THIAZOLIDINEDIONES: REACTIVITY OF THE ACTIVE METHYLENE GROUP

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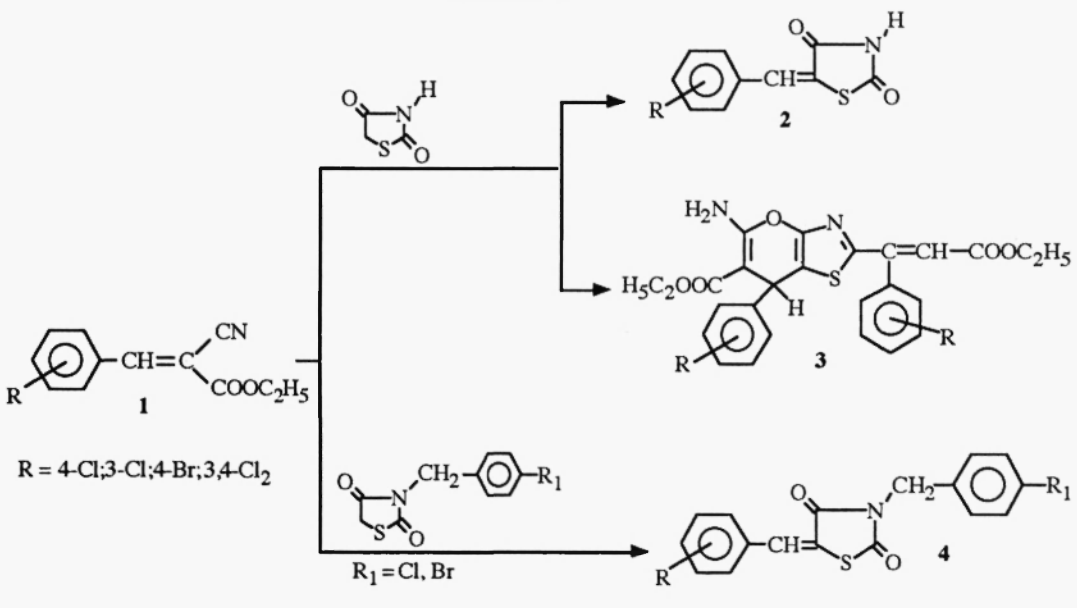
Abstract : The thiazolidine-2,4-diones contain an active methylene group. Thus, they give a nucleophilic addition reaction with alkyl 2-cyanocinnamates. Synthesis, mechanism of the reaction, physical and chemical properties of 5-benzylidene-thiazolidine-2,4-diones and pyrano-thiazoles obtained are described.

Introduction

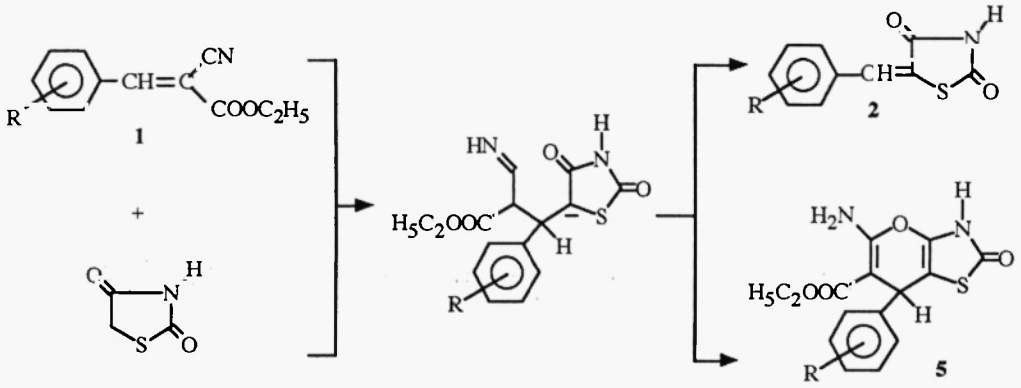
Thiazolidinedione and imidazolidinedione derivatives have been extensively studied because of their reactivity and their pharmacological properties (1,2). The synthesis of 5-benzylidene-thiazolidine-2,4-diones and 5-benzylidene-imidazoline-2,4-diones substituted in the 3-position by a benzyl group has been previously reported (3-7). In continuation of these works, we described here the condensation of the thiazolidine-2,4-dione, substituted or unsubstituted in the 3-position, on the ethylenic carbon of alkyl 2-cyanocinnamates via Michael addition (8,9). This reaction affords 5-benzylidene-thiazolidine-2,4-diones (compounds **2** and **4**) and a side product. The latter is a cycloadduct to which we assigned the structure 2-(1-phenyl-2-ethoxycarbonyl-eth-1-en-1-yl)-5-amino-6-ethoxycarbonyl-7-phenyl-7*H*-pyrano[3,2-d][1,3]thiazole (compounds **3**) on the basis of the spectral data.

