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REACTION OF MERCAPTOACETATE AND HALIDES CONTAINING ACTIVATED METHYLENES WITH THIOCARBAMOYLIMIDATES: A NOVEL APPROACH TO THE SYNTHESIS OF AMINOTHIAZOLE DERIVATIVES

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Abstract: The reaction of *N*-thiocarbamoylimidates **1** with methyl thioglycolate leads to the formation of 4-arylamino-5-methoxycarbonylthiazoles **2**. The condensation of the same imidates **1** on ethyl bromoacetate, benzyl bromide and chloroacetonitrile provides the corresponding 2-arylaminothiazoles **4**.

INTRODUCTION

Aminothiazoles constitute excellent precursors of a large variety of biologically active compounds such as antibiotics (cephalosporins[1-3], β-lactams[4], sulfathiazoles[5]) and bactericides[6]. They also exibit some antitumoral[7] properties.

As a part of our ongoing work on the use of *N*-functionalized imidates in heterocyclic syntheses[8-12], we show in the present paper that the reaction, in basic conditions, of *N*-thiocarbamoylimidates **1** with alkyl thioglycolates, ethyl bromoacetate, benzyl bromide and chloroacetonitrile constitutes a convenient and easy method allowing access to aminoethoxycarbonylthiazole derivatives.

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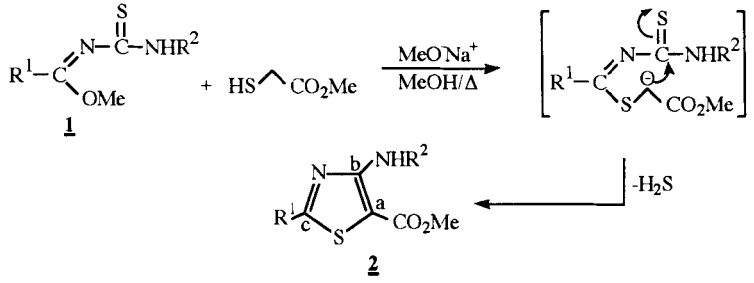
RESULTS AND DISCUSSION

1- Reaction with methyl thioglycolate.

Unlike their *N*-acylated homologues[13] which easily react with thiols, *N*-thiocarbamoylimidates have shown no noticeable reactivity with mercaptan derivatives when the reaction occurs at room temperature. However, refluxing an equimolecular amount of methyl thioglycolate and thiocarbamoylimidate **1** in absolute methanol with an excess of sodium methoxide gives the desired 4-aminothiazoles **2**.

Presumably this is a two step reaction: formation of the *N*-thiocarbamoylthioimidate intermediate whose cyclization affords aminothiazoles **2** (with 54-72% overall yield) (**Scheme 1**).



2a: R^1= Ph R^2= Ph **2c**: R^1=Ph R^2= Ph-CH_2

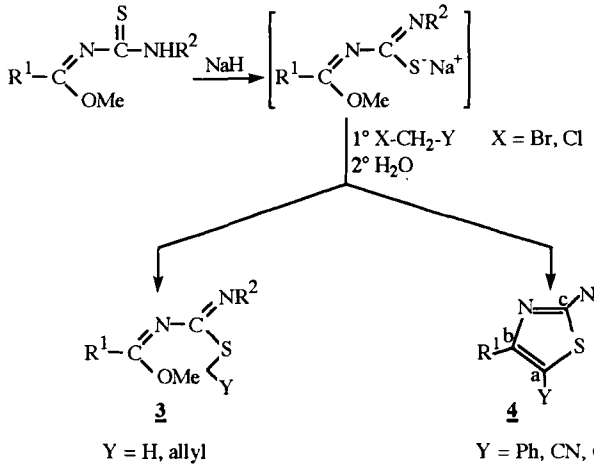
2b: R^1= Ph R^2= pClPh **2d**: R^1=pClPh R^2= Ph

Scheme 1

2- Reaction with halides.

2-Amino-5-ethoxycarbonylthiazoles **4** , isomers to **2**, can be obtained by treating the substrate **1** successively by sodium hydride and ethyl bromoacetate.

It seems that the mechanism of this reaction proceeds by the formation of an imidothioimidate **3** species which subsequently undergoes a cyclization under the effect of base to provide the corresponding aminothiazoles **4** (**Scheme 2**).



