Selectivity of amidrazones towards activated nitriles – synthesis of new pyrazoles and NMR investigation

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DOI: https://doi.org/10.24820/ark.5550190.p009.877

Abstract

N-Arylbenzamidrazones reacted with 2-(ethoxymethylene)malononitriles in ethanol/DMF (20:1), catalyzed by triethylamine (Et_3N), to give 65-81% yields of the corresponding pyrazoles. The structures of the products were proved by IR, mass, and NMR spectra and elemental analyses. Two-dimensional NMR correlations were used to differentiate between possible structures. The reaction mechanism is also discussed.

Keywords: Amidrazones, 2-(ethoxymethylene)malononitriles, pyrazoles, NMR, conjugate addition

Introduction

Amidrazones are convenient building blocks for various heterocycles.[1-5] Recently, we have reported that amidrazones reacted with 2,3-diphenylcyclopropenone via extrusion of ammonia to give 3-(aryl)-2,5,6-triphenylpyrimidin-4(3*H*)-ones.[6]

For a very long time, the usefulness and great therapeutic value of the pyrazole nucleus have been recognized and the activities of this nucleus have been evaluated.[7] Phenazone (antipyrine), a pyrazolin-5-one, was one of the first synthetic drugs.[8] Phenylbutazone, a pyrazolidinedione, is a very potent anti-inflammatory agent, but its use is now banned in some countries.[9] Later on, many modifications of the pyrazole nucleus were attempted and several compounds have been

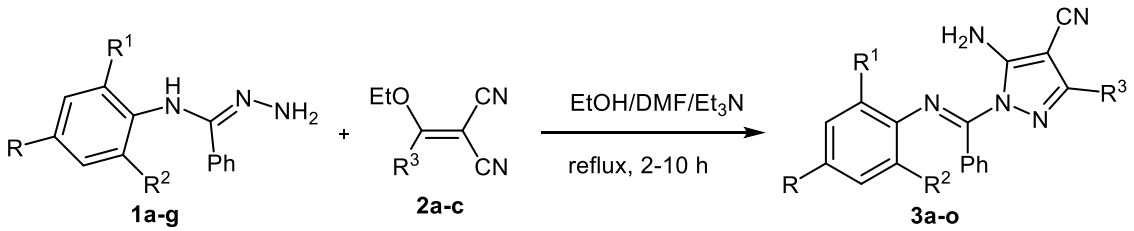
synthesized for the treatment of different conditions like inflammation, pain, cancer, tuberculosis, and diseases caused by bacteria. Some pyrazoles have shown high anti-inflammatory activity compared to indomethacin as the standard drug.[10] Tewari *et al*.[11] have synthesized a series of pyrazoles and evaluated them *in vivo* for their anti-inflammatory activity in carrageenan-induced rat paw edema model using nimesulide as the standard drug. Molecular modeling studies showed that pyrazole analogs interact with the cyclooxygenase-2 (COX-2) active site by classical hydrogen bonding, π-π interaction, and cation–π interaction which increases the residence of the ligand in the active site, consequently augmenting the anti-inflammatory activity of the compounds.[11] Anti-bacterial activity was also tested by Ragavan *et al*.,[12] who have synthesized a group of 1,5-diaryl pyrazoles by altering the active part (amide linkage) and tested the products for anti-bacterial activity against *E. coli* (American Type Culture Collection [ATTC] - 25922), *S. aureus* (ATTC-25923), *Pseudomonas aeruginosa* (ATTC-27853), and *Klebsiella pneumonia*. As anti-cancer agents, pyrazoles have potent anti-angiogenic activity, and inhibit the growth of human breast (MCF-7) and cervical (Hela) carcinoma cells *in vitro*.[13] Also, it was reported that some of a series of 1-arylmethyl-3-aryl-1*H*-pyrazole-5-carbohydrazide derivatives inhibit the growth of A549 cells, and induce cell apoptosis.[14] In addition, two series of pyrazoles were studied as inhibitors of epidermal growth factor receptor (EGFR) kinase; the most potent had an IC_{50} of 0.07 μM, as compared to positive control erlotinib.[15] As antidepressant and anticonvulsant agents, pyrazoles showed good activity as compared to imipramine at a dose level of 10 mg/kg.[16] Pyrazoles have also found use as bifunctional ligands for metal catalysis,[17,18] as model systems to study excited-state intramolecular proton transfers,[19] as artificial receptors,[20,21] and as the backbone to numerous scorpionate ligands.[22] For all these reasons, pyrazole synthesis continues to attract interest. Herein we describe the synthesis of new pyrazoles via the reaction of amidrazones with activated alkenes.

