A NOVEL WAY OF SYNTHESIS OF 1,3,5-TRISUBSTITUTED-2-THIOXOIMIDAZOLIDINONES

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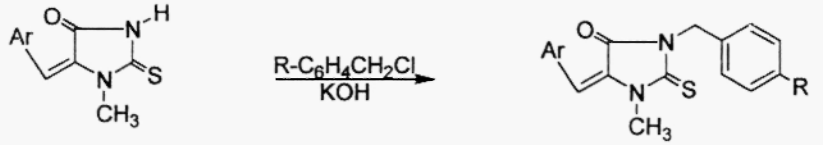
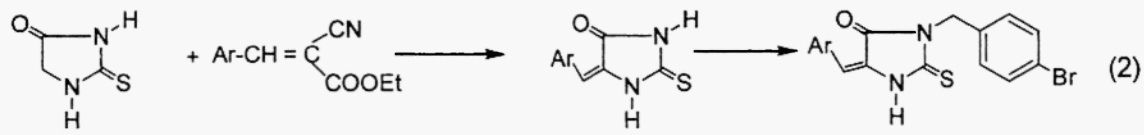
Owing to their pharmacological properties[1-3], imidazolidinediones and thiazolidinediones are widely studied compounds. The synthesis of some 3-benzyl-5-arylidene-imidazolidine-2,4-diones and 5-arylidene-1-methyl-2-thioxo-imidazolidin-4-ones was reported in previous papers[4-7] and we now describe the synthesis and physicochemical data of new 3-(4-bromobenzyl, 4-fluorobenzyl or biphenyl-4-yl-methyl)-1-methyl-2-thioxo-5-arylidene-imidazolidin-4-ones (**2**) as shown in Eq. 1.



1 **2** (1)

a) Ar = C_6H_5, R = Br b) Ar = 3-ClC_6H_4, R = Br c) Ar = 4-ClC_6H_4, R = Br d) Ar = C_6H_5, R = F e) Ar = 3-ClC_6H_4, R = F f) Ar = 4-ClC_6H_4, R = F g) Ar = C_6H_5, R = C_6H_5 h) Ar = 3-Cl-C_6H_4, R = C_6H_5

In addition, some other new 3-(4-bromo-benzyl)-2-thioxo-5-arylidene-imidazolidin-4-ones (**6**) were obtained by nucleophilic Michael addition of 2-thioxoimidazolidin-4-one (**3**) to 3-aryl-2-cyano acrylates (**4**), followed by alkylation (Eq. 2).



3 4 5 6 (2)

a) Ar = 4-ClC_6H_4, b) Ar = 2-BrC_6H_4, c) Ar = 3-ClC_6H_4, d) Ar = 4-$CH_3C_6H_4$, e) Ar = 2-OCH_3,5-BrC_6H_3, f) Ar = C_6H_5-CH_2-O-C_6H_4 g) Ar = 3-indolyl

Chemical and spectroscopic data of compounds (**2**) and (**6**) are gathered in tables 1 to 3.

Table 1.- Physicochemical data of thioxoarylideneimidazolidine compounds.

Cmpd	Yield (%)	mp (°C)	R_f*	IR (νcm^{-1})		MS (m/z)	
				C=O	C=C	M+(%)	(100%)
2a	45	214-216	0.80	1680	1610	386(41.6)	89
2b	75	184	0.88	1685	1610	420(14.6)	89
2c	78	228-230	0.76	1690	1610	420(25.8)	89
2d	76	208-209	0.77	1675	1610	326(41.9)	109
2e	48	150	0.78	1680	1610	360(13.2)	109
2f	55	185-187	0.73	1675	1610	360(17.2)	109
2g	31	92-94	0.93	1690	1615	384(12.7)	116
2b	71	158-160	0.71	1685	1610	418(14.3)	167
5a	56	250-252	0.62	1720	1640	238(8.2)	89
5b	59	237-238	0.34	1720	1655	282(52.4)	89
5c	29	224-226	0.46	1718	1649	238(98.8)	89
5d	62	258-260	0.44	1730	1650	218(36.8)	131
5e	66	251-252	0.55	1745	1650	312(81.2)	314
5f	82	240-241	0.68	1725	1646	310(100)	310
5g	76	285-287	0.40	1711	1638	243(100)	243
6a	95	268-270	0.43	1717	1632	406(41.4)	169
6b	90	205-207	0.52	1700	1620	450(21.8)	90
6c	43	244-245	0.48	1710	1630	406(34.4)	169
6d	95	158-160	0.48	1700	1625	386(60.5)	171
6e	79	250-252	0.50	1720	1633	480(22)	42
6f	87	205-207	0.60	1707	1629	478(7.2)	91
6g	90	217-219	0.51	1674	1605	411(4.7)	89

