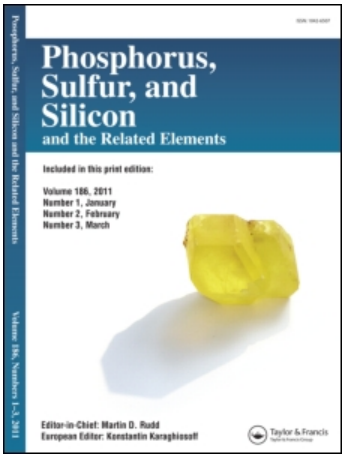

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POTASSIUM FLUORIDE ON ALUMINA: CONDENSATION OF 3-METHYL-2-THIONO-4-THIAZOLIDINONE WITH ALDEHYDES. SYNTHESIS OF α-THIOACRYLIC ACIDS AND PHOSPHONOTHIONOTHIAZOLIDINONES

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POTASSIUM FLUORIDE ON ALUMINA: CONDENSATION OF 3-METHYL-2-THIONO-4-THIAZOLIDINONE WITH ALDEHYDES. SYNTHESIS OF α-THIOACRYLIC ACIDS AND PHOSPHONOTHIONOTHIAZOLIDINONES

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3-Methyl-2-thiono-4-thiazolidinone and aromatic aldehydes adsorbed on potassium fluoride on alumina gave under microwave irradiation 5-arylidene-3-methyl-2-thiono-4-thiazolidinones in 70% to 90% yield. These compounds can be cleaved with sodium hydroxide on alumina into α-thiolacrylic acids in quasi-quantitative yields. Michael addition of diethyl phosphite to 5-arylidene-3-methyl-2-thiono-4-thiazolidinone is described for the first time.

Key words: thiazolidinone; Michael addition; thioacrylic acids; condensation; antiviral; microwave

5-Arylidene-2-thiono-4-thiazolidinones are known for diverse biological activities such as antiviral, bactericidal, fungicidal, antitumoral.[1,2] These compounds are also important intermediates in organic synthesis. Cleavage of the ring leads to β-aryl-α-thioacrylic acids. The exocylic bonds of 5-arylidene-2-thiono-4-thiazolidinones give easily the Michael addition reaction.

Condensation of 3-methyl-2-thiono-4-thiazolidinone with aromatic aldehydes. In the 3-methyl-2-thiono-4-thiazolidinone the methylene group of the ring is very acidic. The carbanion deriving of the methylene group is stabilized by the inductive effect of the carbonyl group and the d orbitals of sulfur. The planar ring of thiazolidinone favours the overlapping of the p-orbital of carbanion with the π orbital of carbonyl.

Condensations of 2-thiono-4-thiazolidinones with aldehydes are described under acidobasic catalytic conditions: with sulfuric acid,[3] sodium hydroxide,[4] ammonia-ammonium chloride,[5] sodium ethylate,[6] ammonium hydroxide,[7] piperidine[8] and sodium acetate-acetic acid[9] as catalysts.

We have reported two examples of the condensation of 3-methyl-2-thiono-4-thiazolidinone with aromatic aldehydes on potassium fluoride on alumina[10] under microwave activation (350 W, 4 mn)[11] obtaining easily and rapidly the arylidene derivatives. The reaction is rapid and the yields are generally excellent (Scheme 1, Table IA).

The arylidenes are extracted with methylene chloride. The products are identified by their ^{1}H NMR, UV and IR spectra (Table IB). The UV spectra gave 3 bands. The first band (256 nm) can be attributed to the carbonyl group and the second

band (290 nm) to the thiocarbonyl group. The third very intense band (370 nm) is due to the double bond conjugated with carbonyl group and with the doublet bond of the sulfur atom. We have not studied the stereochemistry of the condensation products.

