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The application of vinylogous iminium salt derivatives to the regiocontrolled preparation of heterocyclic appended pyrazoles

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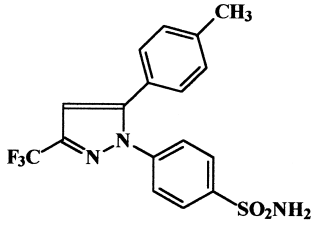
Abstract—A variety of vinylogous iminium salt derivatives have been examined as useful precursors for the regiocontrolled synthesis of heterocyclic appended pyrazoles. The reaction conditions for such processes have been optimized and the regiochemical preferences have been determined. Such reaction sequences represent methodologies which may have useful applications for the preparation of biologically interesting substances.

1. Introduction

Compounds which contain the pyrazole functionality continue to attract great interest due to their varied and significant pharmacological effects. For example, the identification of new and selective cox-2 inhibitors,[1] such as celecoxib (**1**), for the relief of pain and the treatment of the symptoms of arthritis and related diseases has been an important advance in modern anti-inflammatory therapy (Fig. 1). In a related area, heterocycle-appended pyrazoles have been reported[2] to be potent and selective inhibitors of the mitogen-activated protein kinase p38 and consequently provide a novel approach for the treatment of rheumatoid arthritis and related inflammatory diseases. Another significant application of pyrazole chemistry has resulted from the discovery[3] that highly functionalized pyrazoles (such as DPC 423 (**2**)) can act as orally, bioavailable inhibitors of blood coagulation factor Xa. Because of the various side effects associated with current anticoagulants, the identification of orally active substances which require minimal monitoring during treatment has been a priority for drug discovery in this area. Other pyrazole containing compounds have been found to be high-affinity ligands[4] for the estrogen receptor and thereby show promise for menopausal hormone replacement, fertility regulation and the prevention and treatment of breast cancer.



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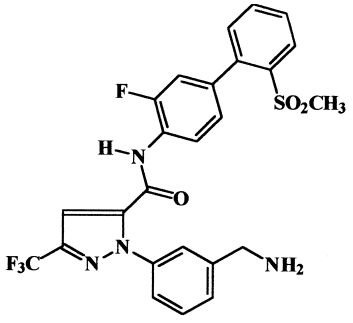

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Figure 1.

Keywords: pyrazoles; vinamidinium salts; chloropropeniminium salts; chlorovinyl aldehydes.
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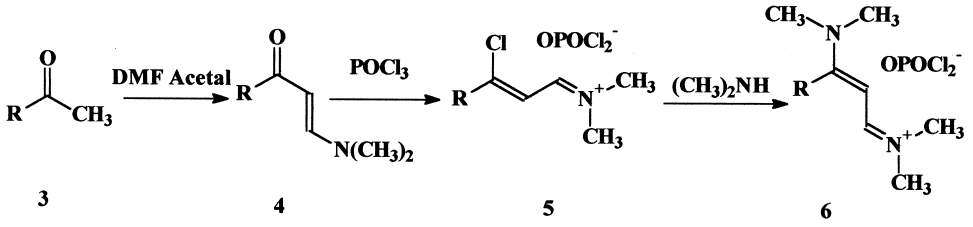


Scheme 1.

The standard approach to the synthesis of pyrazoles has involved the reaction of hydrazine derivatives with 1,3-dicarbonyl compounds. A recent example of such a reaction is described by Nugiel and co-workers[5] in their preparation of indenopyrazoles which were examined as novel inhibitors of cyclin dependent kinases. An alternative strategy is to employ masked 1,3-dicarbonyl compounds such as β-aminoenones as described by Gonzalez-Ortega and co-workers[6] and also by Dominguez et al.[7] In fact β-aminoenones (also known as vinylogous amides) have been recently used by Spivey and co-workers[8] in solid-phase organic synthesis in order to construct a pyrazole library. A related procedure, which uses halovinylaldehydes for the construction of fused pyrazoles has been recently reviewed.[9] A somewhat different approach to pyrazole synthesis developed by Katritzky and co-workers[10] relies on the reaction of hydrazines with α,β-unsaturated ketones, which contain an α-benzotriazole group, such that an addition–elimination sequence results in the desired pyrazole.

