OBSERVATIONS ON THE REACTIONS OF ISOCYANOACETATE ESTERS WITH ISOTHIOCYANATES AND ISOCYANATES

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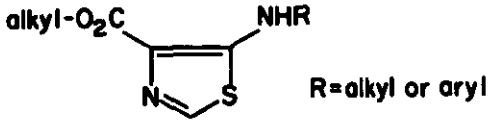
Abstract - The reactions of the metal salts of α-isocyanoacetate esters with isothiocyanates and isocyanates were examined.

The effects of modifying the reaction parameters on the outcome of the reaction (Scheme I) of methyl α-isocyanoacetate (1a) with phenyl isothiocyanate (2a) have been studied, thus providing enhanced understanding of the factors controlling this useful process. Specifically, the substantial influence of reaction temperature and mode of addition of reagents on the yield of main product, thiazole 3a--as well as the novel observation of the formation of imidazole 4 as a minor, but reproducible and significant, side-product--has been documented. Previously reported oxazole formation in the low-temperature reaction of the lithio derivative of 1 with phenyl isothiocyanate (2a) was not observed in the present study; only thiazole (3a) was detected under these conditions. The reaction of isocyano ester 1a with benzyl isothiocyanate (2b) gave thiazole ester 3b or the corresponding carboxylic acid; no imidazole product was isolated, in contrast to the result obtained with phenyl isothiocyanate (2a).

The previously unreported reaction of the salt of an α-isocyanoacetate ester with an isocyanate was shown to produce an amino(alkoxycarbonyl)oxazole in low yield (not optimized). No corresponding hydroxy(alkoxycarbonyl)imidazole was detected. (See Schemes IV and VII.)

Amino(alkoxycarbonyl)thiazoles of type 3 were recently of interest to us as potential intermediates in the preparation of certain fused thiazoles. A search of the literature revealed a



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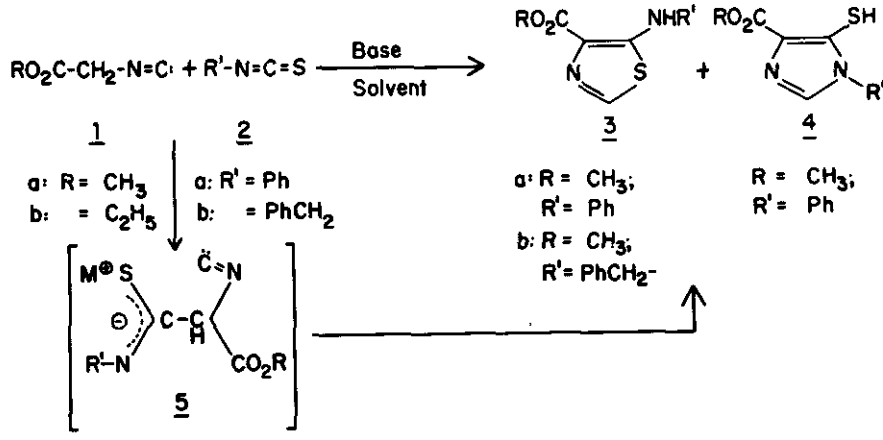
paucity of methodology for the synthesis of the requisite bifunctional thiazoles[1]. However, a recent report by Matsumoto and co-workers[2] addressed this deficiency directly, describing the base-promoted condensation of methyl isocyanoacetate with various isothiocyanates. This approach was of special interest to us because of the great flexibility that it permits in the direct introduction of substituents on the exocyclic nitrogen atom. In particular, the method allows the construction of N-aryl derivatives, which are not otherwise readily preparable.

In the course of utilizing this thiazole synthesis, we have made several observations which clarify certain important points of experimental procedure and provide enhanced understanding of the utility of isocyanoacetate esters.

RESULTS AND DISCUSSION

Thiazole 3a (Scheme I) was of prime interest to us as a synthetic intermediate. Therefore, our

SCHEME I



initially unsuccessful efforts to prepare 3a in the requisite quantities under the reaction conditions reported (potassium t-butoxide in tetrahydrofuran; ambient temperature implied) by Matsumoto and coworkers[2] led us to an investigation of reaction parameters and the observations which form the subject matter of this note. Furthermore, we have examined the reaction of methyl isocyanoacetate (1a) with benzyl isothiocyanate (2b), as well as the corresponding reaction between ethyl isocyanoacetate (1b) and benzyl isocyanate.

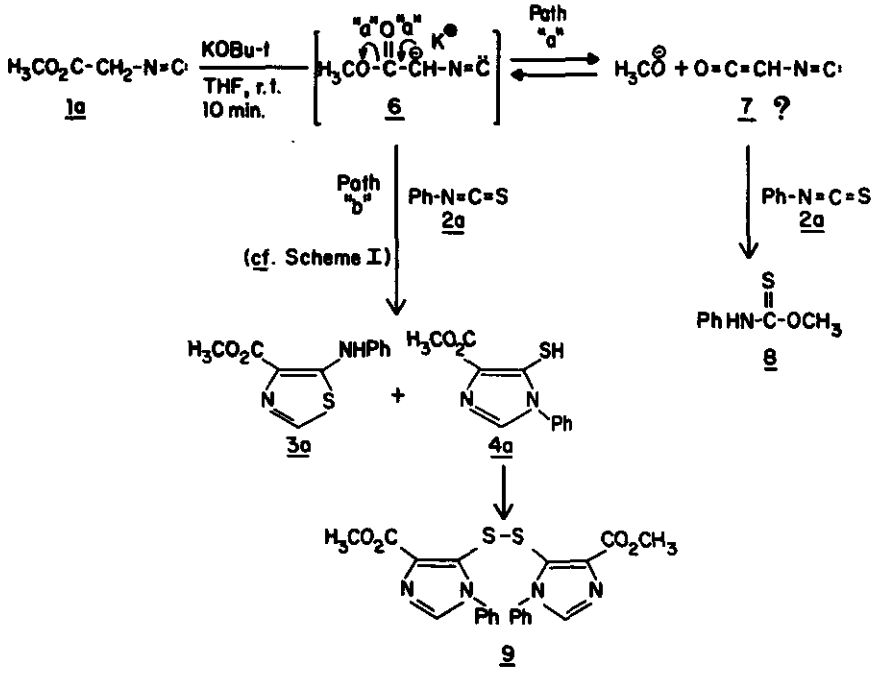
I. Reaction of Methyl Isocyanoacetate with Phenyl Isothiocyanate

In the plausible mechanism for thiazole formation proposed by Matsumoto and coworkers[2], an ambident nucleophilic thiocarboxamide anion (5; Scheme I) is postulated. The more nucleophilic sulfur atom might be expected to react preferentially with the electrophilic C-atom of the isocyanide moiety, thereby producing thiazoles (3), as observed by those authors. However, complete regiospecificity of ring-closure on sulfur as reported by the Matsumoto group[2], would seem unlikely, and formation of some imidazole product (4), resulting from attack of thiocarboxamide nitrogen on isocyanide carbon, would therefore be anticipated. Indeed, we have observed the formation of imidazole 4 in crude isolated yields as high as 24%, depending upon reaction conditions[3].

