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A FRIEDEL-CRAFTS SYNTHESIS OF N-SUBSTITUTED THIOPHENECARBOTHIOAMIDES

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Abstract - The reaction of thiophene and 2,5-dimethylthiophene with isothiocyanates in the presence of aluminum chloride in nitromethane gave rise to the formation of the N-substituted carbothioamides of thiophene-2-carboxylic and 2,5-dimethylthiophene-3-carboxylic acid, respectively. Under similar conditions, 2-ethylthio-5-methylthiophene was attacked by the reagent at the carbon atom adjacent to the ethylthio group, whereas 2-phenyl-5-methylthiophene yielded a mixture of the 3- and 4-carbothioamides.

Only few examples have been reported as yet on the direct, Lewis acid catalyzed substitution of aromatic compounds with the amide or thioamide groups. Leuckart[1,2] was the first to use aluminum chloride as the catalyst in the reaction of an isocyanate with aromatic hydrocarbons and thiophene. However, thiophene was mostly decomposed and the corresponding anilide was obtained in low yield. In 1929, Karrer and Weiss[3] reported on thiocarbamoylation of resorcinol with phenyl isothiocyanate. A detailed study of such reactions was presented by Effenberger and Gleiter[4] who discussed also some mechanistic aspects of the Friedel-Crafts reaction of isocyanates with aromatic hydrocarbons.

Although certainly of potential preparative interest, reactions of this type have not found so far any wider use in the heteroaromatic systems. The known examples are limited to the above-mentioned reactions carried out by Leuckart[1,2] and to the synthesis of thiophene-2-carbothioamide and thiophene-2-carbethoxyamide reported by Papadopoulos[5] who employed tin tetrachloride as the catalyst.

Following our earlier research on a related topic[6] we present now a study aimed at developing a convenient preparative route to thiophenecarbothioamides in the Lewis-acid catalyzed reaction of thiophene and substituted thiophenes with isothiocyanate.

RESULTS AND DISCUSSION

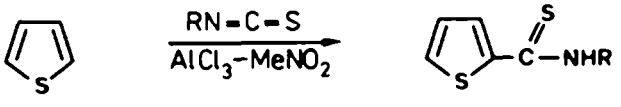
Many Lewis acid were found inapplicable as catalysts of the reaction under study; these include: boron trifluoride diethyl ether and acetic acid complexes, zinc chloride, titanium and tin tetrachlorides and antimony pentachloride. Best results with both aromatic and aliphatic isothiocyanates were obtained when aluminum chloride in a nitromethane solution was used as the catalyst.

In the case of thiophene itself, the substitution invariably occurred at the α-position to yield the appropriate N-substituted thiophene-2-carbothioamides 1-9 (Table 1).

Table 1. Thiophene-2-carbothioamides

Compound	Yields (%)	M.p. (°C) (solvent)	Spectral data[a]
1 R = Me	82.0	87-89 (hexane-benzene)	^{1}H-NMR: 3.10-3.12 (CH_3,d); 6.9-7.7 (thiophene,m);10.0(NH,s).MS:157(M^+) (100);124(M-SH)(16);127(M-RNH)(79); 110(M-RS)(6)
2 R = Et[b]	76.0	50-52 (CCl_4)	^{1}H-NMR:1.12-1.25(CH_3,t);3.47-3.85 (CH_2,q);6.9-7.6(thiophene,m).MS:171 (M^+)(72);138(M-SH)(3);127(M-RNH) (57);111(100);110(M-RS)(29)
3 R = cyclohexyl	78.0	127-129 (CH_3OH-H_2O 3:1)	^{1}H-NMR:1.0-2.2(c-C_6H_{11},m);6.8-7.7 (thiophene,m);10.1(NH,s).MS:225(M^+) (88);224(M-H)(14);192(M-SH)(22);127 (M-RNH)(100);110(M-RS)(80);111(37)
4 R = Ph	92.0	94-95 (CH_3OH-H_2O 3:1)	^{1}H-NMR:6.8-7.6(thiophene,Ph,m);9.0 (NH,s).MS:219(M^+)(39);186(M-SH)(17); 127(M-ArNH)(100);110(M-ArS)(23)
5 R = 4-ClPh	95.0	143-145 (CH_3OH-H_2O 3:1)	^{1}H-NMR:6.9-7.9(thiophene,Ph,m);10.6 (NH,s).MS:253(M^+)(21);255(M+2)(9); 220(M-SH)(14);127(M-ArNH)(100);110 (M-ArS)(19)
6 R = 4-BrPh	98.0	137-139 (CH_3OH-H_2O 3:1)	^{1}H-NMR:6.9-7.8(thiophene,Ph,m);10.7 (NH,s).MS:297(M^+)(13);299(M+2)(14); 264(M-SH)(8);127(M-RNH)(100);110 (M-ArS)(14);109(M-ArSH)(11)
7 R = 4-MePh	90.0	124-126 (CH_3OH-H_2O 3:1)	^{1}H-NMR:3.4(CH_3,s);7.0-7.9(thiophene, Ph,m);11.4(NH,s).MS:233(M^+)(32);232 (M-H)(17);200(M-SH)(22);127(M-ArNH) (100);110(M-ArS)(12)
8 R = 4-MeOPh	89.0	129-130.5 (CCl_4)	^{1}H-NMR:3(OCH_3,s);6.7-7.8(thiophene, Ph,m);10.6(NH,s).MS:249(M^+)(35);216 (M-SH)(41);127(M-ArNH)(100);110 (M-ArS)(11)
9 R = α-naphthyl[c]	9.5	163-164.5 (CCl_4)	^{1}H-NMR:7.1-8.05(thiophene,naphthyl, m);11.8(NH,s).MS:269(M^+)(26);236 (M-SH)(24);127(M-ArNH)(100);110 (M-ArS)(15)

