A convenient one pot preparation of 4-thiazolidinones from enaminolactones

Samia Bouzroura¹, Yamina Bentarzi¹, Rachedine Kaoua¹, Bellara Nedjar-Kolli,*, Sophie Poulain-Martini² and Elisabet Dunach²

¹Laboratory of Applied Organic Chemistry, Houari Boumediene University of Sciences and Technology, Algiers, Algeria.
²Laboratory of Bioactive Molecules and Arums Science, Sophia Antipolis University, UMR 6001 CNRS, France.

(Received September 21, 2009; Revised February 15, 2010; Accepted February 15, 2010)

Abstract: Enaminones 3 and 4, precursors of 4-thiazolidinones, were prepared by condensing tetronic acid (1a) and 4-hydroxy 6-methyl pyrone (1b) respectively with thiosemicarbazide derivatives 2 in refluxing ethanol. The 4-thiazolidinones 6, 7 derivatives were obtained by reacting compounds 3 or 4 with ethyl 2-bromo propionate 5 in the presence of anhydrous sodium acetate in ethalonic medium. Similarly, 9 products were synthesized by action of benzyl 2-bromo acetate 8 on 3.

Keywords: Pyrones; tetronic acid; thiosemicarbazides, enaminones; thiazolidinones.

1. Introduction

The structures of 4-thiazolidinones and 4-imino thiazolidinones are widely studied for their pharmacological properties.¹,² The 4-thiazolidinone derivatives are known to possess antimycobacterial³-⁴, anti-fungal⁵, anti-tuberculosis⁶-⁷, anti-convulsant⁸, anti-inflammatory⁹-¹¹ and anti-HIV¹²-¹⁴ activities. Various synthetic approaches of these molecules were reported.²,³,⁹,¹¹,¹³,¹⁵-²⁰ Nevertheless a common synthetic strategy to construct imino thiazolidinones is the cyclization of thiourea or thiosemicarbazide derivatives with α-halo esters or thioglycolic acids in presence of inorganic base (i.e., NaOAc) in polar solvents using either a conventional³,¹¹-¹⁶ or microwave irradiation methods.²¹,²³

In this paper, we are interested in the construction of this heterocyclic ring system from tetronic acid (n=0, 1a) and 4-hydroxy 6-methyl 2-one-pyran (n=1, 1b) with thiosemicarbazide derivatives 2 which give enaminones 3 and 4 respectively. These reacted with 2-bromo propionate 5 or benzyl 2-bromo acetate 8 leading to 4-thiazolidinones 6, 7 and 9 respectively.

* Corresponding author: Email-address: bellara.kollidz@yahoo.fr
Scheme 1 summarizes the chemical strategy used for the preparation of these compounds.

2. Results and Discussion

The synthesis of enaminolactones 3, 4 was carried out, in good yields as previously reported\textsuperscript{22}, by reacting a suitable tetronic acid (1a) or 4-hydroxy-6-methyl pyrane (1b) with an appropriate substituted thiosemicarbazide 2 in ethanol at reflux.

Enaminolactone thiosemicarbazid group 3 and 4 contains four nucleophilic centers, i.e. N\textsubscript{a}, N\textsubscript{b}, N\textsubscript{c} and the sulphur atom. Cyclisation possibilities of compounds 3 or 4 with ethyl 2-bromo propionate
5 could be achieved either by: nitrogen $N_a$ with sulphur (path way 1) or $N_b$ with sulphur (path way 2) or $N_c$ with sulphur (path way 3) to lead to 6, 7 and 10 or 11 structure respectively. It should be noted that cyclisation reaction of 3 or 4 with ethyl 2-bromo propionate 5 to 10 would not promote due to the $N_a$ free-double bound engaged in a conjugated ring system, that makes this atom less nucleophilic in comparison with $N_b$ and $N_c$ atoms.

In the used operating conditions, sodium acetate captures the nitrogen proton $N_b$ and results in thiol form, allowing the interaction type Soft-Soft between sulphur atom and the electrophile center (CH-Br) according to Pearson’s HSAB (Hard and Soft acids and bases) rules. The interaction Hard-Hard of nitrogen $N_c$ with the carbonyl function leads to 4-thiazolidinones 6, 7 and excludes the formation of structures 11.

Therefore, the cyclization reaction might be summarised in two steps:
First, the reaction is thought to be an S-alkylation of compounds 3 and 4 in its thiol form (due to the sodium acetate used).
The second step involves the ethanol removal and regeneration of acetic acid to give 4-thiazolidinones.

