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Bifunctional Derivative of p,p'-Dichlorochalcone. Part II. Synthesis of a Novel Compound 2-[2-Carboxymethylthio-2-(4-chlorophenyl)ethyl]-2-(4-chlorophenyl)-4-thiazolidinone

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Abstract: The synthesis of 2-[2-carboxymethylthio-2-(4-chlorophenyl) ethyl]-2-(4-chlorophenyl) - 4-thiazolidinone (1) from p, p'- dichlorochalcone using thioglycollic acid in the presence of ammonium carbonate is described. Structural assignment and stereochemistry are discussed.

Keywords: Organic synthesis, chalcone, thiazolidinone, ^{1}H-NMR, ^{13}C-NMR.

Introduction

4-Thiazolidinones substituted in the 2-position, (-)-2-(5-carboxypentyl)-4-thiazolidinone, its derivatives and analogues [1] exhibit unusually high in vitro activity against Mycobacterium tuberculosis. Recently, a number of 2-pyridyl substituted 4-thiazolidinones has been synthesised and found to exhibit highly potent and selective anti-Platelet Activating Factor activity both in vitro and in

vivo [2]. As part of our aim in search of biologically active compounds with sulphur and nitrogen containing heterocycles, we have synthesised a 2-substituted tetrahydro-1,3-thiazin-4-one [3] (its biological screening is under study [4]). Because 4-thiazolidinones substituted in the 2 position were proven to be biologically very potent and selective [1-2], we extended our work on the synthesis of 2-[2-carboxymethylthio-2-(4-chlorophenyl)ethyl]-2-(4-chlorophenyl)-4-thiazolidinone (**1**), a novel compound, from p,p'-dichlorochalcone (**2**) using thioglycollic acid in the presence of ammonium carbonate.

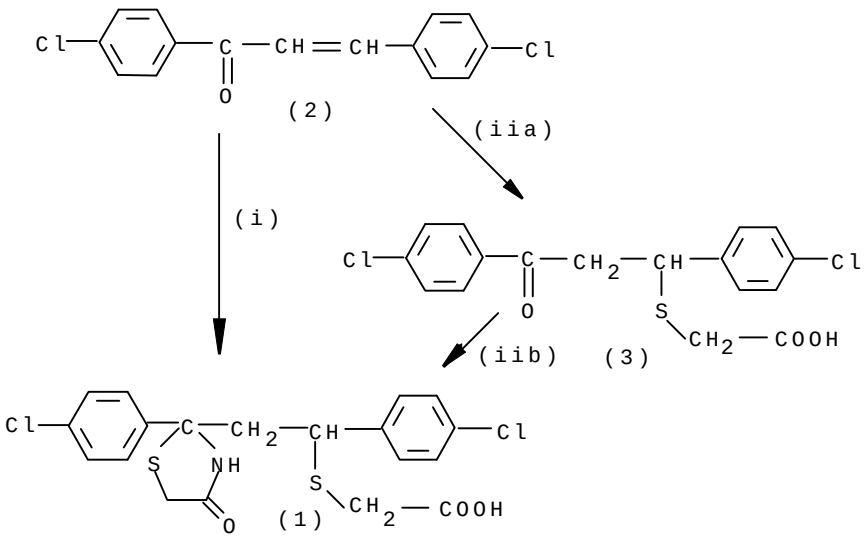
Results and Discussion

We report here the synthesis of compound (**1**) in two ways (Scheme 1):

(i) - a mixture of chalcone (**2**), thioglycollic acid and ammonium carbonate (molar ratio (1:2.5:5) in dry benzene was refluxed for 35 h. Purification of the products by column chromatography over silicagel followed by crystallisation afforded compound (**1**) as colourless globules in good yield (65%).

(ii-a) - a mixture of chalcone (**2**) and thioglycollic acid (molar ratio 1:1.25) in dry benzene was refluxed for 2h; the reaction mixture on crystallisation gave colourless needles of thioether (**3**) in 77% yield.

(ii-b) - the thioether (**3**) in dry benzene was then refluxed with thioglycollic acid and ammonium carbonate (molar ratio 1:1.25:5) for 32 h and the products on purification as above furnished compound (**1**) (64%).