3a: R^1= Ph	R^2= Ph	Y = H	**4a**: R^1= Ph	R^2= Ph	Y = CO_2Et
3b: R^1= Ph	R^2= Ph	Y= vinyl	**4b**: R^1= Ph	R^2= Ph	Y = Ph
			4c: R^1= Ph	R^2= $4ClC_6H_4$	Y = CO_2Et
			4d: R^1= Ph	R^2= $PhCH_2$	Y = CO_2Et
			4e: R^1= $PhCH_2$	R^2= Ph	Y = CO_2Et
			4f: R^1= Ph	R^2= Ph	Y = CN

Scheme 2

Further investigations on the second step (cyclization process) revealed a dependency of the cyclization on the acidity of the hydrogen in the α position with respect to sulfur. It was found that intermediate **3** was isolated only in the case where methyl iodide or allyl bromide was used. This is probably due to the fact that the α hydrogens are not very acidic when Y = CH_3 and -$CH{=}CH_2$. Indeed, the intermediate **3** does not cyclize despite an excessive use of sodium hydride (Scheme 2).

In contrast, replacing the carboxylate ester moiety by any other substituent having electron withdrawing mesomeric effect (-M) such as phenyl and nitrile groups provides 2-amino-5-phenyl thiazoles **4c,d** or 2-amino-5-cyanothiazole **4e** respectively (Scheme 2).

EXPERIMENTAL

1. General procedure for the synthesis of compounds 2.

To 10 mmol (1,06g) of methyl thioglycolate, a 15 mmol (0,81g) of sodium methoxide in absolute methanol (50 ml) was added. The solution was stirred for 6 hours at room temperature , then 10 mmol of imidate 1 were added. The mixture was refluxed for 24 hours. The solvent was removed under reduced pressure and the remaining residue was quenched with distilled water (100 ml). After the usual work up the aminothiazoles 2 were recrystallized from ethanol.

5-Methoxycarbonyl-2-phenyl-4-phenylaminothiazole **2a**

mp = 142°C; yield = 60 %. IR ($CHCl_3$): ν_{NH} = 3394; ν_{CO} = 1627. ^1H NMR ($CDCl_3$): 8.5(s large, 1H); 7.5-7.2(m, 10H); 3.8(s, 3H). ^{13}C NMR ($CDCl_3$): C(OMe) 60.08; C_a 110.53; C_{arom} 122-132; C_c 160.58; C_b 162.17; C(CO) 168.14. Anal. Calcd for $C_{17}H_{14}N_2O_2S$: C 65.80; H 4.51; N 9.03. Found C 65.33; H 4.39; N 8.72.

5-Methoxycarbonyl-4-p-chlorophenylamino-2-phenylthiazole **2b**

mp = 196°C; yield = 72 %. IR ($CHCl_3$): ν_{NH} = 3392; ν_{CO} = 1630. ^1H NMR ($CDCl_3$+$DMSOd_6$): 8.65(m, 1H); 7.5-7.2(m, 9H); 3.8(s, 3H). ^{13}C NMR ($CDCl_3$): C(OMe) 61.12; C_a108.83; C_{arom} 122-132; C_c159.13; C_b 163.29; C(CO) 170.04.

4-Benzylamino-5-methoxycarbonyl-2-phenylthiazole **2c**

mp = 153°C; yield = 67 %. IR ($CHCl_3$): ν_{NH} = 3410; ν_{CO} = 1632. ^1H NMR ($CDCl_3$): 8.3(m, 1H); 7.7-7.2(m, 10H); 3.9(s, 3H). ^{13}C NMR ($CDCl_3$):C (Ph-C-N) 46.13; C(OMe) 59.21; C_a111.31; C_{arom}125-134; C_c156.22; C_b160.09; C(CO) 169.24.

5-Methoxycarbonyl-2-p-chlorophenyl-4-phenylaminothiazole **2d**

mp = 167°C; yield = 54 %. IR ($CHCl_3$): ν_{NH} = 3395; ν_{CO} = 1629. ^1H NMR

($CDCl_3$):8.3-7.4(m, 10H); 3.8(s, 3H). ^{13}C NMR ($CDCl_3$): C(OMe) 58.36; C_a106.75; C_{arom} 125-136; C_c154.12; C_b161.07; C (CO)168.23.

2. Synthesis of thioimidoimidates 3.

To a suspension of 20 mmol (0.48g) of sodium hydride in 50 ml of anhydrous THF, 10 mmol of thiocarbamoylimidate **1a** was added at room temperature and under nitrogen atmosphere. After stirring for one hour, 10 mmol of allyl bromide or methyl iodide in 30 ml of THF was added. The mixture was stirred for an additional 24 hours. Then, the solution was quenched by H_2O. The extraction was carried out with ether. After the usual work up, the solvent was evaporated under reduced pressure. The obtained residue was either distilled (**3b**) or treated with pentane and recrystallized from methanol (**3a**).

***Methyl N-(N'-phenylmethylthioimido)phenylimidate* 3a**

mp = 167°C; yield = 72 %. IR ($CHCl_3$): $\nu_{C=N}$ = 1650, 1658. ^1H NMR ($CDCl_3$):7.8-7.2(m, 10H); 3.85(s, 3H); 2,55(s, 3H).