a) ^{1}H-NMR: δ ppm in acetone-d_6-DMSO-d_6 6:3. MS: m/z (% I_{max}). b) The crude product was distilled under reduced pressure and subsequently recrystallised. c) The crude product was purified on a silica gel column with $CHCl_3$ and then recrystallised.



1-9

Their yields were highest when the thiophene-isothiocyanate-aluminum chloride ratio was 1.2:1:2 and the temperature of the reaction mixture, 0-5°C at the beginning, was allowed to gradually increase to room temperature. Only *t*-butyl isothiocyanate failed to react under such conditions.

Basing on the yield of the carbothioamides 1-9 and on observations made while monitoring the reaction course by TLC, the reactivity of isothiocyanates decreased in the following order: p-bromophenyl ≥ p-chlorophenyl > phenyl > p-tolyl ≥ p-metoxyphenyl > methyl > cyclohexyl > ethyl > 1-naphtyl > isothiocyanate.

In accord with an earlier mechanistic concept[3], the reaction may involve an intermediate formation of thiocarbamoyl chloride. It seems, however, more likely

that activation of the isothiocyanate molecule depends on the formation of an $AlCl_3$ complex on the nitrogen or sulfur atom. Similar concepts have been advanced for isocyanates.[4,7] In our case, the IR spectrum of methyl isothiocyanate recorded in nitromethane reveals two absorption bands attributable to $\nu_{N=C=S}$: at 2112 and 2190 cm^{-1}, respectively. Those bands do not shift on addition of $AlCl_3$ though their intensity decreases to quite a considerable extent. As no $\nu_{C=N}$ absorption bands appear in the spectrum, the sulfur atom seems to be not the site of the complex formation. Consequently, the activation of isothiocyanate may be considered as being due to the formation of an $AlCl_3$ complex on the nitrogen atom.

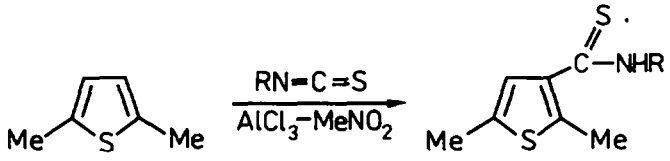
$$R-\overset{\overset{AlCl_3}{|}}{\underset{+}{N}}=C=S \longleftrightarrow R-\overset{\overset{AlCl_3}{|}}{\underset{+}{N}}-C\equiv S$$

The complete unreactivity of t-butyl isothiocyanate, in which steric factors make nitrogen complexing hardly possible, exactly corresponds with that mechanism.

Infrared and ultraviolet spectroscopy revealed that thiophene-2-carbothioamides are not planar and that their predominant conformation is trans(Z)-s-trans.[8]

An analogous reaction with isocyanates gave thiophene-2-carboxamides in poor yields. It seems that alternation of the catalytic conditions should be necessary in that case.

2,5-Dimethylthiophene reacted with isothiocyanates under exactly the same conditions as applied with thiophene although the N-substituted 2,5-dimethylthiophene-3-carbothioamides (10–15) were obtained in lower yields (Table 2).



