Facile Rearrangements of Alkynylamino Heterocycles with Noble Metal Cations

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A number of 2-(alkynylamino)-substituted heterocycles have been synthesized. These heterocycles rearrange in the presence of silver(I) and gold(I) salts to give novel 2*H*-pyrimido[2,1-*b*]benzoxazoles, 2*H*-pyrimido[2,1-*b*]benzothiazoles, and a 2*H*-pyrimido[2,1-*b*]benzoselenazole. Two of the the 2*H*-pyrimido[2,1-*b*]benzoxazoles were isolated in good yield. The kinetics of the silver tetrafluoroborate-catalyzed rearrangements of selected (alkynylamino)benzoxazoles and benzothiazoles have been examined by ^{1}H NMR in CD_3CN. 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.

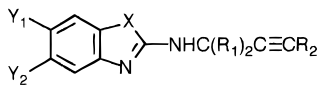
Introduction

The utility of metal ions in the reaction of alkynes is well known. These reactions include the conversion of alkynes to either aldehydes or ketones in the presence of mercuric ion salts[1] and a number of rearrangement reactions.[2] Mercuric acetate is observed to catalyze the rearrangement of acetylenic thioethers leading to nitrogen and sulfur heterocycles.[3] Cu(I) ions have been employed for the rearrangement of acetylenic halides to their isomeric allenes.[4] Landor and Landor showed the rearrangement of acetylenic esters to acetoxyallenes in the presence of zinc salts.[5] A propargylaniline was reported to give a quinoline compound in the presence of a catalytic amount of cuprous chloride.[6]

Silver-catalyzed rearrangements of acetylenes are perhaps the most common. Silver perchlorate has been employed in a facile synthesis of steroidal allenes from the corresponding acetylenic steroids in refluxing acetone.[7] Silver ions catalyze the rearrangement of acetylenic esters to their allenic esters.[8] The rearrangement of propargyl phenyl ethers, catalyzed by silver ion, has been described by Schmid and co-workers.[9] Thus, the use of metal cations has facilitated the conversion of acetylenic compounds to a variety of products, which would have been difficult to obtain. But, to date, no noble metal-catalyzed reactions of acetylenic amines have been reported.

In this paper, we report the rearrangement of heterocyclic acetylenic amines in the presence of silver(I) and gold(I) salts. These rearrangements have led to the synthesis of novel dihydropyrimidines.

Table 1. Alkynylamino Heterocycles Prepared from 2-Chlorobenzazoles and Alkynylamines



compd	X	R_1	R_2	Y_1	Y_2
1	O	H	H	H	H
2	O	H	H	H	Me
3	O	H	H	H	Cl
4	O	H	H	Cl	Cl
5	O	H	H	H	CN
6	O	H	H	H	CO_2Me
7	O	H	H	H	SO_2Me
8	O	H	H	H	OMe
9	O	H	Me	H	H
10	O	H	Me	H	Me
11	O	H	Me	H	CN
12	O	H	Ph	H	H
13	O	Me	H	H	H
14	S	H	H	H	H
15	S	H	Me	H	H
16	Se	H	H	H	H

Results and Discussion

Preparation of Alkynylamino Heterocycles. The compounds investigated in this study are 2-(alkynylamino)-substituted benzoxazoles, benzothiazoles, and a benzoselenazole **1**−**16** (see Table 1). The (alkynylamino)-benzoxazoles were prepared by treatment of the substituted 2-chlorobenzoxazoles **17** with an alkynylamine in the presence of triethylamine (see Scheme 1). The 2-chlorobenzoxazoles were made by treatment of thiones **18** with either phosphorus pentachloride or with thionyl chloride. The thiones, in turn, were obtained from *o*-aminophenols **19** with potassium *O*-ethylxanthate in refluxing pyridine.

The aminophenols **19a** and **19b** are commercially available; **19e** and **19f** were obtained from Eastman Kodak Company Synthetic Chemicals Division. Other aminophenols were made from their corresponding nitrophenols by either catalytic reduction or conversion with iron in acetic acid. 4,5-Dichloro-2-nitrophenol (**20c**) and 4-cyano-2-nitrophenol (**20d**) were prepared by nitration of 3,4-dichlorophenol and of 4-hydroxybenzonitrile. 4-Methoxy-2-nitrophenol (**20g**) resulted from mild nitra-

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(1) For reviews, see: Martell, A. E.; Khan, M. M. T. *Homogeneous Catalysis by Metal Complexes*; Academic: New York, 1974; Vol. 2, pp 91−95.

(2) See review by: Theron, F.; Verny, M.; Vessiere, R. In *Rearrangements Involving Acetylenes*; Patai, S., Ed.; The Chemistry of the Carbon−Carbon Triple Bond, Part 1; John Wiley and Sons: New York, 1978; Chapter 10.

(3) Balasubramanian, K. K.; Nagarajan, R. *Synthesis* **1976**, 189.

(4) Hennion, G. F.; Sheehan, J. T.; Maloney, D. E. *J. Am. Chem. Soc.* **1950**, *72*, 3542.

(5) Landor, P. D.; Landor, S. R. *J. Chem. Soc.* **1956**, 1015.

(6) Easton, N. R.; Cassady, D. R. *J. Org. Chem.* **1962**, *27*, 4714.

(7) Benn, W. *J. Org. Chem.* **1968**, *33*, 3113.

(8) Verny, M.; Vessiere, R. *Bull. Soc. Chim. Fr.* **1969**, *5*, 1729. Ramakrishnan, V. T.; Narayanan, K. V.; Swaminathan, S. *Chem. Ind.* **1967**, 2082.

(9) Koch-Pomeranz, U.; Hansen, H. J.; Schmid, H. *Helv. Chem. Acta* **1973**, *56*, 2981−3004.

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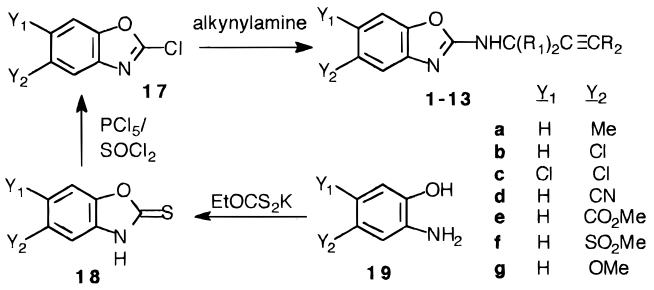
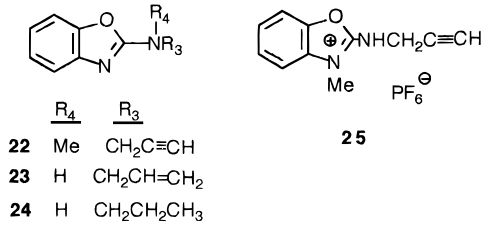
Scheme 1



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*-toluenesulfonate salt of 1-amino-2-butyne. 2-Chlorobenzoselenazole (**21**) was synthesized from 2-mercaptobenzoselenazole 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



