THE BEHAVIOUR OF VICINAL ALKYL AMINOTHIOPHENECARBOXYLATES IN THE SANDMEYER AND SCHIEMANN REACTIONS

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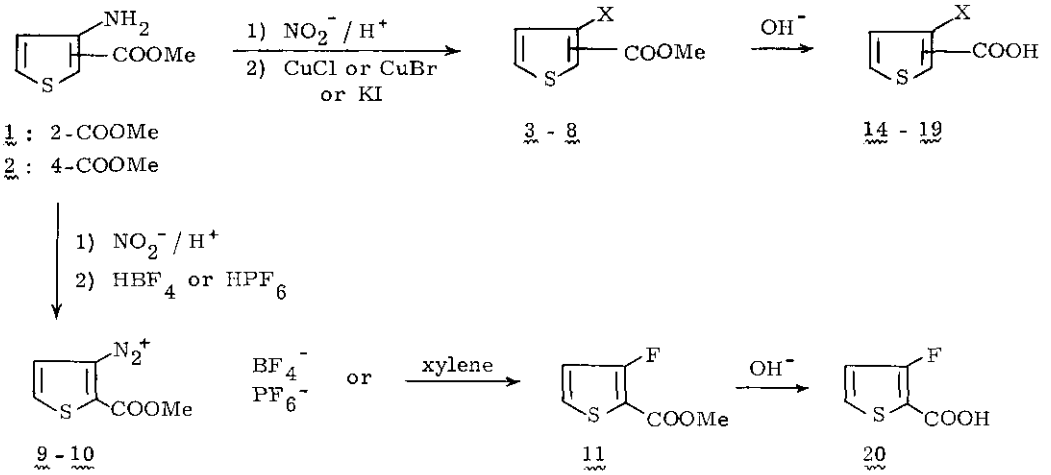
Abstract — The diazotization of vicinal alkyl aminothiophenecarboxylates has been studied. 3-Amino compounds gave clear diazonium salts which yielded the expected halo derivatives in the Sandmeyer and Schiemann conditions. However, 2-amino compounds yielded self-coupling products.

In order to study the Ullmann reaction for the preparation of thiophenic xantones, thioxantones and acridones, we were interested in the syntheses of the three possible isomeric vicinal halothiophenecarboxylic acids, easier than those described [1-7], in which not easy to handle lithium or magnesium reagents are used.

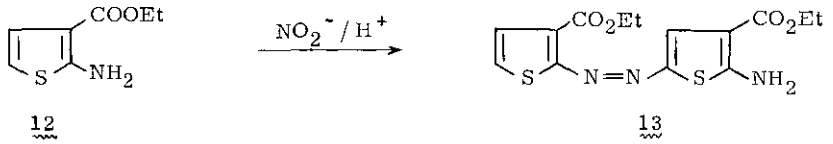
We report here the attempted synthesis of these compounds by hydrolysis of the corresponding esters, which could be obtained by application of the Sandmeyer and Schiemann reaction to the diazonium salts of the three isomeric vicinal alkyl aminothiophenecarboxylates, which are easily available. The synthesis of methyl 3-hydrazinothiophene-2-carboxylate[8] and 3-mercaptothiophene -2 and 4-carboxylic acids[9] are the only examples described in the literature of the use of the diazonium salts of thiophenic aminoesters.

In the case of the 3-aminothiophenes 1 and 2, the diazotization reaction followed the normal course yielding clear and stable diazonium salt solutions from which, the corresponding 3-halo derivatives 3 - 8 were obtained in acceptable yields, by treatment with cuprous chloride, cuprous bromide or potassium iodide.

The fluoro derivative 11 was obtained by thermal decomposition in boiling xylene of the tetrafluoroborate 9 or the hexafluorophosphate 10 compounds, obtained by adding the corresponding inorganic acid to the diazonium solutions of 1. However, methyl 3-fluorothiophene-4-carboxylate could not be obtained in the same manner, because it was not possible to isolate the solid diazonium salts.



The diazonium salt of ethyl 2-aminothiophene-3-carboxylate 12, unlike its isomers, could not be submitted to the Sandmeyer and Schiemann reactions, since it coupled very fast with unreacted 12 to yield the azo compound 13.



12 13

The desired acids 14 - 20 were obtained in nearly quantitative yield by alkaline hydrolysis of the corresponding esters 3 - 8 and 11.