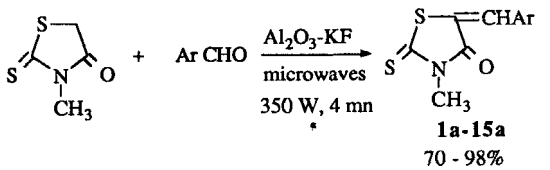
Cleavage of 5-arylidene-3-methyl-2-thiono-4-thiazolidinones. In basic medium the cleavage of 2-thiono-4-thiazolidinone derivatives is similar to the cleavage of 2,4-dioxothiazolidine derivatives.[12] Cleavage takes place with heated alkali hydroxide,[13] barium hydroxide at 100°C[14] or with tetramethylammonium hydroxide.[15] After acidification β-aryl-α-thiolacrylic acids were obtained. We report herein the cleavage of 5-arylidene-3-methyl-2-thiono-4-thiazolidinones by sodium hydroxide on alumina. The 5-arylidene-3-methyl-2-thiono-4-thiazolidinones were adsorbed on sodium hydroxide on alumina and were irradiated with microwaves (210 W, 5 mn) (Scheme 2). Extraction with water and acidification gave β-aryl-α-thiolacrylic acids with quasiquantitative yields. Results are reported in Table IIA.

The β-aryl-α-thiolacrylic acids can exist in two tautomeric forms: β-aryl-α-thiolacrylic acids [form (A)] or as β-aryl-α-thiopyruvic acids [form (B)]. Spectroscopic data and chemical properties (Table IIB) are in favour[16] of the predominance of form (A): In the ^1H NMR spectrum no signal for the benzyl group appears and the resonance at 4.6–4.7 ppm was attributed to the SH. The adsorption at 2550–2580 cm^{-1} in the infrared spectrum was attributed to the thiol group. The UV spectra show two bands, the first at 230–238 nm and the second at 310–340 nm. The same adsorption at 310 nm was found by Bowden *et al.*[17] for α-thiolcinnamic acid.

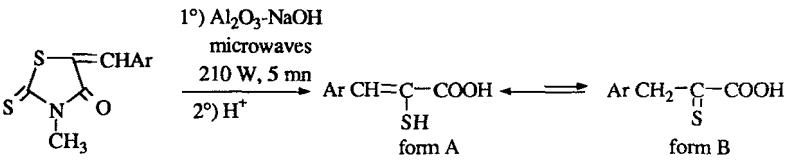
The β-aryl-α-thiolacrylic acids are interesting for their complexing properties toward Zn^{+2}[18] and Mg^{+2}.[19] The complexation with ferric chloride which gives a blue-green coloration is used as a detection test for these acids.[20] These acids are useful for the colorimetric determination of traces of molybdenum or titanium.[21] The β-aryl-α-thiolacrylic acids are also useful intermediates in the synthesis of numerous products like aminoacids, nitriles, α-thiolacids and α-thioacids.[22]

Cleavage by sodium ethylate on alumina. Esterification of β-aryl-α-thiolacrylic acids is extremely difficult.[23] According to the mechanism, we tried to synthesize esters by using ethylate in place of hydroxide, but only the acids were obtained after acidification. We believe that ethoxide on alumina led to the formation of aluminate (Scheme 3). Sodium ethylate without alumina does not give the ring cleavage.

Addition of phosphite to 5-arylidene-3-methyl-2-thiono-4-thiazolidinones under microwave irradiation. The exocyclic double bond of 5-arylidene-3-methyl-2-thiono-4-thiazolidinones is a good olefin for Michael addition. Mustapha *et al.*[24] have shown that Grignard reagents add to 5-arylidene-3-methyl-2-thiono-4-thiazolidi-



SCHEME 1 Condensation of 3-methyl-2-thiono-4-thiazolidinone with aromatic aldehydes on $KF:Al_2O_3$.



SCHEME 2

nones according to Michael addition. Additions of diethylphosphite to cyano[25] or nitro-olefins[26] were recently described.

Continuing the precedent work on Michael addition,[27] we have studied the addition of diethylphosphite to 5-arylidene-3-methyl-2-thiono-4-thiazolinones catalysed by potassium fluoride on alumina (Scheme 4). Under microwave activation (450 W, 5 mn) we observed a clean addition to 5-arylidene-3-methyl-2-thiono-4-thiazolidinones without ring cleavage. The UV spectra of the addition product contain two bands at 250 nm and 290 nm. The ^1H NMR and ^{31}P NMR spectra allow the determination of the ratio of enol and keto form (70/30).

The addition products were obtained in 76 to 92% yield. Enol form is favoured by the formation of an hydrogen bond between P=O and OH (Scheme 4). The results are summarized in Table III.

