A number of 2-alkynylamino)-substituted heterocycles have been synthesized. These heterocycles rearrange in the presence of silver(l) and gold(l) salts to give novel 2H-pyrimido[2,1-b]benzoxazoles, 2H-pyrimido[2,1-b]benzothiazoles, and a 2H-pyrimido[2,1-b]benzoselenazo. Two of the the 2H-pyrimido[2,1-b]benzoselenazo were isolated in good yield. The kinetics of the silver tetrafluoroborate-catalyzed rearrangements of selected (alkynylamino)benzoxazoles and benzothiazoles have been examined by 1H NMR in CD3CN. Factors affecting the electron densities of the triple bond and of the nitrogen atom in the heterocycle are important in influencing the rate of rearrangement.

### Results and Discussion

#### Preparation of Alkynylamino Heterocycles. The compounds investigated in this study are 2-alkynylamino)-substituted benzoxazoles, benzothiazoles, and a benzoselenazo (see Table 1). The (alkynylamino)benzoxazoles were prepared by treatment of the substituted 2-chlorobenzoxazoles with potassium tert-butoxide in refluxing pyridine. The aminophenols obtained from Eastman Kodak Company Synthetic Chemicals Division. Other aminophenols were made from their corresponding nitrophenols by catalytic reduction or conversion with phosphorus pentachloride or with thionyl chloride. The aminophenols 19a and 19b are commercially available; 19c and 19f were obtained from Eastman Kodak Company Synthetic Chemicals Division. Other aminophenols were made from their corresponding nitrophenols by catalytic reduction or conversion with iron in acetic acid. 4,5-Dichloro-2-nitrophthalic (20c) and 4-cyano-2-nitrophthalic (20d) were prepared by nitration of 3,4-dichlorophenol and of 4-hydroxybenzonitrile. 4-Methoxy-2-nitrophthalic (20g) resulted from mild nitro-

#### Table 1. Alkynylamino Heterocycles Prepared from 2-Chlorobenzoxazoles and Alkynylamines

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<tr>
<th>Compd</th>
<th>X</th>
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tion of 1,4-dimethoxybenzene followed by selective hydrolytic removal of the methoxy ortho to the nitro group in refluxing sodium hydroxide.10

Benzothiazoles 14 and 15 and benzoselenazole 16 were accessed from the 2-chloro-substituted heterocycles by treatment with either propargylamine or the p-toluene-sulfonate salt of 1-amino-2-butyne. 2-Chlorobenzoelenazole (21) was synthesized from 2-mercaptobenzoelenazole using sulfur monochloride.

The comparison compounds 2-(N-methyl-N-propargylamino)benzoxazole (22) and 2-(allylamino)benzoxazole (23) were prepared by treatment of 2-chlorobenzoxazole with the respective amines, N-methylpropargylamine and allylamine. Catalytic reduction of 23 provided 2-(propylamino)benzoxazole (24). The quaternary salt 2-(propargylamino)-3-methylbenzoxazolium hexafluorophosphate (25) was obtained by refluxing 1 with excess methyl iodide and subsequent anion exchange with potassium hexafluorophosphate.

Both 1-amino-2-butyne and 3-phenylpropargylamine were prepared by a Gabriel synthesis from their corresponding halides as reported in the literature.11,12

Cyclization of Alkynylamino Heterocycles. In the absence of catalyst, N-propargynaphthylamines undergo thermal Claisen rearrangement reactions at 250 °C to give mixtures of benzoquinolines and tetrahydrobenzoquinolines.13 Iwai and Hirsooka14,15 reported the rearrangement of alkynylammonium salts and alkynyl amines in refluxing sodium ethoxide and ethanol to give a variety of products.

In our work, we found that compounds 1–16 rearranged smoothly to their respective fused dihydropyrimidines in the presence of catalytic amounts of silver tetrafluoroborate in acetonitrile. These reactions were monitored by NMR, and the transformations were complete in less than 48 h at 40 °C.

Except for products 26 and 27, which were isolated, all other dihydropyrimidines were identified by their NMR spectra. Figure 1 illustrates the decreasing resonances from the propargylmethylene protons of 9 and the increasing signals from the dihydropyrimidine ring protons of 27 as a function of time. The kinetic parameters for the rearrangements were obtained from changes in the H resonance signals as a function of time at 40 °C. The first-order kinetics of the rearrangement were measured by fitting the peak intensities (integrals) to a monoexponential curve. Figure 2 shows the curves from which the rate constants for the conversion of 9 to 27 are extracted.