EXPERIMENTAL

Melting points were determined on a Büchi melting point apparatus and are uncorrected. All the new compounds gave satisfactory microanalytical data (± 0.3 %). Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer, ν values in cm^{-1}. ^1H-NMR spectra were recorded on a Varian EM-390 90 MHz spectrometer, using deuteriochloroform or hexadeuteriodimethylsulphoxide (14 - 20) as solvents; signals are reported in δ units with TMS as internal standard.

Alkyl aminothiophenecarboxylates

Methyl 3-aminothiophene-2-carboxylate 1[10], methyl 3-aminothiophene-4-carboxylate 2[11], and ethyl 2-aminothiophene-3-carboxylate[12] were prepared according to the literature procedures.

Methyl 3-halo(chloro, bromo or iodo)thiophene-2-carboxylates (3 - 5)

Methyl 3-aminothiophene-2-carboxylate (9.4 g, 60 mmol) was added gradually to a vigorously

stirred 6M hydrochloric acid solution (25 ml) for the cases of chloro and iodo derivatives or concentrated hydrobromic acid (20 ml) for the case of bromo derivative. The reaction mixture was stirred for 30 min at room temperature and once cooled below 0° C (ice-salt bath), and then diazotised with sodium nitrite (4.2 g, 60 mmol) in water (10 ml). The resulting diazonium salt was stirred for 1 h at this temperature and was poured at once onto a well stirred solution of cuprous chloride (60 mmol in concentrated hydrochloric acid (25 ml)), cuprous bromide (60 mmol in concentrated hydrobromic acid (25 ml)) or potassium iodide (60 mmol in concentrated hydrochloric acid (25 ml)), cooled below 0° C. The reaction mixture was heated at 60° C until evolution of nitrogen had ceased and once cooled, and then repeatedly extracted with ether. The ethereal extracts were washed with water, dried over magnesium sulfate and evaporated to dryness, and the residue was purified by distillation and/or crystallization.
The compounds obtained following this procedure are shown in the Table.

Methyl 3-halo(chloro, bromo or iodo) thiophene-4-carboxylates (6 - 8)

These compounds were obtained as described above, starting from methyl 3-aminothiophene-4-carboxylate (2), shown in the Table.

Methyl 3-fluorothiophene-2-carboxylate (11)

To the cooled diazonium salt solution, prepared as above, from methyl 3-aminothiophene-2-carboxylate (60 mmol), a 36.6% tetrafluoroboric acid solution (18 ml) or a 60% hexafluorophosphoric acid solution (20 ml) were added. The solid diazonium salt was filtered, washed with the corresponding acid solution, methanol and ether and dried "in vacuo", under sulphuric acid to yield respectively methyl 3-diazothiophene-2 carboxylate tetrafluoroborate (9) (Yield, 68%; mp 142-143° C (d)) and hexafluorophosphate (10) (Yield, 89%; mp 162-163° C (d)).
A well stirred suspension of compound 9 or 10 (50 mmol) in dry xylene (100 ml) was heated for 4 h at 150-160° C. The solvent was removed and the residue treated with a 10% sodium carbonate solution and extracted with ether. The ethereal extracts were washed with water, dried with magnesium sulphate, evaporated and the residue was crystallized from ethanol (see the Table).

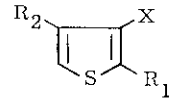
Diazotization reaction of ethyl 2-aminothiophene-3-carboxylate (12)

Ethyl 2-aminothiophene-3-carboxylate (6.8 g, 40 mmol) in concentrated hydrochloric acid (50 ml) was diazotised as described above and from the clear diazonium salt solution formed, a black-violet solid precipitated spontaneously. This solid was filtered, washed with water and recrystallized from ethanol to yield the self-coupling compound 13 (6.8 g, 60% yield). Mp 191-193° C (d). IR (KBr): 3440, 3310 (NH_2), 1710 (C=O), 1645 (N=N). Mass m/z: M^+, 353.

Hydrolysis of methyl 3-halothiophene-2-(or 4)-carboxylates

To a stirred solution of compounds 3 - 8 and 11 (40 mmol) in ethanol (90 ml) a 1N sodium hydroxide solution (90 ml) was added. The mixture was refluxed for 30 min and the solvent