These new compounds may be of interest for their complexing properties and biological activities (potential antiviral properties[28]).

TABLE IA

Physical data of 5-acrylidene-3-methyl-2-thiono-4-thiazolidinone

N°	R	Yield	colour	Mp(°C)	Mp(°C)	Lit.
1a	C_6H_5	82	yellow	170	168-169	13
2a	o-ClC_6H_4	80	orange	148	146-148	15
3a	p-ClC_6H_4	94	orange	201-2	200 15	
4a	m-$NO_2C_6H_4$	91	yellow	242	239-240	13
5a	p--$NO_2C_6H_4$	98	brown	210	210-211	14
6a	o-$CH_3OC_6H_4$	92	orange	190	188-190	15
7a	p-$CH_3OC_6H_4$	78	yellow	180	179-180	15
8a	3,4$(CH_3O)_2C_6H_3$	93	orange	180		
9a	3,4$(CH_2O_2)_2C_6H_3$	90	orange	202-204		
10a	3,4,5$(CH_3O)_3C_6H_2$	91	orange	178-182		
11a	p-$CH_3C_6H_4$	78	orange	169	170	16
12a	C_6H_5CH=CH	73	brown	236	234-235	13
13a	2-thienyl	84	orange	171-2	170 16	
14a	2-furanyl	86	yellow	142	138-139	13
15a	2-furanylCH=CH	70	orange	160-162		

TABLE IB

Spectroscopic data of 5-acrylidene-3-methyl-2-thiono-4-thiazolidinones

N°	IR(KBr)	PMR($CDCl_3$) δ:	UV (EtOH) λ_{max} (log ε)
1a	1700 (ν C=O) ; 1615 (ν C=C)	3.50 (s, 3H, CH_3-N) , 7.50 (s, 5H, H arom),7.75 (s, 1H, CH=).	252 (4.09), 270 (4.14), 298 (4.02) ,
2a	1700 (ν C=O) ; 1605 (ν C=C)	3,60 (s, 3H, CH_3-N) ; 7,2-7,6 (m, 4H,Harom) ; 8,00 (s ,1H, CH=C)	252 (3,16) ; 292 (4,21) ; 385 (4,45)
3a	1700 (ν C=O) , 1620 (ν C=C)	3.55 (s, 3H, CH_3-N) , 7.50 (m, 4H, H arom) , 7.70 (s, 1H, CH=CH)	256 (4.03) , 290 (4.14) , 382 (4.51)
4a	1700 (ν C=O) ; 1620 (ν C=C)		231 (4.21) , 254 (4.17) , 262 (4.19) ,
5a	1695 (ν C=O) , 1605 (ν C=C)	3.50 (s, 3H, NCH_3) , 7.45 (d, J = 8 Hz, 2H, H arom) , 7.70 (s, 1H, CH=C)8.15 (d, J = 8 Hz, 2H, H arom)	254 (3.76) , 281 (4.15) , 384 (4.40)
6a	1700 (ν C=O) , 1610 (ν C=C)	3.60 (s, 3H, CH_3-N) , 6.90-7.70 (m, 4H, H arom) , 8.30 (s, 1H, CH=C)	256 (4.00) , 286 (4.21) , 386 (4.45)
7a	1700 (ν C=O) , 1620 (ν C=C)	3.50 (s, 3H, NCH_3) , 3.85 (s, 3H, OCH3) , 6.95 (d, J = 8 Hz, 2H, H arom) , 7.45 (d, J = 8 Hz, 2H, H arom) , 7.70 (s, 1H, CH=C)	252 (3.85) , 286 (4.01) , 394 (4.48)
8a	1700 (ν C=O) , 1615 (ν C=C)	3.50 (s, 3H, N-CH_3) , 4.00 (s, 6H, OCH_3) , 7.00 (m, 2H, H arom) , 7.40 (s, 1H, H arom) , 7.65 (s, 1H, CH=C)	262 (4.06) , 285 (4.11) , 311 (4.00) ,