Results and Discussion

Amidrazones[23] **1a-g** reacted with 2-(ethoxymethylene)malononitriles **2a-c** in ethanol/DMF (20:1), in presence of triethylamine (Et_3N) to furnish the pyrazoles **3a-o** in 65-81% yields (Scheme 1). We chose amidrazones **1a–g** having aryl groups with either electron-donating or electron withdrawing substitutents on the benzene ring, in order to examine their effect on the reaction. Amidrazones bearing electron-donating groups in the phenyl group attached to N^3 such as *p*-Me (**1b**), 2,6-di-Me (**1c**) or 2-Me (**1g**), or moderately electron-withdrawing substituents such as *p*-Cl (**1d**) or *p*-Br (**1f**), all underwent the reaction smoothly to give the respective pyrazoles (**3b-d,f-h,j-m,o**) in 70-81% yields. For amidrazones bearing strong electron-withdrawing substituents in N^3-Ar such as *p*-NO_2 (**1e**), the reactions proceeded slowly to give 65-67% yields of the corresponding pyrazoles (**3e**,**i**,**n**).

Elemental analyses and IR, NMR, and mass spectra were in good agreement with the assigned product structures. Structures were elucidated with the aid of 1D ^1H and ^{13}C NMR spectra, and

^{1}H-^{1}H COSY and ^{1}H-^{13}C and ^{1}H-^{15}N HSQC and HMBC correlations. Figure 1 shows the positional designations used throughout the series.



1a: R = R^1= R^2 = H;
1b: R = CH_3, R^1= R^2 = H;
1c: R = H, R^1= R^2 = CH_3;
1d: R = Cl, R^1= R^2 = H;
1e: R = NO_2, R^1= R^2 = H;
1f: R = Br, R^1= R^2 = H;
1g: R = R^2 = H, R^1 = CH_3

2a: R^3 = H;
2b: R^3 = CH_2CH_3;
2c: R^3 = CH_3

3a: R = R^1 = R^2 = R^3 = H (70%);
3b: R = CH_3, R^1 = R^2 = R^3 = H (72%);
3c: R = R^3 = H, R^1 = R^2 = CH_3 (79%);
3d: R = Cl, R^1 = R^2 = R^3 = H (71%);
3e: R = NO_2, R^1 = R^2 = R^3 = H (65%);
3f: R = Br, R^1 = R^2 = R^3 = H (73%);
3g: R = H, R^1 = R^2 = CH_3, R^3 = CH_2CH_3 (79%);
3h: R = Cl, R^1 = R^2 = H, R^3 = CH_2CH_3 (73%);
3i: R = NO_2, R^1 = R^2 = H, R^3 = CH_2CH_3 (67%);
3j: R = Br, R^1 = R^2 = H, R^3 = CH_2CH_3 (76%);
3k: R = R^2 = H, R^1 = R^3 = CH_3 (78%);
3l: R = H, R^1 = R^2 = R^3 = CH_3 (81%);
3m: R = Cl, R^1 = R^2 = H, R^3 = CH_3 (72%);
3n: R = NO_2, R^1 = R^2 = H, R^3 = CH_3 (67%);
3o: R = Br, R^1 = R^2 = H, R^3 = CH_3 (74%)

Scheme 1. Synthesis of pyrazoles **3a-o** by the reaction of amidrazones **1a-g** with **2a-c.**

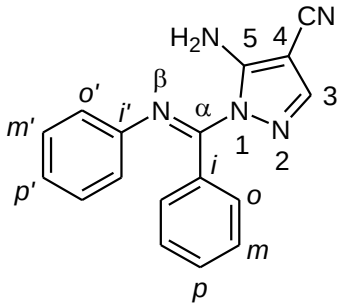


Figure 1. Positional designations for compounds **3.**

Compound **3c** illustrates the method. Mass and elemental analyses indicated that the molecular weight is consistent with the molecular formula $C_{19}H_{17}N_4$. The IR spectra showed absorbance for amino, nitrile and C=N groups at ν_{max} (cm^{-1}) = 3384-3265 (NH_2), 2217 (CN), 1651, 1610 (C=N). For assigning the NMR spectra, the 2,6-dimethylphenyl ring provides a convenient starting point. The methyl protons and their attached carbon are distinctive at δ_H = 2.05 and δ_C = 18.3 respectively. The methyl carbon gives HMBC correlation with a 2H doublet at δ_H = 6.92, assigned as H-*m'*; the attached carbons appear at δ_C = 127.7. H-*m'* gives COSY correlation with a 1H triplet at δ_H = 6.81, assigned as H-*p'*; the attached carbon appears at δ_C = 123.5. H-*m'*, H-*p'*, and CH_3 all give HMBC