The effects of altering a variety of reaction parameters on the yield of desired thiazole 3a are discussed below. This study reveals that the mode of addition of the reagents, the reaction temperature, and the specific base-solvent combination employed are all important factors influencing the outcome of the reaction.

Mode of Addition. The metalated derivative (6) of the isocyanide ester (1a) is unstable under the reaction conditions (Scheme II). That the decomposition of 6 is accompanied by the elimination

SCHEME II



of a methoxyl equivalent is supported by the results of an experiment in which the isocyanoacetate ester (1a) was allowed to stir in contact with a solution of potassium t-butoxide in tetrahydrofuran for 10 min at room temperature prior to the addition of phenyl isothiocyanate (2a). The only isolable product of this reaction was the carbamothioate 8[4]. This result illustrates the importance of minimizing the time interval between generation of the metalated isocyanoacetate and the introduction of the isothiocyanate, which can then capture the anion 6 and shunt it along the desired reaction pathway before 6 can decompose extensively. This requirement dictates either a rapid sequential addition of isocyanide ester, followed by isothiocyanate, or a simultaneous addition of the reagents to the solution of base. As the data in Table I indicate (cf. experiments 2 and 3), sequential addition with a one-minute time interval and

TABLE I Effect of Temperature and Mode of Addition of Reagents on Product Distribution in the Reaction of Methyl Isocyanoacetate (1a) with Phenyl Isothiocyanate (2a) [Scheme II]: Base = Potassium t-Butoxide; Solvent = *Tetrahydrofuran*

Experiment Number	Prevailing Temp.[a], °C	Mode of Addition[b]	Approximate Product Distribution,[c] %		
			Thiazole 3a	Imidazole 4a or 9	Carbamothioate 8
1	25	Sequential (10 min Interval)	——[e]	——[e]	Only product detected (PMR)
2[d]	25	Sequential (1 min Interval)	47 (HPLC)	24 (HPLC)	——[e]
3	20-22	Simultaneous	42 (PMR)	42 (PMR)	——[e]
4[d]	-25 to -30	Sequential (1 min Interval)	70 (HPLC) 69 (Isolation)	3 (HPLC) 3 (Isolation	——[e]

[a]Since the reaction was exothermic, application of external cooling was required to maintain a roughly constant temperature. In general, the base-solvent mixture was cooled to below room temperature; 1a, then 2a, or 1a + 2a, was added[b]; and the temperature was allowed to rise to

the "prevailing" level noted, where it was maintained by controlling the rate of addition and continuing cooling as needed.

[b] Sequential: The isocyanoacetate ester was added to the base-solvent mixture and stirred for the time-interval indicated before addition of the isothiocyanate was begun.
Simultaneous: A solution of isocyanoacetate ester and isothiocyanate in the reaction solvent was added to the base-solvent mixture.

[c] The approximate distribution of products (expressed here as a percentage of the theoretical yield) was determined by PMR, HPLC, and/or isolation, as noted in parentheses after the tabulated number.[14] The methods of estimation are described fully in the experimental section.

[d] A separate oxidation step (utilizing oxygen in the presence of catalytic iodine) was performed in order to convert thiol 4a to the more readily detectable and isolable disulfide 9. See experimental section for details.

[e] Not detected, but may be present as a minor constituent of the reaction mixture.

simultaneous addition gave similar results at 20-25°C with respect to thiazole production. The significance of the apparent difference in thiazole: imidazole ratio between the two experiments has not been addressed.

Reaction Time. Although it has not been demonstrated for the potassium t-butoxide-tetrahydrofuran system, it has been shown (vide infra) that in sodium hydride-dimethoxyethane the reaction products are formed rapidly and are stable under the reaction conditions. Thus, following the introduction of the isothiocyanate, reaction time does not appear to be crucial.

Temperature. The reaction process is exothermic, and the temperature rapidly rises above ambient in the absence of external cooling. Precooling the potassium t-butoxide-tetrahydrofuran solution to -30°C and allowing the temperature to rise to ambient before quenching gave a substantially improved yield of thiazole (experiment 4; Table I). Lower temperature also appears to suppress imidazole formation (cf. experiment 4 with 2 and 3) in this system. The markedly improved yield of 3a obtained in the low-temperature experiment, as analyzed by HPLC, was verified by isolation (experiment 4; Table I) of this thiazole[5].

Thus, only by carefully minimizing the interval between isocyanoacetate and isothiocyanate additions and lowering the reaction temperature were we able to duplicate the reported[2] 65% yield of thiazole 3a. Under these conditions, imidazole 4a was also isolated in 3% yield as its disulfide 9.

Substitution of Sodium Hydride-Dimethoxyethane for Potassium t-Butoxide-Tetrahydrofuran. In a fashion similar to that described above for the potassium-t-butoxide-tetrahydrofuran base-solvent system, the effects of the mode of addition of reagents and reaction temperature on the production of thiazole 3a were examined with a sodium hydride-dimethoxyethane system. The results are summarized in Table II.

TABLE II Effect of Temperature and Mode of Addition of Reagents on Product Distribution in the Reaction of Methyl Isocyanoacetate (1a) with Phenyl Isothiocyanate (2a) [Scheme II]: Base = Sodium Hydride; Solvent = Dimethoxyethane

Experiment Number	Prevailing Temp.[a], °C	Mode of Addition[b]	Approximate Product Distribution,[c] %		
			Thiazole 3a	Imidazole 4a or 9	Carbamothioate 8
5	22	Sequential (10 min Interval)	5 (Isolation)	Not Determined; much polar material	17 (Isolation)
6[d]	22	Simultaneous	53 (HPLC)	5 (HPLC)	——[e]
7	20-25	Simultaneous	58 (Isolation)	2.5 (Isolation)	——[e]
8[d]	-25 to -30	Simultaneous	76 (HPLC)	9 (HPLC)	——[e]
9[f]	-25 to -30	Simultaneous	61 (HPLC)	6.5 (HPLC)	——[e]
10	-20 to +22[g]	Simultaneous	(TLC)[g]	(TLC)[g]	——[e]

[a], [b], [c], [d], [e] See the corresponding footnotes in Table I.

[f] 15-Crown-5 present in reaction mixture.

[g] Reaction was monitored by TLC: -20°C (2 h) → 0° to 10°C (34 h) → 22°C (48 h); 3a predominated throughout; no substantial change observed during course of experiment.

In the NaH-DME system, too, allowing a substantial (10-minute) interval between the additions of isocyanoacetate and isothiocyanate was found to have an adverse effect on the yield of thiazole (Expt. 5, Table II). As with KOBu-t-THF, lowering the reaction temperature to approximately -30°C had a beneficial effect on thiazole production (Expt. 8, Table II). The chief differences in results with the two base-solvent systems were the somewhat higher yields of thiazole and substantially reduced yields of imidazole seen at room temperature with the NaH-DME system. At reduced temperature (-30°C), both systems produce their best yields of thiazole 3a, and the results are comparable (70-75%).