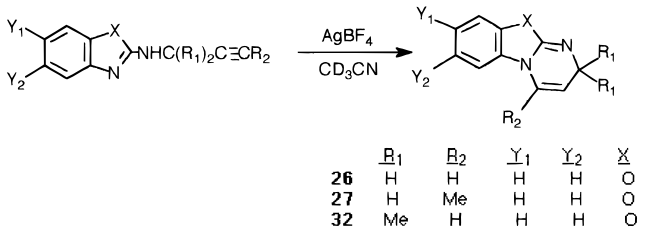
with the respective amines, *N*-methylpropargylamine and allylamine. Catalytic reduction of **23** provided 2-(propylamino)benzoxazole (**24**). The quaternary salt 2-(propargylamino)-3-methylbenzoxazolium hexafluorophosphate (**25**) was obtained by refluxing **1** with excess methyl iodide and subsequent 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*-propargylnaphthylamines undergo thermal Claisen rearrangement reactions at 250 °C to give mixtures of benzoquinolines and tetrahydrobenzoquinolines.[13] Iwai and Hirsoka[14,15] 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 propargylic methylene 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 ^{1}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 (k_{obs}) 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-butynyl 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 Y_2 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 unsubstitiuted 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 D_2O, the dihydropyrimidine **28**, whose vinyl protons are replaced with deuterium, was obtained. In

(10) Robertson, R.; Smith, J. C. *J. Chem. Soc.* **1926**, 392.
(11) MacInnes, I.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1077.
(12) Gensler, W. J.; Rockett, J. C. *J. Am. Chem. Soc.* **1955**, *77*, 3264.
(13) Scheurer, H.; Zsindely, J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 478.
(14) Iwai, I.; Hirsoka, T. *Chem. Pharm. Bull.* **1963**, *11*, 1564.
(15) Iwai, I.; Hirsoka, T. *Chem. Pharm. Bull.* **1964**, *12*, 813.

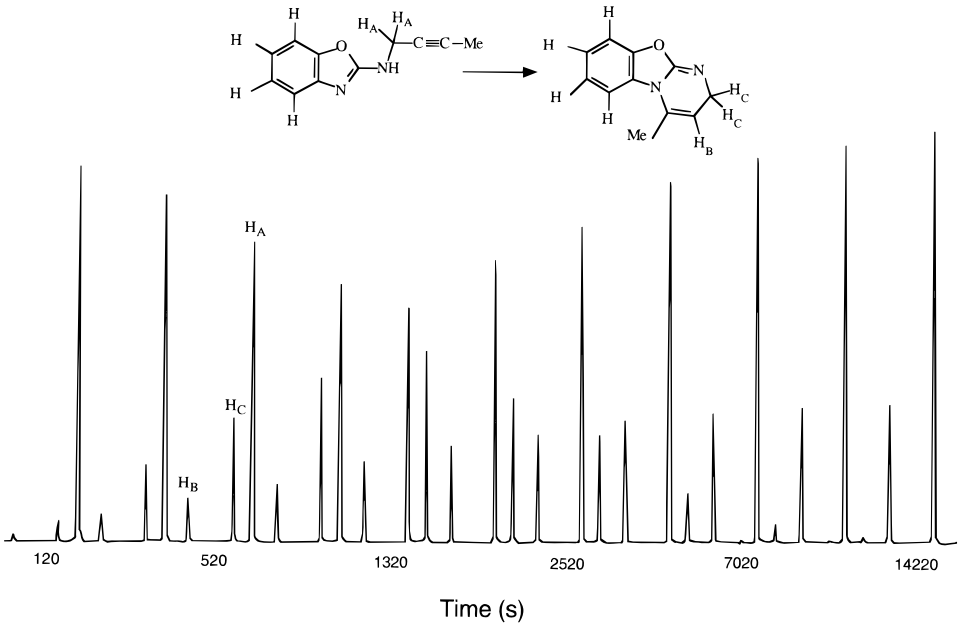


Figure 1. Expansions of the proton NMR spectra of 2-(butynylamino)benzoxazole (**9**) as a function of time during the cyclization reaction.

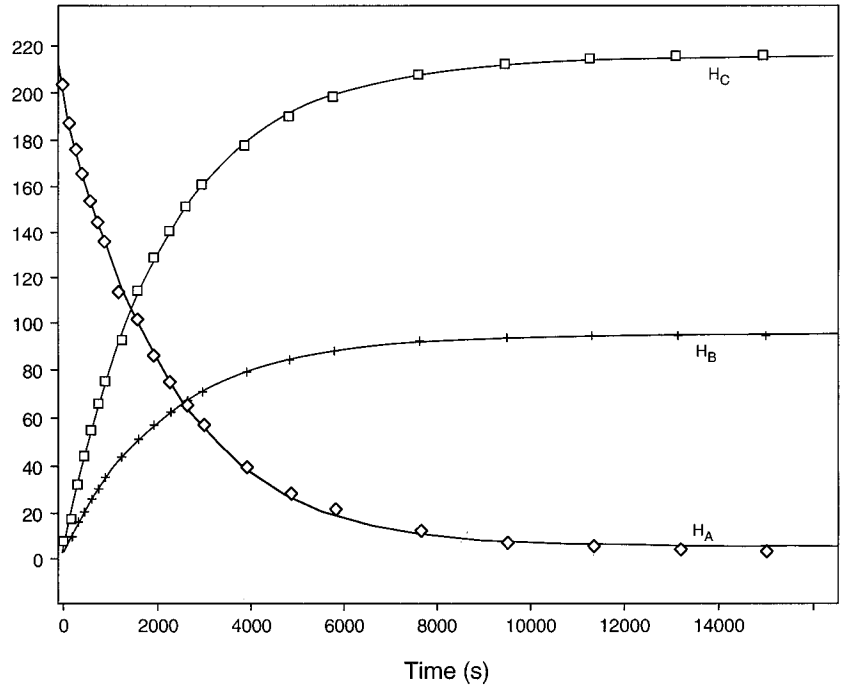
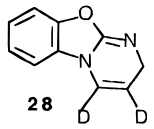


Figure 2. First-order growth and decay curves extracted from the spectra as illustrated in Figure 1.

the absence of the silver catalyst, only the NH proton in **1** exchanged with deuterium.



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Rearrangement with Gold Salts. Aurous bis(pentamethylene sulfide) tetrafluoroborate[16] catalyzed the rearrangement of **9** to the dihydropyrimidine **27** readily in nitromethane. The k_{obs} for this reaction, 24.40×10^{-4}, is nearly identical to the k_{obs}, 24.57×10^{-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[17] in 1986. The methods of preparation generally involve formation of the pyrim-

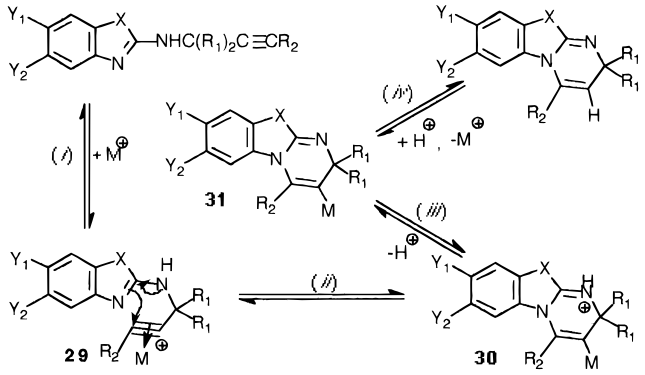
(16) Prepared as per the method of Hill, D. T. US Patent 4,165,380, 1979.

