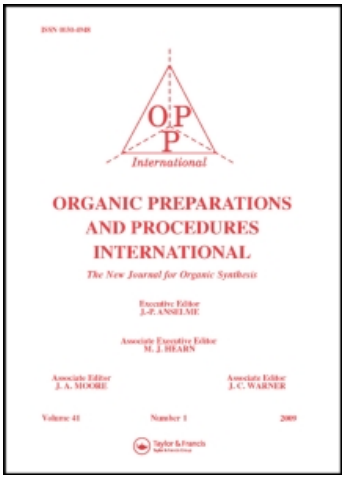

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

THE REACTIONS OF SOME ALKOXYCARBONYL ISOTHIOCYANATES WITH ALCOHOLS, PHENOLS AND AMINES

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To cite this Article Katritzky, Alan R. , Bernard, Marek K. , Long, Qiu-He , Xie, Linghong , Malhotra, Nageshwar and Beltzer, Morton(1993) 'THE REACTIONS OF SOME ALKOXYCARBONYL ISOTHIOCYANATES WITH ALCOHOLS, PHENOLS AND AMINES', Organic Preparations and Procedures International, 25: 1, 83 — 90
To link to this Article: DOI: 10.1080/00304949309457933
URL: http://dx.doi.org/10.1080/00304949309457933

ORGANIC PREPARATIONS AND PROCEDURES INT., 25 (1), 83-90 (1993)

THE REACTIONS OF SOME ALKOXYCARBONYL ISOTHIOCYANATES WITH ALCOHOLS, PHENOLS AND AMINES

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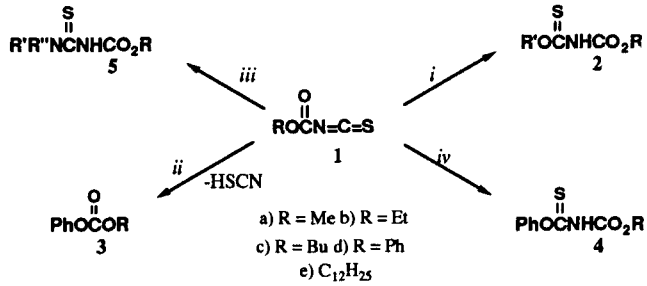
Ethoxycarbonyl isothiocyanate and related compounds (**1**) undergo exothermic additions with compounds containing active hydrogens.[1,2] Alcohols afford N-alkoxythiocarbonylcarbamate esters (**2**) in nearly quantitative yields (Scheme 1) and while methyl alcohol reacts vigorously, benzyl alcohol does so rather slowly.[1] Phenols, on the other hand, usually react with loss of the elements of thiocyanic acid to yield alkoxycarbonyl phenols (**3**);[1] however, if the reaction is carried out in a heterogeneous system (e. g. aluminum chloride in methylene chloride), or if triethylamine is used as a catalyst, the urethane derivatives (**4**) may be obtained.[3] Alkyloxycarbonyl- or aryloxycarbonyl isothiocyanates (**1**) react readily with primary and secondary amines to afford excellent yields of the expected di- and



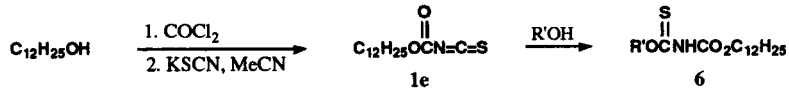
i) R'OH *ii*) PhOH, -HSCN *iii*) R"R'"NH *iv*) PhOH, THF/TEA (or $AlCl_3/CH_2Cl_2$)

Scheme 1

trisubstituted thioureas (**5**).[2] Diphenylamine reacts with alkoxycarbonyl isothiocyanates but fails to do so with aryloxycarbonyl isothiocyanates.[1] The products of these reactions are of considerable industrial importance having been utilized as cytostatic agents [4,5] and as insecticides, *inter alia*.[6] Additionally, these compounds may have use as sulfide mineral flotation agents similar to related commercial products such as dialkylthioisocarbamates.[7,8] The present study was undertaken to widen the range of

products in general and to obtain similar compounds from dodecyloxycarbonyl isothiocyanate for comparison with their ethoxycarbonyl analogues. Our study has demonstrated that the higher homologues can indeed be obtained and that the reactions are general.