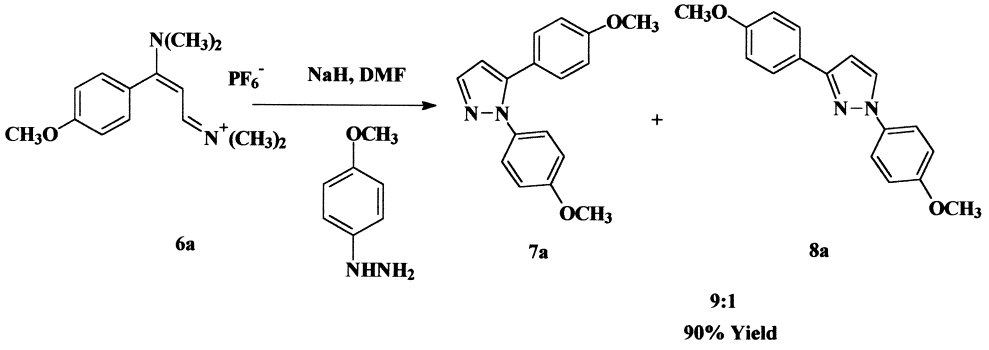
2. Results and discussion

We have previously reported[11] the novel, efficient and regiocontrolled synthesis of highly functionalized pyrroles which used vinylogous iminium salt derivatives as the key synthons. It is also of interest to note that vinamidinium salts, as a consequence of their synthetic utility, have received significant recent attention by Davies and co-workers[12] of the Merck Process Group for the large scale preparation of pyridine-based cox-2 inhibitors. We would now like to report our efforts in applying our pyrrole strategy to the regioselective preparation of heterocyclic appended pyrazoles. The vinylogous iminium salt derivatives that are currently employed in our research program are prepared according to the following general strategy[13] (Scheme 1).

Although β-aminoenones (vinylogous amides, (**4**)) have been studied with regard to their conversion to pyrazoles, chloropropeniminium salts (**5**) and unsymmetrical vinamidinium salts (**6**) have not been thoroughly studied[14] with regard to their efficiency or regiochemical outcome in the preparation of pyrazoles. We have therefore examined a variety of vinylogous iminium salt derivatives for their ability to provide heterocyclic appended pyrazoles in an efficient and regiocontrolled fashion. In order to establish the feasibility of the methodology, we first explored the reaction of vinamidinium salt **6a** with 4-methoxyphenylhydrazine hydrochloride under conditions that had been previously utilized[13] for pyrrole formation (Scheme 2).

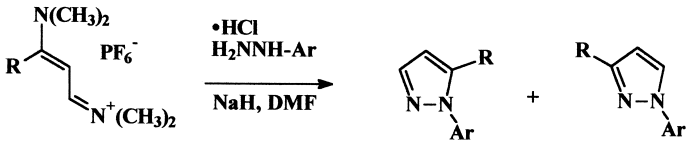
Purification of the reaction mixture by radial chromatography produced both the 1,5- and 1,3-pyrazole isomers, compounds **7a** and **8a**, respectively, in a 9:1 ratio and in a combined yield of 90%. The reaction was subsequently repeated on the 2-thienyl vinamidinium salt (**6b**) in which case an 87% combined yield of pyrazole isomers was obtained after purification. The ratio of isomers was again 9:1 with the 1,5-isomer predominating. The reaction was repeated with several different arylhydrazines and the results are reported in Table 1 (compounds **a**–**d**). In all cases, the reactions produced high yields of the pyrazoles with strong regiochemical preference (9:1) for the 1,5-isomer versus the 1,3-isomer. The yields reported in Table 1 refer to the total yield for both isomers.

With purified samples of compounds **7b** and **8b** in hand, NMR NOE difference spectra were obtained on each isomer. The NMR NOE studies on pyrazole **7b** revealed an interaction between the phenyl protons and thienyl protons which establishes the close proximity of these groups for the 1,5-isomer. No interactions could be observed between either pyrazole hydrogen and the ortho hydrogens of the phenyl group. For pyrazole **8b**, NMR NOE



Scheme 2.

Table 1. Reaction of vinamidinium salts with arylhydrazines



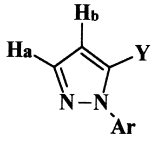
6 **7** **8**

Compound	R	Ar	% Yield	Isomer ratio of **7/8**
a	4-MeOPh	4-MeOPh	90	9/1
b	2-Thienyl	4-MeOPh	87	9/1
c	2-Thienyl	Ph	85	9/1
d	2-Thienyl	4-BrPh	90	9/1
e	3-Thienyl	4-MeOPh	83	9/1
f	2-Furyl	4-MeOPh	86	9/1
g	*N*-Methyl-2-pyrroyl	4-MeOPh	79	9/1
h	*N*-Methyl-2-pyrroyl	4-MeOPh	70	9/1

interactions were observed between the appropriate pyrazole hydrogens and the respective phenyl and thienyl hydrogens thereby establishing the relative relationships of the phenyl and thienyl groups as being 1,3 to each other. In addition, Habraken and co-workers[15] have reported a consistent and useful trend in the chemical shifts of pyrazole hydrogens as a function of the solvent polarity.