10 - 15

A part of the starting 2,5-dimethylthiophene is here presumbly deactivated by forming a σ-complex in the result of α-protonation. A similar phenemenon was observed in the case of 2,5-dimethylthiophene acylation in the presence of aluminum chloride.[9]

The reaction of 2,5-dimethylthiophene with phenyl isocyanate was more complex. In addition to the expected N-phenyl-2,5-dimethylthiophenecarboamide, another product was isolated. Its elemental analysis and mass-spectrometric molecular mass determination were consistent with the concept of isocyanate addition to three molecules of the thiophene. Studies on the reactions of this type are in progress.

So far as 2-phenyl-5-methylthiophene is concerned, the acylation reaction provides a good piece of evidence of the significance of polar and steric effects.[10] Even if one does not consider the difference in the phenyl and methyl group volume, the position 3 seems to be most vulnerable to an electrophilic attack since delocalization of the positive charge in the 3-σ-complex is apparently favored as compared with the isomeric structure, i.e., the 4-σ-complex. According to experimental results[10], however, bulky acylating reagents attacked preferably C-4, the carbon atom adjacent to that bearing the methyl substituent.

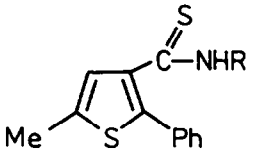
According to our results, steric factors were of no essential importance in the reaction of 2-phenyl-5-methylthiophene with isothiocyanates in a nitromethane solution of aluminum chloride. In general, the yields were rather low and the reaction products invariably contained two isomeric compounds (16 and 17).

Thus, in the reaction with methyl isothiocyanate, 16a and 17a were formed in the 1:1 ratio as estimated by ^{1}H-NMR spectroscopy; and in the reaction with phenyl and p-bromophenyl isothiocyanates, 16b,c and 17b,c were formed in the 7:3 ratio.

Table 2. 2,5-Dimethylthiophene-3-carbothioamides

Compound	Yield (%)	M.p. (°C) (solvent)	Spectral data[a]
10 R = Me	48.0	97-98.5 (CCl_4-hexane)	IR:3420(NH).UV:256.3(4.10);277.3(4.03);357.0(2.62).^{1}H-NMR:2.3(CH_3(5),s);2.42(CH_3(2),s);3.15(N-CH_3,d);6.67(H(4),s);7.45(NH,br.s).MS:185(M^+)(84);155(M-RNH)(18);152(M-SH)(100)
11 R = cyclohexyl	79.0	114-115 (hexane)	IR:3380(NH).UV:255.4(4.05);281.2(4.01);360.9(2.63).^{1}H-NMR:1.1-2.2(c-C_6H_{11},m);2.3(CH_3(5),s);2.42(CH_3(2),s);6.7(H(4),s).MS:253(M^+)(64);220;155(M-RNH)(26);138(M-RS)(100)
12 R = Ph	61.0	92-93.5 (hexane)	IR:3380,3354sh(NH).UV:261.6(4.07);311.5(4.11);400.2(2.70).^{1}H-NMR:2.3(CH_3(5),s);2.4(CH_3(2),br.s);6.77(H(4),br.s);7.1-7.8(arom,m).MS:247(M^+)(72);214(M-SH)(100);155(M-ArNH)(92)
13 R = 4-BrPh	68.0	134-135 (CCl_4-hexane)	IR:3384,3354sh(NH).UV;261.9(4.11);315.3(4.13);400.5sh(2.72).^{1}H-NMR:2.27(CH_3(5),s);2.37(CH_3(2),br.s);6.67(H(4),s);7.3(Ph,m).MS:325(M^+)(29);327(M+2)(29);155(M-ArNH)(100)
14 R = 4-ClPh	66.5	142-144 (CCl_4-hexane)	IR:3390,3360sh(NH).UV:259.9(4.13);314.2(4.15);400.3(2.72).^{1}H-NMR:2.3(CH_3(5),s);2.37(CH_3(2),br.s);6.75(H(4),s);7.62(arom.m).MS:281(M^+)(43);283(M+2)(20);155(M-ArNH)(100)
15 R = 4-MeOPh	81.0	92-93 (CCl_4-hexane)	IR:3390,3370sh(NH).UV:259.1sh(4.09);403.8(4.06);312.9(4,06);400.2sh(2.86).^{1}H-NMR:2.3(CH_3(5),s);2.45(CH_3(2),s);3.55(OCH_3,s);6.5-7.65(arom.m);8.67(NH,s).MS:277(M^+)(54);244(M-SH)(83);155(M-ArNH)(100)

a) IR spectra taken in $CHCl_3$, c = 0.03 mole/dm^3; UV spectra in ethanol: λ_{max} nm (lg ε); ^{1}H-NMR: δ ppm in $CDCl_3$; MS: m/z (% I_{max}).