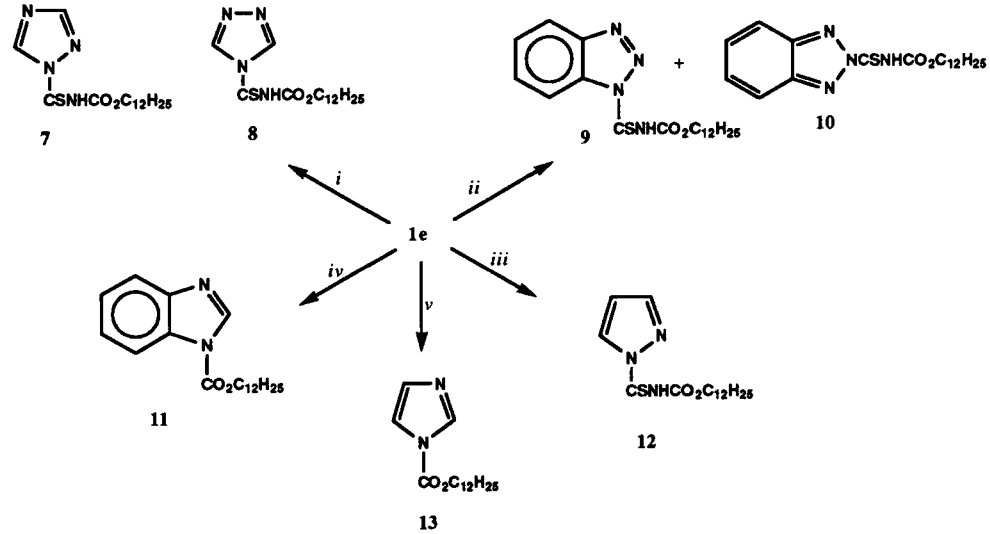
Preparative methods for alkyloxycarbonyl or aryloxycarbonyl isothiocyanates (**1**) are based on the substitution of the halogen atom in chloroformates by the isothiocyanate group. Ethoxycarbonyl isothiocyanate (**1b**) was prepared by Lamon's procedure[9] (reaction of ethyl chloroformate with sodium or potassium thiocyanate in acetonitrile) which has recently been improved by using pyridine or quinoline as catalyst.[10] The reaction of 1-dodecanol with phosgene according to the literature procedure for the synthesis of benzyl chloroformate[11] gave dodecyl chloroformate which, with potassium thiocyanate in toluene, formed dodecyloxycarbonyl isothiocyanate (**1e**) as a yellowish orange oil (78%). It was characterized by HRMS and NMR data (see Experimental Section). Its reaction with



a) R' = 2-pyridylmethyl b) R' = *iso*-Bu c) R' = $C_{12}H_{25}$ d) R' = 3-pyridylmethyl e) 2-pyrrolyl

2-pyridylmethanol in anhydrous THF gave 2-pyridylmethyl dodecyloxythiocarbamate (**6a**) in 45% yield. The corresponding derivatives of isobutanol (**6b**), dodecanol (**6c**), 3-pyridylmethyl (**6d**) and 2-pyrrole (**6e**) were obtained in moderate to good yields by mixing **1e** with the alcohols (Table 1).

Compound **1e** gave a mixture of the 1- and 4-substituted triazoles (**7** and **8**) with 1,2,4-triazole in anhydrous THF. With benzotriazole, similarly **1e** gave a mixture of the 1- and 2-substituted derivatives (**9** and **10**). The reaction of **1e** with benzimidazole, pyrazole and imidazole in anhydrous THF gave the derivatives (**11**, 41%), (**12**, 52%) and (**13**, 41%) respectively (Scheme 2, Tables 1-3).



i) 1,2,4-triazole *ii*) benzotriazole *iii*) imidazole *iv*) benzimidazole *v*) pyrazole

Scheme 2

With the primary amines N-phenyl-1,4-phenylenediamine and 4-aminodiphenyl ether in anhydrous

TABLE 1. Preparation of Compounds **6-20**.