correlation with a carbon at δ_C = 144.2, assigned as H-*i':* this is a three-bond coupling from CH_3 and H-*m',* and a four-bond coupling from H-*p'*. H-*p'* gives HMBC correlation with a carbon at δ_C = 126.6, assigned as C-*o';* this is a three-bond coupling. C-*o'* gives no other HMBC correlation; this signal is the only tall carbon signal lacking attached protons. (The ^{13}C lines from doubly-degenerate carbons are about twice the height of the others: four signals when both phenyl rings are twofold symmetric, two signals in **3k**). The protons of the monosubstituted phenyl ring barely separate into a 1H triplet at δ_H = 7.33, a 2H "triplet" at δ_H = 7.27, and a 2H doublet at δ_H = 7.19; these are assigned as H-*p,* H-*m,* and H-*o* respectively. The attached carbons appear at δ_C = 130.0 (C-*p),* 128.0 (C-*m),* and 128.2 (C-*o).* H-*m* gives HMBC correlation with a non-protonated carbon at δ_C = 131.2, assigned as C-*i;* this is a three-bond coupling.

Table 1. NMR assignments of compound **3c**

^{1}H NMR (DMSO-d_6)	**^{1}H-^{1}H COSY**		**Assignment**
8.20 (bs; 2H)			NH_2
7.74 (s; 1H)			H-3
7.33 (t, *J* 7.3; 1H)	7.27,7.19		H-*p*
7.27 (dd, *J* 7.7, 7.2; 2H)	7.33,7.19		H-*m*
7.19 (d, *J* 7.3; 2H)	7.33, 7.27		H-*o*
6.92 (d, *J* 7.5; 2H)	6.81		H-*m*'
6.81 (t, *J* 7.3; 1H)	6.92		H-*p*'
2.04 (s; 6H)			Ar-CH_3
^{13}C NMR (DMSO-d_6)	**HSQC**	**HMBC**	**Assignment**
156.2		7.27, 7.19, 2.04	C-α
154.6		7.74	C-5
144.2		6.92, 6.81, 2.04	C-*i'*
141.7	7.74		C-3
131.2		7.27	C-*i*
130.0	7.33	7.19	C-*p*
128.2	7.19	7.33, 7.19	C-*o*
128.0	7.27	7.27, 2.04	C-*m*
127.7	6.92		C-*m*'
126.6		6.81	C-*o*'
123.5	6.81		C-*p*'
114.2		7.74	C-4a
72.9		8.20, 7.74	C-4
18.3	2.18	6.92, 6.81	Ar-CH_3
^{15}N NMR (DMSO-d_6)	**HSQC**	**HMBC**	**Assignment**
-94.9		7.74	N-2
-178.0		8.20, 7.74	N-1
-310.4	8.20		NH_2

This leaves the pyrazole ring. The amino protons give a broadened singlet at δ_H = 8.20, whose attached nitrogen appears at δ_N = 70.0. The amino protons give HMBC correlation with a carbon at δ_C = 72.9, assigned as C-4. (The upfield shift arises because this carbon is part of a push-pull system.[24]) C-4 also gives HMBC correlation with a singlet at δ_H = 7.74, assigned as H-3; its attached carbon appears at δ_C = 141.7. H-3 also gives HMBC correlation with a carbon at δ_C = 154.6, assigned as C-5, and with the nitrile carbon at δ_C = 114.2. H-3 gives HMBC correlation with a nitrogen at δ_N = -178.0; this nitrogen also gives HMBC correlation with N**H**$_2$**.** These are both three-bond correlations if this nitrogen is N-1, which is also consistent with its chemical shift (between the normal sp^3 and sp^2 ranges). H-3 also gives HMBC correlation with a nitrogen at δ_N = -94.9, which is assigned as N-2; this is a two-bond correlation, but two-bond H-N couplings are larger than four-bond couplings (like that between H-3 and the nitrile nitrogen, which is not observed). The remaining carbon, at δ_C = 156.2, is assigned as C-α based on chemical shift; it gives HMBC correlation with H-*m* (four bonds), H-*o* (three bonds), and CH_3 (five bonds). Table 1 summarizes the NMR assignments of compound **3c**.

The regiochemical assignment depends on the ^{1}H-^{15}N correlations. Nitrogen signals were measured for thirteen of the fifteen products. Nitrogen signals were observed indirectly *via* the proton channel, using gradient-enhanced HSQC and HMBC experiments;[25] HMBC experiments utilized a standard mixing time of 65 ms; this is supposed to equal 1/[2*J*(N,H)], corresponding to *J* 7.7 Hz. Because ^{1}H-^{15}N coupling constants are smaller than the corresponding ^{1}H-^{13}C couplings,[26] the intensity and observability of cross-peaks are sensitive to the mixing time,[27] and we could not detect all the nitrogen atoms; however, the signals detected suffice to prove the regiochemistry. Table 2 lists the observed ^{15}N signals, together with the protons to which they give HSQC or HMBC correlations; Figure 2 shows the general structures of products **3** and possible regioisomers **4**.

