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AN EFFICIENT SYNTHESIS OF 5-ARYL(or ALKYL)AMINO-4-ETHOXYCARBONYL-2-METHYLTHIO-1,3-THIAZOLES FROM DIMETHYL N-(ETHOXYCARBONYLMETHYL)IMINODITHIOCARBONATE AND ISOTHIOCYANATES.

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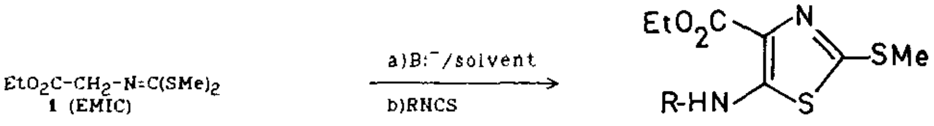
Abstract- An efficient synthesis of perfunctionalyzed 1,3-thiazoles **2a-2b** with good yields has been carried out by a cyclocondensation reaction between the α-metallated dimethyl N-(ethoxycarbonylmethyl)iminodithiocarbonate and aryl or alkylisothiocyanates.

In this paper we give account of an efficient synthesis of 5-aryl(or alkyl)amino-4-ethoxycarbonyl-2-methylthio-1,3-thiazoles **2a-2f**. These perfunctionalyzed 1,3-thiazoles can be used as building blocks to obtain other heterocyclic structural complex systems by a convergent connection with specific synthons. Thus, the methylthio on C2 can be substituted by halogen, O-, N-, and C-nucleophiles by or without a previous oxidation of the sulfide.[1] This strategy can be used, for instance, to obtain the famotidine, an interesting antiulcer agent.[2] By other hand, the ethoxycarbonyl on C4 can be the starting point for a new heterocyclization[3] to azadiaryl compounds that can be used as target molecules to obtain compounds of biological interest.[4] Additionally, the presence of the amine substituent on C5 can make possible the fusion of other hetero- or homocycles of variable topology with 1,3-thiazole moiety.

We have previously reported that the dimethyl N-(ethoxycarbonylmethyl)iminodithiocarbonate (EMIC), **1**, is an useful synthetic equivalent of the EtO_2C-C4-N=C2-SMe synthon that is a structural unit present into 1,3-thiazoles whose substituents on C5 position come from an unsaturated electrophile.[5] Thus, 5-alkylthio-4-ethoxycarbonyl-2-methylthio-1,3-thiazoles have been obtained by a cyclocondensation reaction of EMIC with carbon disulfide, and later alkylation of intermediate 1,3-thiazole-5-thiolate with alkyl halides.[5,6]

We describe now an efficient synthesis of 5-aryl(or alkyl)amino-4-ethoxycarbonyl-2-methylthio-1,3-thiazoles, **2a-2f**, by a cyclocondensation reaction between the α-metallated EMIC and aryl and alkyl isothiocyanates (Scheme 1).



2a-2f

R: **a**, Ph; **b**, p-FC_6H_4; **c**, p-MeC_6H_4; **d**, p-$MeOC_6H_4$; **e**, Et; **f**, n-Bu

-Scheme 1-

Different base/solvent systems, base/EMIC proportions, and reaction conditions for metallation of **1**, and condensation of α-metallated EMIC with phenyl isothiocyanate were tested. The results have been gathered in Table 1.

Table 1. Observed yields for 4-ethoxycarbonyl-2-methylthio-5-phenylamino-1,3-thiazole, **2a**, from **1** and phenyl isothiocyanate.

Run	Base/solvent	Base/EMIC/PhNCS	reaction conditions metallation	 condensation	yield(%)[a]
1	KBu^tO/THF	1.1/1/1	20°C/0.5 h	20°C/0.5 h	36
2	KBu^tO/THF	1.1/1/1	-78°C/0.5 h	-78°C/0.5 h 20°C/2 h	49
3	KBu^tO/THF	1.4/1/1	-78°C/0.5 h	-78°C/0.5 h 20°C/2 h	90
4	NaH/DMSO	1.5/1/1	20°C/2 h		b)
5	NaH/DME	1.5/1/1	0°C/0.5 h	20°C/0.5 h	c)
6	NaOH[d]	---/1/1	20°C/2 h		19

[a] Isolated product. Except in the indicated cases none other product was detected by TLC except **1**. [b] Bis(4-ethoxycarbonyl-2-methylthio-1-phenyl imidazolyl)disulfane was obtained (10%) by acidification to pH 5 of the reaction crude after of the extraction with diethyl ether at basic pH with negative result.[7] [c] Methyl N-phenyldithiocarbamate was obtained with a yield of 45%. [d] The following conditions were used: $CH_2Cl_2/NaOH-H_2O$ (4%)/n-Bu_4N^+, Br^-.