Scheme 2. Mechanism reaction of 4-thiazolidinones 6 and 7 from enaminolactones and ethyl 2-bromo propionate

Compounds 9 were obtained with a similar reaction mechanism using benzyl 2-bromo acetate 8 as reagent. Both analytical and spectral data of all the synthesized compounds are in full agreement with the formation of 4-thiazolidinones structures 6 and 7.

The IR spectra of 4-thiazolidinones 6, 7 and 9 gave lactam (C=O) stretching bands of the thiazolidinones ring at 1700-1705 cm$^{-1}$ in addition to the bands stretching (C=O) at 1651 and 1650 cm$^{-1}$ of enaminolactones.

The $^1$H-NMR spectra of these 4-thiazolidinone derivatives, reveal the absence of $N_c$-H and $N_b$-H of enaminolactones 3 or 4 commonly observed at 9-10 ppm and the presence of two new signals at 1.52 ppm as a doublet ($J=9$ Hz) and 4.50 ppm as a quadruplet ($J=9$Hz) attributed respectively to the methyl group -CH$_3$ and SCHCO proton of thiazolidinone moiety in structures 6 and 7. On the other
Preparation of 4-thiazolidinones from enaminolactones

hand, peaks at 19, 158 and 176 ppm in the $^{13}$C-NMR spectrum of structures $6a$-$c$ and $7a$-$c$ are assigned to the methyl group $-\text{CH}_3$, the imine $\text{C}=\text{N}$ and carbonyl $\text{C}=\text{O}$ functions respectively.

In conclusion, a series of 4-thiazolidinones $6$, $7$ were synthesized from enaminolactones $3$ or $4$ and ethyl 2-bromo propionate $5$ in the presence of anhydrous sodium acetate and acetic acid in refluxing absolute ethanol. Similarly, these enaminolactones react with benzyl 2-bromo acetate $8$ to lead $9$ derivatives. The reaction mechanism of these molecules shows a regiospecific cyclisation, involving the $\text{N}_c$ nitrogen and the sulphur atom.

3. Experimental

(Melting points were measured on a Buchi 512 apparatus and were uncorrected. FTIR were taken in Nujol on a Perkin –Elmer spectrometer. The $^1$H NMR spectra (250 MHz) and $^{13}$C NMR (63 MHz) were run on a Bruker spectrometer in DMSO- $d_6$ or CDCl$_3$ using tetramethyl silane as internal standard. The impact ionisation (IE) mass spectra were recorded on a Nermag R-10-10C at 70 ev. The elemental analysis data were performed on a Thermo Electron Flash EA 1112. Chemicals were purchased from Aldrich and Fluka.

The preparation of enamine derivatives $3$ and $4$ were previously described by us.

3.1. General procedure for the formation of 4-thiazolidinones $6a$-$c$ and $7a$-$c$.

10 mL of appropriate thiosemicarbazide $3$ or $4$ and 12 mL of ethyl bromo propionate $5$ were refluxed in 30 mL for 8-9 hours of absolute ethanol in the presence of 4 mL of anhydrous sodium acetate and 10 drops of acetic acid. The reaction mixture was cooled and concentrated under reduced pressure. Then, 30 mL of water was added to the residue and was extracted with 40 mL of ethyl acetate. The organic phase was dried over anhydrous Na$_2$SO$_4$. The product was isolated and separated on chromatography column employing different eluants ($7a$-$c$: CH$_2$Cl$_2$/ ethyl acetate (7:3); $6a$: petroleum ether / CH$_2$Cl$_2$ (5:1); $6b$: CH$_2$Cl$_2$/ ethyl acetate (9:1); $6c$: ethyl acetate).

Py: pyrone; Th: thiazolidinone.

5-methyl-1,3-thiazolidine-2,4-dione 2-[(5-oxo-2,5-dihydrofuran-3-yl)hydrazone] ($6a$):

Yield: 30 %; yellow crystal; m.p. 110-112 °C. IR (Nujol, cm$^{-1}$) 1650 (C=O$_{\text{py}}$), 1701 (C=0$_{\text{Th}}$); $^1$H NMR (250 MHz, DMSO- $d_6$) ($\delta$/ppm): 1.52 (d, 3H, Th, $\text{CH}_3$, $J$= 9 Hz), 4.33 (q, 1H, Th, CH, $J$=9Hz), 4.67 (s, 1H, py =CH), 4.74 (s, 2H, py CH$_2$), 9.78 (s, 1H, NH$_a$), 11.72 (s, 1H, NH); $^{13}$C NMR (63 MHz, DMSO- $d_6$) ($\delta$/ppm): 19.78 (CH$_3$), 45.13 (CH), 67.16 (CH$_2$), 81.93 (=CH), 158.61 (N=C), 167.06 (NC=), 175.05 (OC=O), 176.30 (NC=O). MS. (IE, 70eV): m/z  227([M+.], 22%), 183(33), 129(60), 100(15), 85(100), 83(23). Anal. Calcd. for C$_8$H$_9$N$_3$O$_3$S: C, 42.28;  H, 3.99, N, 18.49; O, 21.12; S, 14.11. Found: C, 42.40;  H, 3.85,  N, 18.30.