The proton NMR chemical shifts for pyrazoles **7** and **8**, as a function of solvent, behaved similarly to pyrazole **9**, reported by Habraken et al., with the exception that the chemical shift of the corresponding Hc proton for pyrazole **8** exhibited a larger shift differential. It was also noted by Habraken that the Hc proton always appears downfield from the Ha proton with both protons having consistently different (albeit small) coupling constants. With the regiochemical assignments established, various heterocycle appended vinamidinium salts were prepared in the standard manner and they were treated with 4-methoxyphenylhydrazine to yield the anticipated pyrazoles in good yield with a 9:1 preference for the 1,5 disubstituted system (Table 1, compounds **e**–**h**). These analogs represent structurally interesting biheterocyclic systems whereby thiophene, furan and pyrrole rings are appended in a regiocontroled fashion at either the 3 or 5 position of the pyrazole ring system. A summary of proton NMR chemical shifts and accompanying coupling constants of the pyrazole hydrogens for the analogs prepared are listed in Table 2. The proton chemical shifts and coupling constants (pyrazole hydrogens) for the analogs listed follow the pattern described by Habraken for 1,5- and 1,3-disubstituted pyrazoles thereby confirming the NOE based structure assignments.

Table 2. Summary of chemical shifts and coupling constants for pyrazole hydrogens for the 1,5- and 1,3-isomers



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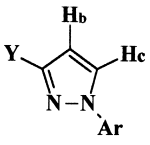

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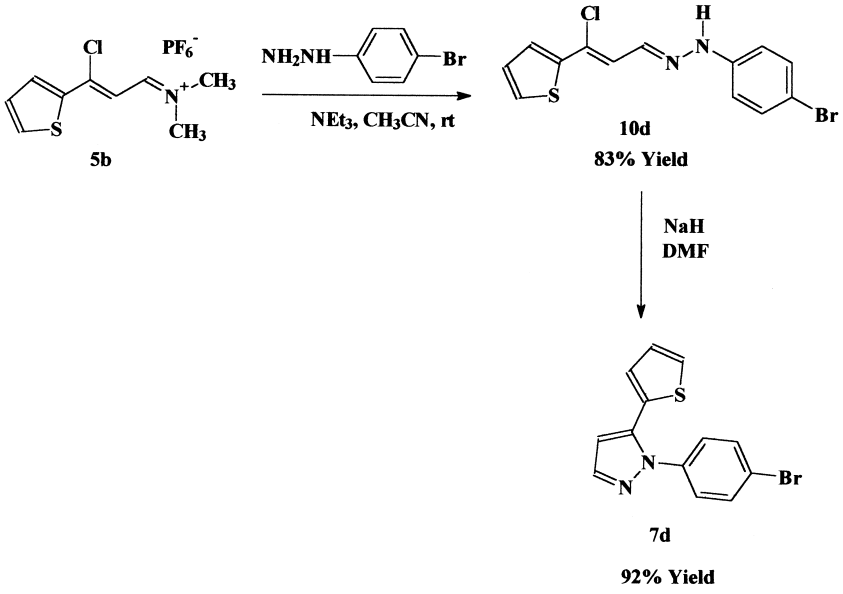
Compound	Y	Ar	H_a (ppm)[a]	H_b (ppm)[a]	J_{ab} (Hz)
9 (Lit. value)	H	5-Pyrazolyl	7.82	6.46	1.7
7a	4-MeOPh	4-MeOPh	7.69	6.55	1.6
7b	2-Thienyl	4-MeOPh	7.68	6.73	1.9
7c	2-Thienyl	Ph	7.74	6.73	1.8
7d	2-Thienyl	4-BrPh	7.77	6.74	1.8
7e	3-Thienyl	4-MeOPh	7.67	6.67	1.8
7f	2-Furyl	4-MeOPh	7.71	6.72	1.9
7g	2-Pyrrolyl	4-MeOPh	7.74	6.57	1.6
7h	3-Pyrrolyl	4-MeOPh	7.54	6.6	1.7
			H_c (ppm)[a]		J_{bc} (Hz)
9 (Lit. value)	H	5-Pyrazolyl	8.22	6.46	2.4
8a	4-MeOPh	4-MeOPh	8.42	6.91	2.2
8b	2-Thienyl	4-MeOPh	8.42	6.9	2.4
8c	2-Thienyl	Ph	8.57	6.96	2.4
8d	2-Thienyl	4-BrPh	8.61	6.99	2.4
8e	3-Thienyl	4-MeOPh	8.42	6.88	2.5
8f	2-Furyl	4-MeOPh	8.46	6.79	2.4
8g	2-Pyrrolyl	4-MeOPh	8.39	7	–

[a] DMSO-d_6 was used as the solvent.

It has already been mentioned that chloropropeniminium salts (**5**) also function as useful three carbon synthons for the preparation of heterocyclic compounds. Such substances have received attention[14] for the preparation of pyrazoles but have not been examined carefully with regard to regiochemical control features and to applications for the synthesis of biheterocyclic systems. Consequently, chloropropeniminium salt **5b** was treated with 4-bromophenylhydrazine under a somewhat milder set of reaction conditions involving triethylamine/acetonitrile at room temperature. A hydrazone intermediate of the vinamidinium salt was produced as a single regioisomer and this was cyclized to the 1,5-disubstituted pyrazole in a second step with sodium hydride/DMF (Scheme 3). No evidence of any 1,3-pyrazole isomer could be detected in the crude reaction product.

