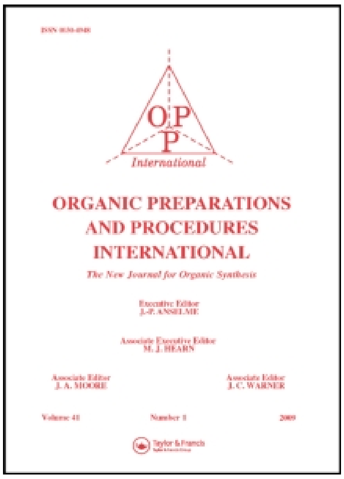

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THE FRIEDEL - CRAFTS REACTION OF PHENOLS WITH CARBETHOXY ISOTHIOCYANATE

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THE FRIEDEL-CRAFTS REACTION OF PHENOLS WITH CARBETHOXY ISOTHIOCYANATE

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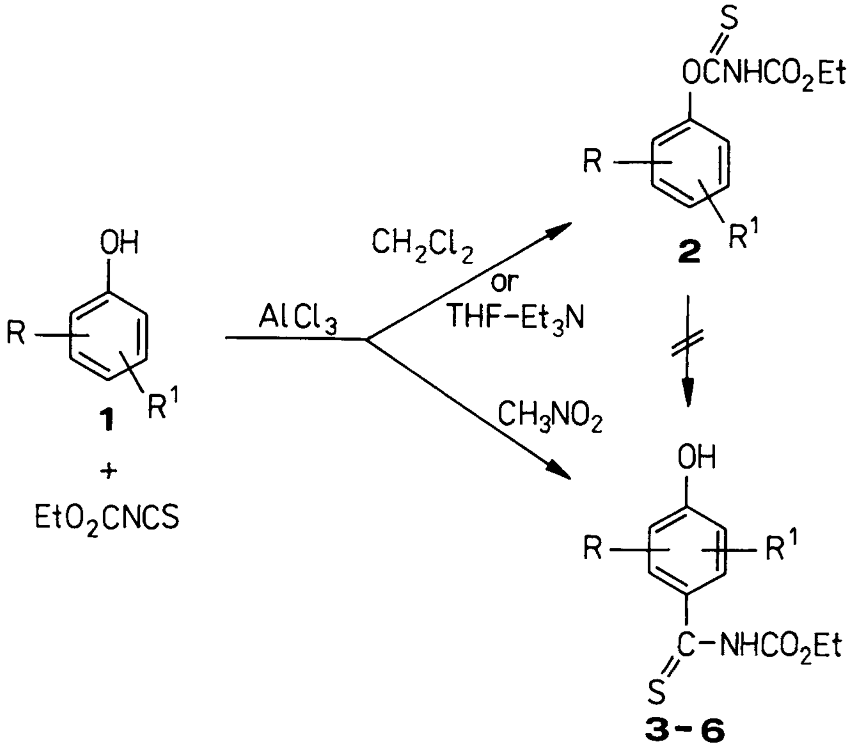
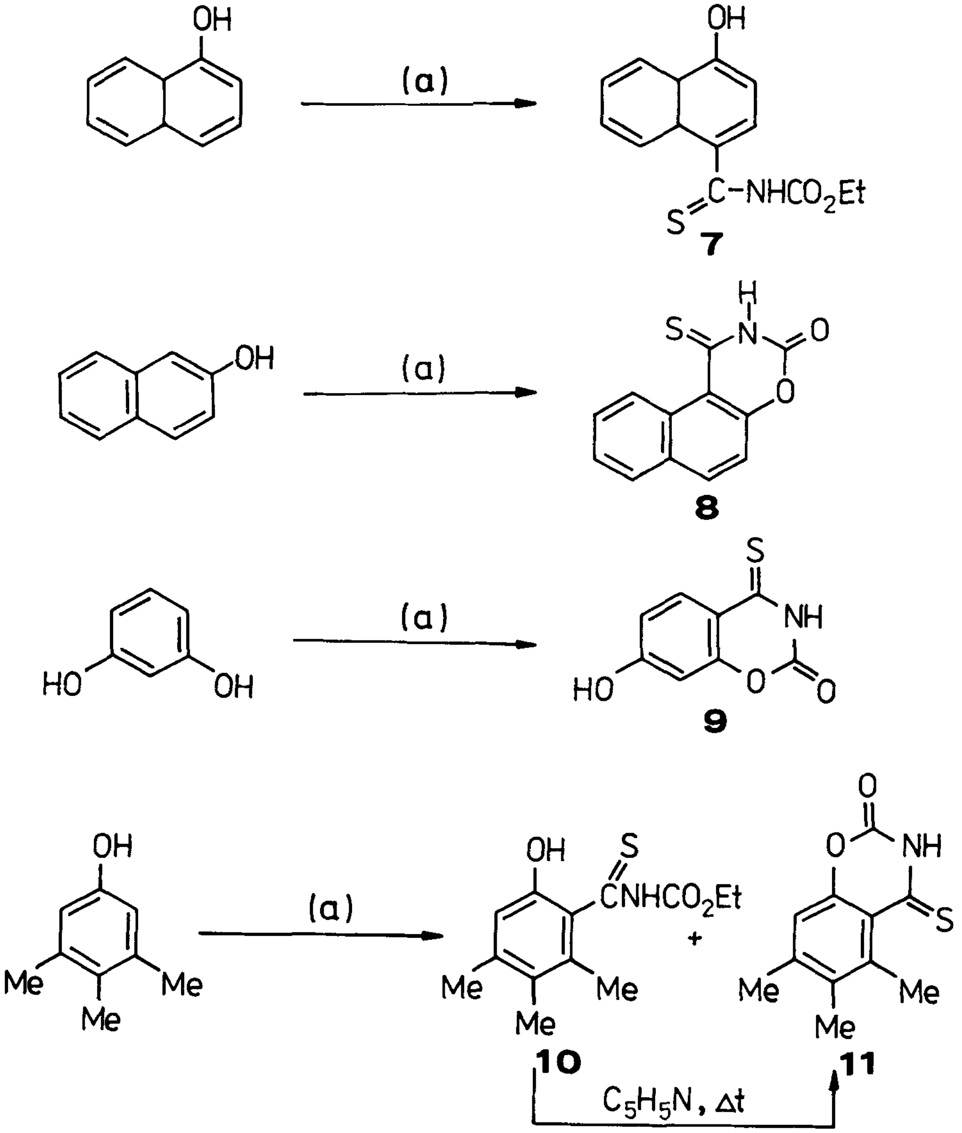
A facile procedure for the Friedel-Crafts synthesis of secondary aromatic thioamides[1] and of 2- and 3-benzo[b]thiophenecarboxylic acids[2] has been developed earlier in this laboratory. The homogeneity of the reaction mixture (a solution of aluminum chloride in nitromethane was used) simplified the isolation of the products and consequently the yields improved considerably. The present investigation is concerned with a similar reaction of phenols with carbethoxy isothiocyanate, which had been used earlier by Papadopoulos[3] with aromatic hydrocarbons. By working in a heterogeneous system (aluminum chloride in methylene chloride), Papadopoulos obtained either N-carbethoxythioamides or primary thiobenzamides. It was recently shown[3] that the hydroxy group is the major site of attack in such a heterogeneous system to give a thiocarbamoyloxy derivative (2) and not a thioamide.