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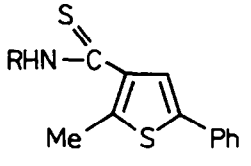

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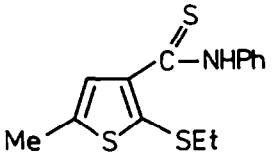

18

a) R=Me b) R=Ph c) R= 4-BrPh

The isomers were separated by column chromatography on silica gel with $CHCl_3$-CCl_4 1:1 as the mobile phase. It seems noteworthy that the proportions of the isolated thioamides 16a-c and 17a-c were by far inconsistent with the NMR analysis data (Table 3) for crude product mixtures. In the case of 16b,c and 17b,c roughly equal amounts of the isomers were isolated, whereas the 16a-to-17a by weight ratio was 1:2.3. If one depends, therefore, only on the isolable output the S_E reaction orientation may be easily misestimated.

The reaction of 2-phenyl-5-methylthiophene with isothiocyanates appears, therefore, to be controlled mostly by stabilization of the σ-complex. Steric factors seem to be of no much importance as the nitrogen-attached group is quite free in taking its position beyond the thioamide plane. Nonplanarity of the thiophene-2-carbothioamide derivatives has been demonstrated by spectroscopic methods.[8]

Table 3. Carbothioamides 16a-c and 17a-c

Compound	Yield (%)[a]	M.p. (°C) (solvent)	Spectral data[b]
16a R = Me	13.5	103.5-104.5 (hexane)	IR:3408(NH).UV:258.7(4.19);270sh(4.18). ^{1}H-NMR:2.35(CH_3(5),s);2.93(N-CH_3,d);6.93-7.42(arom.m).MS:247(M^+)(89);246(M-H)(100);217(M-RNH)(17);214(M-SH)(40)
17a R = Me	31.0	101-102 (hexane)	IR:3415(NH).UV:267.9(4.30);298.2(4.22);393.3sh(2.57). ^{1}H-NMR:2.47(CH_3(5),s);3.12(N-CH_3,d);7.05-7.45(arom.m).MS:247(M^+)(55);214(M-SH)(100);199(M-RSH)(23)
16b R = Ph	10.0	92-93 (hexane)	IR:3387(NH).UV:264.8(4.26);315.0(4.16);400.0sh(2.79). ^{1}H-NMR:2.37(CH_3(5),s);6.7-7.45(arom.m);8.37(NH,br.s).MS:309(M^+)(69);308(M-H)(50);217(M-ArNH)(100)
17b R = Ph	10.0	136-137 (hexane-CCl_4)	IR:3390,3365sh(NH).UV:268.5(4.47);297.9(4.39);393.9sh(2.56). ^{1}H-NMR:2.47(CH_3(5),br.s);7.0-7.75(arom.m).MS:309(M^+)(56);276(M-SH)(100);217(M-ArNH)(66)
16c R = 4-BrPh	23.0	142.5-143.5 (hexane)	IR:3374(NH).UV:265.3(4.33);320.0(4.21);400.1sh(2.82). ^{1}H-NMR:2.37(CH_3(5),s);6.87-7.6(arom.m);8.35(NH,br.s).MS:387(M^+)(26);389(M+2)(27);217(M-ArNH)(100)
17c R = 4-BrPh	23.0	166-167.5 (hexane-CCl_4)	IR:3388,3358sh(NH).UV:268.7(4.51);295.0sh(4.38);400.1sh(2.77). ^{1}H-NMR:2.5(CH_3(5),br.s);7.1-7.7(arom.m).MS:387(M^+)(40);389(M+2)(45);354(M-SH)(100);217(M-ArNH)(90)

a) Yields refer to purified products isolated by column chromatography. b) IR spectra taken in $CHCl_3$, c = 0.03 mole/dm^3; UV spectra in ethanol: λ_{max} nm (lg ε); ^{1}H-NMR: δ ppm in $CDCl_3$; MS: m/z (% I_{max}).

High selectivity of the electrophilic substitution was reported for 2-alkyl-5--alkylthiothiophene.[11] No steric effects were observed there and unlike in the former reactions, the reagent attacked almost exclusively the C-4 carbon atom. According to other reports[12,13], activation of the adjacent carbon atom by an alkylthio group was also much more effective than that by the methyl group. This may be explained, so as it was in the case of 2-phenyl-5-methylthiophene, in terms of greater stability of the 4-σ-complex, in which the cationic center is localized close to the substituent with a distinct +M effect as compared with the complex formed on protonation at C-3.