Table 2 summarizes the observed rates of ring closure (kobs) for the pairs of compounds 1, 9, 2, 10, 5, 11; and 14, 15 with either a hydrogen or a methyl group on the terminus of the alkynyl chain. The benzoxazoles 9–11 having a methyl group at the terminus show accelerated rates of cyclization compared to their hydrogen analogs regardless of the substituent on the benzene ring. This rate increase is much greater for the 5-methyl- (2, 10) than for the 5-cyano-substituted (5, 11) benzoxazoles. For the benzothiazoles, there is no rate difference between the 2-butylnyl and 2-propargyl compounds 15 and 14.

The effects of aromatic ring substitution can be seen for the cyano and the methyl groups in both the propargyl and butynyl series. In each series, the presence of a cyano substituent results in a rate decrease for the cyano compounds 5 and 11 relative to their unsubstituted analogs 1 and 9. Clearly, the rate decrease is greater for the butynyl series than for the propargyl series (ca. 2-fold). Compounds 2 and 10 containing electron-donating methyl groups at Y2 exhibit rate increases compared to 1 and 9.

The data from Table 2 also show that the benzoxazole 13 with a gem-dimethyl group in the propargyl chain exhibits the fastest rate of ring closure. Compound 12 having a phenylpropargyl moiety rearranges at a rate comparable to the unsubstituted propargylamine 1. Comparison of the unsubstituted benzothiazole 14 to the benzoxazole 1 shows a marked rate increase (6.42 vs 1.43), but a similar comparison of the methyl substituted compounds 15 and 9 indicates a slight rate decrease (6.42 vs 7.70). Compound 22 with a N-methyl-substituted propargyl chain exhibits one of the slowest rates of ring closure.

Compounds lacking the acetylenic group such as 2-allylamino 23 and 2-propylamino 24 did not rearrange and neither did the 3-methyl substituted quaternary salt 25.

The rearrangement of 1 was also observed with catalytic amounts of silver trifluoroacetate. When an 8-fold molar excess of silver trifluoroacetate was used, the rearranged material 26 was present only as a minor product. However, an excess amount of silver tetrafluoroborate gave only 26.

When the rearrangement of 1 was carried out in the presence of D2O, the dihydropyrimidine 28, whose vinyl protons are replaced with deuterium, was obtained. In
the absence of the silver catalyst, only the NH proton in 1 exchanged with deuterium.

**Rearrangement with Gold Salts.** Aurous bis(pentamethylene sulfide) tetrafluoroborate\(^\text{(16)}\) catalyzed the rearrangement of 9 to the dihydropyrimidine 27 readily in nitromethane. The \(k_{\text{obs}}\) for this reaction, \(24.40 \times 10^{-4}\), is nearly identical to the \(k_{\text{obs}}\), \(24.57 \times 10^{-4}\), for silver tetrafluoroborate-catalyzed rearrangement in nitromethane. This rate for compound 9 in nitromethane is about three times faster than that in acetonitrile as noted in Table 2. In addition, reaction of 9 with the aurous salt gave a rich gold mirror deposited on the wall of the NMR tube. On the other hand, neither triphenylphosphine Au(I) chloride nor potassium Au(I) dicyanide in acetonitrile reacted with compounds 1 or 9.

**Preparation of Dihydropyrimidines.** The syntheses and stability of dihydropyrimidines have been reviewed by Weis and van der Plas\(^\text{(17)}\) in 1986. The methods of preparation generally involve formation of the pyrim-

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idine ring via cyclization of acyclic carbonyl compounds with nitrogen-containing materials. Conditions for this reaction often include high temperature or strongly alkaline conditions. Other methods call for addition of ammonia to β-dicarbonyl compounds or reduction of aromatic pyrimidines with complex metal hydrides or organometallic reagents. Dihydroheteroaromatics, in general, suffer from instability arising from their propensity to oxidation, hydrolysis, and isomerization. Many of the methods of preparation give low yields resulting from either the harsh reaction conditions employed, the subsequent aqueous workup for isolation of the product, the instability of the particular dihydropyrimidines involved, or all of the above.

Fused tricyclic pyrimidines are accessible by the condensation of 2-amino heteroazoles with unsaturated carbonyl compounds yielding pyrimidinones.18 These tricyclic pyrimidinones are, in fact, hydroxy-substituted heteroaromatic rings having a six π-electron system. A two π-electron system, 3,4-dihydro-2H-pyrimido[2,1-b]-benzothiazole, has been reported by a number of workers.19 Thus far, there have been no reports describing the preparation of fused dihydropyrimidines having a four π-electron system in the pyrimidine ring.

