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Microwave-Assisted Solvent-free Synthesis of Iminothiazolines

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Abstract : Several Imino 4-Thiazolines were prepared by condensation of disymmetric thioureas and α–chloro ketone under microwave irradiation in solvent free conditions. Hydrochlorides precursors were isolated. Iminothiazolines are obtained directly when reactions are performed over alumina.

Imino 4-Thiazolines derivatives have been reported to exhibit significant biological activities such as bactericidal[1], analgesicidal[2], fungicidal[3], insecticidal[4].

The classical synthesis of these compounds involve the Hantzsch condensation reaction[5] of disymmetric thioureas and α chloroketone to give iminothiazolines hydrochlorides which undergo dehydrohalogenation affording iminothiazolines. In the course of our studies related to the development of the synthetic protocol using microwave irradiation under solvent free conditions[6], we report a novel and easy access to imino 4-thiazolines, using a one-pot procedure.

Reactions of thiourea **1** and α-chloro ketone **2** carried out without solvent under microwave irradiation at 80°C afford thiazolinium salts **3** quantitatively (^{1}H NMR). The course of the reaction is easy to follow by observing the reaction mixture during microwave heating and the irradiation should be stopped when the salt precipitates. After treatment with base the free iminothiazoline **4** is recovered.

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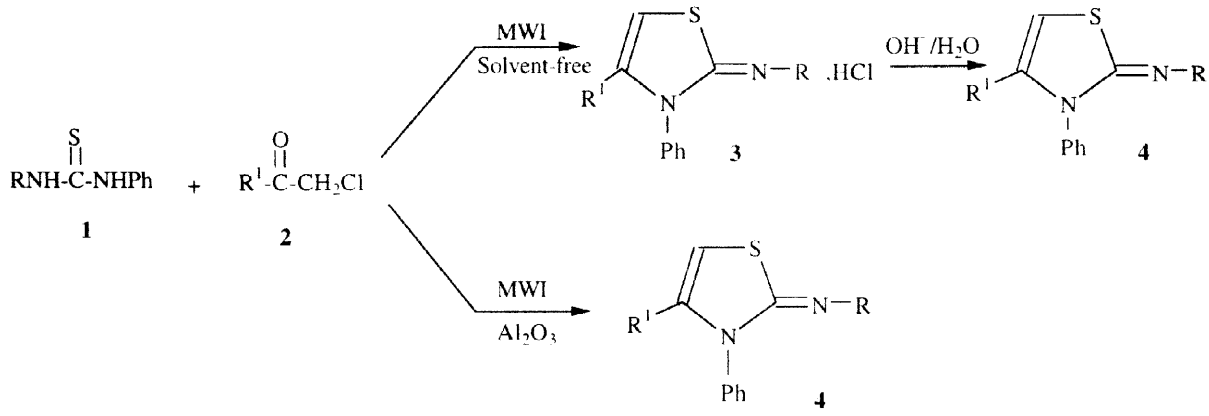

Under classical heating in the same conditions, much lower yields are observed and reaction mixtures are not clean. The results are summarized in table 1.

All thiazolinium salts are isolated with fair yields, high degree of purity, and characterized by their spectroscopic data (^1H and ^{13}C NMR, mass spectra). In two cases (entry 3 and 6) the reaction led to a second adduct which is probably a regioisomer as already described in the literature[7].

Table 1: Synthesis of hydrochlorides salts **3** under microwave irradiation[8]

Entry	R	R^1	T(mn)	Yield%[a]	F(C°)	Classical heating[b]
1	Methyl	Phenyl	10	95	186	65
2	//	Benzyl	10	98	116	70
3	//	Ipr[c]	8	97	153	75
4	//	tBu	5	90	118	70
5	//	TMP	10	94	214	d
6	//	Naphtyl[c]	8	90	d	d
7	Phenyl	Phenyl	10	90	205	45
8	//	Benzyl	5	85	190	30
9	//	Ipr	5	90	138	80
10	//	tBu	4	82	206	40
11	//	TMP	4	77	190	d
12	//	Naphtyl	10	85	d	d

a) Yield of isolated product.b) Yield estimated by ^1H NMR. c) Reactions give a mixture of two adducts, the mixture have an oil aspect.d) In these cases the comparison was not realized.

Alumina as support for dehydrohalogenation in dry media under microwave irradiation was already used in the laboratory[9]. In order to obtain directly iminothiazolines, we have performed the reaction in the presence of basic alumina in solvent-free conditions, under microwave irradiation.

Experiments realized in these conditions show that dehydrohalogenation is achieved by varying the quantities of alumina. The best results are obtained for 5g of alumina and 5.10^{-3} mole (table 2) of products. The effect of the different reaction conditions can be rationalized by the above scheme .

Table 2 : Synthesis of iminothiazolines **4** over alumina under microwave irradiation[10]

Entry	R[1]	Conditions reactions	% Salts **3**	% Imines **4**[a]	F(C°) Imines **4**
1	Phenyl	MWI	100	0	
2		MWI (Al_2O_3)	0	100	136
3	Benzyl	MWI	100	0	
4		MWI (Al_2O_3)	0	100	112
5	Ipr	MWI	100	0	
6		MWI (Al_2O_3)	0	100	b
7	Naphtyl	MWI	100	0	
8		MWI (Al_2O_3)	0	100	b

a) In this case the comparison with classical heating has not been realized. b) product obtained as an oil

In conclusion we have demonstrated that coupling microwave irradiation with alumina supported reaction is synthetically useful in the one-pot synthesis of iminothiazolines.This reaction represents a simple and quick method leading to fair yields.

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8 Typical synthetic procedure : the thiourea (1.2 eq) and the α chloro ketone (1eq) were mixed, placed in quartz tube, and introduced into a Synthewave 402® (Prolabo) single mode apparatus (4cm, ϕ, reactor)[11] with a temperature monitored at 80°C. The mixture was irradiated for the time given in table 1. Thiazolinium salts precipitate in the tube. Products were isolated by crystallization from ether. The free iminothiazoline is obtained by treatment with aqueous ammonia followed by extraction with CH_2Cl_2. Reactions under classical heating are carried out without solvent in an oil bath previously set at 80°C during the same time.

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10 Reaction with Al_2O_3 : Substrates were mixed with alumina (5g). The mixture was treated in similar conditions. After usual work up, iminothiazolines were isolated and identified by their spectroscopic data.

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