A variety of reaction conditions were also studied in order to optimize the formation of the 1,3-disubstituted pyrazole isomer versus the 1,5-isomer. As part of this process, chloropropeniminium salts (such as **5b**) were examined as



Scheme 3.

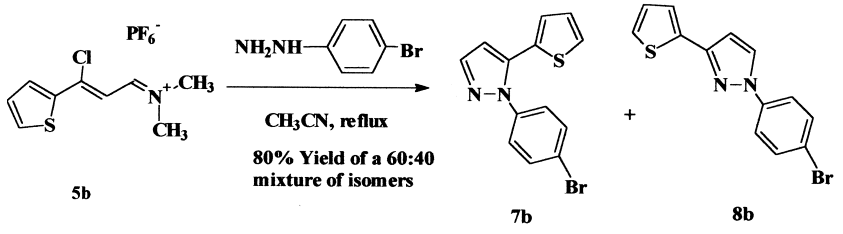
possible precursors. The most useful results are represented in Scheme 4 which suggest that the relative amount of the 1,3-isomer can be increased significantly by running the reaction in the absence of base.

Interestingly, if the arylhydrazine and the chloropropeniminium salt are refluxed in glacial acetic acid, the 1,5-isomer is produced as the only product (Scheme 5). The nature of the controlling mechanistic features of this set of reaction conditions is not clear.

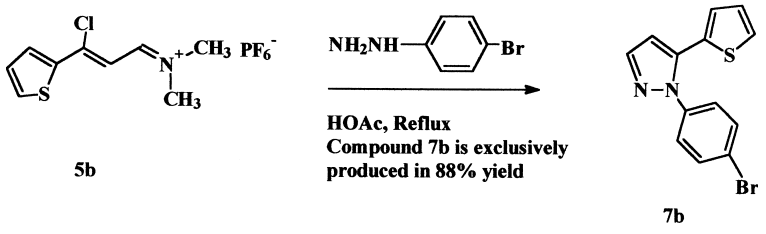
Since chloropropeniminium salts are easily hydrolyzed to the corresponding chlorovinylaldehydes (e.g. **11**), we have also examined these substances as precursors to disubstituted pyrazoles. The initial results (Scheme 6) established the feasibility for this process and since the chloropropeniminium salts and the chlorovinylaldehydes should behave in a somewhat similar fashion, we decided to examine both substrates in greater detail.

Conditions which were employed utilized acetonitrile as the solvent and involved varying the amounts of arylhydrazine and base (DABCO) used in the pyrazole formation. Acetonitrile was chosen for this study since it had been the most effective solvent for the earlier reactions. These trials are listed in Table 3 and there are several trends which stand out.

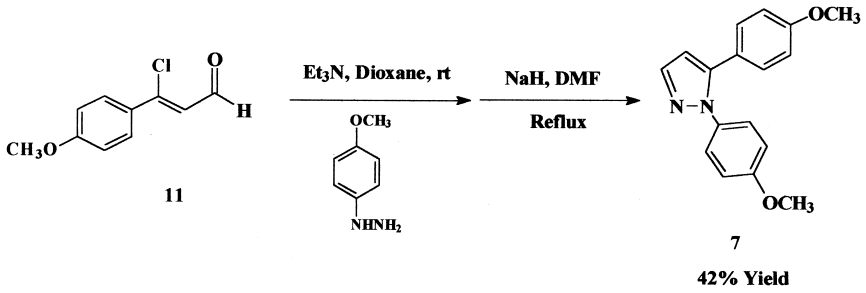
Pyrazole formation is relatively clean and efficient for both chloropropeniminium salt and chlorovinylaldehyde substrates when reactions are conducted in the absence of base (DABCO). If the stoichiometry of the hydrazine is increased by 2:1 relative to the substrate, the yield of pyrazole from the chloropropeniminium salt is improved



Scheme 4.



Scheme 5.



Scheme 6.

but this is not the case for the chlorovinylaldehyde. When the amount of hydrazine is increased[17] relative to the substrate, the pyrazole isomer ratio does not appear to change. The amount of the major isomer tends to increase when the chlorovinylaldehyde is used as the starting material. In an overall sense, both the chloropropeniminium salt and the chlorovinylaldehyde serve as useful and efficient precursors to the 1,5-disubstituted pyrazoles.