In our work, the conditions for preparing the dihydropyrimidines are mild with no heating required and no aqueous workup necessary. For example, 2H-pyrimido[2,1-b]benzoxazole (26) can be made by mixing compound 1 with silver tetrafluoroborate in acetonitrile at rt. Isolation involved simple addition of sodium iodide followed by filtration of the silver iodide formed. The final product was purified by sublimation. Yields ranged between 40 and 60%. Similarly, 2H-4-methylpyrimido[2,1-b]benzoxazole (27) was prepared from 9.

Mechanism of Rearrangement. A plausible mechanism for the rearrangements of the alkynylamino heterocycle to the dihydropyrimidine is depicted in Scheme 2. Step i is a rapid complexation of the triple bond with the noble metal ion to form the complex 29. Step ii is the nucleophilic attack of the ring nitrogen on the triple bond–metal complex resulting in the protonated cyclic intermediate 30. Loss of a proton in step iii is expected to be rapid and results in the vinylsilver or vinylgold intermediate 31. Protonation of the vinyl metal species 31 gives the final dihydropyrimidine in step iv. Though the current work does not permit an absolute determination of the rate-determining step, changes in the NMR spectra upon addition of silver tetrafluoroborate indicate that silver complexation is rapid. Depending on the nature of X, Y1, Y2, R1, and R2, steps ii or iv could be rate determining. If one assumes that the ring closure step ii is rate determining, then most of the experimental observations can be accounted for.

The increased rate of ring closure for the 2-(butynylamino)benzoxazoles 9–11 relative to the 2-(propargylamino)benzoxazoles 1, 2, and 5 can be understood in terms of the electron-donating effect of the methyl group on the triple bond. This results in a stronger interaction with the metal ion, which leads to a more rapid ring closure. Compound 12 containing a phenylpropargyl group exhibits no rate enhancement over compound 1. Since a phenyl group is only a weak electron donor, there should be little change in the electron density of the triple bond and no rate enhancement would be expected.

The rates of rearrangement for the cyano-substituted compounds 5 and 11 are decreased compared to 1 and 9. The electron-withdrawing cyano group depletes the electron density of the benzoxazole. This depletion reduces the nucleophilicity of the azole nitrogen and retards the rate of cyclization. Conversely, compounds 2 and 10, both containing electron-donating methyl groups, exhibit faster rates of cyclization than those observed for 1 and 9.

The rate of cyclization for 2-(propargylamino)benzothiazole 14 is ca. 4.5 times greater than that for the corresponding benzoxazole 1. The electronegativity of sulfur is less than that of oxygen, so that sulfur would be less electron withdrawing. Consequently, the nitrogen atom in benzothiazole should be more nucleophilic and rate enhancing. The fact that the butynyl analog 15 rearranges at the same rate as 14 is unclear.

Compound 13 with a gem-dimethyl group exhibits the fastest rate of rearrangement. This rate enhancement may be due to the "gem-dialkyl effect" proposed by Allinger and Zalkow in terms of enthalpies and entropies of open-chain vs ring compounds.20 That is, the gem-dimethyl chain in 13 has a more favorable enthalpy of ring closure and reduces the rotational entropy of the open-chain dimethylpropargylamine as compared to the unbranched propargylamine 1.

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The deuterium-labeling experiment is also consistent with Scheme 2. Initial exchange of the amino proton by deuteron leading to 33 should be diffusion controlled. Complexation of the triple bond with silver ion labilizes the terminal acetylenic proton, which then undergoes proton—deuterium exchange. Alternatively, a transient silver acetylide may be formed followed by deuteron silver exchange. In the absence of silver, only 33 was observed. Subsequent steps of metal—deuterium exchange according to Scheme 2 convert 34 to the deuterated material 28.

\[ \text{1} \xrightarrow{D_2O} \text{33} \xrightarrow{AgBF_4, D_2O} \text{34} \xrightarrow{Ag^+} \]

The appearance of only a minor amount of cyclization product from 1 in the presence of excess silver tetrafluoroborate can be understood in terms of the equilibrium shown below. Excess trifluoroacetate, a weakly basic anion, causes deprotonation of the terminal proton and forces the equilibrium toward the right with formation of a silver acetylide 35 and trifluoroacetic acid. A similar interaction between an alkyn and metal ion has been suggested in the dissociation of a proton and the formation of an acetylide.\(^{21}\) The acetylide, once formed, would not be able to participate in the ring closure as in step i shown in Scheme 2. Tetrafluoroborate, on the other hand, is not at all basic and cannot deprotonate the acetylenic proton. The rearrangement reaction proceeds as expected even in the presence of excess silver tetrafluoroborate.

