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The Preparation and Some Reactions of a Benzotriazole Substituted Vinamidinium Salt

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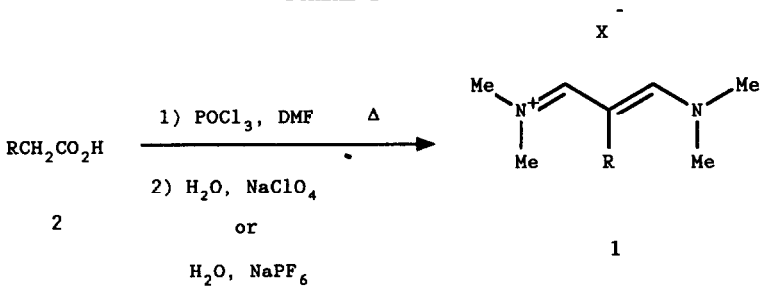
Abstract: A three step synthesis of a novel 2-(1-benzotriazolyl)-vinamidinium salt is described along with its direct conversion to a series of unusual 5-(1-benzotriazolyl)pyrimidines, 4-(1-benzotriazolyl)-pyrazoles, and 4-(1-benzotriazolyl)pyrroles.

In recent years, one of the focuses for our research group has been to expand the synthetic utility of vinamidinium salts by creating new vinamidinium salts with novel substituents and to study the reactions of these new salts with a variety of reagents. Recently, we synthesized a 2-(arylsulfonyl)vinamidinium salt **(1a)** and reacted it with a variety of nucleophiles, reducing agents and organometallic reagents to produce a series of unique molecules incorporating the synthetically and biologically intriguing phenylsulfonyl moiety[1]. We now wish to describe an extension of this work to the benzotriazole moiety.

SCHEME 1



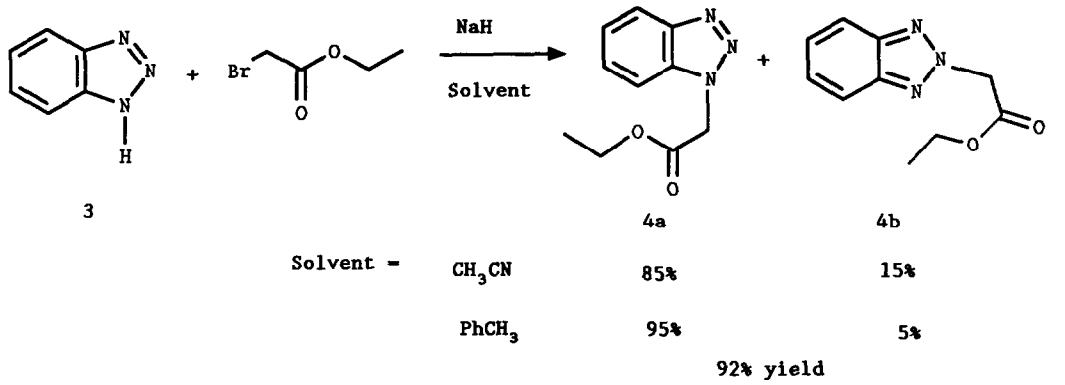
If one examines the literature of vinamidinium salts[2], their potential utility as three-carbon building blocks for a wide array of carbocycles and heterocycles becomes apparent. Vinamidinium salts can regioselectively incorporate an appended substituent onto a new ring system, making them attractive starting materials for the synthesis of new medicinal[3] and agricultural agents[4]. Also, many 2-substituted vinamidinium salts can be readily prepared in a one step reaction from the corresponding substituted acetic acids (**2**) under Vilsmeier-Haack conditions[2,5] (SCHEME 1).

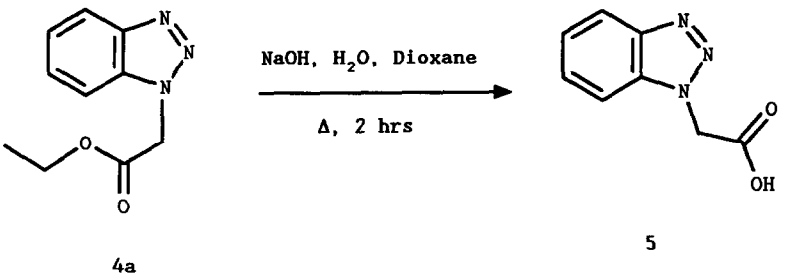
When targeting new substituents to append to the vinamidinium salt skeleton, a number of factors must be considered. First, the necessary substituted acetic acid that serves as the precursor must be easily obtained. Also, a substituent should be chosen that will impart interesting properties to the carbocycles and heterocycles that will be formed from the vinamidinium salt. Finally, it may also be important to choose a substituent that could later be functionalized or selectively displaced from the final cyclic compounds. An important synthetic auxiliary that fills many of these criteria and that has captured the attention of Katritzky and coworkers[6] is benzotriazole. The benzotriazole group has been shown to be a pharmacophore[7] and it can be easily manipulated and replaced by other groups such as Grignard reagents. It also has the potential to serve as a ligand for metal coordination and could, therefore, be used as a directing group for heteroatom directed metallation reactions. In addition, examples of heterocyclic appended vinamidinium salts are rare[3] and those that are attached through a nitrogen atom have not received appropriate attention either[8]. For these reasons, it appeared to us that a 2-(1-benzotriazole) substituted vinamidinium salt (**1b**) would be a worthy synthetic target.