Table 2. Nitrogen chemical shifts of products, and their ^{1}H correlations

Compound	**N**H$_2$[a]	N-1[b]	N-2[b]	N-β[b]	NO$_2$[b]
3a	-310.7 (N**H**$_2$)	-177.7 (H-3)	n/o[c]	n/o	--[d]
3b	-310.8 (NH$_2$)	-177.3 (NH$_2$, H-3)	-94.7 (H-3)	-101.6 (H-*o'*)	--
3c	-310.4 (NH$_2$)	-178.0 (NH$_2$, H-3)	-94.9 (H-3)	n/o	--
3d	-310.2 (NH$_2$)	n/o	n/o	n/o	--
3f	-309.6 (NH$_2$)	-177.5 (NH$_2$, H-3)	-95.0 (H-3)	-104.5 (H-*o'*)	--
3g	-310.5 (NH$_2$)	n/o	-102.2 (H-3a)[e]	n/o	--
3i	-310.5 (NH$_2$)	n/o	-102.7 (H-3a)	-106.8 (H-*o'*)	-10.2 (H-*m'*)
3j	-309.9 (NH$_2$)	n/o	-102.6 (H-3a)	n/o	--
3k	-310.1 (NH$_2$)	-181.6 (NH$_2$)	-101.6 (H-3a)	-103.2 (H-3')[f]	--
3l	-310.4 (NH$_2$)	-182.4 (NH$_2$)	-101.4 (H-3a)	n/o	--
3m	-309.5 (NH$_2$)	-181.5 (NH$_2$)	-101.9 (H-3a)	-107.1 (H-*o'*)	--
3n	-308.6 (NH$_2$)	n/o	-101.9 (H-3a)	-107.1 (H-*o'*)	n/o
3o	-309.5 (NH$_2$)	-181.6 (NH$_2$)	-101.8 (H-3a)	-106.6 (H-*o'*)	--

[a] HSQC correlation. b: HMBC correlation. c: Not observed. d: No such nitrogen. [e] Pseudo-benzylic methyl or methylene protons attached to C-3. [f] Non-symmetric ring: same position as H-*o'* in other rings.

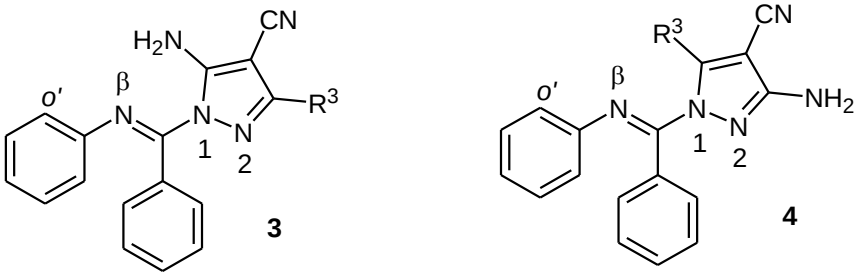
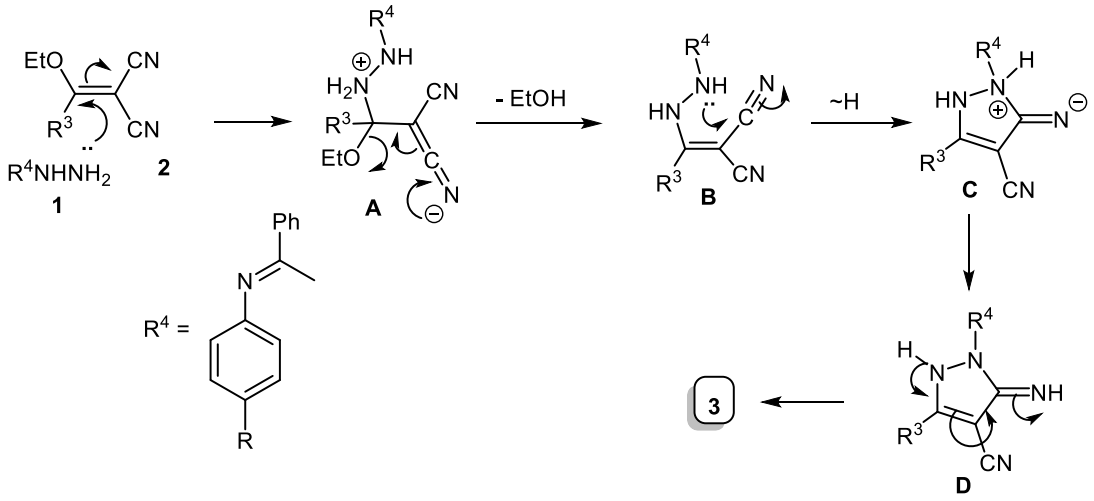