3. Conclusions

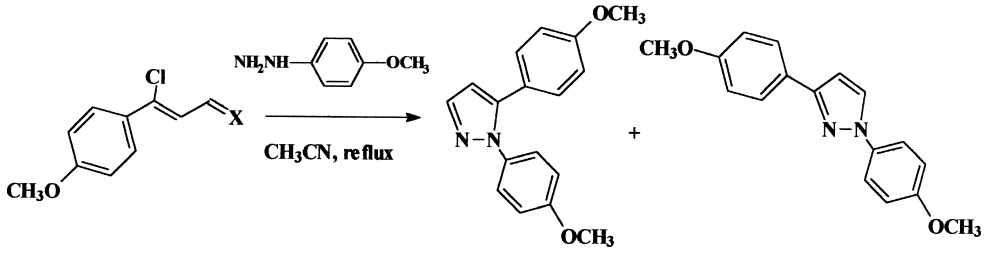
In summary, we have demonstrated that vinamidinium salts, chloropropeniminium salts and chlorovinylaldehydes can be effectively used for the regioselective preparation of heterocyclic appended 1,5-disubstituted pyrazoles. The 1,5-isomer has been found to predominate in most cases and can be exclusively formed by running the reaction in acetic acid or by using a stepwise process where the intermediate hydrazone is obtained and subsequently cyclized. The amount of the 1,3-isomer can be increased by carrying out such reactions in acetonitrile under reflux and in the absence of base. Vinamidinium salts, chloropropeniminium salts and chlorovinylaldehydes can be conveniently and efficiently prepared from a variety of readily available ketones and they serve as chemo-differentiated three carbon building blocks with predictable regiochemical selectivity. Consequently, this synthetic method should provide ready access to structurally and biologically interesting biheterocyclic substances and complement the existing, available procedures for the regioselective preparation of highly functionalized pyrazoles.

4. Experimental

4.1. General

The following procedures are typical of the experimental conditions used for the preparation of pyrazoles. All chemicals were used as received from the manufacturer (Aldrich Chemicals and Fisher Scientific) and all reactions were carried out under a nitrogen atmosphere. NMR spectra were obtained on a Varian Gemini 2000 spectrometer in

Table 3. Reaction of chloropropeniminium salts and chlorovinylaldehydes with 4-methoxyphenylhydrazine



7a **8a**

5a X = $N^+(CH_3)_2$

11a X = O

Substrate[a] (equiv.)	Hydrazine (equiv.)	DABCO (equiv.)	% Yield of pyrazole[b]	Isomer ratio of **7a/8a**[c]
5a (1)	(1)	(0)	69	2/1
5a (1)	(1)	(1)	Trace	–
5a (1)	(2)	(0)	95	2/1
5a (1)	(2)	(2)	Trace	–
11a (1)	(1)	(0)	68	12/1
11a (1)	(1)	(1)	Trace	–
11a (1)	(2)	(0)	53	12/1
11a (1)	(2)	(2)	Trace	–

[a] All reactions were run in refluxing acetonitrile for approximately 14 h.
[b] The yield of total pyrazole was determined by gas chromatography.
[c] The ratio of pyrazole regioisomers was determined by ^{1}H NMR integration.

either $CDCl_3$ or d_6-DMSO solutions. IR spectra were recorded on a Perkin–Elmer 1420 spectrometer as either nujol mulls or KBr pellets. High resolution mass spectra were provided by the Midwest Center for Mass Spectrometry at the University of Nebraska at Lincoln. Melting points and boiling points are uncorrected. Radial chromatographic separations were carried out on a Harrison Chromatotron using silica gel plates of 2 mm thickness with a fluoresecent backing. The vinylogous iminium salt derivatives were prepared by standard methods.[16] All purified compounds gave a single spot upon tlc analysis on silica gel 7GF using an ethyl acetate/hexane mixture as eluent. All chromatographed compounds gave ^{13}C NMR spectra indicative of compounds greater than 95% pure. Gas chromatographic analyses were carried out on a Shimadzu QP5050A GC–MS system equipped with a Restek 30 m, XTI-5 capillary column.