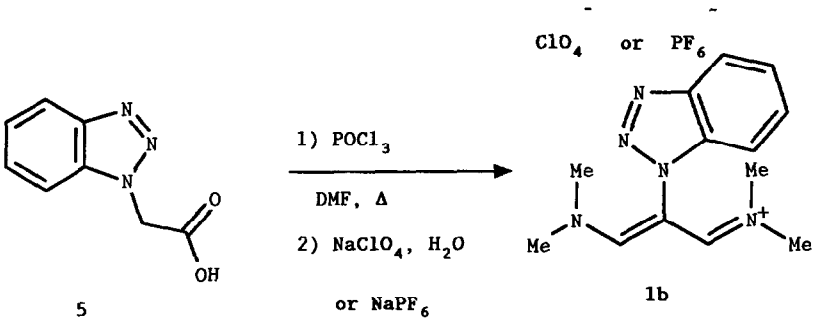
The requisite (1-benzotriazolyl)acetic acid (**5**) is readily available from the corresponding ethyl 2-(1-benzotriazolyl)acetate (**4a**), which is in

turn made from ethyl 2-bromoacetate and benzotriazole[7] (SCHEME 2).

SCHEME 2







In our initial trials to make ethyl 2-(1-benzotriazolyl)acetate, we used acetonitrile as the solvent and found a mixture of isomers had been produced [85:15 mixture with the N-1(**4a**) isomer predominating]. We attempted to improve the isomeric ratio by using a different solvent and

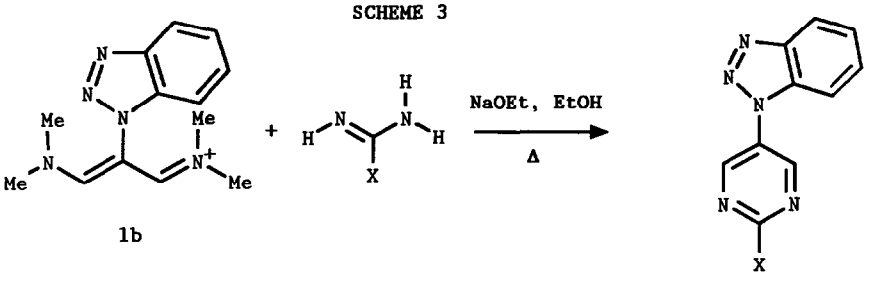
found that in toluene, the reaction produced a 95:5 ratio of the desired isomer as determined by ^{1}H NMR. The isomers were separated by radial chromatography and could be easily differentiated by the symmetrical features of the ^{1}H NMR of the minor isomer (**4b**). If we took this crude mixture of isomers and subjected it to the next 2 steps in the vinamidinium salt synthesis, the 2-isomer completely disappeared during the subsequent purification processes thereby eliminating the need for any chromatographic purification at the ester stage. After the ethyl ester (**4a**) was obtained, it was hydrolyzed to the benzotriazole substituted acetic acid in excellent yield (SCHEME 2).

Finally, the (1-benzotriazolyl)acetic acid was reacted with phosphorus oxychloride and DMF at 105-110°C until carbon dioxide evolution ceased (approximately 3 hrs) to produce the desired vinamidinium salt (SCHEME 2). Traditionally we have precipitated our vinamidinium salts as perchlorates, but the possible safety hazards involved with perchlorate salts have motivated us to find a new, and potentially safer counter ion for our work. Recently, Wudl[9] reported utilizing sodium hexafluorophosphate to precipitate several vinamidinium salts in excellent yields. Application of this methodology resulted in the hexafluorophosphate salt (**1b**) being obtained in 89% yield. This salt is a well defined, stable solid that is somewhat hygroscopic and has a long shelf life if it is stored in an anhydrous environment. The NMR spectral properties (^{1}H and ^{13}C) of the benzotriazole group were clearly observed for the salt and a molecular ion could be seen in the mass spectrum for the cation portion of the salt.