Figure 2. General structures of products **3** and possible regioisomers **4.**

In all structures, the broadened amino protons give HSQC correlation with an sp^3 nitrogen, which is assigned as **N**H_2. In seven of the products, the same broadened protons also give HMBC correlation with a nitrogen at δ_N = -177 to -183; this chemical shift corresponds to the formally sp^3 nitrogen of an amidine,[28] and the signal is assigned as N-1, consistent with structure **3**. In the regioisomer **4,** the nitrogen three bonds from the amino protons would be sp^2 hybridized, and would have a chemical shift of approximately δ_N = -110. Consistent with the assignment of structures **3** is the HMBC correlation observed, in products **3g-o**, between H-3a and an sp^2 nitrogen at δ_N = -101 to -103, assigned as N-2. No nitrile nitrogen atoms were observed: they are all at least four bonds from the nearest protons. The presence of the nitrile groups is deduced from observations of the nitrile *carbons* in the ^{13}C NMR spectra, and of nitrile absorptions in the IR spectra.

Mechanistically, the reaction can be described (Scheme 2) as due nucleophilic attack of the hydrazine group to C-1 to form salt **A**.



Scheme 2. Mechanism of pyrazole formation from reaction of **1a-g** with **2a-c**

The observation of products **3,** rather than **4**, requires that this attack occur at C-1 instead of one of the nitrile carbons. Elimination of ethanol would then give intermediate **B**. Subsequently, internal cyclization of **B** would give **C**, which would be in tautomerism with **D** and ultimately give product **3** after proton transfer.

Experimental Section

General. NMR spectra were measured on a Bruker AV-400 spectrometer (Bruker BioSpin Corp., Billerica, MA, USA) (400 MHz for ^{1}H, 100 MHz for ^{13}C, and 40.55 MHz for ^{15}N) at Florida Institute of Technology, USA. The ^{1}H and ^{13}C chemical shifts are given relative to internal standard TMS = 0; ^{15}N shifts are reported versus external neat nitromethane = 0.[29] For preparative thin layer chromatography (PLC), glass plates (20 x 48 cm) were covered with a slurry of silica gel Merck PF254 and air dried and developed using the solvents listed. Zones were detected by quenching of indicator fluorescence upon exposure to 254 nm UV light. Elemental analyses were carried in the National Research center, Dokki, Cairo, Egypt. Mass spectrometry was performed by electron impact at 70 eV, with a Finnigan Mat 8430 spectrometer in the National Research center, Dokki, Cairo, Egypt. IR spectra using KBr pellets, were run on a FT-IR (Bruker), Minia University, El-Minia, Egypt. Amidrazones **1a-g** were prepared according to reference 23.

Reaction of amidrazones 1a-g with 2a-c (Scheme 1)

General procedure. A 100 mL round-bottom flask was flame-dried. Dry absolute ethyl alcohol (20 mL) containing a few drops of triethylamine Et_3N and 1 mL of DMF, a mixture of **1a-g** (1 mmol) and **2a-c** (1 mmol) was added. The mixture was stirred under reflux for 2–10 h (the reaction was followed by TLC analysis). The solvent was then removed under vacuum and the residue was separated. The products **3a-o** were obtained and were recrystallized from the stated solvents.

(*E*)-5-Amino-1-(phenyl(phenylimino)methyl)-1*H*-pyrazole-4-carbonitrile (3a). Pale yellow crystals (EtOH), yield: 0.23 g (70%)); mp 204-205 ºC. IR (KBr; ν_{max}, cm^{-1}): 3369-3273 (NH_2), 3057 (CH aromatic), 2218 (C≡N), 1644, 1618 (C=N), 1552 (C=C). ^{1}H NMR (DMSO-d_6): δ_H 8.25 (bs, 2H; NH_2), 7.75 (s, 1H; H-3), 7.31 (m, 5H; H-*o*,*m*,*p*), 7.19 (t, *J* 7.4 Hz, 2H; H-*m'*), 6.98 (t, 1H, *J* 7.2 Hz; H-*p'*), 6.82 (d, 2H, *J* 7.6 Hz; H-*o*). ^{13}C NMR (DMSO-d_6): δ_C 157.7 (C-α), 154.4 (C-5), 146.4 (C-*i'*), 141.9 (C-3), 130.8 (C-*i*), 129.4 (C-*p*), 129.2 (2C; C-*o*), 128.5 (2C; C-*m'*), 127.6 (2C; C-*m*), 123.8 (C-*p'*), 121.5 (2C; C-*o'*), 114.2 (C≡N), 72.7 (C-4). ^{15}N NMR: Table 2. MS (EI, 70 eV): *m/z* (%) 287 (M^+, 10), 180 (100), 77 (59). Anal. Calcd for $C_{17}H_{13}N_5$ (287.12): C, 71.06; H, 4.56; N, 24.37. Found: C, 70.90; H, 4.49; N, 24.30.