The N-methyl-N-propargylamino material 22 exhibited one of the slowest cyclization rates of all the compounds. In step iv, the metal ion is replaced with a proton, which may be supplied by the NH of the starting material. In 22, where the N atom contains a methyl instead of hydrogen, the proton for step iv will have to come from an external source. This may come from the acetylenic proton of another molecule of 22, from the solvent CD\(_3CN\) (CD\(_3CN\), though dried before use, may still contain a trace amount of moisture), or from the somewhat hygroscopic silver tetrafluoroborate (as evidenced by H\(_2\)O in the \(^1H\) NMR spectrum). This process may be slow depending on the concentration of 22 and the state of dryness of the reaction components.

The reaction of gold ions with alkynylamino heterocycles depends on the nature of the Au(I) complex and on how tightly the gold ion is bound to the ligand. The gold ion in triphenylphosphine Au(I) chloride, or potassium Au(I) dicyanide, complexes very tightly to the ligands. Thus, these complexes will not yield free gold ion under most conditions. On the other hand, the thioether of the highly labile aurous bis(pentamethylbenzenesulfide) forms an unstable sulfonium bond and gives up the Au(I) ion readily. This Au(I) ion is then free to catalyze the rearrangement of 9 to 27. The rate difference observed in the rearrangement of 9 between nitromethane and acetonitrile is not understood. Both solvents have nearly identical dipole moments and dielectric constants.

The gold mirror seen on the NMR tube is a consequence of the reduction of Au(I) ion, potentially by the dihydropyrimidine 27, which itself may be oxidized to the aromatic system 37. The latter compound, presumably hydrolytically unstable, could not be clearly identified in the NMR spectrum. The fact that no silver mirror was observed in the silver-catalyzed rearrangement is not surprising. Thermodynamically, the reduction potential of Au(I) is more favorable than Ag(I) by about 0.9 V.\(^{22}\)

\[
\begin{align*}
\text{Au}^{+} + e^- & \rightarrow \text{Au}^0 & 1.692 \text{ V} \\
\text{Ag}^{+} + e^- & \rightarrow \text{Ag}^0 & 0.799 \text{ V}
\end{align*}
\]

The inactivity of comparison compounds 23–25 is completely consistent with the proposed mechanism. The former two do not contain an acetylenic bond, and the latter cannot cyclize because of the quaternization of the azolium nitrogen.

**Conclusion**

A number of 2-(propargylamino)benzoxazoles, benzothiazoles, and a benzoselenazole have been prepared. These compounds rearranged in the presence of a catalytic amount of silver tetrafluoroborate in deuterated acetonitrile to dihydropyrimidines. \(^1H\) NMR has been utilized to study the kinetics of these rearrangements. An electron-donating group on the alkyn terminal, or on the benzene ring, accelerated ring closure. An electron-withdrawing group on the benzene ring of the heterocycles retarded the ring closure rate. A reactive Au(I) salt also catalyzes the rearrangement of 2-(butynylamino)benzoxazole with a concomitant gold mirror formation. Two novel tricyclic dihydropyrimidines can now be obtained simply by treatment of the alkynylamino heterocycles with silver tetrafluoroborate.

**Experimental Section**

Melting points were determined on a capillary melting point apparatus and are uncorrected. Infrared spectra were obtained from KBr disks. Mass spectra were determined on an electron impact mass spectrometer. NMR spectra were taken in CDCl\(_3\), DMSO-\(_d_6\), or CD\(_3CN\) with a 90 or 300 MHz spectrometer for \(^1H\) and at 22.63 MHz for \(^13C\). TMS was used as an internal standard, and chemical shifts are reported as \(\delta\) values (ppm from TMS). All kinetics measurements were obtained at 300 MHz and at 40 °C using a 5 mm four-nucleus probe (\(^1H, ^13C, ^19F, \text{and} ^31P\)). The acquisition conditions were


Typical reactant concentrations were 2.1 benzoxazolesilver tetrfluoroborate by weight using 5 mg of the silver salt in 0.8 mL of deuterated acetonitrile. The sample was thermally equilibrated in the magnet, and the requisite amount of silver tetrfluoroborate was added. After shaking, the sample was returned to the probe and allowed to reequilibrate to temperature. This process was performed within 120–180 s. During the temperature reequilibration period, the sample was locked and shimmed prior to acquiring the necessary NMR spectra.