3,5-dimethyl-1,3-thiazolidine-2,4-dione 2-[(5-oxo-2,5-dihydrofuran-3-yl)hydrazone] ($6b$):

Yield: 68 %; Yellow crystal; m.p. 200-202 °C. IR (Nujol, cm$^{-1}$) 1651 (C=O$_{\text{py}}$), 1702 (C=0$_{\text{Th}}$); $^1$H NMR (250 MHz, DMSO- $d_6$) ($\delta$/ppm): 1.55 (d, 3H, Th, $\text{CH}_3$, $J$= 9 Hz), 3.06 (s, 3H, NCH$_3$), 4.38 (q, 1H, Th, CH, $J$=9Hz), 4.79 (s, 1H, py =CH), 4.81 (s, 2H, py CH$_2$), 10.17 (s, 1H, NH$_a$); $^{13}$C NMR (63 MHz, DMSO- $d_6$) ($\delta$/ppm): 19.75 (CH$_3$), 31.25 (CH$_3$), 45.16 (CH), 67.20 (CH$_2$), 81.95 (=CH), 158.63 (N=C), 167.10 (NC=), 175.07 (OC=O), 176.35 (NC=O). MS. (IE, 70eV): m/z  227([M+.], 22%), 183(33), 129(60), 100(15), 85(100), 83(23). Anal. Calcd. for C$_9$H$_{11}$N$_3$O$_3$S: C, 42.28;  H, 3.99, N, 18.49; O, 21.12; S, 14.11. Found: C, 42.40;  H, 3.85,  N, 18.30.
5-methyl-1,3-thiazolidine-2,4-dione-2-[(5-oxo-2,5-dihydrofuran-3-yl)hydrazone] (9a): Yield: 30 %; White crystal; m.p. 230-232 °C. IR (Nujol, cm⁻¹) 1651 (C=O pyr), 1705 (C=Oth), 1700 (C=Oth); ¹H NMR (250 MHz, DMSO- d₆) (δ/ppm): 4.02 (s, 2H, Th CH₂), 4.67 (s, 1H, py =CH), 4.74 (s, 2H, py CH₂), 9.98 (s, 1H, NH₂); ¹³C NMR (63 MHz, DMSO- d₆) (δ/ppm): 158.60 (C=O), 167.09 (C=n), 173.49 (C=O), 175.06 (C=O). S.M (IE, 70eV): m/z 213([M+], 17%), 197(4), 143(100), 117(32), 98(44), 87(12). Anal. Calcd. for C₃H₇N₂O₃S: C, 39.43; H, 3.31; N, 19.71; O, 22.51; S, 15.04. Found: C, 39.50; H, 3.28; N, 19.68.

3.2. Synthesis of 4-thiazolidinones compounds 9a-b.

A (10 mL) suspension of enaminolactones 3a-b and 12 mL of benzyl 2-bromo acetate 8 were refluxed in 30 mL of absolute ethanol in the presence 4 mL of anhydrous sodium acetate and 10 drops of acetic acid for 4 hours. The precipitate obtained was filtered and recrystallized in ethanol.

5-methyl-3-phenyl-1,3-thiazolidine-2,4-dione-2-[(2-methyl-6-oxo-3,6-dihydro-2H-pyran-4-yl)hydrazone] (7a): Yield: 34 %; Yellow crystal; m.p. 195-197 °C. IR (Nujol, cm⁻¹) 1650 (C=O pyr), 1702 (C=Oth); ¹H NMR (250 MHz, CDCl₃), (δ/ppm): 1.45 (d, 3H, py, CH₃), 1.62 (d, 3H, Th, CH₃, J=9 Hz), 2.50-2.65, (m, 2H, py CH₂), 2.41 (m, 1H, py CH), 4.52 (q, 1H, Th, CH, J=9Hz), 4.88 (s, 1H, py =CH), 9.50 (s, 1, 1H, NH₂), 11.92 (s, 1H, NH); ¹³C NMR (63 MHz, CDCl₃) (δ/ppm): 19.14 (CH₃), 20.78 (CH₂), 31.84 (CH₃), 44.29 (CH), 71.80 (CH), 83.35 (C=CH), 158.0 (N=C), 167.24 (NC=), 176.17 (C=O), 177.10 (NC=). S.M (IE, 70eV): m/z 255([M+], 14%), 211(40), 131(100), 112(55), 102(23), 87(24). Anal. Calcd. for C₁₀H₁₅N₃O₅S: C, 47.05; H, 5.13; N,16.46 ; O,18.80; S, 12.56. Found: C, 42.50; H, 3.91, N, 18.32.