Once the 2-(1-benzotriazolyl)vinamidinium salt was obtained, it was condensed with a wide variety of substituted amidines in an ethanol/sodium ethoxide mixture to produce a series of pyrimidines in excellent purified yields after ethanol/water recrystallization. Although the preparation of pyrimidines from vinamidinium salts is a well-known process[2], this particular reaction is novel in that it incorporates the benzotriazolyl group onto the pyrimidine ring. As a result, a highly functionalized biheterocyclic system is obtained with a specific regiochemical relationship between the two rings. To achieve an alternative synthesis of pyrimidines substituted in this fashion would be quite difficult as a result of the inability to selectively halogenate the 5 position of the pyrimidine ring[10]. The spectral properties (^{1}H and ^{13}C NMR) of the 5-benzotriazole substituted pyrimidines were consistent with other 5-substituted pyrimidines that we have previously prepared[11] and the incorporation of the benzotriazole group was clearly demonstrated. Additionally, the preparation of analog **6e** was carried out in the absence of base to avoid the reaction of any liberated dimethylamine with the

thiomethyl group.

SCHEME 3



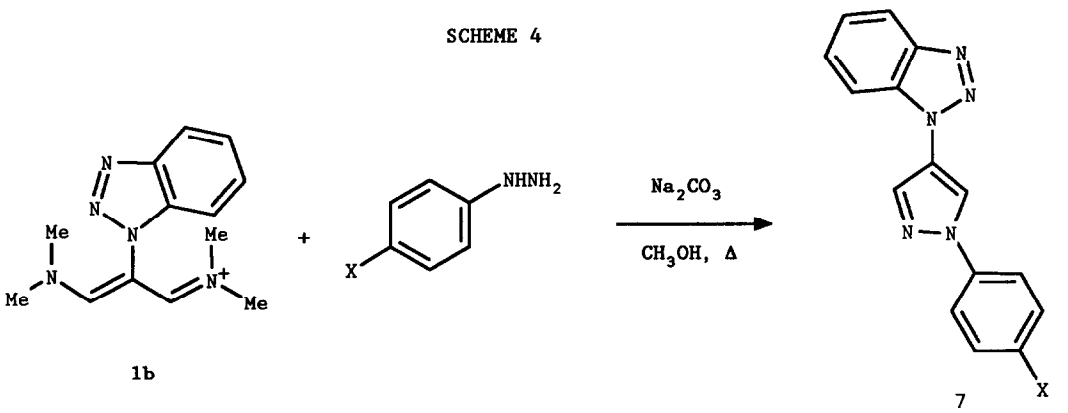
1b

6

Compound	X	% Yield
6a	NH_2	85
6b	CH_3	88
6c	Ph	95
6d	OCH_3	90
6e	SCH_3	85
6f	$N(CH_3)_2$	75
6g	H	60

In a reaction very similar to the pyrimidine formation, the 2-(1-benzotriazolyl)vinamidinium salt (**1b**) was condensed with a variety of substituted phenyl hydrazines in an ethanol/sodium carbonate mixture to yield a series of pyrazoles in good purified yields after ethanol/water recrystallization. As in the previous case, a significant feature of this reaction is the regioselective formation of a unique biheterocyclic system. Pyrazoles with a substituent at the 4 position represent a significant category of agrochemical agents[12] and the methodology depicted in SCHEME 4 provides ready access to a unique class of materials. The spectral properties of these substances were also consistent with those reported[11] for similarly substituted pyrazoles which have been obtained from symmetrically substituted vinamidinium salts.

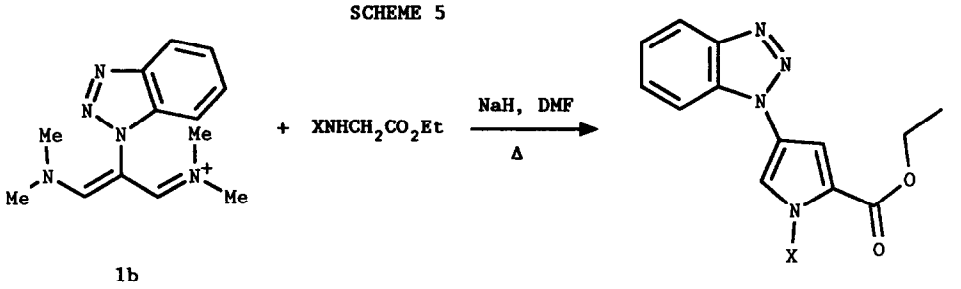
SCHEME 4



Compound	X	% Yield
7a	CH_3O	75
7b	CH_3	80
7c	H	82
7d	Br	91
7e	Cl	85

We have recently demonstrated[13] that condensing 2-substituted vinamidinium salts with glycine ethyl ester and sarcosine ethyl ester yields the corresponding 2,4-disubstituted pyrroles. This reaction presumably occurs via an azomethine ylid. When this methodology was applied to the 2-(1-benzotriazolyl)vinamidinium salt (**1b**), regioselectively substituted pyrroles were obtained in excellent purified yields after radial chromatography (SCHEME 5). Selective substitution at the 4 position of a pyrrole is difficult to achieve[14] as a result of the ring being deactivated towards nucleophilic substitution and being activated at the 2 and 5 positions for electrophilic substitution. Highly functionalized pyrroles have also received much attention recently as insecticidal[15] and fungicidal agents[15]. The spectral properties of the 4-benzotriazole substituted pyrroles were consistent with analogs previously reported[13] by our group.