In all cases, except runs 4 and 5, the 1,3-thiazole **2a** was the unique isolated product. The best result in **2a** was obtained with the KBu^tO/THF system (Table 1, run 3). From run 4 a solid with a melting point of 200°C was isolated and identified as bis[5-(4-ethoxycarbonyl-2-methylthio-1-phenyl)imidazolyl]disulfane by according with ir, ^1H- and ^{13}C-nmr data.[7] A related result has been described in the literature[8] for the cyclocondensation reaction of N-tosylmethylisocyanide and isothiocyanates with tha NaH/DMSO system.

From the results gathered in Table 1, the synthesis of 5-aryl(or alkyl)amino-4-ethoxycarbonyl-2-methylthio-1,3-thiazoles, **2a-2f**, was verified with an 40% excess of KBu^tO, and π-defficient and π-excess aryl isothiocyanates, and alkyl isothiocyanates. The results have been collected in Table 2.

All new compounds have been fully characterized from their ir, ^1H-nmr, ^{13}C-nmr, and ms data together a satisfactory analytical data. The ir, ^1H-, ^{13}C-nmr, and ms key data have been gathered in Table 3.

The ir data support the presence of an amine and conjugated carbonyl groups. The single band at 3220-3420 cm^{-1} can be assigned to a NH group,[9] and the band at 1660-1730 cm^{-1} to a carbonyl group of a conjugated ester with an unsaturated system (Ref. 9, p. 177).

Table 2. Observed yields by the synthesis of 5-aryl(or alkyl)amino-4-ethoxycarbonyl-2-methylthio-1,3-thiazoles 2a-2f.

1,3-thiazol	R	Yield(%)[a]	M p(°C)
2a	Ph	90	79-80[b]
2b	p-FC_6H_4	65	54-55[c]
2c	p-MeC_6H_4	73	64-65[b]
2d	p-$MeOC_6H_4$	55	57-58[b]
2e	Et	59	liquid[d]
2f	n-Bu	77	liquid[d]

[a]Yield in purified product. [b]Recrystallized from methanol. [c]Recrystallized from hexane. [d]Purified by silica gel flash chromatography.

Table 3. Ir, ^{1}H-Nmr, ^{13}C-Nmr, and Ms key data of 1,3-thiazoles 2a-2f.

			δ(ppm)								
	Ir(cm^{-1})		^{1}H-Nmr		^{13}C-Nmr					Ms	
Compound	NH(s)	CO(s)	NH	SCH_3	C2	C4	C5	CO	SCH_3	$M^{\cdot +}$(100%)	MeS-C≡S$^+$(%)
2a	3400	1660	9.80[a]	2.65	164.72[b]	140.64	122.90	164.76	17.56	294	20
2b	3280	1690	9.58[a]	2.62	156.89	146.20	122.80	164.49	17.59	312	44
2c	3220	1730	9.60[a]	2.62	156.44	145.50	122.15	164.35	17.32	308	13
2d	3300	1700	9.47[a]	2.59	158.17	133.84	121.54	164.34	17.37	324	25
2e	3310	1710	7.40[c]	2.56	161.83	142.50	117.87	162.96	16.51	246	15
2f	3420	1700	7.27[c]	2.52	162 73	143.02	118.33	163.56	17.08	274	12