A series of NMR spectra were acquired generally using a series of 20 preacquisition delays. Most of the spectra were acquired every 20 min in the early stages of the growth kinetics for the first 3 h of the experiment. For the remaining 12 h of the accumulation, spectra were acquired every hour. If the series of preacquisition delays utilized in the kinetics determination were inappropriate as evidenced by either faster or slower conversion to products, the experiment was repeated using a more appropriate series of delays. The time for conversion of half of the reactants to the product, $t_{1/2}$, was measured directly by fitting the peak heights (integrals) to a monoeponential curve using the VNMR software (Varian VNMR software Version 4.3B). Errors were estimated to be ±0.5%.

2-(Propargylamino)benzoxazole (1). Propargylamine (5.50 g, 0.10 mol) and triethylamine (15.15 g, 0.15 mol) were mixed in dry acetonitrile (100 mL) and stirred at rt under a nitrogen atmosphere. A solution of 2-chlorobenzoxazole (15.35 g, 0.10 mol) in dry acetonitrile (40 mL) was added dropwise and the mixture refluxed. After 4 h, the mixture was cooled to rt and filtered. The filtrate was diluted with ethyl acetate, and the solvent was removed in vacuo. This gave an oil which was recrystallized from heptane (200 mL). The product was dried in a vacuum oven overnight at 45 °C: yield 9.3 g (94%), white solid; mp 118 °C; TLC (silica gel; dichloromethane/MeOH, 98:2) single spot at $R_f$ 0.5, was followed using a more appropriate series of delays. The time for the first 3 h of the experiment. For the remaining 12 h of the accumulation, spectra were acquired every 1 hour. If the series of preacquisition delays were inappropriate as evidenced by either faster or slower conversion to products, the experiment was repeated using a more appropriate series of delays. The time for conversion of half of the reactants to the product, $t_{1/2}$, was measured directly by fitting the peak heights (integrals) to a monoeponential curve using the VNMR software (Varian VNMR software Version 4.3B). Errors were estimated to be ±0.5%.

5-Chlorobenzoxazole-2-thione (18b). The procedure described for 18a was followed using 19b (7.2 g, 0.05 mol), potassium O-ethylxanthate (8.8 g, 0.055 mol), and pyridine (120 mL): yield 6.7 g (94%), tan powder; mp 259–262 °C dec; TLC (silica gel; dichloromethane/MeOH, 95:5) major spot at Rt 0.70, minor spot at Rt 0.40; $^1$H NMR (DMSO-d$_6$, 7.2 (m, 1 H), 7.4 (1 H), 7.7 (d, 1 H).

2,5-Dichlorobenzoxazole (17b). The procedure described for 17a was followed using 18b (4.6 g, 0.025 mol), phosphorus pentachloride (5.2 g, 0.025 mol), and dry acetonitrile (40 mL). This gave a white solid; mp 109 °C; TLC (silica gel; dichloromethane/ethyl acetate, 98:2) single spot at $R_f$ 0.90, trace spot at Rt 0.70; $^1$H NMR (CDCl$_3$) 7.1 (d, 1 H), 7.4 (1 H), 7.7 (d, 1 H).

45-Dichloro-2-nitrophenol (20c). The nitrophenol (16.3 g, 0.10 mol) was dissolved in glacial acetic acid (100 mL); the solution was stirred and heated to 40 °C. A solution of 90% nitric acid (9.1 g, 0.13 mol) in glacial acetic acid (30 mL) was added dropwise at a rate such that the pot temperature was maintained between 50 and 55 °C. The mixture was stirred for 0.5 h at rt and poured into ice–water (500 mL). The aqueous mixture was filtered and the collected solid washed with water and air-dried in the hood overnight at rt. This gave a yellow solid that showed two major spots on TLC (silica gel; dichloromethane/ethyl acetate, 98:2) at Rt 0.90 and 0.10. The crude product was chromatographed on silica gel using dichloromethane/ethyl acetate (98:2) as the eluant. The fractions containing the Rt 0.90 component were combined, and the solvent was removed in vacuo. This gave an oil which solidified on standing: yield 8.2 g (39%), yellow solid; mp 63–65 °C; TLC (as above) major spot at Rt 0.90, trace spot at Rt 0.50; $^1$H NMR (CDCl$_3$) 7.1 (s, 1 H), 8.2 (s, 1 H), 10.45 (s, O H).