* Eluent: **2**,$CHCl_3$:MeOH, 96:4; **5a**, CH_2Cl_2:MeOH, 99:1; **5b**, CH_2Cl_2; **5c-5e**,**6a**, *n*-Hex:AcOEt 70:30; **5f**, C_6H_6/MeOH, 90:10; **5g**, *n*-Hex:AcOEt, 60:40; **6b**, **6d**, **6g**, CH_2Cl_2:MeOH, 95:5; **6c**, **6e**, $CHCl_3$:MeOH, 95:5; **6f**, nHex:AcOEt 50:50.

Table 2. ^{1}H NMR Chemical Shifts of Thioxoarylidene-1-methylimidazolidines (**2**).

Cmpd	NCH_3	CH_2	=CH	Ar	R
2a	3.30	4.55	6.81	8.21(2H,m) / 7.40(3H,m)	7.54(2H,d) J=8.2 / 7.44(2H,d) J=8.2
2b	3.30	4.55	6.81	8.46(1H,s) / 8.06(1H,m) 7.43(2H,m)	7.54(2H,d) J=8.4 / 7.43(2H,d) J=8.4
2c	3.29	4.55	6.,82	8.25(2H,d) J=8.7 7.48(2H,d) J=8.9	7.54(2H,d) J=8.5 / 7.43(2H,d) J=8.8
2d	3.30	4.56	6.81	8.22(2H,m) / 7.40(3H,m)	7.52(2H,m) / 7.16(2H,m)
2e	3.28	4.56	6.79	8.46(1H,s) / 8.06(1H,m) 7.42(2H,m)	7.52(2H,m) / 7.16(2H,m)
2f	3.29	4.56	6.81	8.25(2H,d) J=8.0 7.47(2H,d) J=7.9	7.52(2H,m) / 7.16(2H,m)
2g	3.24	4.50	6.77	8.19(2H,m) 7.27-7.62(3H,m)	7.27-7.62(12H,m)
2h	3.22	4.50	6.76	8.44(1H,s) / 8.04(1H,m) 7.27-7.62(2H,m)	7.27-7.62(9H,m)

Table 3. ^{1}H NMR Chemical Shifts of Thioxoarylidene imidazolidines (**5, 6**).