9a	1700 (ν C=O) , 1620 (ν C=C)	3.50 (s, 3H, N-CH_3) , 6.10 (s, 2H, OCH_2O) , 6.85 - 7.30 (m, 3H, H arom) , 7.70 (s, 1H, CH =C)	252 (3.95), 295 (4.03) , 401 (4.38)
10a	1700 (ν C=O) , 1615 (ν C=C)	3.50 (s, 3H, NCH_3), 3.90 (s, 9H, OCH_3) , 6.65 (s, 2H, H arom), 7.60 (s, 1H, CH=C)	255 (3.87), 287 (4.05), 396 (4.49)
11a	1700 (ν C=O) , 1620 (ν C=C)	2.30 (s, 3H, CH_3), 3.50 (s, 3H, NCH_3), 7.35 (m, 4H, H arom), 7.80 (s, 1H, CH=C)	254 (4.01), 284 (4.14), 376 (4.50)
12a	1695 (ν C=O) , 1600 (ν C=C)	3.50 (s, 3H, NCH_3), 6.65-7.75 (m, 8H, CH= and H arom)	254 (3.8), 296 (4.11), 231 (3.9), 262 (3.81), 398 (4.41)
13a	1700 (ν C=O) , 1620 (ν C=C)	3.45 (s, 3H, CH_3-N), 7.10 (m, 1H, H arom), 7.30 (d, 1H, H arom), 7.60 (d, 1H, H arom) , 7.80 (s, 1H, CH=C)	254 (3.72), 288 (4.11), 395 (4.60)
14a	1705 (ν C=O) ; 1610 (ν C=C)	3.50 (s, 3H, N-CH_3), 6,50 (dd, 1H, H arom), 6,75 (d, 1H, H arom), 7.40 (s, 1H, CH =), 7.60 (d, 1H, H arom)	252 (3.98), 286 (4,18), 400 (4.67)
15a	1700 (ν C=O), 1590 (ν C=C)	3.50 (s, 3H, N- CH_3), 6.45-7.00 (m, 4H), 7.35-7.70 (m, 2H)	254 (3.81), 305 (4.08), 418 (4.66)

TABLE IIA

Physical data of α-thiolacrylic acids

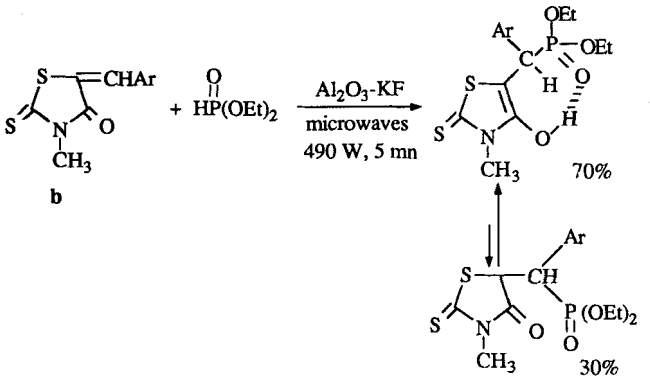
N°	R	Yield	colour	Mp(°C)	Mp(°C)	Lit.
1b	C_6H_5	96	yellow	133-4	133-134	17
3b	p-ClC_6H_4	95	orange-yellow	172	168-170	13
11b	p-$CH_3C_6H_4$	91	yellow	167-8	167-168	19
13b	2-thienyl	99	yellow	114-6	115-117	17
14b	2-furanyl	96	yellow	188	188	18

