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A NOVEL SYNTHESIS OF THIAZOLES FROM DIMETHYL N-(ETHOXYCARBONYLMETHYL)IMINO DITHIOCARBONATE, CARBON DISULFIDE AND ALKYL HALIDES.

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We report a new synthesis of thiazoles from a cyclocondensation reaction between dimethyl N-(ethoxycarbonylmethyl)iminodithiocarbonate (EMIC), carbon disulfide and alkylation of intermediate thiazole-2-thiolate with alkyl halides.

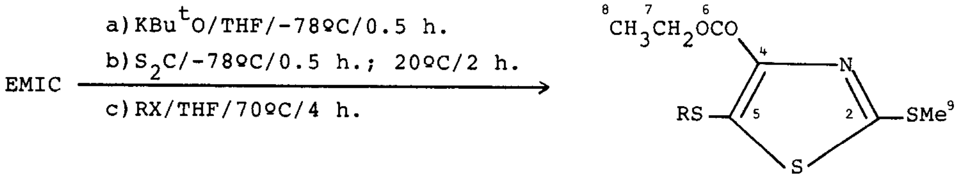
We have recently studied the reaction of carbanion from dimethyl N-(ethoxycarbonylmethyl)iminodithiocarbonate (EMIC)[1,2] with aromatic aldehydes[2,3]. Our interest in this ambident carbanion is due to its utility for transfer the C-N=C unit to unsaturated electrophiles C=Z (Z:O,N,S) and to obtain heterocyclic compounds and/or acyclic compounds by base induced open ring of preformed heterocycles as observed with aromatic aldehydes[4,5]. In this paper we report a new synthesis of thiazoles by an one-pot cyclocondensation reaction from EMIC, carbon disulfide and alkylation of 4-ethoxycarbonyl-2-methylthiothiazole-5-thiolate with alkyl halides.

EMIC was obtained from glycine ethyl ester hydrochloride, carbon disulfide and methyl iodide using the phase transfer catalyst technique with triethylbenzylammonium chloride (TEBA) as catalyst and NaOH-H_2O/benzene as two-phase system. This procedure is more convenient than other methods described previously in the literature[1,2] because the EMIC is obtained in an one-pot reaction in 15 min. with a purity of 97-99%[6].

$$EtO_2C-CH_2-\overset{+}{N}H_3,Cl^- \xrightarrow[20ºC/TEBA/15-20\ min.]{NaOH\ 22\ M/benzene/S_2C/MeI} EtO_2C-CH_2-N=C(SMe)_2$$

EMIC (33-39%)

5-Alkylthio-4-ethoxycarbonyl-2-methyltiothiazoles, Ia-h, are obtained in an one-pot reaction from EMIC, carbon disulfide and alkyl halides.



Ia-h

R: a: $PhCH_2$; b: p-$MeC_6H_4CH_2$; c: p-$FC_6H_4CH_2$; d: p-$ClC_6H_4CH_2$; e: p-$NO_2C_6H_4CH_2$; f: CH_3; g: $CH_3(CH_2)_3$; h: $(CH_3)_2CHCH_2$

The reaction is most conveniently performed as follows. To a stirred suspension of 2.0 eq. of KBu^{t}O in 50 ml. of dry THF[7] (at -78ºC under N_2) is added dropwise a solution of 1 eq. (5 mmol) of EMIC in 4 ml. of dry THF[7] (-78ºC/0.5 h.) and 1.2 eq. of S_2C in 4 ml. of dry THF[7] (-78ºC/0.5 h. and 20ºC/15 min.). A solution of 1 eq. of benzyl chloride or 10 eq. of alkyl halide in 10 ml. of dry THF[7] is added (70ºC/4 h.). The product is obtained upon dilution of reaction mixture with water and is purified by precipitation with pentane and recrystallized from hexane (Ia-f) or from silica gel chromatography (hexane/ethyl acetate: 80/20 v/v) (Ig-h).