Experiment 10 established that the products are formed rapidly (within 2 h) at -20°C and that no significant change in their apparent ratio or the overall composition of the reaction mixture (as judged by thin-layer chromatography) occurred even after 48 h at room temperature -- i.e, the products appear to be stable under the reaction conditions.

Effect of Solvent with Sodium Hydride as Base. Substitution of tetrahydrofuran or N,N-dimethylformamide for dimethoxyethane with sodium hydride as base (simultaneous addition; 20-24°C) resulted in decidedly inferior yields of thiazole 3a (Table III).

Although crude imidazole yields were concomitantly enhanced, especially in tetrahydrofuran, the reactions produced a more complex array of side-products than those in dimethoxyethane.

TABLE III Effect of Solvent on Yield and Product Distribution in the Reaction of Methyl Isocyanoacetate (1a) with Phenyl Isothiocyanate (2a) [Scheme II]: Base = Sodium Hydride.

Experiment Number	Solvent*	Prevailing Temp.[a], °C	Mode of Addition[b]	Approximate Product Distribution,[c] %		
				Thiazole 3a	Imidazole 4a or 9	Carbamothioate 8
6[d]	DME	22	Simultaneous	53 (HPLC)	5 (HPLC)	——[e]
11	THF	20	Simultaneous	26 (PMR)	63 (PMR)	——[e]
12	N,N-DMF	20-24	Simultaneous	14 (Isolation)	12 (Isolation)	——[e]

*DME = dimethoxyethane; THF = tetrahydrofuran; N,N-DMF = N,N-dimethylformamide.

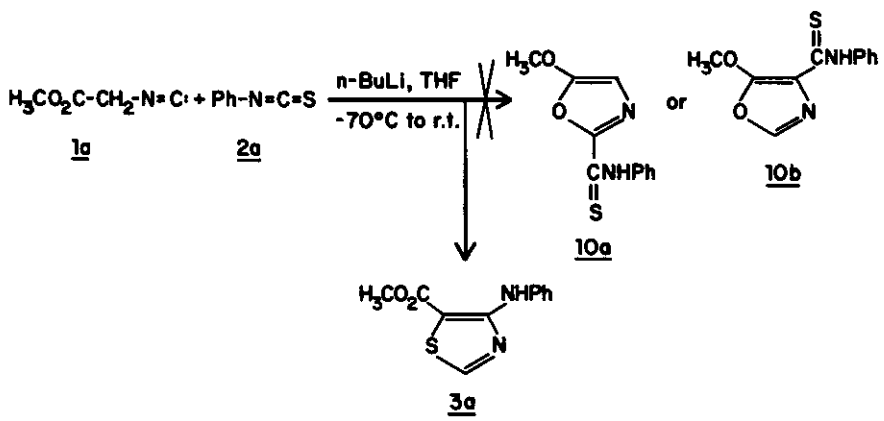
a, b, c, d, e See the corresponding footnotes in Table I.

Effect of the Cation of the Base. To examine the effect of changing the cation of the base on reaction outcome, we substituted lithium hydride for sodium hydride with dimethoxyethane as solvent, employing simultaneous addition of reagents. For reasons unknown, there was no discernible reaction at room temperature. Heating the reaction mixture at 50°C overnight resulted in an approximately 30% crude yield of thiazole 3 -- substantially poorer than the results generally obtained with sodium hydride.

Effect of Crown Ether. The addition of 10 mole percent 15-crown-5 to a sodium hydride-dimethoxyethane reaction mixture (simultaneous addition; -30°C) appeared to reduce significantly the yield of thiazole 3a (cf. Expts. 8 and 9, Table II). There was also an apparent reduction in the yield of imidazole, but the observed difference between the absolute yields of imidazole in the two experiments is probably not significant.

Low Temperature Reaction of the Lithium Derivative of Methyl Isocyanoacetate (1a) and Phenyl Isothiocyanate (2a) in THF. The reaction of the lithium derivative of ethyl isocyanoacetate with phenyl isothiocyanate has been reported[6a] to yield neither thiazole nor imidazole products, but rather the 2- or 4-N-phenylthiocarbamoyl-5-alkoxyoxazole (cf. Scheme III; 10a, b) that would result from participation by the isocyano ester oxygen in oxazole ring closure.

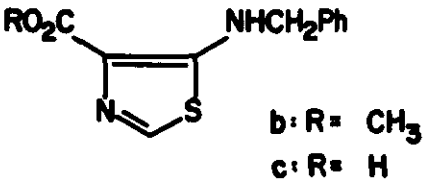
SCHEME III



In our hands, the reaction of equimolar quantities of methyl isocyanoacetate (1a) and phenyl isothiocyanate (2a) under the prescribed conditions (1 equivalent of n-BuLi; THF; -70 to -60°C; sequential addition with a one-minute time interval; quench at room temperature) gave a low yield of thiazole (3a) as the only detectable product. The main constituents of the reaction mixture were unchanged starting materials 1a and 2a. No oxazole was observed.

II. Reaction of Methyl Isocyanoacetate (1a) with Benzyl Isothiocyanate (2b).

We examined the reaction (Scheme I) of methyl isocyanoacetate (1a) with benzyl isothiocyanate (2b) in two base-solvent systems. With sodium hydride in dimethoxyethane (20-25°C maintained by cooling; simultaneous addition) a 32% crude yield of thiazole (3b) was isolated.



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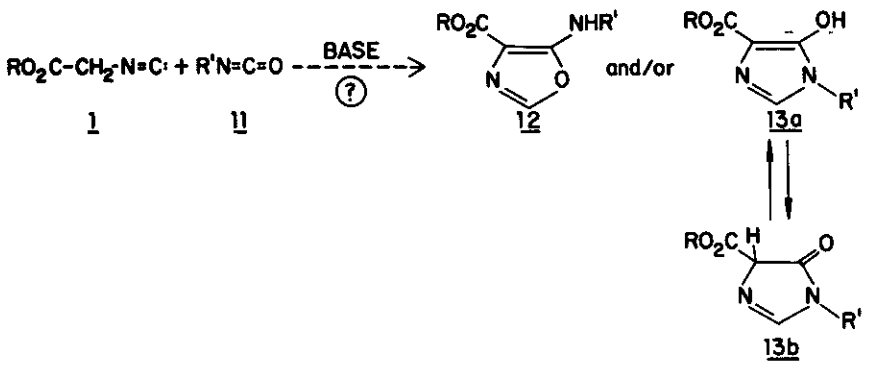
When potassium t-butoxide in tetrahydrofuran was used, the ester (3b) was not isolated; instead, a 46% yield of a crude product containing the carboxylic acid (3c) was obtained. In neither case was any imidazole detected. Despite that fact, the presence of imidazole in the form of an N-benzylthiol derivative analogous to imidazole 4a (Scheme II) in the substantial polar fraction of the reaction mixture cannot be definitively ruled out. However, the detection of some disulfide resulting from spontaneous oxidation would be expected, based on our results with the imidazolethiol 4a (see A.4. of the Experimental Section), had any significant amount of thiol been formed in the reaction. No deliberate effort was made to oxidize the polar fraction.