TABLE IIB

Spectroscopic data of α-thiolacrylic acids

N°	IR(KBr)	PMR($CDCl_3$) δ:	UV (EtOH) λ_{max} (log ε)
1b	2640, 2560 (ν SH) , 1680 (ν C=O) , 1590 (ν C=C)	4.65 (s, 1H, SH), 7.15-7.8 (m, 5H, H arom), 7.95 (s, 1H, CH=), 9.00 (m, 1H, CO_2H)	231 (3.85) , 254 (3.60) , 271 (3.63) , 312 (4.08)
3b	2640, 2560 (ν SH) , 1680 (ν C = O) , 1595 (ν C=C)	4.60 (s, 1H, SH) , 7.30 (d, 2H, H arom) , 8,00 (d, 2H, H arom) , 7.90 (s, 1H, CH=) , 9.45 (m, 1H, CO_2H)	232 (3.79) , 254 (3.60) , 270 (3.60) , 324 (4.16)
11b	2640, 2560 (ν SH) , 1670 (ν C = O) , 1600 (ν C=C)	2.35 (s, 3H, CH_3) , 4.70 (s, 1H, SH) , 7.20 (d, 2H, H arom) , 7.50 (d, 2H, H arom) , 7.85 (s,1H,CH=) , 8.70 (m, 1H, CO_2H)	234 (3.81) , 254 (3.57) , 272 (3.61) , 316 (4.11)
13b	2580 , 2640 (ν SH) , 1675 (ν C=O) , 1600 (ν C=C)	4.65 (s, 1H, SH) , 7.05-7.65 (m, 3H, H arom) , 8.10 (s, 1H, CH) , 8.70 (m, 1H, CO_2H)	235 (3.67) , 254 (3.56) , 264 (3.55) , 272 (3.56) , 330 (4.14)
14b	2640 ; 2550 (ν SH) , 1680 (ν C = O) , 1600 (ν C=C)	4.70 (s, 1H, SH) , 6.60 (m, 1H, H arom) , 6.90 (d, 1H, H arom) , 7.60 (m, 1H, H arom) , 7.85 (s, 1H, CH=) , 9.50 (m, 1H, CO_2H)	232 (3.72) , 254 (3.50) , 264 (3.72) , 271 (3.47) , 326 (4.17)

SCHEME 3



SCHEME 4

TABLE III

Michael addition of $HP(O)(OEt)_2$ catalysed by Al_2O_3-KF under microwave irradiation (490 W, 5 mn)

Products	Aryl	Yield (%)
1c	Phenyl	76
13c	2-Thienyl	84
14c	2-Furyl	92

EXPERIMENTAL

Proton NMR spectra (PMR) were recorded in ppm downfield from internal Me_4Si on a Varian EM 360 instrument (60 MHz). ^{13}C NMR spectra were recorded in ppm downfield from internal Me_4Si on a Brucker WP 60, as were the ^{31}P NMR spectra, in ppm downfield from external H_3PO_5. Mass spectra (MS) were recorded on a Nermag R10-10H spectrometer. Infrared spectra were recorded in KBr or between NaCl plates on a Perkin Elmer 684 IR spectrophotometer, absorptions are in cm^{-1}. UV spectra were recorded on Beckman Acta M VI spectrometer. Alumina-KF is prepared as previously described.[10]

Sodium hydroxide on alumina. Sodium hydroxide (6 g) was dissolved in water (40 ml) and mixed with neutral chromatographic alumina (Woelm-N, 2087; 34 g). The mixture was evaporated with rotary evaporator under vacuum at 100°C. Ethanol (4 × 50 ml) was added for removing the last traces of water. The white solid was placed in an oven at 100°C and stored in a closed flask.

Condensation of 3-methyl-2-thiono-4-thiazolidinone with aldehydes

General procedure. Potassium fluoride on alumina (2 g) was added to a mixture of N-methylrhodamine (5 mmol, 0.736 g) and aldehyde (5 mmol) in the minimum amount of methylene chloride. After evaporation of the solvent under vacuum, the solid is irradiated with microwaves (350 W, 4 mn). The solid is extracted with methylene chloride (40 ml and 3 × 10 ml) and filtered on Celite. The solvent is evaporated under vacuum and the solid is crystallized from ethanol.

Cleavage of 5-arylidene-3-methyl-2-thiono-4-thiazolidinones with sodium hydroxide on alumina

General procedure. Sodium hydroxide on alumina is added to a solution of 5-arylidene-3-methyl-2-thiono-4-thiazolidinone (5 mmol) in methylene chloride. After evaporation of the solvent under vacuum, the solid is irradiated with microwaves (210 W, 5 mn). Water (20 ml) was added and filtered. The filtrate was acidified to pH = 2 with hydrochloric acid and the α-thiolacrylic acid was isolated by filtration. The acid is crystallized in ethanol.

