Preparation of Ethoxycarbonyl Isothiocyanate Using a Pyridine or Quinoline Catalyst

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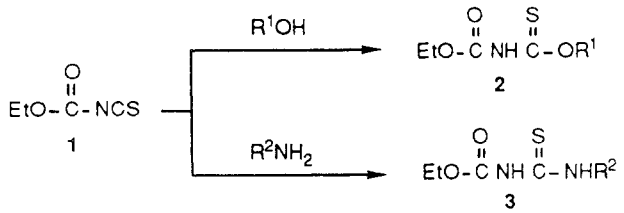
A process for the preparation of ethoxycarbonyl isothiocyante using pyridine or quinoline as a catalyst in an aqueous medium is presented. This process leads to high yields of the desired product with only trace amounts of the thiocyanate being formed. Reaction of ethoxycarbonyl isothiocyanate, prepared *in situ*, with nucleophiles can be carried out in with yields and purity.

Introduction

Ethoxycarbonyl isothiocyanate (1) has been shown to be a very useful reagent for the synthesis of a variety of compounds.[2] It was our desire to use this reagent for the starting material in preparing a series of ethoxycarbonyl thionocarbamates **2** and thioureas **3** for use in mineral processing applications.[3,4]



The best literature method for preparing this material was that of Lamon, where ethyl chloroformate was reacted with sodium or potassium thiocyanate in aprotic polar solvents such as acetonitrile or ethyl acetate.[5] In our hands, this method gave yields of only 63% of the desired product with about 10% ethoxycarbonyl thiocyanate also being produced. The low yields are in part due to the fact that the thiocyanate ion is an ambident nucleophile, providing attack by either the nitrogen or the sulfur depending on the conditions.[6] The low yields and the use of solvents such as acetonitrile were unacceptable for our purpose since we needed to be able to scale up to large-scale production. Therefore, we explored the possibility of a catalyst for this reaction. In this report we detail our findings.

Results and Discussion

Goerdeler reported the use of pyridine as a catalyst for the preparation of ethoxy(thiocarbonyl) isothiocyanate from ethyl chlorothioformate and sodium thiocyanate in carbon tetrachloride with a yield of 52%.[7] Although the reported yield was low, we examined the use of pyridine and quinoline in the preparation of 1 at first in toluene as a solvent and later in water. Ethoxycarbonyl isothiocyanate will hydrolyze in water at room temperature; however, we found that by keeping the temperature low (generally 8–12 °C) good to excellent yields of the ethoxycarbonyl isothiocyanate can be obtained with only traces of the thiocyanate being formed. By extracting the product into cold hydrocarbon solvent, drying over magnesium sulfate, and distilling, a yield of 80% with 98% purity was obtained.

Table I. Effect of Substitution on Catalysis Performance of Pyridine and Quinoline

catalyst (g/mol)	time (h)	temp (°C)	yield[a] (%)
none	24	25	0
pyridine (4.5)	5.5	10	95
pyridine (3.0)	7.5	10	95
2-methoxypyridine (4.6)	6.0	10	0
2-chloropyridine (2.4)	7.0	10	30
4-chloropyridine (2.4)	3.0	10	82
quinoline (4.0)	7.5	10	95
6-methoxyquinoline (4.8)	6.0	10	95
6-chloroquinoline (7.1)	6.0	10	93

[a] Overall yields of the thionocarbamate from the reaction of 1 with isobutyl alcohol based on GC analysis.

However, because of the severe lachrymator properties, we have found it to be much simpler to react the ethoxycarbonyl isothiocyanate in situ with a suitable nucleophile, such as an alcohol or an amine, to obtain excellent yields of 85–95% of the desired thionocarbamate or thiourea. This can be accomplished by maintaining the temperature at such a level so that the nucleophile will react in preference to water (generally 10–15 °C for primary alcohols and 0–5 °C for amines). Isolation is a simple matter of adding enough water to dissolve the salts and separating the layers. Sometimes a small amount of an organic solvent (such as an alcohol or hydrocarbon) is needed for good phase separation.