***Methyl N-(N'-phenylallylthioimido)phenylimidate* 3b**

bp_1 = 123°C; yield = 65 %. IR ($CHCl_3$): $\nu_{C=N}$ = 1650, 1657; $\nu_{C=C}$ = 1600. ^1H NMR ($CDCl_3$):7.8-7.2(m, 10H); 5.6(m, 1H); 4.8(m, 2H); 3.85(s, 3H); 3.1(m, 3H).

3. Synthesis of 2-aminothiazoles 4.

To the suspension of sodium hydride (20 mmol) in THF (50ml) was added dropwise under nitrogen atmosphere with stirring at room temperature a solution of thiocarbamoylimidate (10 mmol) in THF (10 ml). After stirring for 1h, ethyl bromoacetate (10 mmol) dissolved in THF (30 ml) was added. The reaction mixture was stirred for a period of 14h and hydrolyzed with water (10 ml). The organic layer was extracted with chloroform, dried over $MgSO_4$ and concentrated under reduced pressure to give the 5-ethoxycarbonyl-2-phenylamino-4-phenylthiazole **4a**.

5-Ethoxycarbonyl-2-phenylamino-4-phenylthiazole **4a**

mp = 141°C; yield = 77 %. IR ($CHCl_3$): ν_{NH} = 3392; ν_{CO} = 1707. ^1H NMR($CDCl_3$): 10(s large, 1H); 7-7.6(m, 10H); 4.2(q, 4H); 1.22(t, 3H). ^{13}C RMN ($CDCl_3$): C(CH_3)14.13; C(CH_2-O-) 60.73; C(CO)168.31;C_a161.63;C_b 158.57; C_c139.22; C_{arom} 120-134.

2-Phenylamino-4,5-diphenylthiazole **4b**

mp = 136 °C; yield = 68 %. IR ($CHCl_3$): ν_{NH} = 3397. ^1H NMR ($CDCl_3$): 10 (s large, 1H); 7.6-7(m, 15H). ^{13}C NMR ($CDCl_3$): C_a145.44; C_b163.58; C_c 140.30; C_{arom}122-134.

2-(4-Chlorophenyl)amino-5-ethoxycarbonyl-4-phenylthiazole **4c**

mp = 160°C; yield = 54 %. IR ($CHCl_3$): ν_{NH} = 3402; ν_{CO} = 1692. ^1H NMR ($CDCl_3$+$DMSOd_6$): 7-8(m, 10H); 4.2(q, 4H); 1.26(t, 3H). ^{13}C NMR ($CDCl_3$+$DMSOd_6$): C(Me) 14.82; C(CH_2-O-) 59.92; C_{arom}120-134; C_c 142.12; C_b 156.02; C_a 160.34; C(CO) 168.23.

4-Benzyl-5-ethoxycarbonyl-2-phenylaminothiazole **4d**

mp = 51°C; yield = 80 %. IR ($CHCl_3$): ν_{NH} =3393; ν_{CO} =1697. ^1H NMR ($CDCl_3$): 9.25(s large, 1H); 7.2(m, 10H); 4.5(s, 2H); 4.2(q, 2H); 1.3(t, 3H). ^{13}C NMR($CDCl_3$): C(Me) 14.52; C(CH_2-Ph) 45.36; C(CH_2-O-) 60.38; C_{arom} 120-134; C_c 141.21; C_b 158.81; C_a 162.03; C(CO) 168.57; Anal. Calcd for $C_{19}H_{18}N_2O_2S$: C 67.45; H 5.32; N 8.28. Found C 67.16; H 5.54; N 8.13;.

2-Benzylamino-5-ethoxycarbonyl-4-phenylthiazole **4e**

mp = 123°C; yield = 64 %. IR ($CHCl_3$): ν_{NH} =3408; ν_{CO} =1703. ^1H NMR ($CDCl_3$): 8-7(m,11H); 4.6(s, 2H); 4.2(q, 4H); 1.32(t, 3H). ^{13}C NMR ($CDCl_3$): C(Me) 14.25; C(-N-CH_2-Ph) 36.05; C(CH_2-O-) 60.66; C_{arom} 120-134; C_b 139.32; C_c 150.69; C_a 162.60; C(CO) 168.10.

5-Cyano-2-phenylamino-4-phenylthiazole **4f**

mp = 150°C; yield = 82 %. IR ($CHCl_3$): ν_{NH} =3395; $\nu_{C\equiv N}$ =2225. ^1H NMR

($CDCl_3$+ $DMSOd_6$): 10.6(s large, 1H); 7.6-7 (m, 10H). ^{13}C NMR ($CDCl_3$): C(CN) 114.12; C_{arom} 120-132; C_b 139.21; C_c 148.52; C_a 159.23.

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