2-Amino-4,5-dichlorophenol (19c). The nitrophenol (7.5 g, 0.036 mol) was mixed with glacial acetic acid (100 mL) and water (10 mL), stirred, and heated to reflux. Iron powder (10.1 g, 0.18 mol) was added in portions over 15 min (exothermic). After the addition, the mixture was heated for 10 min and immediately filtered through a Celite pad. The filtrate was poured into ice–water (500 mL). The aqueous mixture was extracted three times with ethyl acetate, and the extracts were combined, washed three times with 5% sodium bicarbonate solution and three times with saturated NaCl solution, and then dried over magnesium sulfate and filtered. The solvent was removed in vacuo and the residue dried in a vacuum oven at rt overnight: yield 5.6 g (82%), white powder; mp 218–220 °C dec; TLC (silica gel; dichloromethane/
MeOH, 95:5) major spot at Rf 0.40, trace spot at Rf 0.35; 1H NMR (DMSO-d6) 7.5 (s, 1 H), 8.0 (s, 1 H), 8.4 (d, 1 H).

2-Chloro-5-tribenzoazoles (5). The thione 18c (5.5 g, 0.025 mol) and thionyl chloride (25 mL) were mixed under nitrogen. Two drops of DMF were added, and the mixture was heated to 65–70 °C for 0.5 h. The dark brown solution was cooled to rt and diluted with dichloromethane (150 mL). The solvent and excess thionyl chloride were removed on a rotary evaporator. The solid residue was air-dried in the hood at rt for 1 h: yield 5.5 g (98%), brown solid; TLC (silica gel; dichloromethane/MeOH, 96:4) showed that Rf 0.30; 1H NMR (CDCl3) 7.65 (s, 1 H), 7.80 (s, 1 H). Anal. Calc. for C13H7N2O2: C, 59.0; H, 2.5; N, 11.4; Cl, 28.4.

5-Cyano-2-(propargylamino)benzoazole (5). The procedure described for compound 4 was used with 17d (4.0 g, 0.022 mol), propargylamine (1.3 g, 0.022 mol), and thionyl chloride (3.6 g, 0.025 mol). TLC (silica gel; dichloromethane/MeOH, 96:4) of the crude product showed a major spot at Rf 0.50, a minor spot at Rf 0.40, and trace spots at Rf 0.90, 0.60, 0.35. This solid was chromatographed on silica gel using dichloromethane/MeOH (96:4) as the eluant. The fractions containing the Rf 0.50 component were combined, and the solvent was evaporated. The residue was recrystallized from 120 mL of toluene/MeOH, 95:5) major spot at Rf 0.90, minor spot at Rf 0.35; 1H NMR (CDCl3) 2.4 (t, 1 H), 3.95 (s, 3 H), 4.3 (d, 1 H). Anal. Calc. for C11H11N2O2: C, 62.5; H, 4.5; N, 12.5; O, 12.0. Found: C, 62.5; H, 4.5; N, 12.5.
acetonitrile (65:15) and dried in a vacuum oven at rt over a weekend: yield 1.3 g (21%), beige powder; mp 189--192 °C. TLC (silica gel; dichloromethane/MeOH, 98:2) major spot at Rf 0.25 (t, 1 H), 3.1 (s, 3 H), 4.2 (d, 2 H), 6.6 (bs, NH), 7.5 (d, 1 H), 7.65 (d of d, 1 H), 7.85 (d, 1 H). Anal. Calcld for C11H10N2O: C, 63.3; H, 4.8; N, 13.2. 

2-Amino-4-methoxyphenol (19g). The nitrophenol 20g (10.0 g, 0.059 mol) and palladium on charcoal (10%, 0.20 g) were mixed with ethanol (100 mL) and ethyl acetate (100 mL). The mixture was hydrogenated on a Parr shaker apparatus at rt until hydrogen uptake ceased. The mixture was filtered, and the solvent was removed. The residue was recrystallized from ethanol/ethyl acetate (95:5) as the eluant. The main component were combined, and the solvent was removed. The product was recrystallized from ethyl acetate/ether (1:1): yield 3.4 g (57%), white crystals; mp 126--128 °C; H NMR (CDCl3) 1.8 (t, 3 H), 2.3 (t, 3 H), 4.3 (q, 2 H), 6.9 (d, 1 H), 7.3 (t, 1 H), 7.4 (d, 1 Hz). Anal. Calcld for C7H10NO: C, 77.4; H, 4.9; N, 13.9.