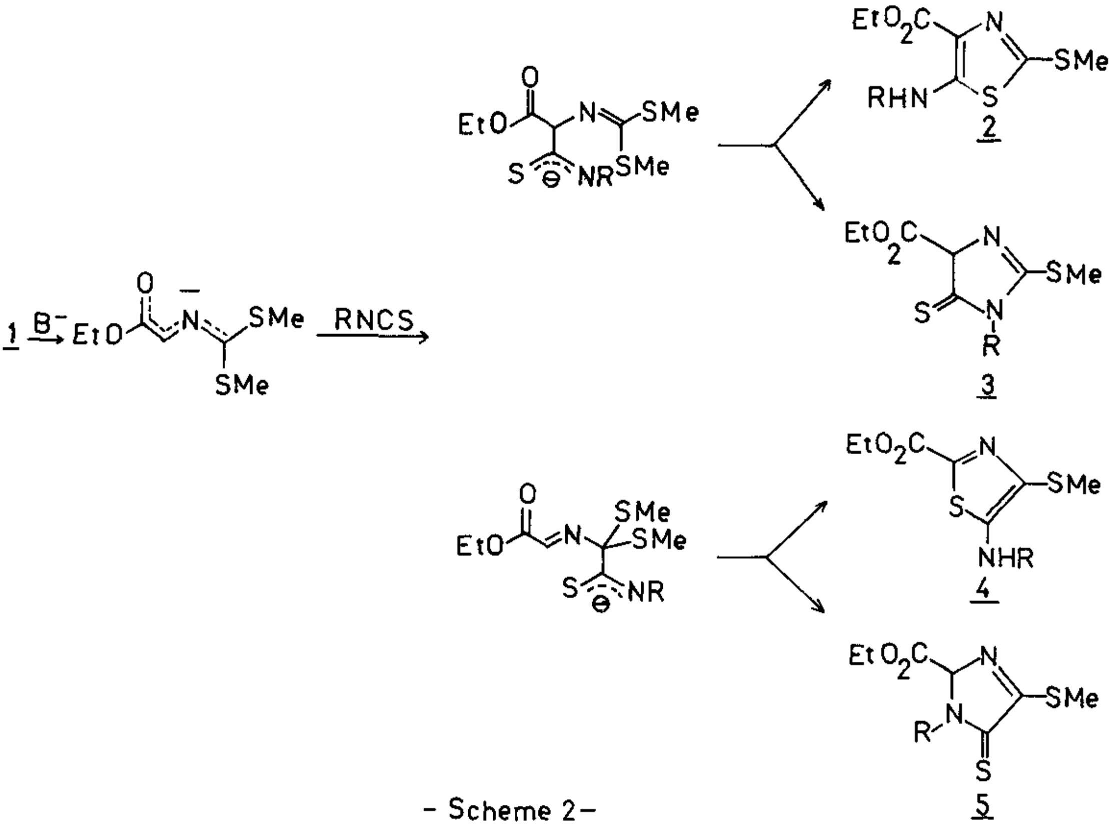
[a]Broadened singlet. [b]Interchangeable assignments. [c]Broadened triplet.

The ^{1}H-nmr data prove the presence of an ethyl ester, a methylthio, and a secondary amine groups. The signals observed at 2.52-2.65 ppm support the presence of a methylthio group bounded to a sp^2 carbon,[10] and the signals at 9.47-9.80 ppm and 7.27-7.40 ppm an aromatic (2a-2d) or aliphatic (2e-2f) secondary amine groups (Ref. 10, p. 118).

The ^{13}C-nmr data support the proposed structure to 2a-2f compounds. The assignment of signals to C2 and C4 carbons is proposed by comparison with the chemical shifts reported by us for C2 and C4 carbons of 5-aryl(or alkylthio)-4-ethoxycarbonyl-2-methylthio-1,3-thiazoles (C2: 161.73-163.74 ppm; C4: 137.74-141.46 ppm).[5]

The ms data are according to the proposed structure to 2a-2f 1,3-thiazoles. In all cases the base peak has been the molecular ion, and a common ion m/z=91 has been detected. This peak can be reasonably assigned to MeS-C≡S$^+$ ion (Ref. 1, p. 244), and its formation precludes any other relative disposition of the sulfur heteroatoms in the molecular ion.

Thus, the synthesis of 1,3-thiazoles by this method has shown to be highly selective because four different products can be originated taking into account the regioselectivities of condensation and cyclization steps[8] (Scheme 2).



- Scheme 2-

Although some related syntheses have been previously described -cyclocondensation reactions of nitrile ylides with monothioesters,[11] α-metallated isocyanides with carbon disulfide,[8] monothio,[12], and dithioesters;[13] EMIC with carbon disulfide,[5,6] and rearrangement of mesoionic 1,3-oxazoles to mesoionic 1,3-thiazoles[14]- none of these methods allows to obtain the perfunctionalyzed 1,3-thiazoles described in this paper.

EXPERIMENTAL

Melting points were determined *in a Büchi 520 apparatus in capillary* tubes and are uncorrected. The ir spectra were recorded on a Perkin Elmer 781 spectrometer. The ^{1}H- and ^{13}C-nmr spectra were recorded on a Varian FT 80A spectrometer (79.542 MHz for ^{1}H and 20.00 MHz for ^{13}C). Solutions in $CDCl_3$ (13% and 25% w/v, respectively) at 303^{o}K were used. Chemical shifts are quoted in δ values using TMS as internal reference. Mass spectra were recorded on a Varian Matt 711 spectrometer by electron impact technique (70 eV). All elemental analyses were satisfactories. Silica gel 60 F_{254} plates (Merck) were used for TLC, and silica gel 273-400 mesh (Merck) was used for conventional *flash column chromatographies.*

Synthesis of 1[13] was accomplished from ethyl ester glycine hydrochloride (Aldrich Chemie), carbon disulfide, and methyl iodide following the procedure described previously by us.[5] α-Metallated 1 was condensed with phenyl isothiocyanate in different base/solvent systems and/or reaction conditions (Table 1). The isolation of products was performed following a general procedure with special features gathered in Table 1.