Compound	RX	M.P.(ºC)[8]	Yield(%)[a]
Ia	$PhCH_2Cl$	78-79	36
Ib	$p\text{-}MeC_6H_4CH_2Cl$	84-86	17
Ic	$p\text{-}FC_6H_4CH_2Cl$	92-94	19
Id	$p\text{-}ClC_6H_4CH_2Cl$	116-118	42
Ie	$p\text{-}NO_2C_6H_4CH_2Cl$	116-118	50
If	MeI	51-53	48
Ig	$CH_3(CH_2)_3Br$	liquid	40
Ih	$(CH_3)_2CHCH_2Br$	liquid	29

[a] Recrystallized product (except Ig-Ih).

All new compounds are fully characterized by their IR[9], ^{1}H-NMR[9,10] (Table 1), ^{13}C-NMR[9,11] (Table 2) and MS[9] together correct elemental analysis. The proposed structure for Ia-Ih thiazoles is according with the multiplicity observed in ^{13}C-NMR coupled spectra (Table 2).

TABLE 1

	^{1}H-NMR. δ(ppm)[a]			
Compound	H7(c,2H)	H8(t,3H)	H9(s,3H)	Other signals
Ia	4.32	0.99	2.63	4.17(s,2H); 7.25(bs,5H)
Ib	4.40	1.39	2.65	2.33(s,3H); 4.14(s,2H); 7.10-7.28(m,4H)
Ic	4.40	1.39	2.65	4.14(s,2H); 6.68(m,2H); 7.42(m,2H)
Id	4.38	1.38	2.64	4.12(s,2H); 7.27(bs,4H)
Ie	4.22	1.31	2.64	4.28(s,2H);7.50-7.61(m,2H);8.11-8.22(m,2H)
If	4.41	1.40	2.60	2.57(s,3H)
Ig	4.41	1.42	2.70	0.96(t,3H); 1.15-1.56(m,4H); 2.98(t,2H)
Ih	4.41	1.41	2.70	1.11(t,3H); 1.65-2.00(m,1H); 2.85(d,2H)

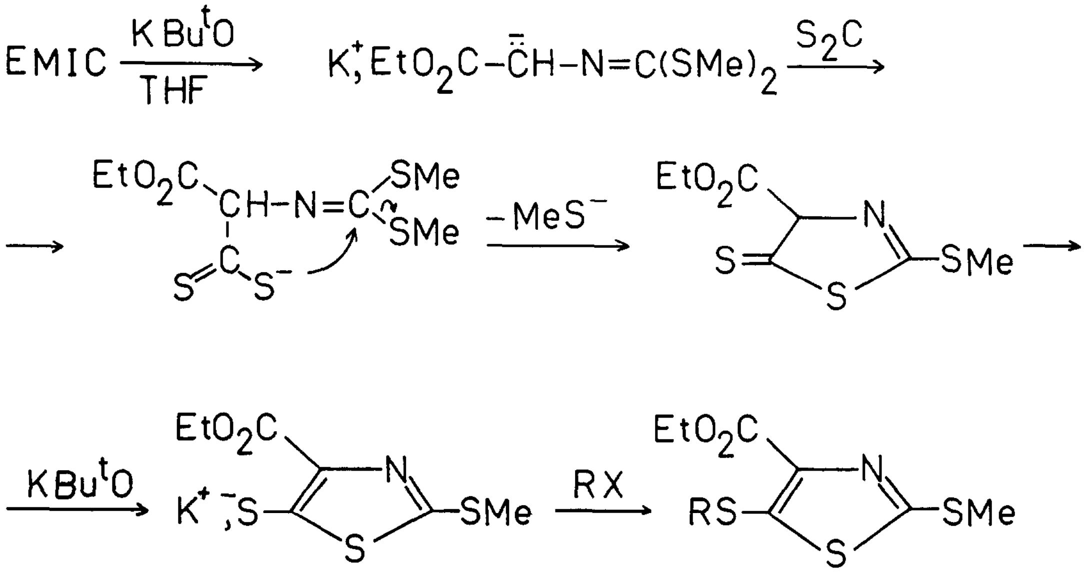
[a] c: cuadruplet; t: triplet; s: singlet; bs: broadened singlet.