Scheme 1. Synthesis of (**1**). (i) (**2**): $HSCH_2COOH$: $(NH_4)_2CO_3$ (molar ratio 1:2.5:5), dry benzene, reflux, 35h. (ii-a) (**2**): $HSCH_2COOH$ (molar ratio 1:1.25), dry benzene, reflux, 2h. (ii-b) (**3**): $HSCH_2COOH$: $(NH_4)_2CO_3$ (molar ratio 1: 1.25:5), dry benzene, reflux, 32h.

The constitution of (**1**) is confirmed by ^{1}H-NMR, ^{13}C-NMR, INEPT, COSY, HETCOR and long-range-HETCOR spectra (Tables 1 and 2). These spectra and an additional NOE-experiment also

suggest that the relative configuration of product (**1**) is most probably *u* (unlike [5]), and the partial conformation of both central bonds C-2-C-1' and C-1'-C-2 ' is antiperiplanar (Figure 1 [6]).

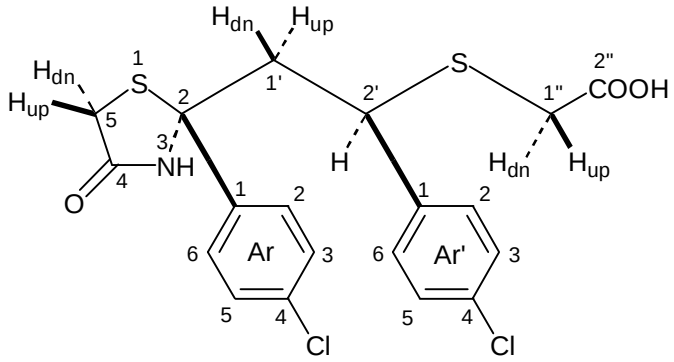


Figure 1.

Table 1. ^{1}H-NMR data of (**1**).

H-nr	δ (ppm)	Integration	Multiplicity	J (Hz)	NOE
5_{up}	3.42	1H	d	$J_{5up,5dn}$ 15.56	
5_{dn}	3.59	1H	d	$J_{5up,5dn}$ 15.56	
NH	9.20	1H	s	-	Ar-2,6; 2 '
$1'_{up}$	2.66	1H	dd	$J_{1'up,1'dn}$ 14.65; $J_{1'up,2'}$ 3.21	
$1'_{dn}$	2.82	1H	dd	$J_{1'up,1'dn}$ 14.65; $J_{1'dn,2'}$ 9.46	
2'	4.14	1H	dd	$J_{1'up,2'}$ 3.21; $J_{1'dn,2'}$ 9.46	
$1''_{up}$	2.85	1H	d	$J_{1''up,1''dn}$ 15.26	
$1''_{dn}$	3.04	1H	d	$J_{1''up,1''dn}$ 15.26	
Ar-2,6	7.29	2H	d	$J_{Ar\text{-}2,6,Ar\text{-}3,5}$ 8.85	$1'_{up}$, $1'_{dn}$, 2', NH
Ar-3,5	7.23	2H	d	$J_{Ar\text{-}2,6,Ar\text{-}3,5}$ 8.85	
Ar'-2,6	7.13	2H	d	$J_{Ar'\text{-}2,6,Ar'\text{-}3,5}$ 8.55	$1'_{dn}$, 2', $1''_{up}$
Ar'-3,5	7.20	2H	d	$J_{Ar'\text{-}2,6,Ar'\text{-}3,5}$ 8.55	

Especially the ^{1}H-NMR spectrum contains stereochemical information. Both the diastereotopic hydrogen atoms as well at C-1" as at C-5 are well separated from each other, one hydrogen atom of each pair, H_{up}, being above the phenyl ring in the shielding cone and the other one, H_{dn}, outside of it. Also the diastereotopic hydrogen atoms at C-1' are well separated. According to Karplus [8] the coupling constants reveal an antiperiplanar torsion angle for H_{dn}-1' and H-2', and a synclinal torsion angle for H_{up}-1' and H-2'. Further, irradiation of the NH-proton results in a NOE-enhancement of H-Ar-2,6, but also of H-2' which means that the NH-proton and H-2' are very near to each other. Irradiation

of H-Ar'-2,6 activates H-2', but also H_{dn}-1' and H_{up}-1", which means that also these protons are very near to each other. Molecular mechanics calculations confirm that the structure as shown in figure 1 is the most stable form of compound (**1**).

Table 2. ^{13}C-NMR data of (**1**).