SCHEME 5



1b

8

X- H, 89% yield

X- Me, 91% yield

In summary, we have demonstrated a high yield, 3 step synthesis of a novel 2-(1-benzotriazolyl)vinamidinium salt. This three carbon building block was then used to construct pyrimidines, pyrazoles and pyrroles with a benzotriazole group attached in a regioselective fashion. These transformations represent an efficient and clean method for producing novel biheterocyclic systems which have the potential to serve as useful bioactive agents. The benzotriazole group may enhance the inherent bioactivity of the parent molecule or in a synthetic sense act as a chelating group for regioselective metalation reactions.

EXPERIMENTAL

Ethyl 2-(1-benzotriazolyl)acetate (4a). A 100-mL, three-neck round-bottomed flask was equipped with a magnetic stir bar, a condenser, and a mineral oil bubbler and placed under a nitrogen atmosphere. Into the flask was placed 0.44 g (0.011 mol) of a 60% mineral oil dispersion of sodium hydride. This dispersion was washed with several portions of dry hexane, and the hexane was removed via cannula. Added to the flask were 20 mL of toluene, and the resulting mixture was allowed to stir with an ice bath until the mixture reached 0°C. Next, 1.82 g (0.011 mol) of ethyl bromoacetate were added to the flask, and the mixture was allowed to stir for five minutes. Subsequently, 1.00 g (0.0084 mol) of benzotriazole was added to the flask, and the ice bath was removed. The reaction was then heated for five hours at 80-90°C. The solvent was removed from the reaction mixture in vacuo and the residue was partitioned between chloroform and water. The chloroform phase was retained, while the aqueous phase was re-extracted several times. The combined chloroform extracts were dried over anhydrous magnesium sulfate and concentrated in

vacuo. A mixture of isomers (2.10 g, 92% yield) was produced in a 95:5 ratio of ethyl (1-benzotriazoyl)acetate **(4a)** and ethyl (2-benzotriazolyl)-acetate **(4b)**. The isomers were separated by radial chromatography on a Harrison Chromatron on a 2-mm-thick plate of silica gel. Elution with a hexane/ethyl acetate mixture afforded the minor isomer as a faster moving band and the major isomer as a slower moving band. The minor isomer (**4b**) exhibited the following properties: mp 121-123°C; ^{1}H NMR (DMSO-d_6) δ 1.23 (t, J = 7.1 Hz, 3 H), 4.20 (q, J = 7.1 Hz, 2 H), 5.84 (s, 2 H), 7.49 (m, 2 H) and 7.98 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 15.7, 58.8, 63.5, 119.8, 128.7, 145.8 and 168.5; IR (KBr pellet) 1740 cm^{-1}; HRMS (EI) for $C_{10}H_{11}N_3O_2$ calcd. 205.0851, found 205.0850. The major isomer (**4a**) exhibited the following properties : mp 84-86°C; ^{1}H NMR (DMSO-d_6) δ 1.23 (t, J = 7.1 Hz, 3 H), 4.20 (q, J = 7.1 Hz, 2 H), 5.80 (s, 2 H), 7.44 (t, J = 8 Hz, 1 H), 7.59 (t, J = 8 Hz, 1 H), 7.87 (d, J = 8 Hz, 1 H), and 8.09 (d, J = 8 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 15.8, 50.4, 63.4, 112.6, 120.9, 125.9, 129.4, 135.3, 146.8, and 169.1; IR (KBR pellet) 1741 cm^{-1}; HRMS (EI) for $C_{10}H_{11}N_3O_2$ calcd. 205.0851, found 205.0852.

(1-Benzotriazolyl) Acetic Acid (5). A one-neck, 100-mL round-bottomed flask was equipped with a stir bar and condenser. Into the flask were placed 1.00g (0.0049 mol) of ethyl (1-benzotriazolyl)acetate **(4a)**, 20 mL of dioxane and 10 mL of 5 M NaOH. The mixture was refluxed for two hours and then cooled to room temperature. The solution was adjusted to a pH of 5 with 2 N HCl and allowed to sit overnight. The product precipitated out of solution and was collected by vacuum filtration. The product was a white crystalline solid (0.82 g, 95% yield) and exhibited the following properties: mp 214-216°C; ^{1}H NMR (DMSO-d_6) δ 5.68 (s, 2 H), 7.43 (t, J = 8 Hz, 1 H), 7.58 (t, J = 8 Hz, 1 H), 7.87 (d, J = 8 Hz, 1 H), and 8.08 (d, J = 8 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 50.5, 112.6, 120.8, 125.7, 129.2, 135.3, 146.8, and 170.5; IR (KBr pellet) 1727 cm^{-1}; mass spectrum, m/z 177 (M^+). Anal. Calcd. for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72. Found: C, 54.02; H, 3.88; N, 23.45.

