Microwave assisted synthesis, the most efficient method for the synthesis of thiazolidin-4-ones from thiosemicarbazones

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Abstract
(2-(pyrazin-2-yl)aminmethylenehydrazono)-thiazolidin-4-one, *HPzAm4DHotaz*, and (2-(pyrazin-2-yl)aminmethylenehydrazono)-3-methylthiazolidin-4-one, *PzAm4Motaz* have been prepared by the reaction of thiosemicarbazones with chloroacetic acid in presence of triethylamine in toluene using a microwave assisted synthesis and a conventional method, at reflux temperature. While the conventional method carried out other side products as triazoles and thiadiazoles, the cyclization of the thiosemicarbazones using microwave irradiation favours the obtaining of the tiazolidinones as only product and gave better yields, shorter times and any side products were formed.

Keywords: thiosemicarbazone, thiazolidin-4-one, microwave synthesis

Introduction

Thiazolidinones are a common structural motif in clinically used drugs such as *ralitoline* as a potent anti-convulsant, *etozoline* as an antihypertensive, *pioglitazone* as a hypoglycemic agent and *thiazolidomycin* against streptomyces. The diversity in the biological response profiles has attracted the interest of many researchers to explore this skeleton as a potentially active scaffold [1-3].

Thiazolidine-4-ones are derivatives of thiazolidine (Fig. 1) with a carbonyl group at the fourth position. This ring is known as a *wonder* nucleus because it belongs to a group of biologically active heterocycles probably due to the presence of sulphur, nitrogen and oxygen in the core structure. Furthermore the possible substitution at positions 2, 3 and 5 enables the introducing of additional handles to synthesize different derivatives. The nature of these substituents can play a crucial role in the compound's biological activity although the greatest influence on structure and property is exerted by the group attached to the carbon atom in the second position [1-6].

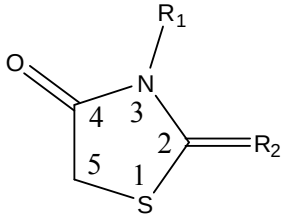
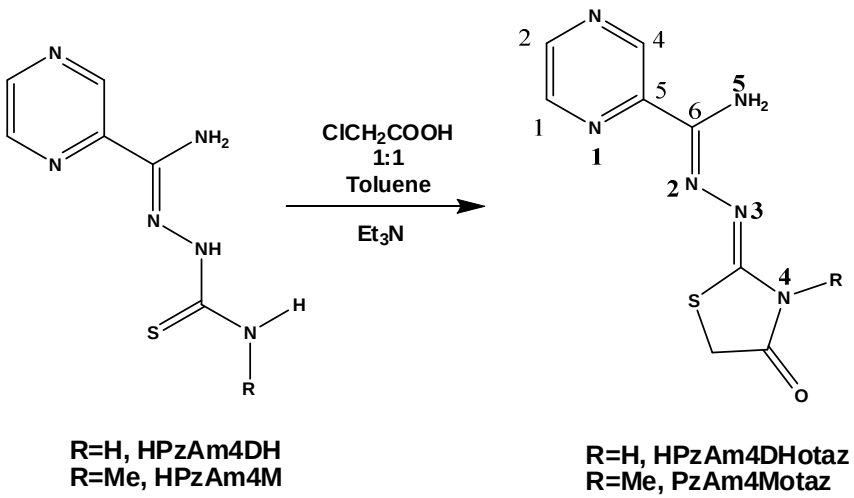


Fig.1

Results and discussion

HPzAm4DHotaz and PzAm4Motaz were synthesized (Scheme 1) by a conventional method and by a microwave method as described in the experimental part and in the Scheme 1.

The compounds were mostly based on analytical, MS, FT-IR and NMR data and were also determined their crystal structures (Fig. 2).



Scheme 1. Synthetic route to thiazolidin-4-ones

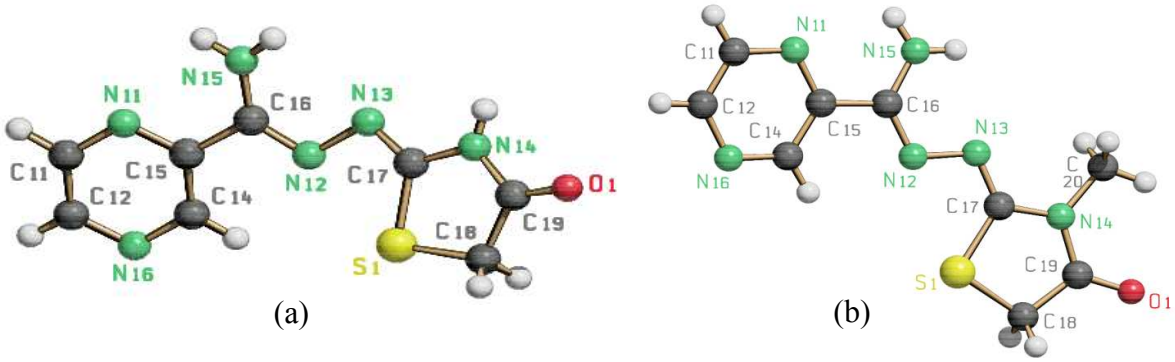


Fig. 2. Molecular structures of HPzAm4DHotaz (a) and PzAm4Motaz (b)

The thiazolidine rings C17/S1/C18/C19/N14 are almost planar with rms mean plane deviations of 0.0431 and 0.0422 Å for HPzAm4DHotaz and PzAm4Motaz, respectively, while the methylenehydrazono moities C16/N12/N13/C17/S/N14 have rms of 0.1246 and 0.0093, and form angles of about 3.9º in both compounds. The mean plane of the pyrazine ring in each compound makes an angle of 29.40º and 4.82º with the mean plane of the methylenehydrazono moiety C16/N12/N13/C17/S/N14. The large angle in HPzAm4DHotaz could be related with the existence of the N(4)H and the possibility to take part in intermolecular bindings.