Cmpd	CH_2	=CH	NH	CH_3/OCH_3	Ar	4-BrC_6H_4
5a		6.45	12.10(2H)		7.77(2H,d)J=8.7 / 7.46(2H,d)J=8.4	
5b		6.56	12.39(2H)		7.76(2H,m) / 7.45(1H,m) 7.32(1H,m)	
5c		6.47	12.35(2H)		7.86(1H,s) / 7.43(2H,m) 7.67(1H,m)	
5d		6.46	12.22(2H)	2.34	7.66(2H,d)J=8.1 / 7.24(2H,d)J=8.1	
5e		6.58	12.34(2H)	3.85	7.82(1H,d)J=2.1 / 7.52(1H,dd) J=9.0-2.4 /7.02(1H,d)J=9.0	
5f	5.18	6.47	12.30(1H) 12.10(1H)		7.74(1H,d)J=9.0 / 7.41(5H,m) 7.06(1H,d)J=8.7	
5g		6.84	12.04(1H) 11.80(2H)		8.48(1H,s) / 7.81(1H,d)J=7.2 7.46(1H,d)J=7.8 / 7.19(2H,m)	
6a	4.51	6.63			8.17(2H,d)J=8.7 / 7.49(2H,d)J=8.7	7.55(2H,d)J=8.1 7.47(2H,d)J=8.4
6b	4.52	6.94			8.79(1H,d)J=7.8 / 7.53(1H,m) 7.71(1H,d)J=8.1 / 7.30(1H,m)	7.54(2H,d)J=8.4 7.46(2H,d)J=8.7
6c	4.53	6.74	12.30(1H)		8.37(1H,s) / 8.04(1H,d)J=6.6 7.45-7.52(2H,m)	7.45-7.52(4H,m)
6d	4.48	6.53		2.33	8.03(2H,d)J=8.4 / 7.53(2H,d)J=8.7	7.23(2H,d)J=7.8 7.47(2H,d)J=8.4
6e	4.50	6.98		3.86	8.89(1H,d)J=2.1 / 7.55(1H,d)J=2.4 7.05(1H,d)J=8.9	7.51(4H,s)
6f	4.51 5.18	6.72	11.75(1H)		8.14(2H,d)J=8.7 / 7.44(5H,m) 7.10(2H,d)J=9.0	7.54(2H,d)J=8.4 7.47(2H,d)J=8.7
6g	4.58	7.14	11.92(1H) 11.60(1H)		8.42(1H,s) / 8.11(1H,d)J=7.8 7.18(1H,m) / 7.47-7.57(2H,m)	7.47-7.57(4H,m)

As shown in these tables, to use 1,4-nucleophilic addition gave a better reaction yield than the classical synthetic way based on a Knoevenagel-type condensation gives.

Moreover, fragmentations and peak intensities observed in electronic impact MS allowed to propose the molecular structures of compounds isolated.

Finally, one must emphasize that the 3-benzyl-1-methyl-2-thioxo-5-arylidene-imidazolidin-4-ones (**2**) and the 3-(4-bromo-benzyl)-2-thioxo-5-arylidene-imidazolidin-4-ones (**6**) were isolated in a single isomer form. It has been previously demonstrated[6,7] that Z isomer was the major derivative obtained in the case of the arylidene imidazolidinones Actually in 5-(3-chloro-benzylidene-1-methyl-2-thioxo-imidazolin-4-ones, value of the vicinal coupling constant between ethylenic proton and 4-carbonyl carbon determined by using coupled ^{13}C-H NMR, *e.g.* 9.93Hz, agrees with that of Z isomer as previously shown for several structurally related compounds[4].

EXPERIMENTAL SECTION

Melting points were measured on a Buchi apparatus. Thin layer chromatography was performed on Merck 60 F254 silica gel plates with a 0.2 mm thickness. Compounds were powdered, mixed with KBr at 1% concentration and pressed into pellets before infrared spectra be recorded on a Perkin-Elmer 1310 spectrometer, apart from compounds **4**, **5e**, **5f**, **5g**, and **6e**, **6f**, **6g**, which were studied on IFS 66 Bruker spectrometer. ^{1}H NMR spectroscopy was carried out on a Bruker AC 300 P spectrophotometer apart from compounds **2** and **6e**, the spectra of which was recorded on a Bruker AC 200 spectrophotometer. DMSO-d_6 was used as solvent and TMS as reference. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in Hertz (Hz). 70eV Electronic impact mass spectra were recorded on a Delsi-Nermag R-1010c spectrometer. Intensity of molecular peaks is given with reference to the most intense peak M+(%).
Synthesis and usual data of compounds **1**[4] and **4a-4d**[10] are given in literature.

5-Arylidene-3-benzyl-1-methyl-2-thioxoimidazolidin-4-ones, (**2**). General procedure:
A solution of 1-methyl-2-thioxo-5-benzylidene-imidazolidin-4-ones (4.6mMol) in methanol (2mL) was stirred at room temperature for 30 min with a solution of potassium hydroxide (0.26g, 4.6mMol) in methanol (3mL). Benzyl halide (5 mMol) was then added and the mixture was left stirring for 24 h. The precipitate obtained was collected and washed with water and then with diethyl ether. 1-Methyl-2-thioxo-3-benzyl-5-benzylidene-imidazolidin-4-ones prepared in this way were used without further purification.