2-(1-Benzotriazolyl)-1,1,5,5-tetramethyl-1,5-diazapentadienium Hexafluorophosphate (1b). A 100-mL, three-neck round-bottomed flask was equipped with a condenser, a stir bar and a mineral oil bubbler and was placed under a nitrogen atmosphere. Into the flask, were placed 2.48 g (0.034 mol) of dry DMF, and an ice bath was placed beneath the flask to cool the DMF down to 0°C. Next, 2.59 g (0.0017 mol) of phosphorus oxychloride were added dropwise, and the mixture was allowed to stir for five minutes. To the flask, 1.00 g (0.0056 mol) of (1-benzotriazolyl) acetic acid **(5)** was added. The ice bath was removed, and the reaction was allowed to proceed for three hours at 105-110°C. After the reaction was

complete, the mixture was cooled to room temperature. In a 500-mL beaker, 100-mL of deionized water containing 1.59 g (0.011 mol) of sodium hexafluorophosphate were cooled to 10°C. The cool reaction mixture was transferred quantitatively to the beaker, and the contents of the beaker were stirred until precipitation was complete. The product, a brown solid (2.20g, 89% yield), was collected by vacuum filtration and exhibited the following properties: mp 211-213°C (dec.); ^{1}H NMR (DMSO-d_6) δ 2.00 (s, 6 H), 3.33 (s, 6 H), 7.56 (t, J = 8 Hz, 1 H), 7.76 (m, 2 H), and 8.23 (m, 3 H); ^{13}C NMR (DMSO-d_6) δ 38.7, 51.1, 99.9, 112.5, 121.8, 127.2, 131.7, 138.8, 146.5, and 163.3; HRMS (FAB, M^+) for $C_{13}H_{18}N_5$ calcd. 244.1562, found 244.1568.

2-Amino-5-(1-benzotriazolyl)pyrimidine (6a). A 100-mL, three-necked round-bottomed flask was equipped with a stir bar and condenser and placed under a nitrogen atmosphere. Added to the flask was 0.34 g (0.0085 mol) of a 60% mineral oil dispersion of sodium hydride. The sodium hydride was washed twice with dry hexane, which was removed via cannula. Next, 20 mL of dry ethanol were slowly added to the flask, and the resulting mixture was allowed to stir for several minutes. To the flask, 0.46 g (0.0026 mol) of guanidine carbonate was added, and the mixture was allowed to stir for fifteen minutes. Finally, 1.00 g (0.0026 mol) of the 2-(1-benzotriazolyl)vinamidinium salt **(1b)** was added, and the reaction was refluxed overnight. Solvent was removed in vacuo, and a small amount of water was added to the residue. The resulting solid was collected by vacuum filtration to yield 0.46 g (85% yield) of the pyrimidine after recrystallization in ethanol/water: mp 191-193°C; ^{1}H NMR (DMSO-d_6) δ 7.31 (s, 2 H), 7.51 (t, J = 8 Hz, 1 H), 7.64 (t, J = 8 Hz, 1 H), 7.83 (d, J = 8 Hz, 1 H), 8.17 (d, J = 8 Hz, 1 H), and 8.68 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 111.0, 119.7, 122.1, 124.8, 128.7, 133.2, 145.6, 154.2, and 163.7; IR (KBr pellet) 3315 and 3181 cm^{-1}; mass spectrum, m/z 212 (M^+). Anal. Calcd. for $C_{10}H_8N_6$: C, 56.60; H, 3.80; N, 39.60. Found: C, 56.29; H, 3.62; N, 39.57.

5-(1-Benzotriazolyl)-2-methylpyrimidine (6b). This compound was prepared in 88% yield in a manner similar to the preparation of 2-amino-5-(1-benzotriazolyl)pyrimidine **(6a)** with the exception that acetamidine was used as one of the starting materials. This compound **(6b)** exhibited the following properties: mp 143-145°C; ^{1}H NMR (DMSO-d_6) δ 2.81 (s, 3 H), 7.58 (t, J = 8 Hz, 1 H), 7.73 (t, J = 8 Hz, 1 H), 8.07 (d, J = 8 Hz, 1 H), 8.26 (d, J = 8 Hz, 1 H), and 9.31 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 27.9, 111.4, 122.9, 127.1, 131.3, 132.1, 134.1, 148.6, 152.5, and 170.3; HRMS (EI) for $C_{11}H_9N_5$ calcd. 211.0858, found 211.0863.