4.1.1. 1-(4-Methoxyphenyl)-5-(2-thienyl)pyrazole (7b). A 100 mL three-neck round-bottom flask was equipped with a stir bar, condenser, and placed under a nitrogen atmosphere. Into the flask was placed 0.226 g (5.6 mmol) of a 60% mineral oil dispersion of sodium hydride. The dispersion was washed twice with hexane, and the hexane was removed via cannula. Dry DMF (10 mL) was added to the flask followed by 0.74 g (4.2 mmol) of arylhydrazine. This solution was allowed to stir for 5 min. Finally, 1.00 g (2.8 mmol) of vinamidinium salt (**6b**) was added along with 30 mL of dry DMF. The reaction was stirred overnight at 100°C and cooled to room temperature. The solvent was removed in vacuo and the residue was partitioned several times between water and chloroform. The combined chloroform extracts were dried and concentrated. The crude product was passed through a short plug of silica gel and purified by radial chromatography using a gradient elution with hexane and ethyl acetate. A 90:10 mixture of 1,5-pyrazole (**7b**)/1,3-pyrazole (**8b**) was obtained in 87% yield (0.65 g). These isomers were easily separated by a second treatment of radial chromatography. The major isomer, 1,5-pyrazole (**7b**), exhibited the following properties: mp 110–112°C; ^1H NMR (DMSO-d_6) δ 3.83 (s, 3H), 6.73 (d, J=1.9 Hz, 1H), 7.00–7.10 (m, 4H), 7.30 (d, J=8.9 Hz, 2H), 7.55 (d of d, J=1.8, 4.6 Hz, 1H), and 7.69 (d, J=1.9 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 57.2, 108.5, 116.1, 129.0, 129.2, 129.3, 129.8, 132.5, 134.2, 138.6, 141.5, and 161.1; FTIR (KBr pellet) 1515, 1251, 834 and 720 cm^{-1}; HRMS calcd for $C_{14}H_{12}N_2SO$ 256.0670 found 256.0678. The minor isomer, 1,3-pyrazole (**8b**), exhibited the following properties: mp 73–74°C; ^1H NMR (DMSO-d_6) δ 3.82 (s, 3H), 6.90 (d, J=2.4 Hz, 1H), 7.00–7.20 (m, 3H), 7.50–7.53 (m, 2H), 7.77 (d, J=9.0 Hz, 2H), and 8.45 (d, J=2.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 57.2, 106.6, 116.4, 121.6, 126.4, 127.2, 129.5, 131.0, 134.9, 137.7, 148.9, and 159.4; FTIR (KBr pellet) 1520 and 1254 cm^{-1}; HRMS calcd for $C_{14}H_{12}N_2SO$ 256.0670 found 256.0676.

4.1.2. 1,5-Bis(4-methoxyphenyl)pyrazole (7a). This compound was prepared in 90% yield as a 90:10 mixture of isomers and the 1,5-isomer (**7a**) exhibited the following properties: mp 104–106°C; ^1H NMR (DMSO-d_6) δ 3.74 (s, 3H), 3.77 (s, 3H), 6.55 (d, J=1.6 Hz, 1H), 6.90 (d, J=8.9 Hz, 2H), 6.96 (d, J=8.9 Hz, 2H), 7.17 (t, J=8.9 Hz, 4H), and 7.68 (d, J=1.6 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 56.9, 57.1, 108.6, 115.8, 115.9, 124.2, 128.5, 131.5, 134.9, 141.4, 144.0, 160.1, and 160.8; FTIR (KBr pellet) 1516, 1252 and 831 cm^{-1}; HRMS calcd for $C_{17}H_{16}N_2O_2$ 280.1212 found 280.1213. The 1,3-isomer (**8a**) exhibited the following properties: mp 190–191°C; ^1H NMR (DMSO-d_6) δ 3.81 (s, 6H), 6.91 (d, J=2.2 Hz, 1H), 7.01 (d, J=9.0 Hz, 2H), 7.07 (d, J=9.0 Hz, 2H), 7.83 (t, J=9.0 Hz, 4H), and 8.42 (d, J=2.2 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 56.9, 57.2, 106.2, 115.9, 116.3, 121.5, 127.3, 128.5, 130.7, 135.2, 153.1, 159.2, and 160.9; FTIR (KBr pellet) 1518 and 1248 cm^{-1}; HRMS calcd for $C_{17}H_{16}N_2O_2$ 280.1212 found 280.1216.

4.1.3. 1-Phenyl-5-(2-thienyl)pyrazole (7c). This compound was prepared in 85% yield as a 90:10 mixture of isomers and the 1,5-isomer (**7c**) exhibited the following properties: bp 86°C at 0.05 torr; ^1H NMR (DMSO-d_6) δ 6.73 (d, J=1.8 Hz, 1H), 6.90–7.10 (m, 2H), 7.30–7.60 (m, 6H), and 7.74 (d, J=1.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 109.3, 128.0, 129.3, 129.4, 130.4, 131.0, 132.3, 138.3, 141.2, and 141.9; FTIR (CCl_4) 1598, 1501, 1390, 927, 764, and 695 cm^{-1}; HRMS calcd for $C_{13}H_{10}N_2S$ 226.0565 found 226.0563.

4.1.4. 1-(4-Bromophenyl)-5-(2-thienyl)pyrazole (7d). This compound was prepared in 90% yield as a 90:10 mixture of isomers and the 1,5-isomer (**7d**) exhibited the following properties: mp 85–87°C; ^1H NMR ($CDCl_3$) δ 6.55 (d, J=1.8 Hz, 1H), 6.83 (d, J=3.6 Hz, 1H), 6.98 (d of d, J=3.6, 5.0 Hz, 1H), 7.26 (d, J=8.8 Hz, 2H), 7.31 (d, J=5.0 Hz, 1H), 7.52 (d, J=8.8 Hz, 2H), and 7.69 (d, J=1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 110.4, 123.9, 128.9, 129.3, 129.5, 132.9, 134.1, 138.7, 140.6, and 142.6; FTIR (CCl_4) 1492, 926, 829 and 704 cm^{-1}; HRMS calcd for $C_{13}H_9N_2SBr$ 303.9670 found 303.9665.

