | 22        |
| 5     | 1:1:1                  | C$_6$H$_5$| CH$_3$| 4e      | 6        | 15        |
| 6     | 1:1:1                  | C$_6$H$_5$| C$_2$H$_5$| 4f     | 5        | 16        |
| 7     | 1:1:1                  | C$_6$H$_5$| C$_6$H$_5$| 4g     | 6        | 37        |
| 8     | 1:1:1                  | CH$_3$| CH$_3$| 4h      | 5        | 25        |
| 9     | 1:1.2:1.2              | H     | H     | 4a      | 2        | 32        |
| 10    | 1:1.2:1.2              | H     | CH$_3$| 4b      | 3        | 25        |
| 11    | 1:1.2:1.2              | H     | C$_6$H$_5$| 4c      | 1        | 33        |
| 12    | 1:1.2:1.2              | C$_6$H$_5$| H     | 4d      | 3        | 29        |
| 13    | 1:1.2:1.2              | C$_6$H$_5$| CH$_3$| 4e      | 2        | 25        |
| 14    | 1:1.2:1.2              | C$_6$H$_5$| C$_6$H$_5$| 4f    | 2        | 20        |
| 15    | 1:1.2:1.2              | C$_6$H$_5$| C$_6$H$_5$| 4g    | 3        | 41        |
| 16    | 1:1.2:1.2              | CH$_3$| CH$_3$| 4h      | 2        | 29        |
| 17    | 2:2:1                  | H     | H     | 4a      | 1        | 52        |
| 18    | 2:2:1                  | H     | CH$_3$| 4b      | 2        | 38        |
| 19    | 2:2:1                  | H     | C$_6$H$_5$| 4c      | 1        | 48        |
| 20    | 2:2:1                  | C$_6$H$_5$| H     | 4d      | 1.5      | 40        |
| 21    | 2:2:1                  | C$_6$H$_5$| CH$_3$| 4e      | 1        | 43        |
| 22    | 2:2:1                  | C$_6$H$_5$| C$_6$H$_5$| 4f    | 1        | 42        |
| 23    | 2:2:1                  | C$_6$H$_5$| C$_6$H$_5$| 4g    | 1.5      | 50        |
| 24    | 2:2:1                  | CH$_3$| CH$_3$| 4h      | 1        | 38        |

General conditions: thiosemicarbazide 1a–c, maleimides 2a–d, and Meldrum’s acid 3 with 0.1 mmol % of Et$_3$N, in EtOH (20 ml), under reflux.

As an example, the $^1$H NMR spectrum of compound 4c clearly showed a triplet at 1.01 ppm and a multiplet at 3.05 ppm, attributed, respectively to the protons of the alkyl group (CONH-CH$_2$-CH$_3$) of the acetamide part. In addition, an ABX spin system was observed at 2.55 ppm for 1-H$_a$ (1H, dd, $J_{a-b} = 16$ Hz, $J_{a-x} = 12$ Hz, CH$_2$), 2.87 ppm for 1-H$_b$ (1H, dd, $J_{b-a} = 16$ Hz, $J_{b-x} = 4$ Hz, CH$_2$), 4.20 ppm for 5’-HX (1H, dd, $J_{a-x} = 12$ Hz, $J_{b-x} = 4$ Hz, CH), attributed to the aliphatic protons CH$_2$-CH of the thiazolidinone ring (Fig. 3).
The singlet at about 1.92 ppm corresponds to the two equivalent methyl groups on the acid part of the Meldrum’s acid ring. The signal at 10.21 ppm was attributed to the two amine protons (NH₂), confirming the opening of the maleimide ring.

In addition, the ¹³C NMR spectrum revealed two carbonyl function signals at around 169.3 and 176.9 ppm, assigned to the cyclic and acyclic carbonyl functions, respectively, and showed also the appearance of two new signals at 157.3 and 162.7 ppm, relating to the two carbon atoms of the C≡N imine function.

The 2D NMR analysis [Heteronuclear Multiple Bond Correlation (HMBC) and Heteronuclear Single Quantum Coherence (HSQC)] allowed the precise assignment of all protonated aromatic and quaternary carbon atoms.

In the case of the 4-thiazolidinone compounds, the quaternary carbon atoms C-4’ (176.9 ppm) and C-2 (169.3 ppm) were assigned based on HMBC cross-correlations of C-4’/H-x/H-b/H-a and C-2/NH/CH₂/CH₃, respectively. It was also possible to assign a high HMBC correlation of imine function (162.7 ppm) C-2’/H-1’/H-3’. Figure 4 illustrates other important HMBC connectivity.