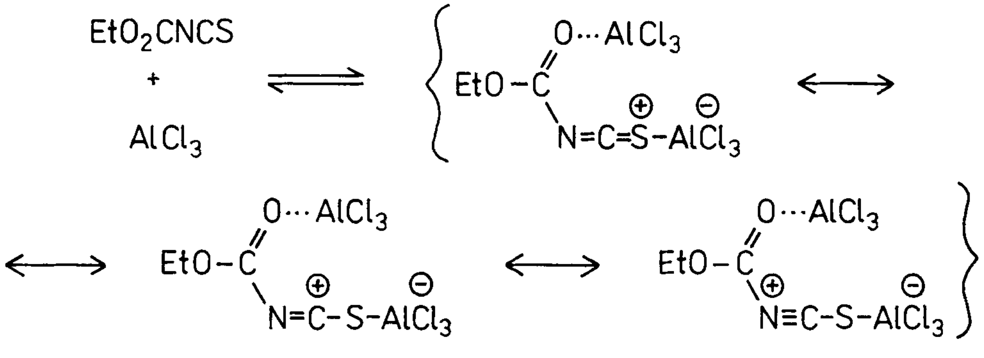
The present study shows that the course of the reaction is highly dependent on the homogeneity of the reaction mixture. Thus, in a heterogeneous system (aluminum chloride in methylene chloride), an urethane-type compound, N-carbethoxythiocarbamoylphenol (2) is formed, whereas in nitromethane, attack occurs primarily on the benzene ring to yield 4-hydroxy-N-carbethoxythiobenzamide (3). Similarly 2 are formed in the reaction carried out in tetrahydrofuran and triethylamine. In nitromethane, small amounts of urethanes 2 are isolated as the reaction by-products; they are not intermediates since no isomerization of 2 to 3 occurs under the reaction conditions. The rate of the reaction is markedly increased with C-alkylated phenols (monitored by TLC). While 1-naphthol reacts similarly to yield the para-substituted product 7, substitution of 2-naphthol occurs, however, at the 1-position to yield the intermediate N-carbethoxythioamide, which cyclizes to 3,4-dihydro-2-oxo-2H-naphth[1,2-e]-1,3-oxazin-4-thione 8; a similar product 9 is obtained with resorcinol. 3,4,5-Trimethylphenol also reacts at the ortho-position to yield a mixture of N-carbethoxythiobenzamide 10 and of 3,4-dihydro-2-oxo-5,6,7-trimethyl-2H-1,3-benzoxazine-4-thione 11 in a 4:1 ratio (^{1}H-NMR). Although chromatographic separation of the mixture failed, pure 11 was obtained on refluxing the mixture in pyridine; attemps to isolate 10 were unsuccessful. A ratio of 1:1:2 of phenol-carbethoxy isothiocyanate -aluminum chloride at 0-5^o was found to be the optimum conditions (Table 1).