TABLE. Yields and physical data of thiophenic derivatives



Compd. No	R_1	R_2	X	Yield (%)	Bp °C (mm Hg)	Mp °C	IR (C=O)	^{1}H-NMR thiophenic protons		
3	CO_2Me	H	Cl	65	113-114(12)	34-35	1730	7.05 (d, 1H, H3);	7.55 (d, 1H, H2);	$J_{2,3} \simeq 5$Hz
4[a]	CO_2Me	H	Br	60	126-127(12)	49-50[b]	1725	7.10 (d, 1H, H3);	7.50 (d, 1H, H2);	$J_{2,3} \simeq 5$Hz
5[c]	CO_2Me	H	I	60	160-161(12)	52-53[b]	1730	7.20 (d, 1H, H3);	7.45 (d, 1H, H2);	$J_{2,3} \simeq 5$Hz
6[d]	H	CO_2Me	Cl	52		48-50[e]	1720	7.65 (d, 1H, H5);	8.45 (d, 1H, H2);	$J_{2,5} \simeq 3.5$Hz
7[f]	H	CO_2Me	Br	50		49-51[e]	1715	7.70 (d, 1H, H5);	8.40 (d, 1H, H2);	$J_{2,5} \simeq 3.5$Hz
8[g]	H	CO_2Me	I	53	118-120(12)[e]		1720	7.85 (d, 1H, H5);	8.35 (d, 1H, H2);	$J_{2,5} \simeq 3.5$Hz
11	H	CO_2Me	F	48/92		110-112[h]	1705	6.85 (m[i], 1H, H3);	7.65 (m[i], 1H, H2);	$J_{2,3} \simeq 5$Hz
14[j]	CO_2H	H	Cl	c.a.100		187-188(d)[k]	1685	7.30 (d, 1H, H3);	8.05 (d, 1H, H2);	$J_{2,3} \simeq 5$Hz
15[l]	CO_2H	H	Br	c.a.100		191-192(d)[k]	1675	7.35 (d, 1H, H3);	8.00 (d, 1H, H2);	$J_{2,3} \simeq 5$Hz
16[m]	CO_2H	H	I	c.a.100		200-201(d)[k]	1675	7.45 (d, 1H, H3);	7.95 (d, 1H, H2);	$J_{2,3} \simeq 5$Hz
17[n]	H	CO_2H	Cl	c.a.100		152-153(d)[k]	1670	7.65 (d, 1H, H5);	8.45 (d, 1H, H2);	$J_{2,5} \simeq 3.5$Hz
18[o]	H	CO_2H	Br	c.a.100		156-158(d)[k]	1670	7.70 (d, 1H, H5);	8.40 (d, 1H, H2);	$J_{2,5} \simeq 3.5$Hz
19[p]	H	CO_2H	I	c.a.100		167-168(d)[k]	1665	7.85 (d, 1H, H5);	8.35 (d, 1H, H2);	$J_{2,5} \simeq 3.5$Hz
20	CO_2H	H	F	c.a.100		157-158(d)[q]	1675	6.90 (m[i], 1H, H3);	7.70 (m[i], 1H, H3);	$J_{2,3} \simeq 5$Hz

[a] Bibliographic[13] mp 50° C; [b] recrystallized from n-hexane; [c] bibliographic[13] mp 54° C; [d] bibliographic[14] mp 48-50° C; [e] recrystallized from benzene-n-hexane; [f] bibliographic[14] mp 50-51° C; [g] bibliographic[14] bp 105-110° C (mm); [h] recrystallized from ethanol; [i] $H_AH_BF_X$ system; [j] bibliographic[3] mp 175-176° C; [k] recrystallized from ethanol-water; [l] bibliographic[1,4,5] mp 190° C, 195-197° C, 193-195° C; [m] bibliographic[2] mp 193-195° C; [n] bibliographic data[7]; [o] bibliographic[1,6] mp 150-152° C, 157-159° C; [p] bibliographic[2,7] mp 169-170° C, 168-169° C; [q] recrystallized from ethyl acetate-n-hexane.

evaporated. The residue was dissolved in water (100 ml) and acidified with a 10% hydrochloric acid solution. The solid thus formed was filtered, washed with water, dried and recrystallized. The compounds obtained according to this procedure are shown in the Table.

Analytical data of new compounds

3	Calc. for $C_6H_5ClO_2S$	:	C, 40.79;	H, 2.83;	S, 18.13	
	Found	:	41.02;	2.63;	18.40	
11	Calc. for $C_6H_5FO_2S$	:	C, 45.00;	H, 3.13;	S, 20.00	
	Found	:	44.82;	3.30;	19.87	
13	Calc. for $C_{14}H_{15}N_3O_4S_2$	:	C, 47.59;	H, 4.24;	N, 11.90;	S, 18.13
	Found	:	47.37;	4.19;	12.03;	18.31
20	Calc. for $C_5H_3ClO_2S$	:	C, 36.92;	H, 1.85;	S, 19.69	
	Found	:	36.69;	1.87;	19.89	

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