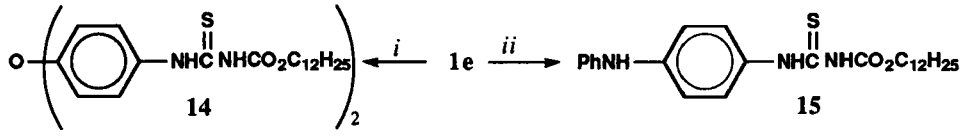
Comp.	Method	Yield	m.p.(RC) (%)	Crystal form	Recryst. solvent	Analysis/HRMS Calcd (Found) C	H	N
6a	B	45	91-92	needles	hexane	63.13 (62.95)	8.48 (8.63)	7.36 (7.51)
6b	A	100	—	oil	—	62.57 (62.47)	10.21 (10.30)	4.05 (4.18)
6c	A	99	52-5	microcryst.	hexane	68.22 (68.35)	11.23 (11.71)	3.06 (3.09)
6d	B	51	—	oil	—	321.2304 (321.2391)		
6e	B	15	72-76	microcryst.	CH_2Cl_2	63.87 (63.38)	8.93 (9.02)	8.27 (7.99)
7 + 8	B	52	65-81	yellow needles	MeCN	56.47 (56.14)	8.24 (8.43)	16.47 (16.08)
9 + 10	B	90	46-51	yellow microcryst	hexane	61.54 (61.15)	7.69 (8.01)	14.36 (14.70)
11	B	41	34-35	yellow microcryst	CH_3CN	72.69 (72.52)	9.15 (9.55)	8.48 (7.97)
12	B	52	42-46	microcryst	CH_2Cl_2	60.14 (61.14)	8.61 (8.73)	12.38 (11.20)[b]
13	B	41	35-36	yellow microcryst	CH_3CN	68.53 (68.91)	10.06 (19.31)	9.99 (9.87)
14	B	59	109-11	yellow microcryst	EtOH	64.66 (64.43)	8.41 (8.51)	7.54 (7.54)
15	B	94	108-09	yellow needles	hexane	68.54 (68.75)	8.18 (8.37)	9.22 (9.26)
16	B	94	156-57	colorless prisms	hexane	62.10 (62.37)	7.95 (8.18)	3.81 (3.68)
17	C	65	133-35	red needles	EtOH:H_2O 3:1	64.06 (63.86)	8.06 (7.94)	4.15 (3.86)
18	D	41	75-77	yellow needles	hexane	51.19 (51.19)	4.30 (4.18)	6.63 (6.52)
19	B	83	111-14	yellow needles	hexane	73.24 (73.34)	9.22 (9.37)	5.34 (5.22)
20	A	100	34-36	microcryst.	hexane	60.53 (60.90)	9.84 (10.35)	4.21 (4.21)

a) lit.[12] mp. 67-68°; b) Satisfactory elemental analysis could not be obtained for this compound. However, the ^1H NMR and ^{13}C NMR spectra were very clean.

TABLE 2. ^{1}H NMR ($CDCl_3$) Data for Compounds **6-20**

Comp.	CH_3 $3H_t$	J	CH_2 of chain m	H	CH_2O $2H_t$	J	NH	ArH	Others
6a	0.88	7	1.62, 1.65	20	4.17	7	8.93	7.22-8.61 (m, 4 H)	5.70 (s, 2H, CH_2-Py)
6b	0.88	7	1.26, 1.65	20	4.15	7	[b]	—	2.13(m, 1H, CH), 4.31 (d, 2H, CH_2CH) 1.01 (d, 6H, i-Pr)
6c	0.88[d]	7	1.30, 1.65 1.79, 4.53[e]	28	4.15	7	8.30	—	—
6d	0.87	6	1.26, 1.66	20	4.15	7	—	7.29-8.68(m,4H)	5.17(s,2H,CH_2-Py)
6e	0.88	7	1.26, 1.69	20	4.22	7	8.78, 9.96	—	
7 + 8[c]	0.86 0.88	7	1.26, 1.52	20	3.88	7	6.39	8.28 (s, 2H), 8.12 (s, 1H) 8.88(s,1H)	—
9 + 10	0.88	7	1.26, 1.75	20	4.33	7	10.82	7.54 (m, 1H), 7.70 (m, 1H) 8.14 (m, 1H), 8.84 (m, 1H) 7.43-7.46 (m, 2H) 7.94-7.97 (m, 2H)	—
11	0.88	7	1.34, 1.83	20	4.48	7	—	8.02, 7.80 (d, 1H) 7.38(m,2H)	8.46 (s, Benzimidazole-CH)
12	0.88	7	1.26, 1.71	20	4.27	6	—	—	8.65, 7.68, 6.46 (m, Pyrrole-CH)
13	0.87	7	1.29, 1.78	20	4.41	7	—	—	
14	0.85[d]	7	1.24, 1.62	40	4.14	7	11.24 11.49(s,2H)	7.02-7.05(m,4H) 7.58-7.61(m,4H)	—
15	0.88	7	1.27, 1.67	20	4.19	7	5.82 8.36 11.31	6.91-7.45(m,9H)	—
16	1.07	7	-	-	4.00[f]	7	7.85	6.90(s,2H)	4.97 (s, 1H, OH), 1.19 (s, 18H, t-Bu) 3.89(s,2H)
17	1.26	7	—	—	4.20[f]	7	7.7	7.56(s,2H)	11.8 (bs, 1H, OH), 1.40 (s, 18H, t-Bu)
18	1.38	7	-	-	3.19[f]	7	9.9	7.39-7.43(m,2H), 8.26-8.30(m,2H)	—
19	1.13	7	-	-	3.98[f]	7	7.65	7.16-1.19(m,4H) 7.34-7.37(m,4H)	0.70(s,18H,t-Bu),1.36 (s, 12H, 2xCH_3), 1.71 (s, 2H)
20	0.88[a]	7	1.26, 1.79	23	4.53,4.22[f]	7	8.39	-	—