General procedure. To a stirred solution of KBu^tO (0.785 g, 7 mmol) in 50 ml dry THF (at -78°C under nitrogen) was added dropwise a solution of 1 (1 g, 5 mmol) in 4 ml dry THF. After 0.5 h. at -78°C, a solution of 5 mmol of isothiocyanate in 4 ml dry THF was slowly added. After 30 min. at -78°C, the mixture was allowed to stand at room temperature for 2 h., and was then quenched with water, and extracted with diethyl ether (4x30 ml). The combined ethereal extracts were dried on $MgSO_4$ (12 h.), and evaporated. The product was isolated by precipitation with pentane and recrystallized (**2a**-**2d**), or from silica gel flash chromatography **2e**: *n*-hexane/ethyl acetate: 90/10 v/v; **2f**: *n*-hexane/ethyl acetate: 95/5 v/v.

4-Ethoxycarbonyl-2-methylthio-5-phenylamino-1,3-thiazol, 2a. Ir (KBr pellet) 3400, 2910-2820, 1660, 1620, 1590, 1570, 1420, 1255, 1205, 790 cm^{-1}. ^{1}H-Nmr, δ(ppm): 1.42 (t, 3H, CH_3CH_2, J=7.0 Hz), 2.65 (s, 3H, SCH_3), 4.41 (q, 2H, CH_2CH_3, J=7.0 Hz), 7.05-7.53 (m, 5H, Ph), 9.80 (bs, 1H, NH). ^{13}C-Nmr, δ(ppm): 14.56 (CH_3CH_2), 17.56 (SCH_3), 60.87 (CH_2CH_3), 118.61 (*p*-C), 122.90 (C5), 123.81 (*o*-C), 129.69 (*m*-C), 140.64 (C4), 155.79 (*ipso*-C), 164.72 (C2), 164.76 (CO_2Et). Ms (%): 296 (9.4), 295 (14.3), 294 (100.0), 248 (37.1), 247 (3.7), 215 (77.1), 214 (19.4), 91 (19.7), 77 (15.1).

4-Ethoxycarbonyl-5-*p*-fluorphenylamino-2-methylthio-1,3-thiazole, 2b. Ir (KBr pellet): 3280, 3100, 2990, 1690, 1670, 1600, 1580, 1470, 1230, 1200, 1190, 860, 780 cm^{-1}. ^{1}H-Nmr, δ(ppm): 1.43 (t, 3H, CH_3CH_2, J=7.0 Hz), 2.62 (s, 3H, SCH_3), 4.41 (q, 2H, CH_2, J=7.0 Hz), 6.81-7.34 (m, 4H, Ar), 9.58 (bs, 1H, NH). ^{13}C-Nmr, δ(ppm): 14.53 (CH_3CH_2), 17.59 (SCH_3), 60.95 (CH_2CH_3), 116.48 (d,*m*-C,$^2J(^{13}C,^{19}F)$=22.6 Hz), 120.28 (d,*o*-C, $^3J(^{13}C,^{19}F)$=11.8 Hz), 122.80 (C5), 137.06 (d, *ipso*-C, $^4J(^{13}C,^{19}F)$=2.6 Hz), 146.20 (C4), 156.89 (C2), 159.38 (d,*p*-C,$^1J(^{13}C,^{19}F)$=244.4 Hz), 164.69 (CO_2Et). Ms (%): 314 (10.3), 313 (19.1), 312 (100.0), 266 (45.6), 265 (4.1), 233 (69.1), 232 (45.6), 95 (19.1), 91 (44.1).

4-Ethoxycarbonyl-5-*p*-methylphenylamino-2-methylthio-1,3-thiazole, 2c. Ir (KBr pellet): 3220, 3000, 2900, 1730, 1660, 1590, 1580, 1420, 1270, 1200, 820, 780 cm^{-1}. ^{1}H-Nmr, δ(ppm): 1.42 (t, 3H, CH_3CH_2, J=7.1 Hz), 2.32 (s, 3H, CH_3-Ar), 2.62 (s, 3H, SCH_3), 4.41 (q, 2H, CH_2CH_3, J=7.1 Hz), 7.10 (m, 4H, Ar), 9.60 (bs, 1H, NH). ^{13}C-Nmr, δ(ppm): 14.22 (CH_3CH_2), 17.32 (SCH_3), 20.46 (CH_3-Ar), 60.47 (CH_2CH_3), 118.38 (*o*-C), 122.15 (C5), 129.84 (*p*-C), 133.48 (*ipso*-C), 137.92 (*m*-C), 145.50 (C4), 156.44 (C2), 164.35 (CO_2Et). Ms (%): 310 (9.2), 309 (14.9), 308 (100.0), 262 (48.6), 261 (8.1), 229 (64.5), 228 (16.7), 91 (13.2).