Experimental procedure

Synthesis of HAmPz4DHotaz

Conventional method. The thiosemicarbazone HPzAm4DH (1.60 g, 8.15 mmol) in toluene (75 ml) with some drops of triethylamine was heated slightly and stirred during a hour and a solution of chloracetic acid (0.77 g, 8.15 mmol) in toluene (25 ml) was added slowly. The mixture was refluxed for 5 hours and a crude product was obtained and HPz4DHotaz was isolated by recrystallisation in MeOH. Yield: 77% (1.48 g). Other side products were formed in the reaction.

Microwave method. A mixture of HPzAm4DH (1.60 g, 8.15 mmol) in toluene (150 ml) was taken in a round bottom flask with an inverted funnel and to it chloroacetic acid (1.67 g, 17.65 mmol) in toluene (50 ml) and some drops of triethylamine were added slowly. The mixture was irradiated in a microwave oven for about 1h and 360W. The yellow solid was washed and recrystallised in MeOH and a white product of HPzAm4DHotaz was obtained. Yield: 96% (1.74 g).

HAmPz4DHotaz: Anal. found: C, 40.67; H, 3.41; N, 35.57; S, 13.57 %. Calc. for $C_8H_8N_6OS$ (236.25): C, 40.40; H, 3.35; N, 35.35; S, 13.62 %. M.p.: 255ºC. IR (KBr, ν_{max}/cm^{-1}): 3428-3320 ν(NH), 1710 ν(C=O), 1637-1523 ν(C=N)+ν(C=C), 1022 ν(NN). MS (IE): *m/z (%)* 236.0 (83) $[M]^+$, 189.0 (91) $[C_7H_5N_6O]^+$, 163.0 (28) $[C_6H_3N_4S]^+$, 106.0 (44) $[C_5H_4N_3]^+$, 80.0 (100) $[C_4H_4N_2]^+$, 79.0 (43) $[C_4H_3N_2]^+$, 52.0 (89) $[C_2N_2]^+$. ^{1}H RMN (DMSO-d_6, ppm): 11.7 (1H, sa, N4H); 9.25 (1H, s, H4); 8.71 (1H, d, H2); 8.67 (1H, d, H1); 6.45 (2H, sa, N5H_2); 3.85 (2H, s, CH_2). ^{13}C RMN (DMSO-d_6, ppm): 174.0 (C=O); 158.6 (C7); 151.5 (C6); 146.0 (C5); 145.6 (C1); 143.5 (C2); 142.8 (C4); 33.0 (CH_2).

Syntesis of PzAm4Motaz

Conventional method. HPzAm4M (1.61 g, 7.66 mmol) in toluene (75 ml) with some drops of triethylamine was heated slightly and stirred for a hour for total solubilisation. A solution of chloroacetic acid (0.79 g, 7.66 mmol) in toluene (25 ml) was added and the mixture was refluxed for 5 hours and a solid was separated by filtration which was washed and recrystallised with MeOH to obtain the white ligand PzAm4Motaz. Yield: 53 % (1.00 g). Other side products were formed in the reaction.

Microwave method. HPzAm4M (1.68 g, 8.00 mmol) in toluene (150 ml) with some drops of triethylamine was heated slightly and stirred for 15 minutes. A solution of chloroacetic acid (1.67 g, 17.65 mmol) in toluene (50 ml) was added. The mixture was irradiated in a microwave oven at 360W of power and for 45 min and the yellow solid was washed and recrystallised in MeOH and corresponds to PzAm4Motaz. Yield: 82 % (1.64 g).

PzAm4Motaz: Anal. found: C, 43.38; H, 4.01; N, 33.61; S, 12.96 %. Calc. for $C_9H_{10}N_6OS$ (250.20): C, 43.19; H, 4.03; N, 33.58; S, 12.81 %. M.p.: 235ºC. IR (KBr, ν_{max}/cm^{-1}): 3464-3315 ν(NH), 1714 ν(C=O), 1614-1523 ν(C=N)+ν(C=C), 1023 ν(NN). MS (IE): *m/z (%)* 250.0 (99) $[M]^+$, 177.0 (100) $[C_7H_9N_6]^+$, 106.0 (16) $[C_5H_4N_3]^+$, 80.0 (20) $[C_4H_4N_2]^+$, 79.0 (17) $[C_4H_3N_2]^+$. ^{1}H RMN (DMSO-d_6, ppm): 9.27 (1H, s, H4); 8.72 (1H, d, H2); 8.69 (1H, d, H1); 6.80 (2H, sa, N5H_2); 3.91 (2H, s, CH_2); 3.22 (3H, s, CH_3). ^{13}C RMN (DMSO-d_6, ppm): 172.5 (C=O); 158.2 (C7); 152.8 (C6); 146.5 (C5); 145.9 (C1); 143.7 (C2); 143.2 (C4); 33.5 (CH_2); 29.8 (CH_3).

Conclusions

A microwave-assisted synthesis of thiazolidinones from thiosemicarbazones has been achieved and compared with a conventional method. While the microwave irradiation is a simple and convenient method for their synthesis, when the conventional method was carried out, the thiazolidinones were also obtained but other side products (triazoles and thiadiazoles) were formed by cyclization of the starting thiosemicarbazone. As conclusion, the microwave assisted synthesis for the

experiments performed to obtain thiazolidine 4-ones by cyclization of the 2-pyrazine thiosemicarbazones with cloroacetic acid in presence of triethylamine was the most effective method because provides shorter reaction time and better yields, simplifies the product purification and any side products are formed.

References

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