C-nr	δ (ppm)	INEPT	Longe-range HETCOR correlation with
2	69.30	C	H-Ar-2,6; $H\text{-}1'_{up}$; H-2'; NH
4	172.45	C	$H\text{-}5_{up}$; $H\text{-}5_{dn}$
5	32.91	CH_2	NH
1'	49.08	CH_2	
2'	44.52	CH	H-Ar'-2,6; $H\text{-}1''_{up}$; $H\text{-}1''_{dn}$
1"	32.91	CH_2	
2"	170.70	C	$H\text{-}1''_{up}$; $H\text{-}1''_{dn}$
Ar-1	143.41	C	H-Ar-3,5
Ar-2,6	126.79	CH	H-Ar-2,6
Ar-3,5	127.78[a]	CH	H-Ar-3,5
Ar-4	131.84	C	H-Ar-2,6
Ar'-1	139.93	C	H-Ar'-3,5; H-1'
Ar'-2,6	129.87	CH	H-Ar-2,6; H-2'
Ar'-3,5	127.86[a]	CH	H-Ar'-3,5
Ar'-4	131.28	C	H-Ar'-2,6

[a] Assignment may be reversed.

Experimental

Melting points were determined on a Koffler hot-plate apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 621 spectrophotometer; ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Unity 400 spectrometer and DCI-mass spectra with a Ribermag R10-10B quadrupole mass spectrometer. Reagents and solvents were of commercial grade and were used without further purification. Column chromatography was performed on Silica Gel 60 (120 mesh) (194013).

p,p'-Dichlorochalcone (**2**) was prepared following a published but slightly modified procedure [9] by condensing *p*-chloroacetophenone with *p*-chlorobenzylidene diacetate (both prepared according to reported procedures [10]) in equimolar ratio in the presence of 2.5 equivalents of sodium hydroxide as light yellow crystalline needles in 85% yield, m.p. 156°C, Rf 0.72 (petroleum ether (40-60°): benzene – 1:1 v/v).

*2-[2-Carboxymethylthio-2-(4-chlorophenyl)ethyl]-2-(4-chlorophenyl)-4-thiazolidinone(***1***)*

(i) A mixture of p,p'-dichlorochalcone (2) (570mg, 2.06 mmol), thioglycollic acid (474 mg, 5.15 mmol) and ammonium carbonate (989 mg, 10.3 mmol) in dry benzene (20ml) was refluxed for 35 h with stirring, and collecting the generated water in an azeotropic collector. The solution was then cooled, washed with water and the organic phase dried over Na_2SO_4. The solvent was distilled off under reduced pressure and the orange oily residue left was chromatographed over a silicagel column (pet. ether (40-60°): diethyl ether 3:7 v/v). The solid product (light orange) obtained was recrystallised from benzene-acetone yielding (**1**) as white crystalline globules, 590 mg (64.9%), m.p. 205°C, Rf 0.19 (pet. ether (40-60°) : diethyl ether - 3:7 v/v).

(ii-a) A solution of p,p'-dichlorochalcone (**2**) (850 mg, 3.07 mmol) and thioglycollic acid (355 mg, 3.84 mmol) in dry benzene (25 ml) was refluxed for 2h, cooled, washed with water and the organic layer dried over Na_2SO_4. The white solid obtained on evaporation of the solvent was crystallised from benzene to furnish white crystalline needles (**3**), 870 mg (76.9%), m.p. 116°C, Rf 0.84 (pet. ether (40-60°) : diethyl ether 3:7 v/v).

(ii-b) To a solution of the thioether (**3**) (450 mg, 1.22 mmol) in dry benzene (15 ml) was added thioglycollic acid (140 mg, 1.52 mmol) and ammonium carbonate (585 mg, 6.1 mmol). This mixture was refluxed for 32 h. The products on usual workup and crystallisation gave (**1**) as white crystalline globules, 340 mg (64%), m.p. 205°C, Rf 0.19 (pet. ether (40-60°) : diethyl ether - 3:7 v/v).

IR (KBr) : ν_{max} 3400 (NH), 3150 (-OH), 1720 (-COOH), 1670 (-CONH-), 1610, 1590 (phenyl), 1480 (S-CH_2), 1410 (C-N), 1270, 1080, 1000, 820 cm^{-1} - DCI-MS (NH3) : m/z 442/444/446 [M^++1].

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Sample Availability: Available from the authors.