(17) Weis, A. L.; van der Plas, H. C. *Heterocycles* **1986**, *24*, 1433.

Table 2. Ring Closure Rates, k_{obs}, of Silver-Catalyzed (Alkynylamino)benzoxazoles

compd	k (s^{-1}) × 10^4	$k_{rel} = k_{butynyl}/k_{propargyl}$
1	1.43	5.38
9	7.70	
2	1.80	4.58
10	8.25	
5	0.60	2.72
11	1.63	
14	6.42	1.0
15	6.42	
12	1.58	
13	38.50	
22	0.95	

Scheme 2



X, Y_1, Y_2, R_1, R_2 are as previously defined; M = Ag, Au.

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. Dihydroheteroaroamatics, 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-2*H*-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, 2*H*-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, 2*H*-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, Y_1, Y_2, R_1, and R_2, 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.

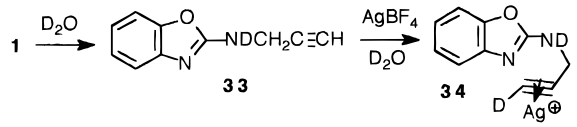
Compound **13** with a *gem*-dimethyl group exhibits the fastest rate of rearrangement. This rate enhancement may be due to the "*gem*-dialkyl effect" proposed by Allinger and Zalkow in terms of enthalpies and entropies of open-chain *vs* ring compounds.[20] That is, the *gem*-dimethyl chain in **13** 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**.

(18) Richardson, A., Jr.; McCarty, F. J. *J. Med. Chem.* **1972**, *15*, 1203. Alaimo, R. *J. Heterocycl. Chem.* **1973**, *10*, 769. Wade, J. J.; Hegel, R. F.; Toso, C. B. *J. Org. Chem.* **1979**, *44*, 1811; *Yakugaku Zasshi* **1968**, *88*, 1003. In the patent literature: Swiss 526,575 and S. African, 6,707,053.

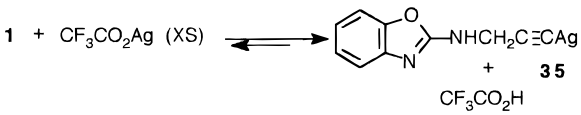
(19) Singh, A; Bahl, A. *Indian J. Chem.* **1969**, *7*, 302. Kost, A. N.; Golubeva, G. A.; Sviridova, L. A. *Khim. Geterotsikl. Soedin.* **1973**, *4*, 495; *Chem. Abstr.* **1973**, *79*, 18623w. In the patent literature: USSR 366,197 and US 4,471,117.

(20) Allinger, N. L.; Zalkow, V. J. *J. Org. Chem.* **1960**, *25*, 701.

The deuterium-labeling experiment is also consistent with Scheme 2. Initial exchange of the amino proton by deuterium 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 deuterium 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 dideuterated material **28**.

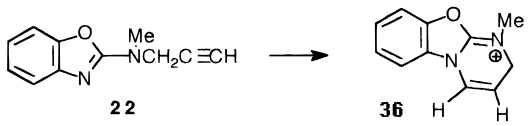


The appearance of only a minor amount of cyclization product from **1** in the presence of excess silver trifluoroacetate can be understood in terms of the equilibrium shown below. Excess trifluoroacetate, a weakly basic



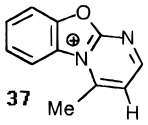
anion, causes deprotonation of the terminal proton and forces the equilibrium toward the right with formation of a silver acetylide **35** and trifluoroacetic acid. A similar interaction between an alkyne and metal ion has been suggested in the dissociation of a proton and the formation of an acetylide.[21] 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_2O 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(pentamethylenesulfide) 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]

$$Au^+ + e^- \rightarrow Au^0 \qquad 1.692\ V$$

$$Ag^+ + e^- \rightarrow Ag^0 \qquad 0.799\ V$$

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 alkyne terminus, 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 ^{13}C. TMS was used as an internal standard, and chemical shifts are reported as δ values (ppm from TMS). All kinetics measurements were obtained at 300 MHz and at 40 °C using a 5 mm four-nucleus probe (^1H, ^{13}C, ^{19}F, and ^{31}P). The acquisition conditions were

(21) See review by: Martell, A. E.; Khan, M. M. T. In *Oxidation of Alkenes and Alkynes*; Academic: New York, 1974; Homogeneous Catalysis by Metal Complexes, Vol. I, Chapter 5.

(22) Values from *Handbook of Chemistry and Physics*, 73rd ed.; Lide, D. R., Ed.-in Chief; CRC: Boca Raton, 1992−1993.

a sweep width of 5800 Hz digitized using 16K points following an acquisition time of 1.412 s with a recycle delay of 1 s and a 40 °C pulse width.

Typical reactant concentrations were 2:1 benzazole:silver tetrafluoroborate 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 tetrafluoroborate 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 accumulating the series of NMR spectra required to characterize the kinetics for conversion. For studies with aurous bis(pentamethylenesulfide) tetrafluoroborate, deuterated nitromethane was used as the reaction solvent.

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, then the experiment was repeated using a more appropriate series of delays. The time for conversion of half of the reactants to the product, $t_{0.5}$, was measured directly by fitting the peak heights (integrals) to a monoexponential curve using the VNMR software (Varian VNMR software Version 4.3B). Errors were estimated to be ±2.5%.

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, washed once with saturated NaCl solution, dried over magnesium sulfate, and filtered. The solvent was evaporated and the residue recrystallized from heptane (200 mL). The product was dried in a vacuum oven overnight at 45 °C: yield 9.3 g (54%), white solid; mp 118−120 °C; TLC (silica gel; dichloromethane/MeOH, 98:2) single spot at R_f 0.50; ^{1}H NMR (CD_3CN) 2.5 (t, 1 H), 4.2 (d, 2 H), 5.2 (bs, NH), 7.05 (m, 1 H). 7.2 (m, 1 H), 7.3 (m, 2 H). Anal. Calcd for $C_{10}H_8N_2O$: C, 69.8; H, 4.7; N, 16.3. Found: C, 69.5; H, 5.0; N, 16.3.

5-Methylbenzoxazole-2-thione (18a). A mixture of **19a** (12.3 g, 0.10 mol) and potassium *O*-ethylxanthate (17.6 g, 0.11 mol) in pyridine (100 mL) was stirred and heated to reflux for 2 h. It was cooled to rt and poured into a mixture of ice−water (400 mL) and concentrated hydrochloric acid (40 mL). The solid was collected, washed with water, and dried in the hood overnight and then in a vacuum oven at 45 °C for several hours: yield 16.0 g (97%), beige powder; mp 220−223 °C; TLC (silica gel; dichloromethane/MeOH, 98:2) single spot at R_f 0.60; ^{1}H NMR (DMSO-d_6) 2.4 (s, 3 H), 7.0 (m, 2 H), 7.3 (d, 1 H).