(*E*)-5-Amino-1-(phenyl(*p*-tolylimino)methyl)-1*H*-pyrazole-4-carbonitrile (3b). Pale yellow crystals (EtOH), yield: 0.23 g (77%); mp 241-242 ºC. IR (KBr; ν_{max}, cm^{-1}): 3438-3294(NH_2), 3061 (CH aromatic), 2921 (CH aliphatic), 2217 (C≡N), 1650, 1607 (C=N), 1548 (C=C). ^{1}H NMR (DMSO-d_6): δ_H 8.22 (bs, 2H; NH_2), 7.71 (s, 1H; H-3), 7.30 (m, 3H; H-*p, m*), 7.26 (m, 2H; H-*o*), 6.96 (d, *J* 7.8 Hz, 2H; H-*m'*), 6.68 (d, *J* 7.7 Hz, 2H; H-*o'*), 2.18 (s, 3H; CH_3). ^{13}C NMR (DMSO-

d_6): δ_C 157.6 (C-α), 154.4 (C-5), 143.8 (C-*i'*), 141.8 (C-3), 132.8 (C-*p'*), 130.9 (C-*i*), 129.4 (C-*p*), 129.2 (2C; C-*o*), 129.0 (2C; C-*m'*), 127.6 (2C; C-*m*), 121.5 (2C; C-*o'*), 114.2 (C≡N), 72.7 (C-4), 20.3 (CH_3). ^{15}N NMR: Table 2. MS (EI, 70 eV): *m/z* (%) 301 (M^+, 10), 238 (100), 214 (80), 194 (30), 135 (67), 77 (50). Anal. Calcd for $C_{18}H_{15}N_5$ (301.13): C, 71.74; H, 5.02; N, 23.24. Found: C, 71.60; H, 5.00; N, 23.10.

(*E*)-5-Amino-1-((2',6'-dimethylphenyl)imino)(phenyl)methyl)-1*H*-pyrazole-4-carbonitrile (3c). Pale yellow crystals (CH_3OH/DCM), yield: 0.25 g (79%); mp 247-248 ºC. IR (KBr; ν_{max}, cm^{-1}) 3384-3265 (NH_2), 3112 (CH aromatic), 2947 (CH aliphatic), 2217 (C≡N), 1651, 1610 (C=N), 1548 (C=C). NMR (DMSO-d_6): Tables 1 and 2. MS (EI, 70 eV): 315 (M^+, 45), 207 (100), 153 (42), 136 (27), 106 (8). Calcd for $C_{19}H_{17}N_5$ (315.15): C, 72.36; H, 5.43; N, 22.21. Found: C, 72.20; H, 5.30; N, 22.10.

(*E*)-5-Amino-1-((4'-chlorophenylimino)(phenyl)methyl)-1*H*-pyrazole-4-carbonitrile (3d). Pale yellow crystals (EtOH), yield: 0.22 g (71%); mp 258-259 ºC. IR (KBr; ν_{max}, cm^{-1}): 3378-3276(NH_2), 3054 (CH aromatic), 2220 (C≡N), 1642, 1618 (C=N), 1550 (C=C). ^{1}H NMR (DMSO-d_6): δ_H 8.22 (s, 2H; NH_2), 7.73 (s, 1H; H-3), 7.31 (m, 5H; H-*o,m,p*), 7.22 (d, *J* 8.2 Hz, 2H; H-*m'*), 6.82 (d, *J* 8.0 Hz, 2H; H-*o'*). ^{13}C NMR (DMSO-d_6): δ_C 158.2 (C-α), 154.4 (C-5), 145.5 (C-*i'*), 142.1 (C-3), 130.6 (C-*i*), 129.5 (C-*p*), 129.2 (2C; C-*o*), 128.4 (C-*p'*), 128.4 (2C; C-*m'*), 127.6 (2C; C-*m*), 123.4 (2C; C-*o'*), 114.2 (C≡N), 72.7 (C-4). ^{15}N NMR: Table 2. MS (EI, 70 eV): *m/z* (%) 323 (M+2, 8), 321 (23, M^+), 214 (100), 111 (12), 75 (13). Anal. Calcd for $C_{17}H_{12}ClN_5$ (321.08): C, 63.46; H, 3.76; N, 21.77. C, 63.34; H, 3.65; N, 10.90.