The reaction of 5-methyl-2-ethylthiothiophene with phenyl isothiocyanate in a nitromethane solution of aluminum chloride gave only one product. This was N-phenyl-5-methyl-2-ethylthiothiophene-3-carbothioamide (18).

The yield was rather low as quite a part of the starting heterocycle decomposed under the reaction conditions. Our reaction has to be carried out at 0-5°C and it is known[9] that aluminum chloride induces decomposition of alkylthiothiophenes at temperatures above -30°C owing to thermal instability of the corresponding σ-complex.

Because of relative simplicity the reactions under study may be recommended for preparative purposes. They may be also adapted to the synthesis of carbothioamides in other heterocyclic systems.

EXPERIMENTAL PART

Analytical. Infrared spectra were taken with a Unicam IR 1100 instrument in $CHCl_3$ solutions (c = 0.03 mole dm^3). A Specord-M40 spectrophotometer was used in the ultraviolet measurements carried out in ethanol (c = 10^{-4} mole dm^3). ^{1}H-NMR spectroscopic measurements were performed on a Tesla BS-487 apparatus (80 MHz) in chloroform-d or a 6:3 mixture of acetone-d_6 and DMSO-d_6 with HMDSO as the internal

standard. Mass spectra were taken with a LKB-2901 instrument with direct inlet (ionization potential 70 eV). Satisfactory analitical data (±0.3 % for C,H,S) were reported for all compounds 1-18.

Thiophene-2-carbothioamides 1-9. General procedure

A thoroughly cooled (0-5°C) solution of aluminum chloride (28.6 g, 0.2 mole) in 220 cm^3 nitromethane was treated dropwise under constant stirring with 0.1 mole isothiocyanate and next with 10.0 g (0.12 mole) thiophene dissolved in 50 cm^3 nitromethane. Stirring was continued 1 hr at 0-5°C and then several hours at room temperature (alternatively, the reaction mixture was left overnight without stirring). The reaction progress was controlled by thin-layer chromatography (silica gel, $CHCl_3$). The reaction mixture was finally poured into ice-water, the product extracted with ethyl acetate and the organic layer repeatedly washed (H_2O) and dried ($MgSO_4$). Upon evaporation of the solvent under reduced pressure the residue was either recrystallized directly from a suitable solvent (Table 1) or additionally purified by dissolving in $CHCl_3$ and filtering trough a 10-cm layer of Al_2O_3. When a CH_3OH-H_2O mixture (3:1) was used for recrystallization a treatment with activated carbon was found of advantage.

Thiocarbamoylation of 2,5-dimethylthiophene (compounds 10-15) and 2-phenyl-5-methylthiophene (compounds 16a-c and 17a-c). General procedure

The reactions were carried out essentially as above with the use of 0.04 mole anhydrous $AlCl_3$ in 30 cm^3 nitromethane, 0.01 mole isothiocyanate and 0.012 mole appropriate thiophene in 20 cm^3 nitromethane. Upon mixing the reagents stirring was continued 30 min at 0-5°C and then 2 hr at room temperature. The crude products were purified as follows: in the case of compounds 10-15, the solid residue was dissolved in chloroform, the solution filtered through a 10-cm layer of Al_2O_3, the filtrate evaporated to dryness and the product left recrystallized from a suitable solvent (Table 2); in the case of compounds 16a-c and 17a-c, the crude products were separated on a silica gel column with $CHCl_3$-CCl_4 1:1 as the eluent and then recrystallized (Table 3).

N-Phenyl-5-methyl-2-ethylthiothiophene-3-carbothioamide 18

The reaction of anhydrous $AlCl_3$ (5.33 g, 0.04 mole) in 30 cm^3 nitromethane, with phenyl isothiocyanate (2.7 g; 0.02 mole) and 2-methyl-5-ethylthiothiophene (3.16 g, 0.02 mole) in 20 cm^3 nitromethane was carried out essentially as above at 0°C (1 hr) and then at 15°C (2 hr). The crude product was purified on a silica gel column; contaminants were eluted first with CCl_4 and then 18 with $CHCl_3$. The product (0.59 g, 10 % yield) m. 75-6.5°C.

IR: 3220, 3270 (NH). UV: 264.6 (4.16); 316.9 (4.03); 400.1 sh (2.79); ^{1}H-NMR: 1.1-1.37 (CH_3,t); 2.35 (CH_3(2),s); 2.62-2.9 (CH_2,q); 7.0-7.82 (arom,m); 10.77 (NH,br.s). MS: 293 (M^+) (3.72); 264 (100.0); 232 (11.79).

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