The mechanism for this process probably involves the formation of *N*-(ethoxycarbonyl)pyridinium (4) or quinolinium (5) chloride as a reactive intermediate, which then is attacked by the thiocyanate ion with a preference for nitrogen attack. These salts were first reported by Hopkins[8] and more recently isolated by Auzou and Rips and shown to be the reactive intermediate in the synthesis of ethyl pyrimidinecarbamates using a pyridine catalyst.[9]

The amount of catalyst used is generally in the range of 3–6 g per mol of ethyl chloroformate. Pyridine provides

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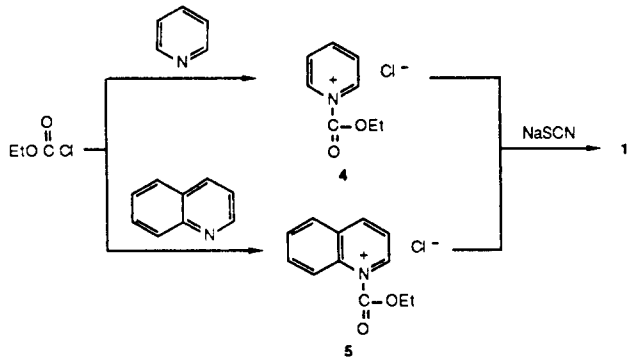

faster reaction rates than does quinoline. However, the faster rate with pyridine is more difficult to control and can lead to side products. It is desirable to neutralize the pyridine with hydrochloric acid before proceeding to react 1 with a nucleophile. This neutralization is generally not necessary for quinoline. Substituted pyridines and quinolines work just as well except for substitution at the 2-position, which may be due to steric hinderance (Table I).

This process can be extended to the reaction of sodium thiocyanate with other alkyl chloroformates, including phenyl chloroformate, with comparable results.

In summary, a process for the preparation of ethoxycarbonyl isothiocyanate has been devised using pyridine or quinoline as a catalyst in an aqueous medium. This process leads to high yields of the desired product with only trace amounts of the thiocyanate being formed.

Experimental Section

All gas chromatography was done on a Hewlett-Packard Model 5840A with a flame ionization detector. In the preparation of 1, a column of 2.5 m × 2 mm stainless steel column packed with 10% OV-17 and 10% SP-2401 on 80/100-mesh Chromosorb W was used. In the reaction of 1 with amines or alcohols, a 0.6 m × 2 mm stainless steel column with the same packing was used. The carrier gas was helium at a flow rate of 60 mL/min. Melting points (uncorrected) were obtained on a Thomas Hoover melting point apparatus. Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were obtained on a Varian VXR400 instrument in $CDCl_3$ with Me_4Si as internal standard. Infrared (IR) spectra were recorded on a Digilab FTS15 or a Beckman IR4240 instrument. Mass spectra were obtained on a Kratos MS50 instrument. Elemental Analyses were obtained by Galbraith Laboratories, Knoxville, TN.

Carbon(isothiocyanatidic) Acid, Ethyl Ester (1). To a 50% aqueous solution of sodium thiocyanate (162 g, 2.0 mol) was added 8 mL of quinoline. Ethyl chloroformate (224.7 g, 2.03 mol) was added dropwise with stirring at 8–12 °C over 40 min. Stirring was continued at 8–12 °C and the reaction was followed by monitoring the disappearance of the ethyl chloroformate by GC. After 7.5 h, less than 2% of the ethyl chloroformate remained. Petroleum ether (100 mL) and 200 mL of water (both chilled to 2–4 °C) were added, followed with 6 mL of chilled concentrated HCl to remove the quinoline from the organic layer. Care was taken to maintain a temperature below 10 °C during the separation of layers and drying the organic layer over $MgSO_4$. After filtration, the organic solution was distilled under vacuum, yielding 211 g of product (80.4% yield, bp 65 °C, 24 mm; lit.[5] bp 51–55 °C 13 mm) with 98% purity by GC.