a) $EtO_2CN{=}C{=}S$, $AlCl_3$-$MeNO_2$

The IR spectra of the nitromethane solutions of carbethoxy isothiocyanate and of its complex with aluminum chloride, in agreement with our earlier conclusions[1], provide evidence of complexation on the sulfur atom, which may account for activation of the carbethoxy isothiocyanate molecule. The spectra also indicate some interaction between the isothiocyanate carbonyl group and aluminum chloride.



EXPERIMENTAL SECTION

Melting points were obtained on a Boetius apparatus and are uncorrected. Infrared spectra were recorded on a Pye Unicam IR-1100 instrument in Nujol and hexachlorobutadiene mulls. ^{1}H-NMR spectra were performed on a Tesla BS 487 C instrument (for solvents cf. Table 1). The results of elemental analyses are presented in Table 2.

4-Hydroxy-N-ethoxycarbonylthiobenzamides (3-7) and 3,4-Dihydro-2-oxo-2H-1,3-benzoxazine-4-thiones (8,9,11). General Procedure.-Carbethoxy isothiocyanate (2.62 g, 20 mmol) was added at 0-5° to a stirred solution of 5.5 g (40 mmol) anhydrous aluminum chloride in 30 mL nitromethane. The appropiate phenol (22 mmol) was then added portionwise at the same temperature. The mixture was stirred at 0-5° for 1 hr (in the case of thiobenzamides 3-7 for 2 hrs), then left overnight in a refrigerator and finally hydrolyzed by pouring onto crushed ice. If the product precipitated in quantity, it was collected and washed with cold water. In case of incomplete precipitation, the mixture was extracted with ethyl acetate and the extract washed with water, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was dissolved in ethyl acetate (50-100 mL) and filtered through a layer (10x2 cm) of aluminum oxide (Broeckman II, neutral, standard), using ethyl acetate as the eluent. Reduced pressure helped to make this operation less time-consuming. The filtrate was again evaporated under reduced pressure and the crude product recrystallized from a suitable