(*E*)-5-Amino-1-((4'-nitrophenylimino)(phenyl)methyl)-1*H*-pyrazole-4-carbonitrile (3e). Pale yellow crystals (CH_3OH/DCM), yield: 0.23 g (71%); mp 270-271 ºC. IR (KBr; ν_{max}, cm^{-1}): 3453-3295 (NH_2), 3095(CH aromatic), 2217 (C≡N), 1659, 1610 (C=N), 1508 (C=C). ^{1}H NMR ($CDCl_3$): δ_H 8.05 (bs, 2H, NH_2), 7.5 (s, 1H, H-3), 7.30-7.20 (m, 5H, H-*o,m,p*), 6.90-6.88 (d, *J* 7.5 Hz, 2H; H-*m'*), 6.80-6.77 (d, *J* 7.5 Hz, 2H; H-*o''*). ^{13}C NMR ($CDCl_3$): δ_C 159.1, 154.6, 152.2, 144.3, 142.1, 130.9, 129.4, 129.2 (2C), 128.3 (2C), 124.7 (2C), 122.3 (2C), 113.3, 75.4. MS (EI, 70 eV): *m/z* (%) 332 (M^+, 25), 225 (100), 179 (37), 76 (53). Anal. Calcd for $C_{17}H_{12}N_6O_2$ (332.10): C, 61.44; H, 3.64; N, 25.29

(*E*)-5-Amino-1-((4'-bromophenylimino)(phenyl)methyl)-1*H*-pyrazole-4-carbonitrile (3f). Pale yellow crystals (CH_3OH/DCM), yield: 0.25 g (70%); mp 280-281 ^{0}C. IR (KBr; ν_{max}, cm^{-1}): 3382-3278 (NH_2), 3100 (CH aromatic), 2220 (C≡N), 1642, 1616 (C=N), 1549 (C=C). ^{1}H NMR (DMSO-d_6): δ_H 8.21 (bs, 2H; NH_2), 7.74 (s, 1H; H-3), 7.36 (m, 2H; H-*m'*), 7.34 (m, 1H; H-*p*), 7.33 (m, 2H; H-*o/m*), 7.29 (m, 2H; H-*m/o*), 6.77 (d, *J* 8.6 Hz, 2H; H-*o'*). ^{13}C NMR (DMSO-d_6): δ_C 158.1 (C-α), 154.4 (C-5), 145.9 (C-*i'*), 142.1 (C-3), 131.3 (2C; C-*m'*), 130.6 (C-*i'*), 129.6 (C-*p*), 129.2 (2C; C-*m/o*), 127.7 (2C; C-*o/m*), 123.8 (2C; C-*o'*), 116.1 (C-*p'*), 114.2 (C≡N), 72.7 (C-4). ^{15}N NMR: Table 2. MS (EI, 70 eV): 367 (M+2, 8), 365 (6, M^+), 306 (36), 288 (17), 245 (14),153 (100), 136 (74), 119 (11), 106 (16). Anal. Calcd for $C_{17}H_{12}BrN_5$ (365.03): C, 55.75; H, 3.30; N, 19.12. C, 55.60; H, 3.15; N, 19.00. Found: C, 55.60; H, 3.20; N, 19.00.

(*E*)-5-Amino-1-(((2',6'-dimethylphenyl)imino)(phenyl)methyl)-3-ethyl-1*H*-pyrazole-4-carbonitrile (3g). Pale yellow crystals (EtOAc), yield: 0.25 g (74%); mp 180-182 ºC. IR (KBr;

ν_{max}, cm^{-1}): 3366-3289 (NH_2), 3055 (CH aromatic), 2967 (CH aliphatic), 2214 (C≡N), 1651, 1618 (C=N), 1553 (C=C). ^{1}H NMR (DMSO-d_6): δ_H 8.16 (bs, 2H; NH_2), 7.33 (t, *J* 7.3 Hz, 1H; H-*p*), 7.26 (dd, *J* 7.7, 7.2 Hz, 2H; H-*m*), 7.18 (d, *J* 7.2, 2H; H-*o*), 6.91 (d, *J* 7.5 Hz, 2H; H-*m'*), 6.80 (t, *J* 7.5 Hz, 1H; H-*p'*), 2.45 (q, *J* 7.6, 2H; CH_2), 2.05 (s, 6H; Ar-CH_3), 1.11 (t, *J* 7.6 Hz, 3H; $CH_2C\mathbf{H_3}$). ^{13}C NMR (DMSO-d_6): δ_C 156.0 (C-α), 155.2, 155.0 (C-3,5), 144.3 (C-*i'*), 131.2 (C-*i*), 130.0 (C-*p*), 128.3 (2C; C-*o*), 127.7 (2C; C-*m'*), 127.4 (2C; C-*m*), 126.7 (2C; C-*o'*), 123.4 (C-*p'*), 114.3 (C≡N), 72.2 (C-4), 20.6 (CH_2), 18.3 (Ar-**C**H_3), 12.2 (CH_2**C**H_3). ^{15}N NMR: Table 2. MS (EI, 70 eV): *m/z* (%) = 343 (M^+, 31), 207 (100), 153 (20), 136 (15), 104 (5). Anal. Calcd for $C_{21}H_{21}N_5$ (343.18): C, 73.44; H, 6.16; N, 20.39. Found: C, 73.24; H, 6.00; N, 20.30.