2-Chloro-5-methylbenzoxazole (17a). The thione **18a** (4.1 g, 0.025 mol) and phosphorus oxychloride (40 mL) were mixed under nitrogen. Phosphorus pentachloride (5.2 g, 0.025 mol) was added in one portion and the mixture heated to 95−100 °C for 2.5 h. The mixture was cooled to rt, excess phosphorus oxychloride was removed, and the residue was vacuum distilled through a short-path distilling head: yield 3.1 g (74%), pale yellow liquid; bp 120−122 °C/24 mm Hg; TLC (silica gel, dichloromethane) single spot at R_f 0.70; ^{1}H NMR ($CDCl_3$) 2.4 (s, 3 H), 7.05−7.40 (m, 3 H).

5-Methyl-2-(propargylamino)benzoxazole (2). Propargylamine (0.98 g, 0.0179 mol) and triethylamine (2.5 g, 0.025 mol) in dry acetonitrile (30 mL) were similarly treated with **17a** (3.0 g, 0.0179 mol) in dry acetonitrile (20 mL) as for the preparation of **1**. The tan residue left after evaporation of the solvent showed a major spot on TLC (silica gel; dichloromethane/MeOH, 98:2) at R_f 0.40 and minor spots at R_f 0.50 and 0.90. 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 in vacuo. The residue was dried in a vacuum oven at rt overnight: yield 1.9 g (58%), white powder; mp 109−112 °C; ^{1}H NMR (CD_3CN) 2.3 (t, 1 H), 2.4 (s, 3 H), 4.3 (d, 2 H), 5.6 (bs, NH), 6.9 (d, 1 H), 7.15 (d of d, 1 H), 7.25 (d, 1 H). Anal. Calcd for $C_{11}H_{10}N_2O$: C, 71.0; H, 5.4; N, 15.0. Found: C, 70.7; H, 5.4; N, 14.9.

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 8.7 g (94%), tan powder; mp 259−262 °C dec; TLC (silica gel; dichloromethane/MeOH, 95:5) major spot at R_f 0.60, trace spot at R_f 0.55; ^{1}H NMR (DMSO-d_6) 7.2 (m, 2 H), 7.4 (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 phosphorus oxychloride (40 mL): yield 1.4 g (30%), yellow liquid; bp 141−143 °C/24 mmHg; TLC (silica gel, dichloromethane) major spot at R_f 0.70, minor spot at R_f 0.40; ^{1}H NMR ($CDCl_3$) 7.4 (d of d, 1 H), 7.45 (d, 1 H), 7.7 (d, 1 H).

5-Chloro-2-(propargylamino)benzoxazole (3). The procedure described for compound **2** was followed using **17b** (1.3 g, 0.0069 mol), propargylamine (0.38 g, 0.0069 mol), triethylamine (1.0 g, 0.010 mol), and dry acetonitrile (40 mL). This gave a tan solid with a major spot on TLC (silica gel; dichloromethane/MeOH, 98:2) at R_f 0.40 and minor spots at R_f 0.90 and 0.60. The crude product was chromatographed on silica gel using dichloromethane/MeOH (98:2) as the eluant: yield 0.90 g (63%), cream colored powder; mp 136−138 °C; ^{1}H NMR ($CDCl_3$) 2.4 (t, 1 H), 4.3 (d, 2 H), 5.85 (bs, NH), 7.0 (d of d, 1 H), 7.2 (d, 1 H), 7.4 (d, 1 H). Anal. Calcd for $C_{10}H_7ClN_2O$: C, 58.1; H, 3.4; N, 13.6; Cl, 17.2. Found: C, 57.9; H, 3.5; N, 13.4; Cl, 16.8.

4,5-Dichloro-2-nitrophenol (20c). 3,4-Dichlorophenol (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 R_f 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 R_f 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 R_f 0.90, trace spot at R_f 0.0; ^{1}H NMR ($CDCl_3$) 7.3 (s, 1 H), 8.2 (s, 1 H), 10.45 (s, O H).

2-Amino-4,5-dichlorophenol (19c). The nitrophenol **20c** (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 5.7 g (89%), dark powder; mp 147−150 °C dec; TLC (silica gel; dichloromethane/ethyl acetate, 98:2) major spot at R_f 0.20, trace spot at the origin; ^{1}H NMR (CD_3CN) 5.1 (bs, NH_2), 6.7 (s, 1 H), 6.8 (s, 1 H).

5,6-Dichlorobenzoxazole-2-thione (18c). The procedure described for **18a** was followed using **19c** (5.5 g, 0.031 mol), potassium *O*-ethylxanthate (5.6 g, 0.035 mol), and pyridine (105 mL). The crude product was isolated and dried as for **18a**. It was further stirred in warm water (200 mL) for 15 min (to remove traces of pyridine) and then the solid collected and washed with more water. The product was dried in a vacuum oven overnight at 45 °C: yield 5.6 g (82%), beige powder; mp 218−220 °C dec; TLC (silica gel; dichloromethane/

MeOH, 95:5) major spot at R_f 0.40, trace spot at R_f 0.35; ^{1}H NMR (DMSO-d_6) 7.5 (s, 1 H), 8.0 (s, 1 H).

2,5,6-Trichlorobenzoxazole (17c). 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) major spot at R_f 0.90, minor spot at R_f 0.85; ^{1}H NMR ($CDCl_3$) 7.65 (s, 1 H), 7.80 (s, 1 H).

5,6-Dichloro-2-(propargylamino)benzoxazole (4). A solution of propargylamine (1.2 g, 0.022 mol) in dry acetonitrile (20 mL) was added dropwise to a mixture of **17c** (5.5 g, 0.025 mol) in acetonitrile (25 mL) with stirring at rt under nitrogen. Then triethylamine (3.3 g, 0.033 mol) in dry acetonitrile (20 mL) was added and the mixture heated to 65−70 °C for 0.5 h. The mixture was cooled to rt, poured into ethyl acetate (250 mL), chilled on ice, and then filtered. The filtrate was washed once with saturated NaCl solution and dried over magnesium sulfate. The mixture was filtered and concentrated in vacuo. This gave a dark brown semisolid that showed two major spots on TLC (silica gel; dichloromethane/MeOH, 98:2) at R_f 0.60 and 0.40. The crude product was chromatographed on silica gel using dichloromethane/MeOH (98:2) as the eluant. Fractions containing the R_f 0.60 component were combined, and the solvent was evaporated: yield 0.80 g (15%), white fluffy solid; mp 136−138 °C; TLC (as above) major spot at R_f 0.60, trace spot at R_f 0.40; ^{1}H NMR (CD_3CN) 2.55 (t, 1 H), 4.2 (d, 2 H), 6.55 (bs, NH), 7.45 (s, 1 H), 7.50 (s, 1 H). Anal. Calcd for $C_{10}H_6Cl_2N_2O$: C, 49.8; H, 2.5; N, 11.6; Cl, 29.4. Found: C, 49.3; H, 2.5; N, 11.4; Cl, 28.4.