***3-Aryl-2-cyanoethyl acrylate,* (4).** General procedure:

An equimolar (23mMol) mixture of aldehyde and ethyl cyanoacetate dissolved in benzene (20mL) with piperidine (3 drops) was heated at 110-120°C for 8-10 h. Upon cooling the product precipitated and was recrystallized from ethanol.

***3-(5-Bromo-2-methoxy-phenyl)-2-cyano-ethyl acrylate*, (4e)**

$C_{13}H_{12}BrNO_2$. M, 293. Yield, 67%. R_f, *n*-hex:AcOEt (70:30), 0.78. F, 101-2°C. IR (cm^{-1}): 3000, 2220, 1708, 1600, 1480, 1464, 1259, 1196, 819, 765. ^1H NMR, δ (ppm): 1.31 (s, CH_3) J=6.9Hz; 3.91 (s, OCH_3); 4.32 (q, CH_2) J=6.9Hz; 7.19 (d, 1H Ar) J=9.3Hz; 7.79 (dd, 1H Ar) J=9 and 2.4Hz; 8.18 (d, 1H Ar) J=2.7Hz; 8.44 (s, ethylenic CH).

***3-(4-Benzyloxy-phenyl)-2-cyano-ethyl acrylate*, (4f)**

$C_{19}H_{17}NO_3$. M, 307. Yield, 80%. R_f, C_6H_6:AcOEt (80:20), 0.5. F, 101-2°C. IR, (cm^{-1}): 2989, 2222, 1714, 1595, 1510, 1245, 1204, 1179, 834, 739. NMR ^1H, δ (ppm): 1.3 (s, CH_3) J=7.21Iz; 4.3 (q, CH_2) J=6.9Hz; 5.24 (s, CH_2); 7.24 (d, 2H Ar) J=9Hz; 8.09 (d, 2H Ar) J=8,7Hz; 7.33-7.50 (m, 5H Ar); 8.31 (s, ethylenic CH).

***2-Cyano-3-(1H-indol-3-yl-methylene)-ethyl acrylate*, (4g)**

$C_{14}H_{12}N_2O_2$. M, 240. Yield, 84%. R_f, C_6H_6:AcOEt (60:40), 0.71. F, 162-5°C. IR (cm^{-1}): 3325, 2985, 2211, 1694, 1587, 1567, 1334, 1244, 1135, 746. ^1H NMR, δ (ppm): 1.31 (s, CH_3) J=6.9Hz; 4.29 (q, CH_2) J=7.2Hz; 7.25-7.37 (m, 2H Ar); 7.58 (dd, 1H Ar) J=6.9 and 2.1Hz; 7.98 (dd, 1H Ar) J=7.2 and 2.4Hz; 8.56 (d, 1H Ar) J=0.6Hz; 8.58 (s, ethylenic CH).

***5-Arylidene-2-thioxoimidazolidin-4-ones*, (5).** General procedure:

A solution of 2-thioxoimidazolidin-4-one, **3**, (0,5g, 4.3mMol), 3-aryl-2-cyanoethyl acrylate (5.1mMol) and piperidine (250μL) in ethanol (8mL) was heated at 80-90°C for 6-8h. After cooling, the product precipitated and was washed with *n*-hexane and then with water. Compounds **5e** and **5f** were enough pure to be used without further purification whilst other derivatives were purified by recrystallization from acetic acid (**5a**, **5b**) or from a mixture of ethanol and water (**5c**, **5d**, **5g**).

***5-Arylidene-3-(4-bromobenzyl)-2-thioxoimidazolidin-4-ones* (6).** General procedure :

A solution of 5-arylidene-2-thioxoimidazolidin-4-one, **5**, (0.4mMol), cesium or potassium carbonate (0.48mMol) in ethanol (3mL) was stirred at room temperature for 1 h. Then 4-bromobenzyl bromide (0.4mMol) was added and the mixture was left stirring for 18-24 h. Upon cooling in ice bath, the product precipitated and was collected and washed with *n*-hexane, toluene and water.

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