5-(1-Benzotriazolyl)-2-phenylpyrimidine (6c). This compound was prepared in 95% yield in a manner similar to the preparation of

2-amino-5-(1-benzotriazolyl)pyrimidine (**6a**) with the exception that benzamidine was used as one of the starting materials. After ethanol/water recrystallization, this compound (**6c**) exhibited the following properties; mp 185-187°C; ^{1}H NMR (DMSO-d_6) δ 7.63 (m, 4 H), 7.75 (t, J = 8 Hz, 1 H), 8.19 (d, J = 8 Hz, 1 H), 8.28 (d, J = 8 Hz, 1 H), 8.55 (m, 2 H), and 9.53 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 113.1, 121.6, 127.0, 129.8, 130.8, 131.0, 132.1, 133.3, 133.7, 138.0, 147.6, 153.2, and 164.5; mass spectrum, m/z 273 (M^+). Anal. Calcd. for $C_{16}H_{11}N_5$: C, 70.31; H, 4.06; N, 25.63. Found: C, 70.14; H, 3.91; N, 25.67.

5-(1-Benzotriazolyl)-2-methoxypyrimidine (6d). This compound was prepared in 90% yield in a manner similar to the preparation of 2-amino-5-(1-benzotriazolyl)pyrimidine (**6a**) with the exception that methylisourea was used as one of the starting materials. After ethanol/water recrystallization, this compound (**6d**) exhibited the following properties: mp 198-200°C; ^{1}H NMR (DMSO-d_6) δ 4.08 (s, 3 H), 7.56 (t, J = 8 Hz, 1 H), 7.70 (t, J = 8 Hz, 1 H), 7.98 (d, J = 8 Hz, 1 H), 8.24 (d, J = 8 Hz, 1 H), and 9.18 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 57.3, 112.6, 121.4, 126.7, 128.7, 130.7, 134.4, 147.3, 156.5, and 166.4; HRMS (EI) for $C_{11}H_9N_5O$ calcd. 227.0807, found 227.0803.

5-(1-Benzotriazolyl)-2-thiomethylpyrimidine (6e). This compound was prepared in 85% yield in a manner similar to the preparation of 2-amino-5-(1-benzotriazolyl)pyrimidine (**6a**) with some exceptions. Methylisothiourea was used as one of the starting materials and no base was employed in the reaction to minimize displacement of the thiomethyl group. After ethanol/water recrystallization this compound (**6e**) exhibited the following properties: mp 166-168°C; ^{1}H NMR (DMSO-d_6) δ 2.66 (s, 3 H), 7.57 (t, J = 8 Hz, 1 H), 7.72 (t, J = 8 Hz, 1 H), 8.06 (d, J = 8 Hz, 1 H), 8.25 (d, J = 8 Hz, 1 H), and 9.25 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 15.9, 112.9, 121.5, 126.9, 130.0, 130.9, 134.0, 147.4, 153.7, and 173.4; HRMS (EI) for $C_{11}H_9N_5S$ calcd. 243.0579, found 243.0577.

5-(1-Benzotriazolyl)-2-N,N-dimethylpyrimidine (6f). This compound was prepared in 75% yield in a manner similar to the preparation of 2-amino-5-(1-benzotriazolyl)pyrimidine (**6a**) with the exception that N,N-dimethylguanidine was used as one of the starting materials. After ethanol/water recrystallization, this compound (**6f**) exhibited the following properties: mp 147-149°C; ^{1}H NMR (DMSO-d_6) δ 3.25 (s, 6 H), 7.52 (t, J = 8 Hz, 1 H), 7.65 (t, J = 8 Hz, 1 H), 7.83 (d, J = 8 Hz, 1 H), 8.18 (d, J = 9 Hz, 1 H), and 8.80 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 38.8, 112.5, 121.3, 122.9, 126.4, 130.3, 134.8, 147.1, 155.4, and 163.0; mass spectrum, m/z 241 (M^+). HRMS (EI) for $C_{12}H_{12}N_6$ calcd. 240.1123, found 240.1127.

5-(1-Benzotriazolyl)pyrimidine (6g). This compound was prepared in a manner similar to the preparation of 2-amino-5-(1-benzotriazolyl)-pyrimidine **(6a)** with a few exceptions. Formamidine was one of the starting materials and the crude residue was partitioned between chloroform and water, with the chloroform phase being retained. The aqueous phase was extracted several more times, and the chloroform extracts were combined and dried over anhydrous magnesium sulfate. Chloroform was removed in vacuo, and the residue dissolved in 100% ethyl acetate and eluted through a short column of silica gel. Finally, the product was subjected to radial chromotography on a Harrison Chromatotron with a 2-mm thick plate of silica gel. Elution with a 50:50 mixture of hexane/ethyl acetate yielded a solid (60% yield) with the following properties: mp 152-154°C; ^{1}H NMR (DMSO-d_6) δ 7.59 (t, J = 8 Hz, 1 H), 7.74 (t, J = 8 Hz, 1 H), 8.14 (d, J = 8 Hz, 1 H), 8.27 (d, J = 8 Hz, 1 H), 9.43 (s, 1 H), and 9.47 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 112.9, 121.6, 127.0, 131.1, 133.7, 133.9, 147.6, 152.6, and 159.7; mass spectrum, m/z 197 (M^+). Anal. Calcd. for $C_{10}H_7N_5$: C, 60.90; H, 3.58; N, 35.52. Found; C, 60.90; H, 3.52; N, 35.33.