4-Cyano-2-nitrophenol (20d). A mixture of nitric acid (90%, 21.0 g, 0.030 mol) and glacial acetic acid (25 mL) was heated to 40 °C. To this mixture was added rapidly a solution of 4-hydroxybenzonitrile (25.0 g, 0.21 mol) in glacial acetic acid (100 mL) until the pot temperature rose to 50 °C. Then the solution was added at a rate such that the pot temperature was maintained between 50 and 60 °C. After the addition, the mixture was stirred for another 20 min at 55 °C and then poured into ice−water (600 mL). The aqueous mixture was filtered and the collected solid washed with water. The product was air dried in the hood at rt overnight: yield 31.9 g (93%), pale yellow powder; mp 142−145 °C; TLC (silica gel; dichloromethane/ethyl acetate, 95:5) single spot at R_f 0.50; ^{1}H NMR (DMSO-d_6) 7.2 (d, 1 H), 7.9 (d of d, 1 H), 8.4 (d, 1 H).

2-Amino-4-cyanophenol (19d). A mixture of **20d** (30.0 g, 0.18 mol), palladium on charcoal (10%, 0.30 g), ethanol (200 mL), and ethyl acetate (100 mL) was hydrogenated on a Parr shaker apparatus at rt until uptake of hydrogen ceased. TLC (silica gel; dichloromethane/ethyl acetate, 95:5) showed that all **20d** at R_f 0.50 was gone. The reaction mixture was transferred to a beaker, ethanol (400 mL) and ethyl acetate (100 mL) were added, and the mixture was warmed to 60 °C until the solid dissolved. The warm mixture was filtered and concentrated. The product was air dried in the hood for a few hours: yield 19.0 g (79%), tan powder; mp 153−156 °C dec; TLC (as above) major spot at R_f 0.40, trace spot at the origin; ^{1}H NMR (CD_3CN) 5.3 (bs, OH and NH_2), 6.8 (m, 3 H).

5-Cyanobenzoxazole-2-thione (18d). The procedure described for **18c** was employed with **19d** (13.4 g, 0.10 mol), potassium *O*-ethylxanthate (17.6 g, 0.11 mol), and pyridine (200 mL). The product was stirred in water (400 mL) at rt and filtered and the collected solid washed thoroughly with water. The product was dried in a vacuum oven at 40 °C for several hours: yield 15.2 g (86%), beige powder; mp 265−268 °C dec; TLC (silica gel; dichloromethane/MeOH, 95:5) major spot at R_f 0.40, trace spots at R_f 0.30 and the origin; ^{1}H NMR (DMSO-d_6) 7.7 (bs, 3 H).

2-Chloro-5-cyanobenzoxazole (17d). The procedure described for **17c** was used with **18d** (4.6 g, 0.026 mol), thionyl chloride (25 mL), and DMF (two drops): yield 4.5 g (98%), tan powder; TLC (silica gel; dichloromethane/MeOH, 98:2) major spot at R_f 0.90, minor spot at R_f 0.30; ^{1}H NMR (DMSO-d_6) 7.6 (d, 1 H), 7.9 (d of d, 1 H), 8.2 (d, 1 H).

5-Cyano-2-(propargylamino)benzoxazole (5). The procedure employed for compound **4** was used with **17d** (4.0 g, 0.022 mol), propargylamine (1.3 g, 0.022 mol), and triethylamine (3.3 g, 0.033 mol). TLC (silica gel; dichloromethane/MeOH, 96:4) of the crude product showed a major spot at R_f 0.50, a minor spot at R_f 0.40, and trace spots at R_f 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 R_f 0.50 component were combined, and the solvent was removed in vacuo. The residue was dried in a vacuum oven at rt overnight: yield 1.10 g (26%), beige powder; mp 190−193 °C; TLC showed a single spot at R_f 0.50; IR spectrum 2220 cm^{-1} (CN); ^{1}H NMR (CD_3CN) 2.6 (t, 1 H), 4.2 (d, 2 H), 6.6 (bs, NH), 7.3 (s, 2 H), 7.65 (s, 1 H). Anal. Calcd for $C_{11}H_7N_3O$: C, 67.0; H, 3.6; N, 21.3. Found: C, 66.3; H, 3.6; N, 21.2.

5-(Methoxycarbonyl)benzoxazole-2-thione (18e). The procedure described for compound **18a** was followed using **19e** (8.35 g, 0.05 mol), potassium *O*-ethylxanthate (8.8 g, 0.055 mol), and pyridine (85 mL): yield 9.6 g (96%), white powder; mp 219−222 °C; TLC (silica gel; dichloromethane/MeOH, 95:5) single spot at R_f 0.50; ^{1}H NMR (DMSO-d_6) 3.9 (s, 3 H), 7.5 (d, 1 H), 7.6 (d, 1 H), 7.8 (d of d, 1 H).

2-Chloro-5-(methoxycarbonyl)benzoxazole (17e). The procedure described for compound **17a** was employed using **18e** (5.2 g, 0.025 mol), phosphorus pentachloride (5.2 g, 0.025 mol), and phosphorus oxychloride (40 mL). After reaction, the mixture was filtered and the filtrate vacuum distilled: yield 1.8 g (34%), yellow liquid (solidified on standing, mp 104−106 °C); bp 160−163 °C/24 mmHg; TLC (silica gel; dichloromethane/MeOH, 98:2) single spot at R_f 0.80; ^{1}H NMR ($CDCl_3$) 4.0 (s, 3 H), 7.55 (d, 1 H), 8.1 (d of d, 1 H), 8.35 (d, 1 H).

5-(Methoxycarbonyl)-2-(propargylamino)benzoxazole (6). The procedure described for compound **2** was followed using propargylamine (0.42 g, 0.0076 mol), triethylamine (1.15 g, 0.011 mol), **17e** (1.6 g, 0.0076 mol), and dry acetonitrile (45 mL). The crude product was recrystallized from 40 mL of toluene/acetonitrile (90:10), washed with pentane, and dried in a vacuum oven at 40 °C for several hours: yield 1.10 g (63%), cream colored fluffy solid; mp 147−149 °C; TLC (silica gel; dichloromethane/MeOH, 98:2) single spot at R_f 0.35; ^{1}H NMR ($CDCl_3$) 2.4 (t, 1 H), 3.95 (s, 3 H), 4.3 (d, 2 H), 5.9 (bs, NH), 7.3 (d, 1 H), 7.85 (d of d, 1 H), 8.1 (d, 1 H). Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.6; H, 4.4; N, 12.2. Found: C, 62.5; H, 4.5; N, 12.5.

5-(Methylsulfonyl)benzoxazole-2-thione (18f). The aminophenol **19f** (9.4 g, 0.05 mol) and potassium *O*-ethylxanthate (8.8 g, 0.055 mol) were refluxed in pyridine (125 mL) for 3 h. The mixture was cooled and poured into a mixture of ice−water (500 mL) and concentrated hydrochloric acid (50 mL). The aqueous mixture was filtered and the product washed with water. The solid was dried and recrystallized from 500 mL of toluene/acetonitrile (75:25). The crystals were washed with pentane and dried in a vacuum oven at 40 °C: yield 6.5 g (57%), pale gray needles; mp 222−224 °C; TLC (silica gel; dichloromethane/MeOH, 95:5) major spot at R_f 0.35, trace spot at R_f 0.40; ^{1}H NMR (DMSO-d_6) 3.25 (s, 3 H), 7.65 (d, 1 H), 7.70 (d, 1 H), 7.80 (d of d, 1 H).