4.1.5. 1-(4-Methoxyphenyl)-5-(3-thienyl)pyrazole (7e). This compound was prepared in 83% yield as a 90:10 mixture of isomers and the 1,5-isomer (**7e**) exhibited the following properties: mp 88–90°C; ^1H NMR (DMSO-d_6) δ 3.82 (s, 3H), 6.67 (d, J=1.8 Hz, 1H), 6.92 (d of d, J=1.3, 5.0 Hz, 1H), 7.02 (d, J=8.8 Hz, 2H), 7.26 (d, J=8.8 Hz, 2H), 7.31 (d of d, J=1.3, 3.0 Hz, 1H), 7.55 (d of d, J=3.0, 5.0 Hz, 1H), and 7.67 (d, J=1.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 57.2, 108.5, 116.0, 125.6, 128.5, 129.0, 129.1, 132.1, 134.8, 140.0, 141.3, and 160.6; FTIR (KBr pellet) 1515, 1250, 840, 805, and 775 cm^{-1}; HRMS calcd for $C_{14}H_{12}N_2SO$ 256.0670 found 256.0673.

4.1.6. 1-(4-Methoxyphenyl)-5-(2-furyl)pyrazole (7f). This compound was prepared in 86% yield as a 90:10 mixture of isomers and the 1,5-isomer (**7f**) exhibited the following properties: bp 101°C at 0.05 torr; ^1H NMR (DMSO-d_6) δ 3.83 (s, 3H), 6.01 (d, J=2.9 Hz, 1H), 6.49 (d of d, J=1.8, 2.9 Hz, 1H), 6.72 (d, J=1.9 Hz, 1H), 7.07 (d, J=9.0 Hz, 2H), 7.33 (d, J=9.0 Hz, 2H), and 7.71 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 57.2, 107.4, 110.5, 113.4, 116.0, 129.0, 134.6, 135.7, 141.6, 145.2, 145.6, and 161.0; FTIR (CCl_4) 1517, 1251 and 836 cm^{-1}; HRMS calcd for $C_{14}H_{12}N_2O_2$ 240.0899 found 240.0913.

4.1.7. 1-(4-Methoxyphenyl)-5-(2-*N*-methylpyrrolyl)pyrazole (7g). This compound was prepared in 79% yield as a 90:10 mixture of isomers and the 1,5-isomer (**7g**) exhibited

the following properties: bp 90°C at 0.1 torr; ^{1}H NMR (DMSO-d_6) δ 3.31 (s, 3H), 3.77 (s, 3H), 5.92 (m, 1H), 6.02 (m, 1H), 6.57 (d, J=1.6 Hz, 1H), 6.85 (m, 1H), 6.94 (d, J=8.9 Hz, 2H), 7.16 (d, J=8.9 Hz, 2H), and 7.74 (d, J=1.6 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 35.9, 57.1, 109.4, 110.6, 112.8, 115.8, 123.4, 125.8, 127.1, 135.0, 136.1, 141.3, and 159.9; FTIR (CCl_4) 1515, 1249, 835 and 722 cm^{-1}; HRMS calcd for $C_{15}H_{15}N_3O$ 253.1215 found 253.1208.

4.1.8. 1-(4-Methoxyphenyl)-5-(3-*N*-methylpyrrolyl)-pyrazole (7h). This compound was prepared in 70% yield as a 90:10 mixture of isomers and the 1,5-isomer (**7h**) exhibited the following properties: mp 94–96°C; ^{1}H NMR (DMSO-d_6) δ 3.60 (s, 3H), 3.82 (s, 3H), 5.73 (m, 1H), 6.40 (d, J=1.7 Hz, 1H), 6.60 (m, 1H), 6.64 (m, 1H), 7.02 (d, J=9.0 Hz, 2H), 7.28 (d, J=9.0 Hz, 2H), and 7.54 (d, J=1.7 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 37.6, 57.2, 105.8, 109.2, 114.4, 115.8, 122.2, 124.2, 129.3, 135.4, 140.8, 141.1, and 160.5; FTIR (CCl_4) 1514, 1260, 830 and 781 cm^{-1}; HRMS calcd for $C_{15}H_{15}N_3O$ 253.1215 found 253.1212.