4-(1-Benzotriazolyl)-1-(4-methoxyphenyl)pyrazole (7a). Into a one-neck, 250-mL round-bottomed flask were placed 1.00 g (0.0026 mol) of the benzotriazolated vinamidinium salt **(1b)**, 0.68 g (0.0039 mol) of p-methoxyphenylhydrazine hydrochloride, and 0.69 g (0.0065 mol) of sodium carbonate. A stir bar and 30 mL of dry ethanol were added, and the flask was attached to a reflux condenser. The reaction was allowed to proceed overnight at reflux. After the reaction was complete, the solvent was removed in vacuo, and the crude product was partitioned between chloroform and water. The chloroform phase was saved, and the aqueous phase was extracted several more times with additional chloroform. After drying the combined chloroform extracts over anhydrous magnesium sulfate, the chloroform was removed in vacuo. The crude solid obtained was purified by recrystallization with ethanol/water. A light tan solid (0.57 g, 75% yield) was collected and dried by vacuum filtration and exhibited the folowing properties: mp 104-106°C; ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3 H), 7.14 (d, J = 9.1 Hz, 2 H), 7.55 (t, J = 8 Hz, 1 H), 7.72 (t, J = 8 Hz, 1 H), 7.93 (d, J = 9.1 Hz, 2 H), 8.10 (d, J = 8 Hz, 1 H), 8.20 (d, J = 8 Hz, 1 H), 8.43 (s, 1 H), and 9.26 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 57.3, 112.9, 116.4, 121.3, 122.1, 123.1, 123.4, 126.5, 130.4, 133.8, 134.7, 135.7, 147.0, and 160.0; IR 1247 cm^{-1}; mass spectrum, m/z 291 (M^+). Anal. Calcd. for $C_{16}H_{13}N_5O$: C, 65.96; H, 4.50; N, 24.16. Found; C, 65.59; H, 4.56; N, 24.16.

4-(1-Benzotriazolyl)-1-(4-methylphenyl)pyrazole (7b). The compound was prepared in an 80% yield in the same fashion as 4-(1-benzotriazolyl)-1-

(4-methoxyphenyl)pyrazole (**7a**) with the exception that p-tolylhydrazine was used as a starting material. The purified product exhibited the following properties: mp 123-125°C; ^{1}H NMR (DMSO-d_6) δ 2.39 (s, 3 H), 7.39 (d, J = 8.4 Hz, 2 H), 7.55 (t, J = 8 Hz, 1 H), 7.72 (t, J = 8 Hz, 1 H), 7.90 (d, J = 8.4 Hz, 2 H), 8.12 (d, J = 8 Hz, 1 H), 8.21 (d, J = 8 Hz, 1 H), 8.46 (s, 1 H), and 9.32 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 22.3, 112.9, 120.4, 121.3, 123.0, 123.6, 126.6, 130.4, 131.8, 133.7, 135.9, 138.3, 138.9, and 147.0; mass spectrum, m/z 275 (M^+). Anal. Calcd. for $C_{16}H_{13}N_5$: C, 69.80; H, 4.76; N, 25.42. Found; C, 69.52; H, 4.62; N, 25.42.

4-(1-Benzotriazolyl)-1-phenylpyrazole (7c). The compound was prepared in an 82% yield in the same fashion as 4-(1-benzotriazolyl)-1-(4-methoxyphenyl)pyrazole (**7a**) with the exception that phenylhydrazine was used as one of the starting materials. After ethanol/water recrystallization, this compound exhibited the following properties: mp 147-149°C; ^{1}H NMR (DMSO-d_6) δ 7.42 (t, J = 8 Hz, 1 H), 7.58 (m, 3 H), 7.73 (t, J = 8 Hz, 1 H), 8.03 (d, J = 7.6 Hz, 2 H), 8.13 (d, J = 8 Hz, 1 H), 8.21 (d, J = 8 Hz, 1 H), 8.50 (s, 1 H), and 9.38 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 112.9, 120.5, 121.4, 123.3, 123.8, 126.6, 128.9, 130.4, 131.4, 133.7, 136.3, 141.1, and 147.0; HRMS (EI) for $C_{15}H_{11}N_5$ calcd. 261.1014, found 261.1015.

4-(1-Benzotriazolyl)-1-(4-bromophenyl)pyrazole (7d). The compound was prepared in an 91% yield in the same fashion as 4-(1-benzotriazolyl)-1-(4-methoxyphenyl)pyrazole (**7a**) with the exception that p-bromophenylhydrazine was used as a starting material. After ethanol/water recrystallization, this compound exhibited the following properties: mp 156-158°C; ^{1}H NMR (DMSO-d_6) δ 7.55 (t, J = 8 Hz, 1 H), 7.73 (t, J = 8 Hz, 1 H), 7.80 (d, J = 9.0 Hz, 2 H), 8.01 (d, J = 9.0 Hz, 2 H), 8.13 (d, J = 8 Hz, 1 H), 8.21 (d, J = 8 Hz, 1 H), 8.52 (s, 1 H), and 9.41 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 112.9, 121.3, 121.4, 122.4, 123.2, 124.0, 126.7, 130.5, 133.6, 134.3, 136.6, 140.3, and 147.0; HRMS (EI) for $C_{15}H_{10}N_5Br$ calcd. 339.0120, found 339.0115.