2-Chloro-5-(methylsulfonyl)benzoxazole (17f). The thione **18f** (3.5 g, 0.015 mol), thionyl chloride (25 mL), and DMF (2 drops) were reacted as for the preparation of **17c**: yield 3.5 g (100%), pale greenish yellow solid; TLC (silica gel; dichloromethane/MeOH, 96:4) major spot at R_f 0.70, trace spots at R_f 0.50, 0.40, and 0.0; ^{1}H NMR ($CDCl_3$) 3.15 (s, 3 H), 7.75 (d, 1 H), 8.0 (d of d, 1 H), 8.35 (d, 1 H).

5-(Methylsulfonyl)-2-(propargylamino)benzoxazole (7). The procedure described for compound **4** was used with **17f** (6.5 g, 0.028 mol), propargylamine (1.4 g, 0.025 mol), triethylamine (3.8 g, 0.038 mol), and dry acetonitrile (65 mL). The reaction gave a product whose TLC (silica gel; dichloromethane/MeOH, 96:4) showed a major spot at R_f 0.40, a minor spot at R_f 0.35, and several other minor spots. The material was chromatographed on silica gel using dichloromethane/MeOH (96:4) as the eluant. The fractions containing mainly the R_f 0.40 component were combined, and the solvent was evaporated. The residue was recrystallized from 120 mL of toluene/

acetonitrile (85:15) and dried in a vacuum oven at rt over a weekend: yield 1.3 g (21%), beige powder; mp 189−192 °C; TLC (as above) single spot at R_f 0.40; ^{1}H NMR (CD_3CN) 2.55 (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. Calcd for $C_{11}H_{10}N_2O_3S$: C, 52.8; H, 4.0; N, 11.2; S, 12.8. Found: C, 52.4; H, 4.1; N, 11.2; S, 11.8.

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, solvent removed, and the residue dried in a vacuum oven at rt: yield 7.6 g (93%), tan powder; mp 133−135 °C dec; TLC (silica gel; dichloromethane/MeOH, 98:2) major spot at R_f 0.30, trace spot at R_f 0.35; ^{1}H NMR (CD_3CN) 3.65 (s, 3 H), 4.0 (bs, NH_2), 6.1 (d of d, 1 H), 6.25 (bs, OH), 6.3 (d, 1 H), 6.6 (d, 1 H).

5-Methoxybenzoxazole-2-thione (18g). The procedure described for **18c** was followed using **19g** (7.5 g, 0.054 mol), potassium *O*-ethylxanthate (9.4 g, 0.059 mol), and pyridine (125 mL): yield 9.3 g (95%), beige powder; mp 212−215 °C dec; TLC (silica gel; dichloromethane/MeOH, 95:5) major spot at R_f 0.60, trace spot at R_f 0.50; ^{1}H NMR (DMSO-d_6) 3.8 (s, 3 H), 6.75 (d, 1 H), 6.8 (d of d, 1 H), 7.4 (d, 1 H).

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; TLC (silica gel, dichloromethane) major spot at R_f 0.45, minor spot at the origin; ^{1}H NMR ($CDCl_3$) 3.8 (s, 3 H), 6.9 (d of d, 1 H), 7.0 (d, 1 H), 7.3 (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 washed twice with saturated NaCl solution. The organic layer was dried over magnesium sulfate and filtered and the solvent removed on a rotary evaporator. This gave a dark brown solid whose TLC (silica gel; dichloromethane/MeOH, 98:2) showed a major spot at R_f 0.40 and minor spots at R_f 0.50 and 0.35. The crude product was chromatographed on silica gel using dichloromethane/MeOH (98:2) as the eluant. The fractions containing the R_f 0.40 component were combined and concentrated. This gave 1.1 g of beige solid, which exhibited a single spot on TLC under the conditions given above. When the product was checked using dichloromethane/MeOH (97:3) as the TLC solvent, two spots were present at R_f 0.40 and 0.45. The product was recrystallized from heptane (30 mL) several times and dried in a vacuum oven at rt: yield 0.25 g (5%), cream colored powder; mp 127−130 °C; TLC (dichloromethane/MeOH, 97:3) major spot at R_f 0.40, trace spot at R_f 0.45; ^{1}H NMR ($CDCl_3$) 2.35 (t, 1 H), 3.8 (s, 3 H), 4.3 (d, 2 H), 5.5 (bs, NH), 6.65 (d of d, 1 H), 7.0 (d, 1 H), 7.2 (d, 1 H). Anal. Calcd for $C_{11}H_{10}N_2O_2 + 0.25H_2O$: C, 63.9; H, 5.1; N, 13.6. Found: C, 63.3; H, 4.8; N, 13.2.

2-(2-Butynylamino)benzoxazole (9). The procedure described for compound **1** was followed using 2-chlorobenzoxazole (2.6 g, 0.017 mol), 1-amino-2-butyne (1.2 g, 0.017 mol), triethylamine (2.6 g, 0.026 mol), and dry acetonitrile (55 mL). The crude product was recrystallized three times from heptane (40−50 mL): yield 1.8 g (56%), white fluffy solid; mp 87−89 °C; TLC (silica gel; dichloromethane/ethyl acetate, 90:10) single spot at R_f 0.30; ^{1}H NMR ($CDCl_3$) 1.8 (t, 3 H), 4.3 (q, 2 H), 5.4 (bs, NH), 7.1 (t, 1 H), 7.2 (t, 1 H), 7.3 (d, 1 H), 7.4 (d, 1 H). Anal. Calcd for $C_{11}H_{10}N_2O + 0.25H_2O$: C, 69.3; H, 5.5; N, 14.7. Found: C, 69.5; H, 5.5; N, 14.8.

2-(2-Butynylamino)-5-methylbenzoxazole (10). Compound **17a** (5.0 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 stirred at rt under nitrogen while a solution of triethylamine (6.1 g, 0.060 mol) in dry acetonitrile (50 mL) was added. The mixture was heated to reflux for 3.5 h. The solvent was removed and the residue diluted with ethyl acetate (100 mL). The mixture was filtered, and the solvent was again removed. The residue was chromatographed on silica gel using 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 3.4 g (57%), white crystals; mp 126−128 °C; ^{1}H NMR (CD_3CN) 1.8 (t, 3 H), 2.3 (s, 3 H), 4.3 (q, 2 H), 6.9 (d, 1 H), 7.3 (s, 1 H), 7.4 (d, 1 H). Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.81; H, 5.95; N, 13.90.

2-(2-Butynylamino)-5-cyanobenzoxazole (11). The procedure described for **10** was followed using **17d** (8.9g, 0.050 mol), *p*-toluenesulfonate salt of 1-amino-2-butyne (12.0 g, 0.050 mol), triethylamine (10.1 g, 0.10 mol), and dry acetonitrile (100 mL). The reaction mixture was filtered through a silica gel plug. The solvent was removed and the residue dissolved in ethyl acetate (150 mL). A solid crystallized from the solution. The mixture was filtered, and the collected solid was dried: yield 3.7 g (35%); ^{1}H NMR (CD_3CN) 1.8 (t, 3 H), 4.2 (q, 2 H), 7.4 (s, 2 H), 7.6 (s, 1 H). Anal. Calcd for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.89. Found: C, 67.85; H, 4.48, N, 19.70.