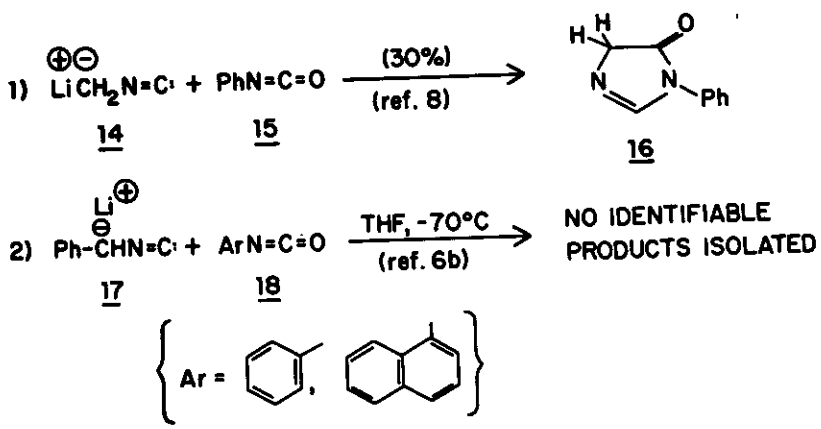
III. Reaction of Ethyl Isocyanoacetate with Benzyl Isocyanate

Since oxazole analogs of the amino(alkoxycarbonyl)thiazoles (3) were also potentially of interest to us, and since no general method for their preparation has been reported, we wished to ascertain

SCHEME IV

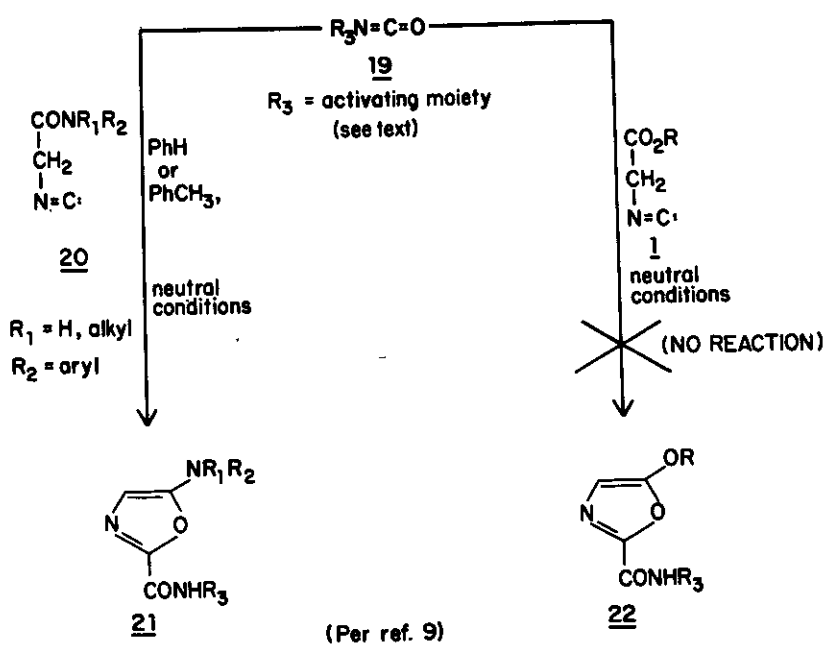


SCHEME V



whether the substitution of an isocyanate for an isothiocyanate in a reaction with the salt of an isocyanoacetate ester might yield the requisite oxazole (12) and/or a substituted imidazole (13), as depicted in Scheme IV. A significant body of literature[7] on the preparation of oxazoles from isocyanides has accumulated over the past decade. However, with respect to the specific process of acylation of an isocyanide with an isocyanate, only three relevant references, none of which suggested a positive prognosis for preparation of the desired substituted oxazoles, were located: 1) (Scheme V, Reaction 1)[9] the reaction of the lithio derivative of methyl isocyanide (14) with phenyl isocyanate (15), from which 3-phenyl-1-imidazolin-4-one (16) (isolated in 30% yield) was the only reported product; 2) (Scheme V, Reaction 2)[6b] the reaction of isocyanobenzyllithium (17) with phenyl or 1-naphthyl isocyanate (18), the products of which could not be purified and were not identified; and 3) (Scheme VI)[9] the reaction of α-isocyanoacetamides (20) with certain reactive aryl (substituted with electron-withdrawing groups) or sulfonyl isocyanates (19) under neutral conditions-- i.e., in the absence of added base--which yielded 5-amino-2-(carbamoyl)-oxazoles (21; in which the oxazole oxygen derives from the carboxamide group of the isocyano-acetamide) as the only detectable products.

SCHEME VI

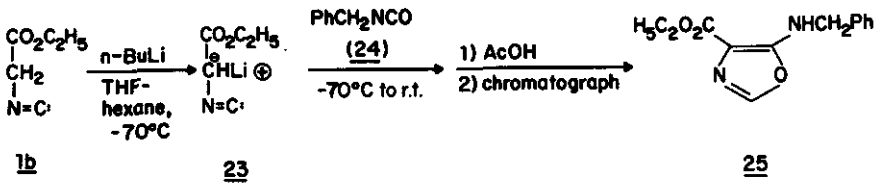


(Per ref. 9)

The authors of this last-cited report on isocyanoacetamides specifically state that α-isocyanoacetates fail to cyclize in the presence of reactive isocyanates under the neutral conditions employed. However, the base-promoted reaction of an α-isocyano ester with an isocyanate has not been reported, and for the reasons cited above, it was to this specific process that we addressed ourselves.

We chose to examine this process with benzyl isocyanate (rather than the phenyl compound), since it would serve to simplify the identification of the possible isomeric products: the PMR spectrum of the N-benzylated imidazole (Scheme IV; 13, R' = $-CH_2Ph$) should exhibit a singlet for the benzyl methylene group, whereas the benzyl methylene of the desired amino(alkoxycarbonyl)oxazole (Scheme IV; 12, R' = $-CH_2Ph$) should appear as a doublet due to the presence of a proton on the adjacent exocyclic nitrogen. The isomeric 5-alkoxy-2-(carbamoyl)oxazole (22; Scheme VI) was considered to be an unlikely product, but would be expected to be distinguishable from the desired 5-amino-4-(alkoxycarbonyl)oxazole on chemical and spectroscopic grounds including the sizeable chemical shift difference exhibited by the 2- versus the 4-methine proton of an oxazole nucleus[9]. The results of this experiment are depicted in Scheme VII.