Michael addition of diethylphosphite on 5-acrylidene-3-methyl-2-thiono-4-thiazolidinones

Diethylphosphite (5.1 mmol) and potassium fluoride on alumina (5 g) are added to a solution of 5-arylidene-3-methyl-2-thiono-4-thiazolidinone (5 mmol) in the minimum amount of methylene chloride. After evaporation of the solvent under vacuum, the solid is irradiated with microwaves (490 W, 5 mn). Water (20 ml) is added and the aqueous filtrate is washed with ether (20 ml). The aqueous phase is acidified to pH = 4 and extracted with methylene chloride (3 × 50 ml). The organic phase is dried on magnesium sulfate, and the solvent evaporated. The produce is crystallized in ethanol. The ratio between ketonic and enolic form is 30/70.

Diethyl (3-methyl-2-thiono-4-thiazolidinon-5-yl) benzyl phosphonate (**1c**)

Yellow solid Mp = 92°; yield = 76%. PMR ($CDCl_3$) δ: 1,20 (m, 6H, $OCH_2\underline{CH_3}$); 3.00 (s, 3H, NCH_3 enolic form); 3.35 (s, 3H, NCH_3 ketonic form); 3.80–4.50 (m, 5H, 4H, OCH_2 and 1H of CH—P=); 4.85 (m, 1H, S—CH—CO); 7.35 (m, 5H, H arom). ^{31}P NMR ($CDCl_3$) δ: 21.70 (ketonic form); 23.60 (enolic form). IR (KBr): 3440 (νOH); 1730 (νC=O); 1295 (νP=O). UV (EtOH) λ_{max}(log ε): 296 (4.31); 260 (4.21). SM. (m/e (%)): M + 2 (1.5); M + 1 (2.5); 373 (12.2) ($M^{+\cdot}$); 288 (3.7); 236 (3.9); 204 (5.4); 149 (14.4); 134 (10.3); 119 (30.8); 91 (12.2); 84 (100).

Diethyl (3-methyl-2-thiono-4-thiazolidinon-5-yl) phosphono-2-furanyl methane (**14c**)

Orange solid Mp = 58–60°, yield = 92%. PMR ($CDCl_3$) δ: 1.25 (m, 6H, $OCH_2\underline{CH_3}$); 3.10 (s, 3H, NCH_3 enolic form); 3.35 (s, 3H, NCH_3 ketonic form); 3.70–4.50 (m, 5H, 4H of OCH_2 and 1H of CH—P=O); 4.80 (m, 1H, S—CH—CO); 6.30 (m, 2H, H arom); 7.10 (m, 1H, H arom). ^{31}P NMR ($CDCl_3$) δ: 19.13 (ketonic form); 20.63 (enolic form). UV (EtOH) λ_{max} (log ε): 296 (4.24); 260 (4.12). IR (KBr): 3460 (νOH); 1735 (νC=O); 1295 (νP=O). SM. (m/e (%)): M + 2 (3.1)); M + 1 (5.6); 363 (23.2) ($M^{+\cdot}$); 226 (11.8); 217 (31.9); 194 (17.7); 189 (12.5); 121 (17.5); 107 (17.3); 97 (13.1); 81 (100).

Diethyl (3-methyl-2-thiono-4-thiazolidinon-5-yl) phosphono-2-thiophenyl methane (**13c**)

Yellow-orange solid, Mp = 78–80°, yield = 84%. PMR ($CDCl_3$) δ: 1.20 (m, 6H, $OCH_2\underline{CH_3}$); 3.10 (s, 3H, NCH_3 enolic form); 3.35 (s, 3H, NCH_3 ketonic form); 3.75–4.50 (m, 5H, 4H de OCH_2 et 1H de CH—P=O); 4.80 (m, 1H, S—CH—CO); 6.70–7.30 (m, 3H, H arom). ^{31}P NMR ($CDCl_3$) δ: 20.00 (ketonic form); 21,60 (enolic form). UV (EtOH) λ_{max} (log ε): 297 (4.13); 262 (4.05); IR (KBr): 3460 (νOH); 1725 (νC=O); 1290 (νP=O). SM. (m/e (%)): M + 2 (7.7)); M + 1 (14.3); 379 (39.7) ($M^{+\cdot}$); 242 (17.0); 233 (67.8); 210 (23.7); 205 (29.5); 140 (29.3); 137 (30.0); 109 (15.83); 111 (23.5); 97 (100).

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