5-methyl-1,3-thiazolidine-2,4-dione-2-[(2-methyl-6-oxo-3,6-dihydro-2H-pyran-4-yl)hydrazone] (7b): Yield: 30 %; Light brown oil; IR (Nujol, cm⁻¹) 1650 (C=O pyr), 1702 (C=Oth); ¹H NMR (250 MHz, CDCl₃) (δ/ppm): 1.45 (d, 3H, py, CH₃), 1.62 (d, 3H, Th, CH₃, J=9 Hz), 2.50-2.65, (m, 2H, py CH₂), 2.41 (m, 1H, py CH), 4.52 (q, 1H, Th, CH, J=9Hz), 4.64 (s, 1H, py =CH), 9.65 (s, 1, 1H, NH₂); ¹³C NMR (63 MHz, CDCl₃) (δ/ppm): 19.49 (CH₃), 20.88 (CH₂), 34.16 (NCH₃), 34.69 (CH₂), 45.94 (CH), 73.08 (CH), 83.35 (C=CH), 158.42 (N=C), 169.11 (NC=), 175.60 (C=O), 176.69 (NC=). S.M (IE, 70eV): m/z 269([M+], 30%), 145(25), 116(70), 112(100), 101(54), 87(5). Anal. Calcd. for C₁₀H₁₅N₃O₅S: C, 47.05; H, 5.13; N,16.46 ; O,18.80; S, 12.56. Found: C, 42.50; H, 3.91, N, 18.32.

5-methyl-3-phenyl-1,3-thiazolidine-2,4-dione-2-[(2-methyl-6-oxo-3,6-dihydro-2H-pyran-4-yl)hydrazone] (7c): Yield: 32 %; Yellow crystal; m.p. 276-278 °C. IR (Nujol, cm⁻¹) 1652 (C=O pyr), 1705 (C=Oth); ¹H NMR (250 MHz, DMSO- d₆) (δ/ppm): 1.31 (d, 3H, py, CH₃), 1.56 (d, 3H, Th, CH₃, J=9 Hz), 2.50 (m, 2H, py CH₂), 4.58 (m, 1H, py CH), 4.76 (q, 1H, Th, CH, J=9Hz), 4.86 (s, 1H, py =CH), 6.90-7.38 (5H, CH₃); 9.78 (s, 1, 1H, NH₂); ¹³C NMR (63 MHz, DMSO- d₆) (δ/ppm): 19.53 (CH₃), 21.46 (CH₂), 32.54 (CH₂), 45.04(CH), 72.28 (CH), 83.26 (=CH), 129.01-129.24-129.35-134.40 (C=aro), 158.79 (N=C), 168.24 (NC=), 176.97 (C=O), 177.88 (NC=). S.M (IE, 70eV): m/z 331([M+], 30%), 207(25), 178(100), 163(44), 112(54), 87(7). Anal. Calcd. for C₁₀H₁₅N₃O₅S: C, 57.99; H, 5.17; N, 12.68; O,14.48; S, 9.68. Found: C, 58.01; H, 5.19; N, 12.60.
3-methyl-1,3-thiazolidine-2,4-dione 2-[2-oxo-2,5-dihydrofuran-3-yl]hydrazone (9b): Yield: 40%; White crystal; m.p. 208-210 °C; IR (Nujol, cm-1) 1650 (C=O), 1704 (C=O); 'H NMR (250 MHz, DMSO-d6) (δ/ppm): 3.10 (s, 3H, NCH3), 4.00 (s, 2H, Th, CH3), 4.58 (s, 1H, py =CH), 4.71 (s, 2H, py CH2), 7.71 (s, 1H, NH); 13C NMR (63 MHz, DMSO-d6) (δ/ppm): 23.56 (NCH3), 33.95 (CH4), 4.71 (s, 2H, py CH2). Anal. Calcd for C8H10N2O3: S: C, 42.28; H, 3.99; N, 18.49; O, 21.12; S, 14.11. Found: C, 42.30; H, 3.91; N, 18.51.

References


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