2-((3-Phenylpropargyl)amino)benzoxazole (12). 3-Phenylpropargylamine hydrochloride (1.2 g, 0.007 mol) and 2-chlorobenzoxazole (1.2 g, 0.0078 mol) were mixed in dry acetonitrile (50 mL). A solution of triethylamine (1.5 g, 0.015 mol) in dry acetonitrile (20 mL) was added and the mixture heated to reflux for 4 h. The solution was cooled and the solvent removed. The residue was taken up in a mixture of ethyl acetate and water. The organic layer was separated, washed twice with water, dried over magnesium sulfate, and filtered. The solvent was removed from the filtrate and the residue recrystallized from ether/ligroin: yield 0.52 g (31%), beige solid; mp 137−138 °C; ^{1}H NMR (CD_3CN) 4.45 (s, 2 H), 7.1 (t, 1 H), 7.2 (t, 1 H), 7.35 (m, 7 H). Anal. Calcd for $C_{16}H_{12}N_2O$: 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 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 on TLC (silica gel; dichloromethane/MeOH, 98:2) a major spot at R_f 0.45, a minor spot at R_f 0.90, and trace spots at R_f 0.60 and 0.40. The crude product was chromatographed on silica gel using dichloromethane/MeOH (98:2) as the eluant. Fractions containing the major component were combined, and the solvent was removed. The residue was dried in a vacuum oven at rt overnight: yield 1.1 g (28%), white powder; mp 113−116 °C; TLC (as above) single spot at R_f 0.40; ^{1}H NMR ($CDCl_3$) 1.8 (s, 6 H), 2.4 (s, 1 H), 5.9 (bs, NH), 7.1 (t, 1 H), 7.2 (t, 1 H), 7.3 (d, 1 H), 7.45 (d, 1 H). Anal. Calcd for $C_{12}H_{12}N_2O + 0.25H_2O$: C, 70.4; H, 6.1; N, 13.7. Found: C, 70.6; H, 6.0; N, 13.6.

2-(Propargylamino)benzothiazole (14). 2-Chlorobenzothiazole (1.69 g, 0.01 mol) and propargylamine (0.55 g, 0.01 mol) were heated in an oil bath at 100 °C for 18 h. Acetone was added to the cooled mixture and the mixture filtered. The filtrate was concentrated and the residue repeatedly extracted with hot ligroin (bp 35−50 °C). Removal of solvent from the combined extracts gave the product: yield 0.17 g (9%), pale yellow solid; ^{1}H NMR (CD_3CN) 2.52 (t, 1 H), 4.25 (d, 2 H), 7.0−7.7 (m, 4 H). Anal. Calcd for $C_{10}H_8N_2S$: C, 63.8; H, 4.3; N, 14.9. Found: C, 63.7; H, 4.5; N, 14.7.

2-(2-Butynylamino)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 (eluant: dichloromethane). Fractions containing the major product 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; ^{1}H NMR (CD_3CN) 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 $C_{11}H_{10}N_2S$: C, 65.32; H, 4.98; N, 13.85. Found: C, 65.10; H, 4.99; N, 13.59.

2-(Propargylamino)benzoselenazole (16). 2-Mercaptobenzoselenazole (20.0 g, 0.093 mol) was added in portions to sulfur monochloride (30.0 g, 0.22 mol) with stirring. After frothing ceased, the mixture was heated to reflux for 1 h. The dark mixture was distilled under vacuum: yield 14.0 g (70%), reddish oil; bp 98−104 °C/0.5 mmHg. ^{1}H NMR data ((CD_3-CN) 7.15−8.0 (m, 4 H)) were consistent with 2-chlorobenzoselenazole (**21**). **21** (2.96 g, 0.014 mol) was added to propargylamine (2.0 g, 0.036 mol) while the reaction flask was chilled in an ice bath. The mixture was warmed to rt and stirred over a weekend. Acetone was added to the solidified mixture, which was filtered, and the filtrate concentrated. The brown residue was recrystallized twice from ligroin (bp 90−110 °C): yield 1.1 g (30%); ^{1}H NMR (CD_3CN) 2.55 (t, 1 H), 4.25 (d, 2 H), 6.9−7.75 (m, 4 H). Anal. Calcd for $C_{10}H_8N_2Se$: C, 51.1; H, 3.4; N, 11.9. Found: C, 51.3; H, 3.4; N, 12.1.

2-(*N*-Methyl-*N*-propargylamino)benzoxazole (22). The procedure described for preparation of compound **1** was followed using 2-chlorobenzoxazole (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%), cream-colored powder; mp 67−70 °C; TLC (silica gel; dichloromethane/MeOH, 98:2) single spot at R_f 0.65; ^{1}H NMR ($CDCl_3$) 2.55 (t, 1 H), 3.2 (s, 3 H), 4.35 (d, 2 H), 6.8 −7.4 (m, 4 H). Anal. Calcd for $C_{11}H_{10}N_2O$: C, 71.0; H, 5.4; N, 15.0. Found: C, 70.5; H, 5.6; N, 15.0.

2-(Allylamino)benzoxazole (23). The same procedure for compound **1** was employed using 2-chlorobenzoxazole (3.07 g, 0.02 mol), allylamine (1.14 g, 0.02 mol), triethylamine (3.03 g, 0.03 mol), and dry acetonitrile (45 mL). This gave an orange oil whose TLC (silica gel; dichloromethane/MeOH, 98:2) showed a major spot at R_f 0.40 and minor spots at R_f 0.90 and 0.50. The crude product was chromatographed on silica gel using dichloromethane/MeOH (98:2) as the eluant. Fractions containing the major component were combined, and the solvent was removed. This gave a clear oil which solidified on standing. The solid was dried in a vacuum oven at rt overnight: yield 1.66 g (48%), white solid; mp 58−61 °C; ^{1}H NMR ($CDCl_3$) 4.1 (d of d, 2 H), 5.1−5.3 (m, 2 H), 5.9 (m, 1 H), 6.4 (bs, NH), 6.8−7.4 (m, 4 H). Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.9; H, 5.8; N, 16.1. Found: C, 68.8; H, 5.8; N, 16.0.

2-(Propylamino)benzoxazole (24). A mixture of **23** (1.0 g, 0.0058 mol), platinum oxide (81%, 0.05 g), and ethyl acetate (80 mL) was hydrogenated on a Parr shaker apparatus at rt. When hydrogen uptake ceased, the mixture was filtered and the solvent removed. The residue was recrystallized from heptane (25 mL): yield 0.51 g (50%), white powder; mp 98−100 °C; TLC (silica gel; dichloromethane/MeOH, 98:2) single spot at R_f 0.60; ^{1}H NMR ($CDCl_3$) 1.05 (t, 3 H), 1.75 (m, 2 H), 3.45 (q, 2 H), 5.1 (bs, NH), 7.05 (t, 1 H), 7.2 (t, 1 H), 7.25 (d, 1 H), 7,4 (d, 1 H). Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.2; H, 6.9; N, 15.9. Found: C, 68.5; H, 7.0; N, 15.9.