TABLE 1. Yields, Physical Properties and Spectral Data of Compounds 2-11

Compd.	Yield[a] (%)	mp.(°C)[b] (solvent)	IR (cm^{-1})	^{1}H-NMR (acetone-d_6/HMDSO$_{int.}$)[c] δ (ppm), J (Hz)
2 R=R^1=H	98	bp.54-56 (3 Torr)	3380 (br) 1760 1740 (sh) 1605 (sh) 1595	1.2 (t,3H,Me,J=6); 4.1 (q,2H,CH_2, J=6); 6.6-7.5 (m,5H,Ar)
3 R=R^1=H	89	175-177 (aq.EtOH)	3380 3320 1742 1600	1.1 (t,3H,Me,J=6); 4.1 (q,2H,CH_2, J=6); 6.7 (d,2H,Ar,J=8); 7.6 (d, 2H,Ar,J=8)
4 R=2-Me R^1=H	93	139-141 (aq.EtOH)	3340 3200 1732 1612	1.1 (t,3H,Me,J=6); 2.1 (s,3H,Me); 4.1 (q,2H,CH_2,J=6); 6.6 (m,2H,Ar); 7.0 (m,1H,Ar); 8.5 (s,1H,OH); 10.7 (br.s,1H,NH)
5 R=3-Me R^1=5-Me	84	154-155 ($MeNO_2$)	3420 3160 1744 1596	1.1 (t,3H,Me,J=6); 2.1 (s,6H,2Me); 4.1 (q,2H,CH_2,J=6); 7.4 (s,1H,Ar); 7.8 (s,1H,Ar); 10.3 (br.s,1H,NH)
6 R=3-Br R^1=H	34	180-182 ($MeNO_2$)	3320 3180 1710 1600	1.2 (t,3H,Me,J=6); 4.1 (q,2H,CH_2, J=6); 6.9 (m,1H,Ar); 7.5-7.9 (m, 2H,Ar); 9.6 (br.s,1H,OH); 10.6 (br.s,1H,NH)
7	82	179-180 ($MeNO_2$)	3276 3184 1714 1585	1.0 (t,3H,Me,J=6); 3.9 (q,2H,CH_2, J=6); 6.8 (m,1H,Ar); 7.4 (m,2H, Ar); 7.8-8.3 (m,3H,Ar); 9.4 (s,1H, OH); 10.9 (br.s,1H,NH)
8	55	251-252 ($MeNO_2$)	3230 3148 1786 1760	7.2-8.3 (m,6H,Ar); 10.3 (br.s,1H, NH)
9	71	260-261 (decompn.) ($MeNO_2$)	3240 (br) 1730 1617	6.5-7.1 (m,2H,Ar); 8.2 (m,1H,Ar); 11.4 (br.s,1H,NH)
11	95	235-236 ($MeNO_2$)	3120 (br) 1770	2.3 (s,3H,Me); 2.4 (s,3H,Me); 2.9 (s,3H,Me); 7.0 (s,1H,Ar)

a) Yields of isolated product based on compound 1.
b) Melting points are uncorrected.
c) Compd. 2 in $CDCl_3$; compds 8 and 9 in DMSO-d_6; compd. 11 in TFA.

TABLE 2. Elemental Analyses of Compounds 2-11

	Calculated				Found			
Compd.	C	H	N	S	C	H	N	S
2	53.32	4.92	6.22	14.23	53.58	5.01	6.32	14.13
3	53.32	4.92	6.22	14.23	53.62	5.10	6.40	14.43
4	55.21	5.48	5.85	13.40	55.11	5.71	6.15	13.78
5	56.90	5.97	5.53	12.66	57.21	6.31	5.79	12.57
6	39.49	3.31	4.60	10.54	39.84	3.26	4.87	10.87
7	61.07	4.76	5.09	11.64	60.83	5.18	5.00	11.92
8	62.87	3.08	6.11	13.98	63.11	3.48	5.98	13.80
9	49.23	2.58	7.17	16.43	49.57	2.91	7.53	16.48
11	59.71	5.01	6.33	14.49	59.62	5.45	6.77	14.53

solvent (Table 1). In the case of compound 11, the crude mixture of 10 and 11 was refluxed 10-15 min with 25 mL pyridine and the solution diluted with water. The precipitated 11 was collected, washed with water, dried and recrystallized from nitromethane.

N-Ethoxycarbonylthiocarbamoyloxybenzene (2).-To a solution of phenol (1.9 g, 20 mmol) in 15 mL dry tetrahydrofuran were added 2.62 g (20 mmol) of carbethoxy isothiocyanate and 1 mL triethylamine. The mixture was left standing 0.5 hr at room temperature in a tightly stoppered flask and then evaporated under reduced pressure. The oily residue was distilled under reduced pressure to give the main fraction, b.p. 54-55°/3 Torr.

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