a) Overlapped with CH_2 protons; b) Not observed; c) in DMSO-d_6; d) (6H); e) (t,2H); f) (q,2H)



i) *p*-$NH_2C_6H_4OC_6H_4NH_2$-*p* *ii*) *p*-(PhNH)$C_6H_4NH_2$-*p*

TABLE 3. ^{13}C ($CDCl_3$) NMR Data Compounds **6 - 20**

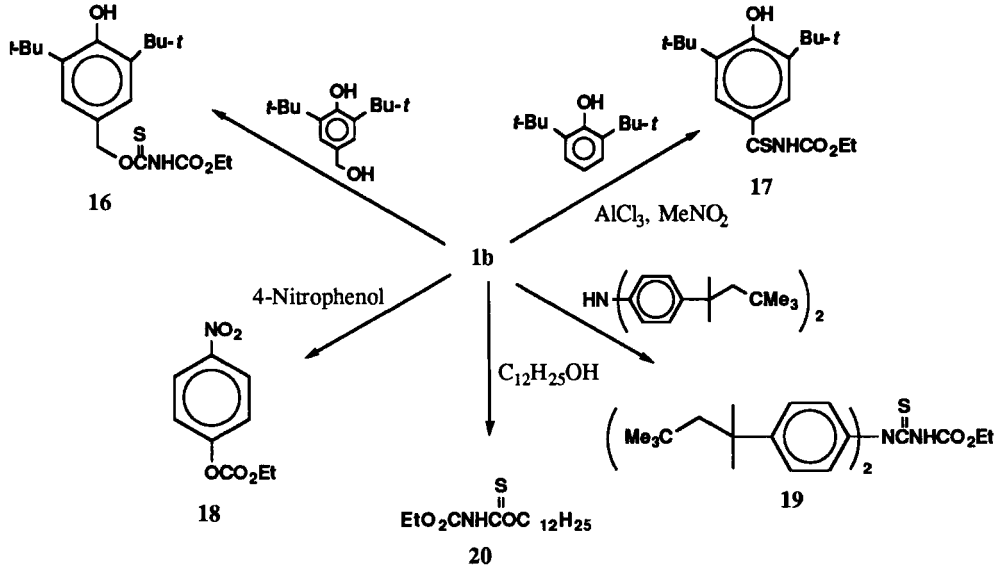
Comp.	CH_3	CH_2	CO	CS	Others
6a	14.0	22.6, 25.6, 28.5, 29.1, 29.3, 29.4, 29.5 29.55, 29.56, 31.8, 66.6, 73.6	149.3	187.9	121.6, 122.9, 137.0, 149.2 (pyridine ring)
6b	14.0, 18.8, 18.9	22.6, 25.6, 27.5, 28.5, 29.1, 29.3, 29.4 29.47, 29.53, 29.55, 31.8, 66.5	149.0	189.1	79.2(CH)
6c	14.1	22.6, 25.7, 28.1, 28.5, 29.2, 29.3, 29.43, 29.45, 29.5, 29.6, 31.8, 66.5, 73.3	149.0	188.9	—
6d	13.9	22.5, 25.5, 28.4, 29.0, 29.1, 29.3, 29.35 29.4, 31.7, 66.5, 68.4	149.3[a]	154.9	123.3, 130.9, 136.1, 149.5[a]
6e	14.0	22.6, 25.7, 28.5, 29.1, 29.2, 29.4, 29.46 29.53, 31.8, 66.7	151.2	184.6	127.6, 127.5, 111.6, 110.6
7 + 8	13.9	22.1, 25.1, 25.2, 27.8, 28.4, 28.6, 28.7, 28.8, 28.9, 29.0, 31.3, 68.8	153.4	168.7	146.1, 146.6, 147.2
9 + 10	14.1	22.6, 25.7, 28.5, 29.9, 29.3, 29.4, 29.5, 29.6, 31.8, 67.2, 69.5	150.7	169.8	116.0, 120.7, 125.8, 126.5, 131.3, 131.9, 147.3
11	14.0	22.6, 25.7, 28.5, 29.1, 29.2, 29.3, 29.4 29.5, 31.8, 68.2	149.5	[b]	143.9, 141.6, 131.2, 125.3, 124.3, 120.6, 114.2
12	13.9	22.5, 25.6, 28.4, 29.0, 29.2, 29.3, 29.4 29.5, 31.7, 66.8	150.6	171.1	142.7, 130.5, 130.4, 110.8
14	13.9	22.1, 25.1, 28.1, 28.6, 28.7, 28.96, 29.02, 29.1, 31.3, 65.8	153.6	178.7	118.5, 126.4, 133.6, 154.4 (Ph)
13	14.0	22.6, 25.6, 28.4, 29.0, 29.3, 29.4, 29.5 31.8, 68.4	148.6	[b]	137.0, 130.4, 117.0
15	14.1	22.6, 25.6, 28.4, 29.1, 29.3, 29.4, 29.6, 31.8, 66.9	152.9	177.8	117.1, 118.2, 121.4, 125.7, 129.3, 130.2, 142.0, 142.4 (Ph)