SCHEME VII



1b 23 25

The lithio derivative of ethyl isocyanoacetate was prepared in tetrahydrofuran-hexane at -70°C. Benzyl isocyanate (24) was added, and the reaction mixture was allowed to come to room temperature before quenching with acetic acid. Chromatography gave a 16% isolated yield of oxazole (25), which was fully characterized and unequivocally distinguished from the possible imidazole isomer

by the appearance in the PMR spectrum ($CDCl_3$) of a benzyl doublet at δ4.55, which collapsed to a singlet upon D_2O exchange. The oxazole methine singlet appeared at δ7.19, significantly downfield of the δ5.8-6.4 region in which the 4-methine of a 5-alkoxy-2-(carbamoyl)oxazole (22; Scheme VI) would be expected (based on the analogy of the 5-amino-2-(carbamoyl)oxazoles (21; Scheme VI) and well within the region expected for the 2-methine of a 5-amino-4-(alkoxycarbonyl)oxazole.[9] No imidazole was detected.[10] The low yield observed in this experiment is probably improvable by modification of reaction time and temperature parameters.

Although only a single example, this reaction suggests a novel access to the otherwise difficult-to-prepare substituted-amino(alkoxycarbonyl)oxazoles (12; Scheme IV) in a fashion analogous to that by which the corresponding thiazoles (3; Scheme I) may be synthesized.

Summary. The reaction of the metal salts of α-isocyanoacetate esters (1) with isothiocyanates (Scheme I) and isocyanates (Schemes IV and VII) were investigated. Examination of the effects of modifying the reaction parameters revealed the importance of temperature and the mode of addition of the reagents in maximizing the yield of thiazoles (3). The isomeric substituted imidazole (4a) has been documented as a side-product in the production of thiazole 3a from isocyanoacetate 1a and phenyl isothiocyanate 2a, but the corresponding imidazole was not detected in the reaction of 1a with benzyl isothiocyanate (2b). The previously unreported reaction of the salt of an α-alkoxycarbonyl isocyanide (1b) with an isocyanate (24) was shown to produce an amino(alkoxycarbonyl)oxazole (25). No hydroxy(alkoxycarbonyl)imidazole (13a) was detected.

EXPERIMENTAL

General. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. ^1H NMR spectra were recorded on a Varian T-60 (60 MHz), CFT-20 (79.5 MHz), or EM-390 (90 MHz) spectrometer, and are expressed as ppm (δ) from Me_4Si internal standard. The solvents in which the spectra were obtained are specified in the text. IR spectra were run on nujol mulls and were recorded on a Nicolet 10 MX fourier transform infrared spectrophotometer. Mass spectra were obtained on a Varian MAT CH5 spectrometer. Microanalyses were performed by the Physical Analytical Services Department of the Schering Pharmaceutical Research Division, and results were within ± 0.4% of theory except as noted in the text. HPLC analyses were performed with a Waters Associates apparatus, consisting of a Model 6000A solvent delivery system, Model 481 ultraviolet absorbance detector, and Model 730 data module.

Unless otherwise indicated, all reagents and chemicals were obtained commercially and were used without pretreatment or further purification. Reaction solvents were dried over type 3A molecular sieves.

REACTION OF METHYL ISOCYANOACETATE WITH PHENYL ISOTHIOCYANATE

A. Potassium t-butoxide-Tetrahydrofuran System--General Procedure

1. Sequential Addition Technique. To a suspension of 17.5 mmoles of potassium t-butoxide in 10 ml of dry tetrahydrofuran was added a solution of 14.9 mmoles of methyl isocyanoacetate (1a) in 20 ml of dry tetrahydrofuran. External cooling was applied as necessary at this stage and during the subsequent addition and reaction of the isothiocyanate. In "room temperature" experiments, an ice-water bath was utilized to maintain the reaction mixture at 20-30°C until any exotherm had abated. An acetone-dry ice bath served to maintain lower temperatures when desired, as noted in Table I.

When addition of the isocyanoacetate was complete, the reaction mixture was stirred at the requisite temperature for the time interval specified in Table I. At this point, a solution of 14.9 mmoles of phenyl isothiocyanate (2a) in 20 ml of dry tetrahydrofuran was added in one portion.

The reaction mixture was allowed to stir at the specified temperature until thin-layer chromatography [silica gel plates; ethyl acetate-hexane (1:4)] indicated the absence of starting materials (generally, 2 to 3 h). Processing of the reaction mixture and isolation, characterization, and quantitative estimation of reaction products are discussed below. Qualitative analysis of the crude reaction mixtures could be performed by means of TLC on silica gel using, in addition to the system cited above, $CHCl_3$-2B ethanol-concentrated ammonium hydroxide in ratios (v/v/v) of 90:2:0.5 and 50:2:0.1.

2. Simultaneous addition technique. To a suspension of 17.5 mmoles of potassium t-butoxide in 10 ml of dry tetrahydrofuran was added a solution containing 14.9 mmoles of methyl isocyanoacetate and 14.9 mmoles of phenyl isothiocyanate in 40 ml of dry tetrahydrofuran. As required, cooling was applied in the manner described in Section 1. The reaction mixture was stirred at the specified temperature (Table I) until starting materials had been consumed, as determined by TLC analysis (see Section 1). Further processing and analysis of the reaction mixture are described below.

3. Quenching and crude isolation of products. The reactions were routinely quenched by acidification (to pH 5-6) with glacial acetic acid. Room temperature reactions were precooled to around 0°C, while lower-temperature reactions were quenched at the prevailing temperature

of the experiment. Solvent was removed under reduced pressure. The residue was partitioned between water and methylene chloride, layers separated, and the aqueous layer extracted with four additional portions of methylene chloride. The combined extracts were washed once with brine, dried over anhydrous sodium sulfate, and solvent removed under reduced pressure to obtain the crude reaction product as a gummy solid, which could then be subjected to direct quantitative analysis or to isolation of the constituents by column chromatography, as detailed below. In some instances, as indicated in Table I, the crude reaction product was subjected to oxidative treatment, which is described in the experimental section that follows.

In those experiments in which it was desired to isolate the thiazole, the following alternative processing scheme was found helpful in effecting a partial separation of thiazole from other reaction components: the reaction mixture was cooled in an ice-water bath and quenched by the addition of water. Solvent was removed under reduced pressure, and the residue was partitioned between water and methylene chloride. The alkaline aqueous phase was extracted four times with methylene chloride, and the combined extracts were washed once with brine, then dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure to obtain a residual solid enriched in the desired thiazole. The remaining components of the reacton mixture could be recovered, if desired, by acidification (acetic acid) and extraction of the aqueous phase.

4. Oxidative treatment of the crude reaction product; conversion of 4a to 9. Control experiments had demonstrated the following facts: a) spontaneous oxidation of the imidazole-sulfhydryl product (4a) to the corresponding disulfide (9) occurred on standing in solution; b) the oxidative treatment described herein had no apparent effect on the thiazole (3a); c) prolonging oxidation beyond the 2 h period employed as standard operating procedure produced no discernible increase in the amount of disulfide (9).

Dry oxygen gas (SOS; extra dry) was bubbled through a stirred solution of the crude reaction product (isolated as described in Section 3), sodium methoxide (ca. 10 mole percent, based on weight of crude product), and a very small, unweighed quantity of iodine in dimethoxyethane for a period of 2 h. Solvent was then removed under reduced pressure, and the residue was triturated with chloroform. Any insoluble solid that remained at this stage was virtually pure imidazole disulfide (9) and was isolated by filtration. The filtrate was washed successively with 25% aqueous ammonium hydroxide and brine and was dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure, and the residual solid was dried under high vacuum. The material thus isolated could then be subjected to quantitative analysis by HPLC (see below).