Scheme 1

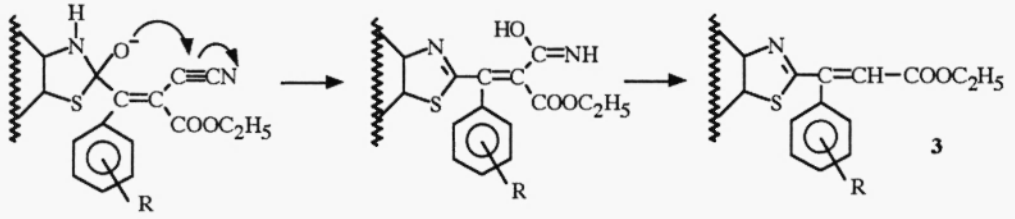


Synthesis and structural study

The alkyl 2-cyanocinnamates **1** were prepared by condensation of benzaldehydes with ethyl cyanoacetate in alcaline medium (8). The nucleophilic addition of the thiazolidine-2,4-dione to the double bond in the cyanocinnamic esters led to 5-benzylidene-thiazolidine-2,4-diones **2**. During this reaction, an intermediate should be formed : the 2-oxo-5-amino-6-ethoxycarbonyl-7-phenyl-7H-pyrano[3,2-d][1,3]thiazole **5**.



This intermediate **5** has not been isolated; it can undergo the nucleophilic attack of another molecule of cyanocinnamic ester on the carbonyl group in the 2-position with elimination of the CN group. Thus, the 2-(1-phenyl-2-ethoxycarbonyl-eth-1-en-1-yl)-5-amino-6-ethoxycarbonyl-7-phenyl-7H-pyrano[3,2-d] [1,3]thiazoles **3** are formed. Structure was assigned by ^{1}H-NMR and mass spectra. Synthesis of closely related compounds, e.g. pyrano-[2,3-c]pyrazoles, has been previously described (10) with a yield of 72 to 95%.



Addition of ethyl 2-cyano-4-chlorophenylacrylate **1a** with N-benzyl-thiazolidine substituted by a chloro or a bromo atom in para position affords the expected 5-benzylidene-N-benzyl-thiazolidine-2,4-diones **4a** and **4c** and a side product, 2-[1-(4-chlorophenyl)-2-ethoxycarbonyl-eth-1-en-1-yl]-5-amino-6-ethoxycarbonyl-7-phenyl-7H-pyrano[3,2-d] [1,3] thiazole **3a**. This compound is obtained after the lateral chain in the 3-position of the compounds **4** has been broken.

If the addition of ethyl 2-cyano-4-chlorophenylacrylate **1a** with 3-(4-chlorobenzyl)-thiazolidine-2,4-dione is carried out in the presence of sodium ethoxide, without heating, the uncyclised product **4c** is only formed, with a yield of 87%.

The condensation of thiazolidines with benzaldehydes in acetic acid medium in the presence of sodium acetate (3-7) can also give the 5-benzylidene-thiazolidine-2,4-diones, substituted or unsubstituted in the 3-position

Experimental protocols

Melting points were determined with a capillary Büchi apparatus and are uncorrected.
I.R. spectra were recorded in 2% KBr tablets with a Perkin-Elmer 1310 spectrophotometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ or in DMSO-d_6 with a Bruker AC-200 spectrometer. Chemical shifts are given in δ values (ppm). Electronic impact mass spectra (70 eV) were obtained with a R-1010C Delsi-Nermag spectrometer. Thin layer chromatography was performed on silica plates pre-coated with Merck Kiesegel $60F_{254}$ and column chromatography, with silica gel (mesh 70-230).

Condensation of ethyl cyanoacetate with benzaldehydes:
In a round-bottomed flask equipped with a Dean-Stark apparatus, a mixture of 0.01 mol of aldehyde, 0.01 mol of ethyl cyanoacetate, 0.8 mL of acetic acid and 0.8 g of sodium acetate in 30 mL of benzene is heated under reflux to complete elimination of water (5 h). After cooling, the solid is filtered off and recrystallized from a suitable solvent. Compounds **1a-d** were prepared according to this procedure.