16	14.2, 30.2	34.2, 62.5	151.6	169.8	34.7 (C, t-Bu), 125.9, 126.7, 136.0, 153.1 (Ph)
17	14.1, 30.0	61.5	152.5	203.2	34.4 (C, t-Bu), 125.6, 133.3, 137.2, 158.2 (Ph)
18	8.5	46.2	152.1	163.4	115.6, 121.6, 125.0, 125.7 (Ph)
19	14.1, 31.2, 31.6	32.3, 62.0	149.6,[a]	180.5	38.5, 57.1 (C), 126.1, 127.1, 127.2, 142.3, 149.4[a] (Ph)
20	14.1, 22.6	25.6, 28.0, 29.1, 29.2, 29.4, 29.46, 29.53, 31.8, 62.3, 73.2	148.9	188.8	—

a Can be reversed; b Could not be observed.

THF, **1e** gave N^1-dodecyloxycarbonyl-N^2-(4-phenylaminophenyl)thiourea (**15**, 94%) and bis(N-dodecyloxycarbonylaminothiocarbonylaminophenyl) ether (**14**, 59%).

The reactions of ethoxycarbonyl isothiocyanate (**1b**) (Scheme 3) with dodecanol, 2,6-di-t-butyl-4-hydroxymethylphenol and di-[4-(1,1,3,3-tetramethylbutyl)phenyl]amine gave the corresponding carbamates **20, 16** and **19** in 100%, 94% and 83% yields respectively. The reaction of **1b** with 4-nitrophenol in the presence of triethylamine gave ethyl 4-nitrophenyl carbonate (**18**) in 41% yield (about 30% of unreacted 4-nitrophenol was detected in the crude reaction mixture by NMR). When the reaction was carried out without triethylamine no reaction occurred, and with a heterogeneous system of aluminum chloride in dichloromethane, only traces of products were formed. The

reaction of **1b** with 2,6-di-t-butylphenol in the presence of aluminum chloride in nitromethane gave N-ethoxycarbonyl-3,5-di-t-butyl-4-hydroxythiobenzamide (**17**) in 65% yield. Compound **17** was characterized by a two-proton singlet (δ 7.56) in the aromatic region and a broad one proton signal (δ 11.8) for the -OH group in the ^{1}H NMR spectrum (Scheme 3).