5-Methoxybenzoxazole-2-thione (18g). The procedure described for 18c was followed using 19g (7.5 g, 0.054 mol), potassium O-ethylxanthylate (9.4 g, 0.059 mol), and pyridine (125 mL); yield 9.3 g (95%), beige powder; mp 133--135 °C dec; TLC (silica gel; dichloromethane/MeOH, 98:2) major spot at Rf 0.30, trace spot at Rf 0.35; H NMR (CDCl3) 3.65 (s, 3 H), 4.0 (bs, NH2), 6.1 (d of d, 1 H), 6.25 (bs, OH), 6.3 (d, 1 H), 6.6 (d, 1 H).

5-Methoxybenzoxazole (19g). The procedure described for compound 1 was followed using 20g (4.6 g, 0.025 mol), thionyl chloride (25 mL), and DMF (two drops): yield 4.5 g (97%), green solid; mp 177--179 °C; TLC (silica gel, dichloromethane) major spot at Rf 0.45, minor spot at the origin; H NMR (CDCl3) 3.65 (s, 3 H), 6.75 (d, 1 H), 6.8 (d of d, 1 H), 7.4 (d, 1 H). Anal. Calcld for C7H7NO: C, 71.98; H, 5.54; N, 13.99. Found: C, 71.81; H, 5.44; N, 13.90.

2-Chloro-5-methoxybenzoxazole (17g). The procedure described for compound 17c was employed with 18g (4.6 g, 0.025 mol), thionyl chloride (25 mL), and DMF (two drops): yield 4.5 g (97%), green solid; mp 177--179 °C; TLC (silica gel, dichloromethane) major spot at Rf 0.40, trace spot at Rf 0.50; H NMR (DMSO-d6) 3.8 (s, 3 H), 7.6 (d, 1 H).

5-Methoxy-(2-propargylamino)benzoxazole (8). The 2-chlorobenzoxazole 17g (4.5 g, 0.025 mol) was mixed with dry acetonitrile (20 mL) and stirred at rt under nitrogen. A solution of propargylamine (1.4 g, 0.025 mol) in dry acetonitrile (20 mL) was added dropwise followed by dropwise addition of a solution of triethylamine (3.8 g, 0.038 mol) in dry acetonitrile (20 mL). The mixture was heated to reflux for 2 h, cooled to rt, and poured into ethyl acetate (150 mL). The mixture was chilled on ice and filtered, and the filtrate was washed twice with water, dried over magnesium sulfate, and filtered. The solvent was removed from the filtrate and the residue recrystallized from ether/lignin: yield 0.52 g (31%), beige solid; mp 113--136 °C; H NMR (CDCl3) 4.45 (s, 2 H), 7.1 (t, 1 H), 7.2 (t, 1 H), 7.35 (m, 5 H). Anal. Calcld for C11H10N2O: C, 77.4; H, 4.9; N, 11.3. Found: C, 77.0; H, 5.3; N, 11.1.

2-(1,1-Dimethylpropargyl)amino)benzoxazole (13). A mixture of 1,1-dimethylpropargylamine (90%, 3.7 g, 0.040 mol) and 2-chlorobenzoxazole (3.1 g, 0.020 mol) under nitrogen was heated to reflux for 4 h. The solution was cooled and the solvent removed. The residue was recrystallized from ethyl acetate/ether (1:1): yield 0.45 g (9%), fluffly crystals; mp 132--134 °C; TLC (as above) 0.40 and 0.45. The crude product was chromatographed on silica gel using dichloromethane/MeOH (98:2) as the eluant. The fractions containing the Rf 0.40 component were combined and concentrated. The residue was heated with stirring to 65--70 °C for 17 h. The resulting semisolid was stirred with ethyl acetate (100 mL), filtered, and dried over magnesium sulfate. The mixture was filtered, and the solvent was removed. The residual yellow oil showed TLC (silica gel; dichloromethane/MeOH, 98:2) a major spot at Rf 0.40, a minor spot at Rf 0.10, and traces spots at Rf 0.90 and 0.45. The crude product was chromatographed on silica gel using dichloromethane/MeOH (98:2) as the eluant. Fractions containing the major component were combined and concentrated. The residue was redissolved in boiling ligroin (bp 90--110 °C): yield 2.6 g (0.030 mol) and the p-toluenesulfonate salt of 1-amino-2-butyne (7.2 g, 0.030 mol) were mixed in dry acetonitrile (100 mL). The mixture was heated to reflux for 4 h. The solution was cooled and the solvent removed. The residue was recrystallized from dichloromethane/ethyl acetate (95:5) as the eluant. The fractions containing the major component were combined, and the solvent was removed. The product was recrystallized from ethyl acetate/ether (1:1): yield 3.3 g (57%), white crystals; mp 126--128 °C; H NMR (CDCl3) 1.8 (t, 3 H), 2.3 (t, 3 H), 4.3 (q, 2 H), 6.9 (d, 1 H), 7.3 (t, 1 H), 7.4 (d, 1 Hz). Anal. Calcld for C7H10NO: C, 77.4; H, 4.9; N, 11.3. Found: C, 77.0; H, 5.3; N, 11.1.