4-Ethoxycarbonyl-5-*p*-methoxyphenylamino-2-methylthio-1,3-thiazole, 2d. Ir (KBr pellet): 3300, 3160, 3110, 2990, 1700, 1660, 1540, 1510, 1480, 1300, 1270, 770, 670 cm^{-1}. ^{1}H-Nmr, ∂(ppm): 1.41 (t, 3H, CH_3CH_2, J=7.0 Hz), 2.59 (s, 3H, SCH_3), 3.78 (s, 3H, OCH_3), 4.42 (q, 2H, CH_2CH_3, J=7.0 Hz), 6.77-7.47 (m, 4H, Ar), 9.47 (bs, 1H, NH). ^{13}C-Nmr, ∂(ppm): 14.26 (CH_3CH_2), 17.37 (SCH_3), 55.19 (OCH_3), 60.44 (CH_2CH_3), 113.92 (*ipso*-C), 114.54 (*m*-C), 121.14 (*o*-C), 121.54 (C5), 133.89 (C4), 156.48 (*p*-C), 158.17 (C2), 164.34 (CO_2Et). Ms (%): 326 (10.6), 325 (15.8), 324 (100.0), 278 (79.0), 277 (5.3), 245 (31.1), 244 (21.6), 91 (25.3).

4-Ethoxycarbonyl-5-ethylamino-2-methylthio-1,3-thiazol, 2e. Ir (film): 3310, 2980, 2860, 1710, 1660, 1550, 1390, 1220, 1150 cm^{-1}. ^{1}H-Nmr, ∂(ppm): 0.93 (t, 3H, CH_3CH_2NH, J=7.1 Hz), 1.35 (t, 3H, CH_3CH_2OCO, J=7.0 Hz), 2.56 (s, 3H, SCH_3), 3.11 (qd, 2H, CH_3CH_2NH, J=7.1 , 5.0 Hz), 4.27 (q, 2H, CH_3CH_2OCO, J=7.0 Hz), 7.40 (bt, 1H, NH,J=5.0 Hz). ^{13}C-Nmr, ∂(ppm): 13.39 (CH_3CH_2OCO, CH_3CH_2NH), 16.51 (SCH_3), 42.88 (CH_3CH_2NH), 58.85 (CH_3CH_2OCO), 117.87 (C5), 142.50 (C4), 161.83 (C2), 162.96 (CO_2Et). Ms (%): 248 (8.3), 247 (9.2), 246 (100.0), 200 (20.2), 199 (3.5), 167 (25.1), 166 (22.1), 91 (15.0).

4-Ethoxycarbonyl-5-*n*-butylamino-2-methylthio-1,3-thiazole, 2f. Ir (film): 3420, 2900, 1700, 1660, 1550, 1460, 1420, 1200, 1150 cm^{-1}. ^{1}H-Nmr, ∂(ppm): 0.93 (t, 3H, $CH_3(CH_2)_3$, J=7.0 Hz), 1.35 (m, 4H, $CH_3(CH_2)_2CH_2NH$), 1.42 (t, 3H, CH_3CH_2OCO, J=7.1 Hz), 2.52 (s, 3H, SCH_3), 3.10 (m, 2H, $CH_3(CH_2)_2CH_2NH$), 4.27 (q, 2H, CH_3CH_2OCO, J=7.1 Hz), 7.27 (bt, 1H, NH, J=7.27 Hz). ^{13}C-Nmr, ∂(ppm): 12.87 ($CH_3(CH_2)_3$), 13.82 (CH_3CH_2OCO), 17.08 (SCH_3), 19.08 ($CH_3CH_2(CH_2)_2$), 30.51 ($CH_3CH_2CH_2CH_2NH$), 48.18 ($CH_3(CH_2)_2CH_2NH$), 59.40 (CH_3CH_2OCO), 118.33 (C4), 143.02 (C5), 162.73 (C2), 163.73 (CO_2Et). Ms (%): 276 (8.7), 275 (10.1), 274 (100.0), 228 (35.3), 227 (4.1), 195 (40.1), 194 (8.3), 91 (12.0).

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