TABLE 2

	^{13}C-NMR[12]. δ (ppm)[a]						
Compound	C2(c)	C4(s)	C5(t)	C6(t)	C7(tc)	C8(ct)	C9(c)
Ia	162.60	140.63	142.92	161.35	66.56	10.62	16.43
Ib	162.70	140.70	143.90	161.65	61.36	14.34	16.85
Ic	162.32	141.21	143.07	161.64	61.53	14.41	16.87
Id	163.39	141.21	142.76	161.58	61.58	14.38	16.84
Ie	163.37	141.53	140.58	160.92	61.12	13.88	16.29
If	162.81	138.93	148.07	161.54	61.35	14.42	17.06
Ig	161.73	139.52	146.00	161.66	61.19	14.23	16.89
Ih	163.08	139.70	146.44	161.78	61.30	14.89	16.96

[a] c: cuadruplet; s: singlet; t: triplet; tc: triplet of cuadruplets; ct: cuadruplet of triplets.

The propensity of methyliminodithiocarbonates to undergo metallation[2,4,5,13] and the presence of a potential leaving group (i.e. thiomethyl) suggests the following reaction path:



Ia-h

In connection with the synthesis of thiazoles using a cyclocondensation reaction between a metallated nucleophile and S_2C the unique method reported is the synthesis of 4-alkyl-5-methylthiothiazoles by reaction of α-metallated isonitriles with S_2C at -60ºC and alkylation of 5-thiazolthiolates with MeI at 60ºC[14]. However, this synthesis has been applied with three isonitriles and MeI has been the unique alkylating reagent used.

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2.- C. Alvarez-Ibarra, J. A. Cereceda, P. Ortiz, A. Vicente and M. L. Quiroga, Tetrahedron Lett., 243 (1985).

3.- The assignment of 5-aryl-2-ethoxycarbonyl-4-methylthio-2,3-dihydrooxazole structure proposed previously by us to products obtained in the condensation of EMIC with aromatic aldehydes in basic media[2] has been revised as 1-(methylthio)carbonylamino-2-arylacrylates (unpublished results). This structural assignment has been proved by isolation and unequivocal characterization of cis and trans-5-aryl-4-ethoxycarbonyl-2-methylthio-3,4-dihydrooxazoles (Ar: phenyl; 2-pyridyl; 2-furyl) and base induced open ring (KBu^tO/THF) of 4-ethoxycarbonyl-2-methylthio-5-phenyl-3,4-dihydroxazole to ethyl 1-(methylthio)carbonylamino-2-phenylacrylate whose physical (melting point and R_f) and spectroscopic (IR, ^{1}H-NMR, ^{13}C-NMR) properties were identical to product described previously by us as 2-ethoxycarbonyl-4-methylthio-5-phenyl-2,3-dihydrooxazole. These unpublished results are in agreement with facts published by Makosza et al.[4].

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6.- The purity of EMIC was tested by GFC (UCC 10% Chromosorb GW-AW-DMCS: length: 3 m.; Φ, 1/8"; carrier gas: (N_2): 20 ml/min.; temperature: 160ºC; retention time: 8 min.).

7.- Recently distilled from $LiAlH_4$.

8.- Melting points are uncorrected.

9.- Spectra were recorded with following apparatus: IR, Perkin-Elmer, model 256; ^{1}H- and ^{13}C-NMR: Varian FT 80A; MS: Varian Matt 711.

10.-$CDCl_3$/TMS. Spectral width: 2000 Hz. Acquisition time: 1.023 s.

11.-$CDCl_3$/TMS. Spectral width: 5000 Hz. Acquisition time: 1.638 s.

12.-^{13}C-NMR spectra of Ia-Ih compounds have additional signals. Ia: 41.26; 127.56; 128.59; 128.69; 135.03. Ib: 41.30; 128.90; 129.37; 132.18; 137.69. Ic: 40.75; 115.71; 130.77; 130.89; 162.38. Id: 40.75; 128.89; 130.38; 133.78; 133.97. Ie: 40.20; 123.57; 129.44; 142.81; 146.90. If: 20.01. Ig: 16.89; 21.75; 30.67; 36.98. Ih: 16.96; 22.02; 28.47; 46.18.

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