2-(Butylaminol)benzothiazole (15). A mixture of 2-chlorobenzothiazole (3.38 g, 0.02 mol), p-toluenesulfonate salt of 1-amino-2-butyne (4.8 g, 0.02 mol), triethylamine (4.0 g, 0.04 mol), and dry acetonitrile (50 mL) was heated to reflux with stirring under nitrogen. After 72 h, the mixture was cooled and the solvent evaporated. The residue was extracted with dichloromethane. After concentration, this solution was chromatographed on silica gel using dichloromethane/ethyl acetate (95:5) as the eluant. Fractions containing the major component were combined, and the solvent was removed. The residue was recrystallized from boiling ligroin (bp 90--110 °C): yield 0.35 g (9%), fluffy crystals;
mp 125–126 °C; 1H NMR (CDCl3) 1.8 (t, 3 H), 4.2 (q, 2 H), 7.15 (t, 1 H), 7.3 (t, 1 H), 7.5 (d, 1 H), 7.7 (d, 1 H). Anal. Calcd for C7H10N2O: C, 71.0; H, 5.4; N, 15.0. Found: C, 71.05; H, 4.98; N, 13.85. 

2-(Propargylamino)benzoselenazole (16). 2-Mercaptobenzoselenazole (20 g, 0.093 mol) was added in portions to sulfur monochloride (30.0 g, 0.22 mol) with stirring. After filtration, the mixture was heated to reflux for 1 h. The sulfur monochloride (30.0 g, 0.22 mol) with stirring. After

The reaction flask was chilled overnight: yield 1.66 g (48%), white solid; mp 58 °C; 1H NMR (CD3CN) 2.55 (t, 1 H), 4.25 (d, 2 H), 6.4 (bs, NH), 6.8 (d of t, 1 H), 7.2 (d, 1 H), 7.35 (2 overlapping d, 2 H). 

2-(Alllylamino)benzoselenazole (23). The same procedure for preparation of compound 1 was followed using 2-chlorobenzoselenazole (3.07 g, 0.02 mol), N-methylpropargylamine (1.38 g, 0.02 mol), triethylamine (3.03 g, 0.03 mol), and dry acetonitrile (45 mL). The crude product was recrystallized from heptane (40 mL): yield 2.30 g (62%), white powder; mp 67 °C; 1H NMR (CD3CN) 2.26 (3d, 3 H), 4.33 (2q, 2 H), 4.76 (2q, 2 H), 6.65 (2q, 2 H), 7.25 (2d, 2 H), 7.35 (s, 1 H). 

2-(Propargylamino)3-methylbenzoxazolium Hexafluorophosphate (25). Compound 1 (0.861 g, 0.005 mol) was refluxed in methyl iodide (10 mL) for 25 h. Excess methyl iodide was evaporated and the residue triturated with ether, yield 0.76 g (48%). To an aqueous solution of this material was added a saturated solution of potassium hexafluorophosphate. The precipitate was collected and dried: 1H NMR (CD3CN) 3.1 (s, 3 H), 4.45 (m, 2 H), 5.2 (d of t, 1 H), 6.8 (d of t, 1 H), 7.2 (d, 1 H), 7.75 (d of d, 1 H). The authors also wish to thank Michael R. Detty and Stephen A. Godleski for reading the manuscript.

Acknowledgment. The authors thank Eastman Kodak Company Analytical Technology Division for combustion analyses. The authors are grateful to C. Y. Chen for the preparation of compounds 10, 11, 12, and 15. The authors also wish to thank Michael R. Detty and Stephen A. Godleski for reading the manuscript.