5. Isolation and purification of reaction products 3a, 8, and 9. The crude reaction product mixture--obtained directly (Section 3) or via oxidative treatment (Section 4)--was subjected to column chromatography, using 'flash'-grade silica gel (Baker 7024). Elution with ethyl acetate-petroleum ether (35-60°C boiling range) mixtures, ranging from 1:4 to 1:1 (v/v), served to isolate 4-methoxycarbonyl-5-(phenylamino)thiazole (3a). Remaining mobile material was then stripped from the column by elution with methanol. This crude more polar fraction was then rechromatographed on silica gel (Baker 7024), eluting with chloroform-2B ethanol-concentrated ammonium hydroxide (9:2:0.25) to obtain dimethyl 5,5'-dithiobis[1-phenyl-1H-imidazole-4-carboxylate] (9).

Recrystallization of thiazole (3a) from ethyl acetate-diisopropyl ether gave a white crystalline solid with mp 90-92.5°C [5] and the following spectroscopic properties. PMR ($CDCl_3$): 3.98 (s, 3H), 7.0-7.5 (m, 5H), 7.97 (s, 1H), 9.76 (broad s, 1H); MS: 234 (49%, M^+), 203 (20%), 202 (100%), 129 (31%), 77 (44%); IR (Nujol): 3270, 3100, 1660 cm^{-1}; Anal. Calcd. for $C_{11}H_{10}N_2SO_2$: C, 56.39; H, 4.30; N, 11.95; S, 13.68. Found: C, 56.44; H, 4.13; N, 11.89; S, 13.65.

Recrystallization of the imidazole disulfide 9 from methanol gave a pale yellow solid with mp 224-228°C. PMR ($CDCl_3$): 3.83 (s, 6H), 7.3-7.6 (m, 10H), 7.79 (s, 2H); MS: 466 (30%, M^+), 233 (36%), 202 (27%), 201 (100%), 146 (17%), 77 (95%); IR: 3100, 1710, 1700, 1600 cm^{-1}; Anal. Calcd. for $C_{22}H_{18}N_4O_4S_2 \cdot 0.3\ H_2O$: C, 55.98; H, 3.97; N, 11.87; S, 13.59. Found: C, 55.79; H, 3.85; N, 11.76; S, 13.75.

From those crude reaction mixtures in which it appeared, the methyl (N-phenyl)carbamothioate 8 could be isolated by means of column chromatography on silica gel (Baker 7024). Elution with 1:9 (v/v) ethyl acetate-petroleum ether (35-60°C boiling range) yielded 8, which appeared before thiazole 3a. Two recrystallizations from methanol gave a pale yellow solid with mp 92-94°C[11] and the following spectroscopic characteristics. PMR ($CDCl_3$): 4.11 (s, 3H); 6.9-7.6 (m, 5H); 9.28 (broad s, 1H); MS: 167 (100%, M^+), 152 (5%), 134 (35%), 135 (10%), 136 (14%), 119 (33%); IR: 3180, 1590, 1535, 1445, 1310, 1285, 1221, 1205, 1136 cm^{-1}; Anal. Calcd. for C_8H_9NOS: C, 57.45; H, 5.42, N, 8.37; S, 19.17. Found: C, 58.00; H, 5.24, N, 8.10; S, 18.65. PMR and mass spectral data are in accord with the structure written. No impurities were detectable by TLC, but carbon and sulfur analyses deviated from theory by slightly more than 0.5%.

B. Sodium Hydride-Dimethoxyethane System -- General Procedure. The methods employed with the NaH-DME system were identical to those described in the preceding sections for the KOBu-t-THF system. Relevant parameters are summarized in Table II. The commercial 60% dispersion of sodium

hydride was washed with petroleum ether prior to use. In the experiment (No.9, Table II) in which crown ether was a constituent of the reaction mixture, 10 mole percent of 15-crown-5 was added prior to the introduction of the isothiocyanate.

C. Sodium Hydride in Tetrahydrofuran or N,N-Dimethylformamide. These experiments were conducted in a fashion directly analogous to that described above in Sections A.2 and A.3. Reaction parameters and results are summarized in Table III.

D. Lithium Hydride in Dimethoxyethane. This experiment was conducted on a 10-mmole scale via the simultaneous addition method described above (Section A.2), using lithium hydride as base in dimethoxyethane solvent. Addition of reagents was performed at 20°C, and the reaction mixture was stirred at room temperature for 24 h. TLC (see A.1 for conditions) showed no evidence of reaction. The reaction mixture was therefore placed in a heating bath at 50°C for 16 h, after which it was quenched and processed as described in Section A.3. This gave a 30% yield of a crude solid, shown to be mainly thiazole 3a by TLC. TLC also showed the presence of a very small, but indeterminate, amount of imidazole disulfide 9.

E. Methods of Quantitative Estimation.

1. PMR analysis. δ-values herein refer to 60-MHz spectra in $CDCl_3$. An estimate of the ratio of thiazole to imidazole in product mixtures was obtained by comparing the integral for H-2 of 4-methoxycarbonyl-5-(phenylamino)thiazole (3a) with the integral for the complex multiplet in the δ7.0-7.8 region, representing the phenyl protons (of both thiazole and imidazole products) plus the H-2 of imidazole disulfide 9 at δ7.79. (Thiol 4a was never isolated and characterized, but it is assumed that its H-2 proton would also appear in this region). The aromatic region was assumed to be free of impurities, and all protons remaining after deducting the thiazole protons were calculated as imidazole protons to obtain the requisite product ratio. We have since learned that in 90-MHz spectra the H-2 proton of 9 is sufficiently separated from the aromatic region to permit a direct comparison of the integrals of the H-2 protons of 3a and 9. These higher field spectra were, however, not available for experiments 3 and 11. Also, in the spectra of the reaction mixtures, the ester methyl groups of thiazole and imidazole overlapped each other and were further overlapped by a broad impurity peak of unknown origin. This region of the spectrum was thus unsuitable for quantitation. The "Approximate Product Distribution" figures reported in the Tables represent percentages of theoretical yield and were obtained by multiplying the percentage of each constituent calculated from the PMR integration by the percent of theoretical yield represented by the total weight of the product mixture from which the analytical sample was obtained. Since recoveries of crude products were less than quantitative,

the percentages of thiazole plus imidazole total less than 100%. The estimates are approximate since minor impurities were generally present along with thiazole and imidazole products.