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: ^{1}H NMR (CD_3CN) 2.8 (t, 1 H), 3.65 (s, 3 H), 4.45 (d, 2 H), 7.3−7.75 (m, 4 H). Anal. Calcd for $C_{11}H_{11}IN_2O$: C, 42.1; H, 3.5; N, 8.9. Found: C, 41.9; H, 3.6; N, 9.1.

2*H*-Pyrimido[2,1-*b*]benzoxazole (26). A mixture of **1** (5.16 g, 0.03 mol) and silver tetrafluoroborate (4.0 g, 0.02 mol) was stirred in dry acetonitrile (150 mL) at rt overnight under nitrogen. The mixture was protected from light by aluminum foil wrapped around the reaction flask. After 16 h, sodium iodide (4.0 g, 0.027 mol) was added to the mixture and the resulting mixture stirred for another 15 min and filtered. The filtrate was concentrated under vacuum leaving behind a dull yellow solid. This material was triturated with methylene chloride several times, each time followed by filtration. The filtrates were combined and concentrated under vacuum. A brownish yellow solid weighing 4.1 g was obtained. This solid was sublimed at 100−125 °C under 0.07 mmHg of pressure, yield 2.9 g (48%). Further purification could be done by slurrrying the solid with a small amount of cold, dry ether. TLC (silica gel, dichloromethane/acetonitrile 5:1) of the solid showed a one-spot homogeneous chromatogram: ^{1}H NMR (CD_3CN) 4.35 (2d, 2 H), 4.95 (2t, 1 H), 6.65 (2t, 1 H), 6.8−7.2 (m, 4 H); ^{13}C NMR ($CDCl_3$) 144.3, 109.6, 123.4, 120.8, 105.7, 129.6 (benzene ring carbons), 121.7 (−N*C*H=C), 104.5 (C=*C*HCH$_2$), 46.7 (C=C*C*H$_2$), 153 (−N*C*=N−); MS *m*/*z* at 172 (MW of **26**). Anal. Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.56; H, 4.89; N, 16.17.

2*H*-4-Methylpyrimido[2,1-*b*]benzoxazole (27). The preparation of **27** followed a similar procedure as for compound **26** using **9** (5.58 g, 0.03 mol) and silver tetrafluoroborate (4.0 g, 0.02 mol). The reaction mixture was stirred for 7 days at rt. The sublimed material (125−130 °C under 0.07 mmHg of pressure) showed a homogeneous one-spot chromatogram (silica gel, methylene chloride/acetonitrile 5:1): yield 2.5 g (47%); ^{1}H NMR (CD_3CN) 2.26 (3d, 3 H), 4.33 (2q, 2 H), 4.76 (3q, 1 H), 7−7.3 (m, 4 H).

2*H*-7-Methylpyrimido[2,1-*b*]benzoxazole: ^{1}H NMR (CD_3CN) 2.3 (s, 3 H), 4.4 (m, 2 H), 5.0 (d of t, 1 H), 6.6 (d of t, 1 H), 6.85 (m, 3 H).

2*H*-7-Chloropyrimido[2,1-*b*]benzoxazole: ^{1}H NMR (CD_3CN) 4.4 (m, 2 H), 5.2 (d of t, 1 H), 6.65 (d of t, 1 H), 6.9−7.2 (m, 3 H).

2*H*-7,8-Dichloropyrimido[2,1-*b*]benzoxazole: ^{1}H NMR (CD_3CN) 4.4 (m, 2 H), 5.2 (d of t, 1 H), 6.7 (d of t, 1 H), 7.25 (s, 1 H), 7.35 (s, 1 H).

2*H*-7-Cyanopyrimido[2,1-*b*]benzoxazole: ^{1}H NMR (CD_3CN) 4.4 (m, 2 H), 5.2 (d of t, 1 H), 6.7 (d of t, 1 H), 7.25 (d, 1 H), 7.4 (d, 1 H), 7.45 (d of d, 1 H).

2*H*-7-(Methoxycarbonyl)pyrimido[2,1-*b*]benzoxazole: ^{1}H NMR (CD_3CN) 3.85 (s, 3 H), 4.4 (m, 2 H), 5.2 (d of t, 1 H), 6.8 (d of t, 1 H), 7.2 (d, 1 H), 7.7 (d, 1 H), 7.75 (d of d, 1 H).

2*H*-7-(Methylsulfonyl)pyrimido[2,1-*b*]benzoxazole: ^{1}H NMR (CD_3CN) 3.1 (s, 3 H), 4.45 (m, 2 H), 5.2 (d of t, 1 H), 6.8 (d of t, 1 H), 7.3 (d, 1 H), 7.65 (2 overlapping d, 2 H).

2*H*-7-Methoxypyrimido[2,1-*b*]benzoxazole: ^{1}H NMR (CD_3CN) 3.8 (s, 3 H), 4.45 (m, 2 H), 5.2 (d of t, 1 H), 6.65 (d of d, 1 H), 6.75 (d of t, 1 H), 6.8 (d, 1 H), 7.1 (d, 1 H).

2*H*-4,7-Dimethylpyrimido[2,1-*b*]benzoxazole: ^{1}H NMR (CD_3CN) 2.25 (m, 3 H), 2.35 (s, 3 H), 4.3 (m, 2 H), 4.75 (m, 1 H), 6.85 (d, 1 H), 7.0 (d, 1 H), 7.15 (s, 1 H).

2*H*-7-Cyano-4-methylpyrimido[2,1-*b*]benzoxazole: ^{1}H NMR (CD_3CN) 2.2 (s, 3 H), 4.3 (t, 2 H), 4.8 (s, 1 H), 7.2 (d, 1 H), 7.4 (d, 1 H), 7.5 (s, 1 H).

2*H*-7-Phenylpyrimido[2,1-*b*]benzoxazole: ^{1}H NMR (CD_3CN) 4.5 (m, 2 H), 5.0 (m, 1 H), 5.65 (d, 1 H), 6.8 (t, 1 H), 6.95 (t, 1 H), 7.15 (d, 1 H), 7.50 (m, 5 H).

2*H*-2,2-Dimethylpyrimido[2,1-*b*]benzoxazole (32): ^{1}H NMR (CD_3CN) 1.4 (s, 6 H), 5.15 (d, 1 H), 6.75 (d, 1 H), 7.15 (m, 4 H).

2*H*-Pyrimido[2,1-*b*]benzothiazole: ^{1}H NMR (CD_3CN) 4.35 (m, 2 H), 5.15 (m, 1 H), 6.8 (d, 1 H), 7.1 (m, 2 H), 7.3 (t, 1 H), 7.4 (d, 1 H).

2*H*-4-Methylpyrimido[2,1-*b*]benzothiazole: ^{1}H NMR (CD_3CN) 2.25 (s, 3 H), 4.15 (m, 2 H), 4.85 (m, 1 H), 7.15 (t, 1 H), 7.25 (t, 1 H), 7.35 (d, 1 H), 7.45 (d, 1 H).

2*H*-Pyrimido[2,1-*b*]benzoselenazole: ^{1}H NMR (CD_3CN) 4.35 (m, 2 H), 5.35 (d of t, 1 H), 6.85 (d of t, 1 H), 7.1−7.7 (m, 4 H). Other peaks in the spectrum were not identified.

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