Addition of the thiazolidine-2,4-diones to cyanocinnamates:
An equimolar mixture of 2,5 mmol of thiazolidine and ethyl cyanocinnamate is dissolved in 20 mL of absolute ethanol with 0.25 mL of piperidine and refluxed for 90 min. After cooling, the reaction mixture is poured into cracked-ice and neutralized with acetic acid up to pH7. The precipitate is filtered off and purified either by crystallization or by column chromatography to give compounds **2** and **4**. The filtrate was brought to dryness *in vacuo*. The oily residue is taken up with $CHCl_3$. After filtration and evaporation, the residue is purified either by column chromatography with chloroform or by two recrystallizations from acetic acid. Compounds **3a-c** were obtained with 1.5 - 6.6% yield. The spectroscopic data are given in Table **1**.

Ethyl 2-cyano-4-chlorophenylacrylate **1a** : recrystallized from ethanol/water ; yield 86% ; mp 95°C lit 92°C (11) ; Rf $CHCl_3$ 0.89
Ethyl 2-cyano-3-chlorophenylacrylate **1b** : recrystallized from absolute ethanol ; yield 62% ; mp 108°C lit 101.2-101.6°C (12) ; Rf C_6H_6/CH_3OH 4/1 0.69
Ethyl 2-cyano-4-bromophenylacrylate **1c** : recrystallized from absolute ethanol.; yield 57% ; mp 115°C litt. (13) mp 97.5°C ; Rf C_6H_6/CH_3OH 4/1 0.62
Ethyl 2-cyano-3,4-dichlorophenylacrylate **1d** : recrystallized from ethanol/water ; yield 87% ; mp 137-8°C lit 124°C (14) ; Rf $CHCl_3$ 0.85
5-(4-chlorobenzylidene)-thiazolidine-2,4-dione **2a** : recrystalllized from acetic acid ; yield 21% ; mp 235°C lit 223-5°C (15) ; Rf C_6H_6/CH_3OH 4/1 0.35

Table 1 : Spectroscopic data

N°	IR (ν cm^{-1}) KBr	^{1}H NMR (δ ppm)	Mass M$^+$(%)
1a	2208 (CN); 1695 (CO); 1587 (C=C)	1.40 (t, 3H) J = 7.1; 4.39 (q, 2H) J = 7.2; 7.48 (d, 2H2,6), J = 8.6; 7.93 (d, 2H3,5) J = 8.5; 8.19 (s, =CH)	
1b	2220 (CN), 1715 (CO); 1610 (C=C)	1.30 (t, 3H) J = 7.1; 4.32 (q, 2H) J = 7.1; 7.61 (q, H5) J = 7.5; 7.68 (m, H4); 7.99 (d, H6) J = 7.5; 8.07 (m, H2); 8.38 (s, =CH).	
1c	2220 (CN); 1720 (CO); 1610 (C=C)	1.40 (t, 3H) J = 7.1; 4.39 (q, 2H) J = 7.1; 7.64 (d, 2H2,6) J = 8.6; 7.85 (d, 2H3,5) J = 8.5; 8.18 (s, =CH).	
1d	2222 (CN); 1712 (CO); 1603 (C=C)	1.41 (t, 3H) J = 7.4, 4.40 (q, 2H) J = 7.4, 7.60 (d, H5) J = 8.5, 7.90 (dd, H5) J = 8.5 et J = 2.2); 8.01 (d, H2) J = 2.2; 8.15 (s, =CH).	
2a	1720, 1750 (CO); 1610 (C=C)	7.59 (s, 4H); 7.77 (s, =CH); 12.64 (s, NH).	
2b	1675, 1745 (CO); 1615 (C=C).	7.54 (m, 3H4,5,6); 7.66 (s, H2); 7.77 (s, =CH); 12.67 (s, NH).	
2c	1720, 1745 (CO); 1610 (C=C)	7.52 (d, 2H2,6) J = 8.2, 7.72 (d, 2H3,5) J = 8.2; 7.74 (s, =CH).	
3a	3390, 3280 (NH); 1705, 1685, 1665 (C=O); 1620 (C=C)	1.19 (t, CH3) J = 7.1; 1.25 (t, CH3) J = 7.1; 4.08 (q, CH2) J = 7.1; 4.16 (q, CH2) J = 7.2; 4.90 (s, CH), 7.67 (s, =CH); 7.14 (d, 2H2,6) J = 8.6, 7.19 (d, 2H3,5) J = 8.6, 7.44 (d, 2H2,6) J = 8.6; 7.55 (d, 2H3,5) J = 8.6; 8.68 (s, NH2).	544 (5.4) 433 (100)
3b	3390, 3260 (NH); 1705, 1690, 1660 (CO); 1620 (C=C)	1.19 (t, CH3) J = 7.1; 1.26 (t, CH3) J = 7.1; 4.08 (q, CH2) J = 7.1; 4.19 (q, CH2) J = 7.1; 4.89 (s, CH), 7.66 (s, =CH); 7.09 (d, 2H6) J = 8.4; 7.34 (d, H5) J = 8.4; 7.48 (d, 2H2) J = 8.6; 7.61 (d, 2H5) J = 8.6; 8.68 (s, NH2).	632 (48.6) 634 (100)
3c	3400, 3260 (NH); 1715, 1695, 1665 (CO); 1630 (C=C)	1.19 (t, CH3) J = 7.1; 1.26 (t, CH3) J = 7.1; 4.15 (m, 4H, CH2); 4.90 (s, CH); 7.66 (s, =CH); 7.12 (m, 4H); 7.48 (m, 4H); 8.69 (s, NH2).	544 (1.6) 433 (100)
4a	1670, 1730 (CO); 1600 (C=C)	4.80 (s, CH2); 7.27 (d, 2H2,6, 4Cl-Ph) J = 8.3; 7.54 (d, 2H3,5) J = 8.2; 7.63 (dd, 4H, 4Br-Ph), 7.96 (s, =CH).	407 (26.5) 168 (100)
4b	1682, 1743 (CO); 1618 (C=C);	4.85 (s, CH2); 7.32 (d, 2H3,5, 4Br-Ph), J = 8.5; 7.48 (d, 2H2,6) J = 8.5; 7.32 (d, H6, 3,4Cl2-Ph) J = 8.5, 7.55 (d, H5) J = 8.8, 7.57 (d, H2) J = 2.5; 7.78 (s, =CH).	441 (26.8) 169 (100)
4c	1682, 1737 (C=O); 1610 (C=C)	4.86 (s, CH2); 7.30 (d, H2,6, 4Cl-C5H4CH2), J = 8.8); 7.38 (d, 2H3,5) J = 8.6) 7.43 (s, 4H, 4-ClC5H4CH), 7.84 (s, =CH)	363 (33.1) 125 (100)