Scheme 3

The structures of all the products are supported by elemental analyses (Table 1) and NMR spectral data (Tables 2 and 3). The most significant signals in the ^{13}C NMR spectra are those of carbonyl and thiocarbonyl groups which usually appeared in the ranges 148-154 and 163-189 ppm, respectively. A downfield shift of the signal of the thiocarbonyl group for compound **17** to 203.2 ppm is due to the shielding effect of the phenyl ring.

EXPERIMENTAL SECTION

Melting points were determined on a Fisher-Johns hot-stage melting point apparatus and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian VXR-300 FT mode NMR spectrometer. The chemical shifts of the proton signals are in parts per million downfield from tetramethylsilane (TMS) as internal standard and those of the ^{13}C signals are referenced to the deuterated solvent ($CDCl_3$ or DMSO-d_6). Thin-layer chromatography (TLC) was performed on precoated silica gel $60F_{254}$ plastic sheets (Kodak Co.). Mass spectra were recorded on an AEI MS-30 mass spectrometer. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. Column chromatography was conducted over silica gel (230-400 mesh). Tetrahydrofuran was pre-dried over 4 Å molecular sieves and distilled from sodium/benzophenone under nitrogen. Ethoxycarbonyl isothiocyanate **1b** was prepared according to a literature method.[10]

Dodecyloxycarbonyl Isothiocyanate (1e).- 1-Dodecanol (18.6 g, 0.1 mol) was added to an ice-cold solution of phosgene in toluene (20%, 58.0 g, 0.1 mol) over 1 min. The solution was stirred for 30

min. at ice bath temperature, and kept at room temperature for 6 hrs. The toluene was distilled off at a temperature not exceeding 60°. The residue was added dropwise to a warm solution of potassium thiocyanate (9.7 g, 0.1 mol) in 100 mL of anhydrous acetonitrile. The mixture was stirred at room temperature for 12 hrs, filtered and the solvent distilled off at 40-45°. The residual yellow orange oil was filtered to yield 21.2 g (78%) of **1e**. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H, CH_3, J = 7 Hz), 1.26 (m, 18H, CH_2), 1.68 (m, 2H, CH_2) and 4.20 (t, 2H, CH_2, J = 7 Hz); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 22.7, 25.6, 28.2, 29.1, 29.3, 29.4, 29.5, 29.6, 31.9, 69.3 (CH_2), 147.2 (C=O), 149.3 (C=S); HRMS 272.1685 (M+1) calcd. for $C_{14}H_{25}NO_2S$ 272.1684 (M+1).

Reactions of Dodecyloxycarbonyl Isothiocyanate (1e) or Ethoxycarbonyl Isothiocyanate (1b) with Alcohols, Phenols or Amines. -

Method A. - A mixture of **1e** or **1b** (0.1 mol) and the appropriate alcohol (0.1 mol) was either stirred or left at room temperature for 12 hrs and the product recrystallized from hexane.

Method B. - Isothiocyanate **1e** or **1b** (0.1 mol 50% solution in THF) was added dropwise to a stirred solution of the alcohol or amine (0.1 mol or for compound **14**, 0.2 mol) in anhydrous THF (100 mL). The product was stirred at room temperature for 12-24 hrs. The solvent was distilled off and the residue purified either by recrystallization or by flash column chromatography.

Method C. - Ethoxycarbonyl isothiocyanate **1b** (2.6 g, 20 mmol) was added slowly to a stirred solution of anhydrous aluminum chloride (5.5 g, 40 mmol) in nitromethane (30 mL) at 0-5°. 2,6-Di-*t*-butylphenol (4.1 g, 20 mmol), in nitromethane (10 mL), was added slowly dropwise while maintaining the temperature at 0-5°. The mixture was stirred at this temperature for 2 hrs and left overnight in the refrigerator. It was poured onto crushed ice, extracted with ethyl acetate (3x200 mL) and the combined extract washed with water and dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by recrystallization.

Method D. - Anhydrous triethylamine (7 mL) followed by ethoxycarbonyl isothiocyanate **1b** (13.1 g, 0.1 mol) was added to a solution of 4-nitrophenol (13.9 g, 0.1 mol) in THF (150 mL). The mixture was left at room temperature for 7 days and the solvent distilled off to give ethyl 4-nitrophenyl carbonate (**15**) in 41% yield (Tables 1-3).

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(Received March 16, 1992; in revised form August 9, 1992)