Carbamic Acid, [(2-Methylpropoxy)(thiocarbonyl)]-, Ethyl Ester (2, R^1 = iBu). This preparation is typical of the reaction of 1 prepared in situ with a primary alcohol. 1 (starting with 2.0 mol of sodium thiocyanate) was prepared in the same manner as above without isolation. At the completion of the reaction, isobutyl alcohol (284 g, 3.8 mol) was added dropwise at 12–15 °C over 20 min. The mixture was allowed to stir overnight while slowly being warmed to room temperature. Water (200 mL) was added to dissolve the salts and the layers were separated. The oil layer (544 g) contained 71.1% of the desired product by GC analysis (94.3% yield): bp 98–99 °C (0.3 mm); IR 3250, 2960, 2870, 1765, 1500, 1395, 1375, 1250, 1160, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) 8.31 (1 H, br s, *NH*), 4.31 (2 H, d, OCH_2CH), 4.23 (2 H, q, OCH_2CH_3), 2.13 (1 H, m, $CH(CH_3)_2$), 1.30 (3 H, t, CH_3CH_2O), 1.02 (6 H, d, $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$) 189.1, 148.9, 79.3, 62.4, 27.6, 19.0, 14.2. Anal. Calcd for $C_8H_{15}NO_3S$: C, 46.81; H, 7.37; N, 6.82; S, 15.62. Found: C, 46.98; H, 7.48; N, 7.10; S, 15.28.

Carbamic Acid, [(Butylamino)(thiocarbonyl)]-, Ethyl Ester (3, R^2 = nBu). This preparation is typical of the reaction of 1 prepared in situ with an amine. 1 (starting with 1.0 mol of sodium thiocyanate) was prepared in the same manner as above using 4 mL of pyridine as the catalyst. The reaction was completed in 4.5 h and the product was not isolated. While maintaining the temperature at 8–10 °C, 18.1 g of 10% HCl was added to neutralize the pyridine followed with 100 mL of water to dissolve the salt. Toluene (50 mL) was added and the mixture cooled to 0–5 °C. *n*-Butylamine (73 g, 1.0 mol) was added dropwise over 2 h at 0–5 °C, followed by 2 h of stirring at room temperature. The layers were separated, yielding 241 g of an oil layer containing 81.9% of the desired product by GC analysis (96.8% yield): mp 37–39 °C (lit.[10] mp 38–39 °C); IR (KBr) 3240, 3180, 2960, 2940, 2870, 1730, 1540, 1250, 1230, 1195, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) 9.69 (1 H, br s, $NHCH_2$), 8.30 (1 H, br s, *NH*), 4.22 (2 H, q, OCH_2CH_3), 3.65 (2 H, dt, $HNCH_2$), 1.65 (2 H, m, CH_2), 1.41 (2 H, m, CH_2CH_3), 1.31 (3 H, t, OCH_2CH_3), 0.96 (3 H, t, CH_2CH_3); ^{13}C NMR ($CDCl_3$) 179.0, 152.9, 62.7, 45.4, 30.3, 20.1, 14.2, 13.7; exact mass calcd for $C_8H_{16}N_2O_2S$ 204.0939, found 204.0936. Anal. Calcd for $C_8H_{16}N_2O_2S$: C, 47.04; H, 7.89; N, 13.71; S, 15.69. Found: C, 47.48; H, 7.95; N, 13.87; S, 15.83.

Effect of Substitution on Catalysis Performance of Pyridine and Quinoline. The ethoxycarbonyl isothiocyanate preparations were conducted as above, using 1.0 mol each of sodium thiocyanate and ethyl chloroformate. The catalyst amount and reaction temperature are given in Table I. The catalyst was neutralized with a stoichiometric amount of HCl and the ethoxycarbonyl isothiocyanate, without isolation, was reacted with isobutyl alcohol (128 g, 2.0 mol) at 10–15 °C to give the thionocarbamate. The yields were determined by GC analysis.

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Registry No. 1, 16182-04-0; 2 (R^1 = *i*-Bu), 103122-66-3; 3 (R$_2$ = *n*-Bu), 6121-29-5; sodium thiocyanate, 540-72-7; ethyl chloroformate, 541-41-3; isobutyl alcohol, 78-83-1; *n*-butylamine, 109-73-9; pyridine, 110-86-1; 2-methoxypyridine, 1628-89-3; 4-chloropyridine, 626-61-9; quinoline, 91-22-5; 6-methoxyquinoline, 5263-87-6; 6-chloroquinoline, 612-57-7; 2-chloropyridine, 109-09-1.

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