4.1.9. 1-(4-Bromophenyl)-5-chloro-5-(2-thienyl)-1,2-diazapenta-2,4-diene (10d). To a 100 mL one-neck round-bottom flask were added 1.00 g (2.8 mmol) of chloropropeniminium salt (**5b**), 0.63 g (2.8 mmol) of arylhydrazine, 0.28 g (2.8 mmol) of triethylamine, 40 mL of dry acetonitrile, and a stir bar. The solution was stirred for 1 h at room temperature. The solvent was removed in vacuo and the residue was partitioned several times between water and chloroform. The combined chloroform extracts were dried and concentrated. The crude product was passed through a short plug of silica gel and purified by radial chromatography using a gradient elution with hexane and ethyl acetate. An 83% yield (0.79 g) of a yellow solid was obtained and exhibited the following properties: mp 120–122°C; ^{1}H NMR (DMSO-d_6) δ 6.97 (d, J=8.9 Hz, 2H), 7.04 (d, J=8.9 Hz, 1H), 7.13 (d of d, J=5.0, 3.7 Hz, 1H), 7.39 (d, J=8.9 Hz, 2H), 7.52 (d, J=3.7 Hz, 1H), 7.65 (d, J=5.0 Hz, 1H), 7.94 (d, J=8.9 Hz, 1H), and 10.91 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 112.3, 116.0, 123.1, 127.0, 127.8, 129.5, 130.3, 133.6, 137.2, 142.9, and 145.3; FTIR (KBr pellet) 3310, 1474 and 826 cm^{-1}; HRMS calcd for $C_{13}H_{10}N_2SBrCl$ 339.9437 found 339.9434.

4.2. Preparation of pyrazole (7d) using hydrazone (10d) as starting material

A 50 mL three-neck round-bottom flask was equipped with a stir bar, condenser and placed under nitrogen. Into the flask was placed 0.112 g (2.8 mmol) of a 60% mineral oil dispersion of sodium hydride. The dispersion was washed twice with dry hexane, and the hexane was removed via cannula. Dry DMF (10 mL) was added to the flask followed by 0.50 g (1.4 mmol) of hydrazone (**10d**) which had been dissolved in 10 mL of DMF. The solution was heated at 100°C overnight. The reaction was cooled to room temperature and the solvent was removed in vacuo. The residue was partitioned several times between water and chloroform. The combined chloroform extracts were dried and concentrated. The residue was passed through a short plug of silica gel and purified by radial chromatography using a gradient elution with hexane and ethyl acetate. Pyrazole **6c** was the only isomer obtained in 92% yield (0.39 g). This product was characterized by tlc and proton NMR spectra and compared to an authentic sample.

4.3. Preparation of pyrazole (7d) under acidic conditions

A 100 mL one-neck round-bottom flask was equipped with a condenser and stir bar. Into the flask were placed 1.00 g (2.8 mmol) of chloropropeniminium salt (**5d**), 1.25 g (5.6 mmol) of arylhydrazine, and 40 mL of acetic acid. The reaction was heated at reflux overnight. The reaction was cooled, neutralized with sodium bicarbonate, and partitioned several times between water and chloroform. The combined chloroform extracts were dried and concentrated. The residue was passed through a short plug of silica gel and purified by radial chromatography using a gradient elution with hexane and ethyl acetate. Pyrazole **6c** was the only isomer obtained in 88% yield (0.74 g). This product was characterized by tlc and proton NMR spectra and compared to an authentic sample.

4.4. Preparation of pyrazoles (7d) and (8d) under neutral conditions

A 100 mL one-neck round-bottom flask was equipped with a condenser and stir bar. Into the flask were placed 1.00 g (2.8 mmol) of chloropropeniminium salt (**5d**), 0.63 g (2.8 mmol) of arylhydrazine, and 40 mL of dry acetonitrile. The reaction was stirred at room temperature for 2 h followed by heating at reflux overnight. The reaction was cooled and partitioned several times between water and chloroform. The combined chloroform extracts were dried and concentrated. The residue was passed through a short plug of silica gel and purified by radial chromatography using a gradient elution with hexane and ethyl acetate. A 3:2 ratio of pyrazole **7d**: pyrazole **8d** was obtained in 80% yield (0.68 g). The isomers were separated by a second treatment of radial chromatography. These products were characterized by tlc and proton NMR spectra and compared to an authentic sample.

4.5. Preparation of 1,5-bis(4-methoxyphenyl)pyrazole (7a) from the β-chlorovinylaldehyde (11)

β-Chlorovinylaldehyde (**11**) (0.60 g, 3.0 mmol) was placed in a round bottom flask equipped with a condensor and stir bar followed by 4-methoxyphenylhydrazine hydrochloride (1.54 g, 15.2 mmol) and dioxane (100 mL). The mixture was stirred for 2.5 h at room temperature and then heated at reflux for 15 h. The solvent was removed in vacuo and the residue was partitioned between chloroform (35 mL) and water (35 mL). The aqueous phase was extracted with additional chloroform (3×35 mL) and the combined chloroform extracts were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to yield a dark, viscous oil. This oil was placed in a round bottom flask equipped with a reflux condensor and stir bar and 50 mL of DMF were added. The resulting mixture was refluxed for 15 h and concentrated in vacuo. The resulting residue was subjected to the usual chloroform/water work up and subsequent purification by radial chromatography. A 42% yield (0.35 g) of the bis(4-methoxyphenyl)pyrazole (**7a**) was

obtained which was identical by proton NMR spectra and tlc analysis to a sample prepared via the vinamidinium salt method.

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