The formation of compound 4 could be explained with a reaction sequence, such as condensation, cyclization, and elimination, presented in Scheme 2.

The suggested mechanism involves a nucleophilic attack on the C≡C double bond of maleimide 2 by the sulfur atom of thiosemicarbazide 1. The non-isolated intermediate I is recycled by a double attack of the amine formed on the carbonyl of maleimide with a ring opening, followed by the addition of Meldrum’s acid 3 to give the intermediate II. The intramolecular condensation of the non-isolated intermediate II and the removal of the diacid lead to the thiazolidinones 4, as shown in Scheme 2.

An X-ray diffraction study carried out on a crystal of the thiazolidinone 4d, obtained after recrystallization from a mixture of ethanol and ethyl acetate 1:1 at room
temperature, shows that the compound 4d crystallizes in a monoclinic space group P21/c. The asymmetric unit is composed of an entire molecular unit as shown in Figure 5.

It is noteworthy that the structural characteristics revealed by the X-ray crystallographic studies are in perfect agreement with the data from the 2D NMR studies.

In conclusion, the one-pot three-component reactions for the synthesis of a new series of thiazolidin-4-one derivatives were developed, starting from thiosemicarbazide 1, maleimide 2, and Meldrum's acid 3. The optimal reaction conditions were studied and

Scheme 2. Plausible mechanism for the formation of thiazolidinone 4.

Figure 5. X-ray crystal structure of compound 4d.
amounts of 1a–c, 2a–d, and Meldrum’s acid 3 in the ratio of 2:2:1 mmol afforded compounds 4 in good yields (38–52%) with shorter reaction time (1–1.5 h). This work has made it possible to elucidate the structure of thiazolidin-4-one derivatives by a combination of AT-IR, 1D, and 2D NMR analysis and X-ray diffraction on a single crystal. A reaction mechanism is proposed to explain the formation of compounds 4.

**Experimental section**

**General considerations**

The synthetic starting material, reagents (Thiosemicarbazide, methyl thiosemicarbazide, and phenyl thiosemicarbazide), (Maleimide, methyl maleimide, ethyl maleimide, and phenyl maleimide) and solvents were purchased from Aldrich Company.

All melting points were measured on a Melting Point SMP 1 Stuart Scientific apparatus. The $^1$H-NMR spectra (400 MHz), $^{13}$C-NMR (75 MHz), HMBC, and HSQC were obtained in dimethyl sulfoxide on a Bruker spectrometer, using TMS as an internal standard from the Research Center Scientific and Technical in Analyzes Physico-Chimiques (CRAPC). Chemical shifts are reported as δ units and coupling constants (J) are reported in Hertz (Hz). IR-ATR apparatus used is a Fourier Transform spectrometer. ATR platinum Diamond Brucker Alpha module, the frequency range studied is between 3500 and 500 cm$^{-1}$. HRMS spectra were recorded on a QStar Elite (Applied Biosystems SCIEX, Foster City, CA) spectrometer. TLC analysis was carried out on 0.2-mm silica-gel plates (Alu foils, Fluka, Germany). UV light was used for detection.

**Typical procedure for the synthesis of 2-[4-oxo-2-(propan-2-ylidenehydrazinylidene)-1,3-thiazolidin-5-yl]acetamide (4a)**

In ethanol (20 ml), under reflux and with magnetic stirring, the thiosemicarbazide 1a (0.182 g, 2 mmol), reacts with maleimides 2a (0.194 g, 2 mmol), Meldrum’s acid 3 (0.144 g, 1 mmol) in the presence of 0.1 mmol% of triethylamine (Et$_3$N) in the ratio 2:2:1. The reaction was monitored by thin layer chromatography (TLC) using chloroform-ethyl acetate (1:1). After a reaction time, which varies according to the radicals $R_1$ and $R_2$, the products 4 are isolated and recrystallized in ethanol.

2-[4-Oxo-2-(propan-2-ylidenehydrazinylidene)-1,3-thiazolidin-5-yl]acetamide (4a)

White solid, mp 230–232 °C, Yield: 52%. IR (ν cm$^{-1}$) 3412 (NH), 3145 (NH$_2$), 1215 (C¼N), 1411 (C¼N), 161.6 (CH 2-CO), 175.7 (CO). HRMS m/z calcd. For C$_8$H$_{13}$N$_4$O$_2$S $[M + H]^+$: 229.0681. Found: 229.0651.

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