2. HPLC analysis. In order to remove small amounts of polar impurities from the crude reaction products to be analyzed, the following washing scheme was employed prior to injection onto the HPLC column: a weighed amount of the sample was dissolved in methylene chloride, washed successively with 25% aqueous ammonium hydroxide and brine, and dried over anhydrous sodium sulfate. The sample was concentrated under reduced pressure and thoroughly dried under high vacuum. The percentage recovery was then calculated. The sample thus prepared was analyzed on a Porasil column (Waters; P/N 27477), using $CHCl_3$-2B ethanol-concentrated ammonium hydroxide (90:2:0.1) as the solvent system, with a flow rate of 2 ml/min at 1080-1100 psi. Note that the conditions utilized were capable of detecting thiazole 3a (retention time: 1.7 minutes) and imidazole disulfide 9 (retention time: 6.7 min), but not the significantly more polar imidazole thiol 4a. (Any thiol should, however, have been removed in the preparative base wash described above). The "Approximate Product Distribution" figures reported in the Tables were calculated by multiplying the percentage of each constituent obtained by integration[12] of the liquid chromatogram by the percentage recovery described above, as well as by the percent of theoretical yield represented by the total weight of the product mixture from which the original analytical sample was derived. That is, e.g.,

$$\%\ \underline{3a} = \left[\begin{array}{l}\%\ \text{Yield of}\\ \text{Crude Rxn.}\\ \text{Mixture}\\ \text{after}\\ \text{Workup}\end{array}\right] \times \left[\begin{array}{l}\%\ \text{Recovery}\\ \text{of Material}\\ \text{from}\\ \text{Base Wash}\end{array}\right] \times \left[\begin{array}{l}\%\ \underline{3a}\ \text{from}\\ \text{Integration}\\ \text{of Liquid}\\ \text{Chromatogram}\end{array}\right]$$

Since recoveries of products were less than quantitative, the percentages of thiazole plus imidazole total less than 100%.

F. Low Temperature Reaction of the Lithium Derivative of Methyl Isocyanoacetate (1a) and Phenyl Isothiocyanate (2a) in THF. This experiment was performed as described by Porsch.[6a] A suspension of the lithium derivative of methyl isocyanoacetate was prepared at -70°C (acetone-dry ice bath) from 32.6 ml (50.5 mmoles) of a 1.55M hexane solution of n-butyllithium and 5.0 g (50.5 mmoles) of methyl isocyanoacetate in 35 ml of tetrahydrofuran. To this suspension, maintained at -70°C, was added dropwise over 30 min a solution of 6.82 g (50.5 mmoles) of phenyl isothiocyanate in 30 ml of tetrahydrofuran. The reaction mixture was stirred for 1 h at -70°C and was then quenched at that temperature by the addition of 2.87 ml (50.5 mmoles) of glacial acetic

acid. When the mixture had come to room temperature, it was poured into 400 ml of water and extracted with several portions of methylene chloride. The combined extracts were washed successively with water and brine, then dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure gave 11.1 g (94% of theory) of residual oil. PMR ($CDCl_3$) of this crude product showed mainly the two starting materials plus a small amount of 4-methoxycarbonyl-5-(phenylamino)thiazole (3a). TLC [silica gel; ethyl acetate-hexane (1:4)] corroborated this finding, showing spots corresponding to starting materials and thiazole 3a, along with a small orgin spot.

The following scheme was devised to isolate for identification purposes a pure sample of the reaction product from the mixture containing mostly the starting materials. No attempt was made to obtain a quantitative recovery of the product. The crude oil was stirred vigorously with hexane, and the hexane phase--containing virtually all the phenyl isothiocyanate, along with some of the methyl isocyanoacetate and product--was decanted. The residual oil was taken up in ether and the solution filtered through a pad of silica gel (Baker; 60-200 mesh) on a sintered glass funnel. Solvent was removed under reduced pressure from the filtrate, leaving 4.06 g (34%) of an oil which TLC showed to be essentially a mixture of methyl isocyanoacetate and thiazole 3a. This oil was partitioned between 3M aqueous HCl and ether with vigorous stirring for 1 h. The layers were separated, and the aqueous phase was made weakly alkaline with 2.5 N NaOH and extracted with methylene chloride. Combined extracts were washed successively with water and brine, dried over anhydrous sodium sulfate, and stripped of solvent under reduced pressure to give 229 mg (ca. 1.9%) of a solid with mp 80-85°C. TLC showed essentially one spot with an R_f equivalent to that of thiazole 3a. Comparison of the PMR and mass spectra of this product with those of authentic material showed it to be 4-methoxycarbonyl-5-(phenylamino)thiazole (3a).

REACTION OF METHYL ISOCYANOACETATE WITH BENZYL ISOTHIOCYANATE

A. Sodium Hydride-Dimethoxyethane System. To a suspension of 1.02 g (25 mmoles) of 60% sodium hydride (washed twice with petroleum ether prior to use) in 45 ml of dimethoxyethane was added dropwise a solution of 2.0 g (20 mmoles) of methyl isocyanoacetate and 3.01 g (20 mmoles) of benzyl isothiocyanate in 85 ml of dimethoxyethane. Temperature was maintained around 25°C. by the application of external cooling (ice-water bath), as required. The reaction mixture was then allowed to stir at room temperature with periodic monitoring by TLC [silica gel; ethyl acetate-petroleum ether, 35-60°C fraction (1:4)]. When the benzyl isothiocyanate had been consumed (approximately 2 h), the reaction was quenched with water, and solvent was removed

under reduced pressure. The semisolid residue was partitioned between water and methylene chloride, and the aqueous layer was separated and re-extracted with methylene chloride. Combined extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain 3.01 g (60% of theory) of a crude solid, which was stirred with diisopropyl ether and filtered to obtain 1.6 g (32%) of a solid with mp 81.5-86.5°C. PMR and mass spectral data, summarized below, identified this product as 5-benzylamino-4-(methoxycarbonyl)thiazole (3b)[2]. PMR ($CDCl_3$): 3.90 (s, 3H), 4.48 (d, 2H, J ≃ 5Hz; collapses to singlet on D_2O exchange), 7.33 (s, 5H), 7.80 (s, 2H; overlaps a second broad unresolved multiplet, which collapses on D_2O exchange); MS: 248 (45%, M^+), 215 (31%), 183 (27%), 187 (13%), 91 (100%).

The original aqueous phase was acidified (acetic acid; pH 5-6) and extracted with methylene chloride to obtain after washing, drying, and reduced-pressure evaporation 1.9 g (38% based on molecular weight of thiazole) of a crude solid, which was shown by TLC [silica gel; methanol-chloroform (1:9) or chloroform-ethanol-0.5% aqueous ammonium hydroxide (1:1:1)] to be a mixture of polar materials. Attempted crystallization of this crude material was unsuccessful, and the components were not identified.