(Solvents: CDCl3: **1a, 1c, 1d, 3a, 3b, 3c, 4b, 4c**; DMSO-d6: **1b, 2a, 2b, 2c, 4a**)

5-(3-chlorobenzylidene)-thiazolidine-2,4-dione **2b** : recrystalllized from acetic acid ; yield 30% ; mp 222°C lit 214-5°C (16); Rf C_6H_6/CH_3OH 4/1 0.42

5-(4-bromobenzylidene)-thiazolidine-2,4-dione **2c** : recrystalllized from acetic acid ; yield 51.5% ; mp 247°C ; Rf C_6H_6/CH_3OH 4/1 0.60

2-[1-(4-chlorophenyl)-2-ethoxycarbonyl-eth-1-en-1-yl]-5-amino-6-ethoxycarbonyl-7-(4'-chlorophenyl)-7H-pyrano[3,2-d] [1,3]thiazole **3a** : purified by column chromatography with $CHCl_3$; yield 6.6% ; mp 246-7°C ; Rf $CHCl_3$ 0.40

2-[1-(4-bromophenyl)-2-ethoxycarbonyl-eth-1-en-1-yl]-5-amino-6-ethoxycarbonyl-7-(4'-bromophenyl)-7H-pyrano[3,2-d] [1,3]thiazole **3b** : purified by column chromatography with $CHCl_3$; yield 2,2% ; mp 228°C ; Rf $CHCl_3$ 0.38

2-[1-(3-chlorophenyl)-2-ethoxycarbonyl-eth-1-en-1-yl]-5-amino-6-ethoxycarbonyl-7-(3'-chlorophenyl)-7H-pyrano[3,2-d] [1,3]thiazole **3c** : purified by column chromatography with $CHCl_3$; yield 1,5% ; mp 222°C ; Rf $CHCl_3$ 0.40

3-(4-bromobenzyl)-5-(4-chlorobenzylidene)-thiazolidine-2,4-dione **4a** : recrystallized from absolute ethanol ; yield 62% ; mp 173-4°C lit 176-7°C (6) ; Rf $CHCl_3$ 0.82

3-(4-bromobenzyl)-5-(3,4-dichlorobenzylidene)-thiazolidine-2,4-dione **4b** : purified by column chromatography with hexane/methylene chloride then recrystallized from absolute ethanol ; yield 23% ; mp 192-3°C ; Rf $CHCl_3$ 0.94

3-(4-chlorobenzyl)-5-(4-chlorobenzylidene)-thiazolidine-2,4-dione **4c** : recrystallized from absolute ethanol ; yield 79% ; mp 185°C ; Rf CH_2Cl_2 0.90

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