4-(1-Benzotriazolyl)-1-(4-chlorophenyl)pyrazole (7e). The compound was prepared in an 85% yield in the same fashion as 4-(1-benzotriazolyl)-1-(4-methoxyphenyl)pyrazole (**7a**) with the exception that p-chlorophenylhydrazine was used as one of the starting materials. After ethanol/water recrystallization, this compound exhibited the following properties: mp 150-152°C; ^{1}H NMR (DMSO-d_6) δ 7.56 (t, J = 8 Hz, 1 H), 7.68 (d, J = 8.5 Hz, 2 H), 7.73 (t, J = 8 Hz, 1 H), 8.07 (d, J = 8.5 Hz, 2 H), 8.14 (d, J = 8 Hz, 1 H), 8.22 (d, J = 8 Hz, 1 H), 8.53 (s, 1 H), and 9.41 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 122.9, 121.4, 122.1, 123.3, 124.0, 126.7, 130.5, 131.4, 133.0, 133.6, 136.6, 139.9, and 147.0; HRMS (EI) for $C_{15}H_{10}N_5Cl$ calcd.

295.0625, found 295.0627.

4-(1-Benzotriazolyl)-2-carbethoxypyrrole (8a). A three-neck, 100-mL round-bottomed flask was equipped with a condenser, a stir bar and a nitrogen atmosphere. To the flask, 0.180 g (0.0045 mol) of a 60% mineral oil dispersion of sodium hydride was added. The sodium hydride was washed several times with dry hexane, and the hexane was removed via cannula. Dry DMF (20 mL) was added to the flask, followed by 0.45 g (0.0032 mol) of glycine ethyl ester hydrochloride. The mixture was allowed to stir for five minutes before 0.500 g (0.0013 mol) of benzotriazolated vinamidinium salt **(1b)** was added. The reaction was allowed to proceed at 120°C for 20 hours. After the reaction was complete, the solvent was removed in vacuo. The crude material was partitioned between chloroform and water, and the chloroform phase was saved. The aqueous phase was reextracted several times with additional chloroform, and the combined chloroform phases were dried over anhydrous magnesium sulfate. After removing the magnesium sulfate by gravity filtration, the chloroform was removed in vacuo. The crude material was dissolved in 100% ethyl acetate and run through a short column of silica gel. Product purification was completed by radial chromotography on a Harrison Chromatotron with a 2-mm thick silica gel plate. Elution with 80:20 hexane/ethyl acetate yielded a solid (0.29 g, 89% yield) with the following properties: mp 158-160°C: ^{1}H NMR ($CDCl_3$) δ 1.41 (t, J = 7.1 Hz, 3 H), 4.40 (q, J = 7.1 Hz, 2 H), 7.29 (s, 1 H), 7.39 to 7.59 (m, 3 H), 7.71 (d, J = 8 Hz, 1 H), 8.13 (d, J = 8 Hz, 1 H), and 9.72 (broad s, 1 H); ^{13}C NMR (DMSO-d_6) δ 16.1, 62.0, 110.1, 112.8, 119.0, 121.2, 123.9, 126.2, 130.1, 133.9, 146.9, and 161.8; IR (KBr) 3156 and 1716 cm^{-1}; mass spectrum, m/z 256 (M^+). Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.92; H, 4.72; N, 21.87. Found; C, 60.87; H, 4.67; N, 21.87.

4-(1-Benzotriazolyl)-2-carbethoxy-1-methylpyrrole (8b). With reaction conditions similar to those for 4-(1-benzotriazolyl)-2-carboethoxy-pyrrole **(8a)** and using glycine as the condensing agent, a solid (0.31g, 91% yield) was produced with the following properties: mp 116-117°C; ^{1}H NMR ($CDCl_3$) δ 1.39 (t, J = 7.3 Hz, 3 H), 4.10 (s, 3 H), 4.35 (q, J = 7.3 Hz, 2 H), 7.30 (s, 2H), 7.42 (t, J = 8 Hz, 1 H), 7.54 (t, J = 8 Hz, 1 H), 7.70 (d, J = 8 Hz, 1 H), and 8.12 (d, J = 8 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 16.0, 38.7, 61.8, 111.7, 112.7, 121.3, 123.6, 124.6, 126.3, 130.2, 133.7, 147.0, and 161.8; IR 1721 cm^{-1}; mass spectrum, m/z 270 (M^+). Anal. Calcd. for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found; C, 62.23; H, 5.19; N, 20.85.

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