B. Potassium t-Butoxide-tetrahydrofuran System. To a suspension of 1.24 g (11 mmoles) of potassium t-butoxide in 80 ml of tetrahydrofuran was added dropwise a solution of 1.0 g (10 mmoles) of methyl isocyanoacetate and 1.5 g (10 mmoles) of benzyl isothiocyanate in 20 ml of tetrahydrofuran. The temperature was maintained around 20-22°C by controlling the rate of addition. When addition was complete, the reaction mixture was stirred at room temperature. Within 1.5 h, TLC [silica gel; ethyl acetate-petroleum ether, 35-60°C fraction (1:4)] indicated that starting materials had been consumed. The reaction mixture appeared to consist of a relatively nonpolar component plus origin material when examined in the above system. The reaction mixture was allowed to stir at room temperature for approximately 60 h. No change was detectable by TLC. The reaction was quenched with water and solvent removed under reduced pressure. The residual oil was partitioned between water and methylene chloride. The layers were separated, and the aqueous phase was extracted with several portions of methylene chloride. The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain 0.6 g (24%) of a red oil, which appeared to be a mixture of several components by TLC [ethyl acetate-petroleum ether (1:4)]. Column chromatography on silica gel (Baker 7024), eluting with mixtures of ethyl acetate and petroleum ether (35-60°C) in ratios ranging from 1:9 to 1:4 (v/v), yielded one partially purified component, which was tentatively

identified as methyl(N-benzyl)carbamothioate on the basis of the following spectroscopic evidence. PMR ($CDCl_3$): 3.70 (s, 3H), 4.36 (d, 2H; J = 6 Hz), 5.05 (broad unresolved multiplet, 1H), 7.3 (s, 5H); MS: 181 (6%, M^+), 165 (82%), 150 (85%), 106 (90%), 91 (100%).

The original aqueous phase was acidified to pH 5-6 with acetic acid and extracted with several portions of methylene chloride. The combined extracts were washed with brine and dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure to obtain 1.17 g (46%) of a gummy solid, which was a mixture of components, as analyzed by TLC [silica gel; $CHCl_3$-methanol-acetic acid (90:10:0.5)]. A portion of this dark, gummy solid was dissolved in boiling methylene chloride containing activated carbon (Darco; grade G-60). The mixture was filtered through Celite, and the filtrate was diluted with hexanes. Thus was obtained a few milligrams of off-white solid (mp 138.5°C, dec), virtually homogeneous as judged by TLC in the above system. On the basis of the following spectroscopic data, this product was identified as 5-benzylamino-4-(carboxy)thiazole (3c)[2]. PMR (DMSO-d_6): 4.44 (d, 2H), 7.32 (broad s, >5H), 8.00 (s, 1H; overlapped by a broad exchangeable s [NH?]), ~12.2 (broad exchangeable unresolved multiplet, 1H); MS: 234 (8%, M^+), 216 (6%), 190 (22%), 149 (7%), 91 (100%).

REACTION OF ETHYL ISOCYANOACETATE WITH BENZYL ISOCYANATE

5-Benzylamino-4-(ethoxycarbonyl)oxazole (25). This reaction was performed in flame-dried glassware under an atmosphere of argon. A solution of 12.9 ml (20.0 mmoles) of n-butyllithium (1.55M in hexane) in 12 ml of tetrahydrofuran was cooled to -70°C in an acetone-dry ice bath. With the temperature maintained at -70°C, a solution of 2.26 g (20.0 mmoles) of ethyl isocyanoacetate[13] was added over a period of 30 min. Immediately upon completion of the addition of the isocyanoacetate, a solution of 2.66 g (20.0 mmoles) of benzyl isocyanate in 12 ml of tetrahydrofuran was added dropwise over 10 min to the cold (-70°C) orange-brown suspension of the lithio derivative of ethyl isocyanoacetate. The reaction mixture was allowed to stir at -70°C for 2.5 h. The cooling bath was then removed and the mixture stirred at room temperature for 2.5 h. The brown reaction suspension was then recooled to -70°C and quenched by the addition of 1.2 ml. (21.1 mmoles) of glacial acetic acid.

Filtration (medium sintered glass funnel) of the reaction mixture gave a tan hygroscopic powder, which was triturated for 16 h in ether containing ≤ 5% by volume methylene chloride. Filtration of the trituration mixture and evaporation of the filtrate under reduced pressure gave approximately 0.6 g (12% of theory) of a yellow solid, which by TLC [ethyl acetate-cyclohexane (1:1); silica gel] was similar in composition to the bulk of the crude product obtained as described below.

Solvent was removed under reduced pressure from the original filtrate of the reaction mixture, and the residue was partitioned between methylene chloride and saturated aqueous sodium chloride solution. The organic layer was separated, washed with aqueous sodium chloride solution, and filtered through a 20-mm layer of silica gel on a 60-ml medium sintered glass funnel. Solvent was removed under reduced pressure from the filtrate, yielding 4.25 g (86% of theory) of a reddish oil. This oil and the yellow solid isolated as described above were combined and chromatographed on silica gel, eluting with ethyl acetate-petroleum ether, 35-60°C fraction (1:2). Two products were thus obtained: Product "A" was a light yellow powder, homogeneous to TLC, with mp 105.5-108°C, weighing 770 mg (15.5% yield). Product "A" was recrystallized and characterized as described below. Product "B" was a dark brown gum, weighing 330 mg (7% of theory), and showing a predominant spot plus at least one impurity on TLC. Efforts to crystallize this gum were unsuccessful, and the main component could not be identified based on the spectra of the semipurified sample.

Product "A" was recrystallized from isopropyl ether to obtain large off-white, needlelike crystals (69% recovery) with mp 108-109°C, which were identified as the title oxazole based on the data summarized below. PMR ($CDCl_3$): 1.36 (t, 3H, J ≈ 7Hz), 4.31 (q, 2H, J ≈ 7Hz); 4.55 (doublet collapsing to a singlet on shaking with D_2O/DCl, 2H, J ≈ 6.5Hz), ≈ 6.5 (NH? poorly resolved), 7.19 (s, 1H), 7.30 (s, 5H); The following chemical shifts were observed in DMSO-d_6: 1.23 (t, 3H, J ≈ 7Hz); 4.17 (q, 2H, J ≈ 7Hz); 4.43 (d, 2H, J ≈ 6.5Hz); 7.26 (s, 5H); 7.60 (s, ∿ 1H); ∿ 7.7 (broad unresolved multiplet, 1H). MS: 246 (41%, M^+), 217 (6%), 200 (13%), 141 (14%), 91 (100%), 65 (22%); IR (Nujol): 3344, 1670, 1635, 1615 cm^{-1}; Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.42; H, 5.54; N, 11.29.

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10. The apparent absence of imidazole may be an artifact of the isolation process. A second mobile (TLC) product was obtained (approximately 7% yield) from the reaction as a partially purified oil, which was not identified; however, the spectroscopic characteristics of this oil did not fit the isomeric imidazole structure 13a, b; Scheme IV), though the presence of such an imidazole could not be definitely ruled out.

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14. For those experiments in which the products were not isolateed, quantitative HPLC data were used to calculate the approximate product yields. A cross-check of the distribution figures produced by HPLC and isolation was made in one experiment (#4, Table I) and suggested a close correspondence between the methods. In two experiments in which neither isolation nor HPLC analysis was performed, PMR integration data were used. Inasmuch as our objective was to delineate broad trends in product distribution, rather than to establish highly precise comparisons of relatively close results, data obtained by the PMR method were regarded as sufficiently comparable to justify their inclusion.

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