(*E*)-5-Amino-1-((4'-chlorophenylimino)(phenyl)methyl)-3-ethyl-1*H*-pyrazole-4-carbonitrile (3h). Pale yellow crystals (EtOAc), yield: 0.27 g (72%); mp 215-216 ºC. IR (KBr; ν_{max}, cm^{-1}): 3369-3273 (NH_2), 3060 (CH aromatic), 2980 (CH aliphatic), 2223 (C≡N), 1647, 1620 (C=N), 1556 (C=C). ^{1}H NMR (DMSO-d_6): δ_H 8.18 (bs, 2H, NH_2), 7.35-7.25 (m, 5H, H-*o,m,p*), 7.20-7.18 (d, *J* 8.5 Hz, 2H; H-*m*\), 6.80-6.77 (d, *J* 8.5 Hz, 2H; H-*o*'), 2.45-2.40 (q, *J* 7.6 Hz, 2H; CH_2), 1.09-1.05 (t, *J* 7.5 Hz, 3H; CH_3). ^{13}C NMR (DMSO-d_6): δ_C 158.1, 155.4, 155.1, 145.6, 130.6, 129.5, 129.2 (2C), 128.6, 128.3 (2C), 127.6 (2C), 123.4 (2C), 114.3, 72.0, 20.5, 12.2. (EI, 70 eV): *m/z* (%) = 350 (M^+, 8), 349 (30), 314 (22), 238 (100), 162 (18), 77 (40). Anal. Calcd for $C_{19}H_{16}ClN_5$ (349.11): C, 65.24; H, 4.61; N, 20.02. Found: C, 65.20; H, 4.55; N, 19.90.

(*E*)-5-Amino-3-ethyl-1-((4'-nitrophenylimino)(phenyl)methyl)-1*H*-pyrazole-4-carbonitrile (3i). Pale yellow crystals (EtOAc), yield: 0.26 g (71%); mp 262-263 ºC; IR (KBr; ν_{max}, cm^{-1}): 3335-3237 (NH_2), 3109 (CH aromatic), 2968 (CH aliphatic), 2216 (C≡N), 1651, 1600 (C=N), 1559 (C=C). ^{1}H NMR (DMSO-d_6): δ_H 8.18 (bs, 2H; NH_2), 8.05 (d, *J* 8.8 Hz, 2H; (H-*m'*), 7.31 (m, 5H; H-*o,m,p*), 7.03 (d, *J* 8.8 Hz, 2H; H-*o'*), 2.44 (q, *J* 7.6 Hz, 2H; CH_2), 1.09 (t, *J* 7.6 Hz, 3H; CH_3). ^{13}C NMR (DMSO-d_6): δ_C 157.8 (C-α), 155.9 (C-3), 155.1 (C-5), 153.4 (C-*p'*), 143.2 (C-*i'*), 130.4 (C-*i*), 129.8 (C-*p*), 129.3 (2C), 127.7 (2C; C-*o,m*), 124.2 (2C; C-*m'*), 122.6 (2C; C-*o'*), 114.2 (C≡N), 72.1 (C-4), 20.6 (CH_2), 12.2 (CH_3). ^{15}N NMR: Table 2. MS (EI, 70 eV): *m/z* (%) = 360 (M^+, 45), 225 (20), 224 (100), 153 (78), 135 (55), 106 (16), 90 (13). Anal. Calcd for $C_{19}H_{16}N_6O_2$ (360.13): C, 63.32; H, 4.48; N, 23.32. Found: C, 63.20; H, 4.40; N, 23.20.

(*E*)-5-Amino-1-((4'-bromophenylimino)(phenyl)methyl)-3-ethyl-1*H*-pyrazole-4-carbonitrile (3j). Pale yellow crystals (EtOAc), yield: 0.28 g (72%); mp 200-201 ºC. IR (KBr; ν_{max}, cm^{-1}): 3367-3272 (NH_2), 3050 (CH aromatic), 2990 (CH aliphatic), 2222 (C≡N), 1647, 1613 (C=N), 1556 (C=C). ^{1}H NMR (DMSO-d_6): δ_H 8.1 (bs, 2H; NH_2), 7.30 (m, 5H; H-*o,m,p*), 7.20 (d, *J* 8.3, 2H; H-*m*\), 6.79 (d, *J* 8.2, 2H; H-*o'*), 2.43 (q, *J* 7.5 Hz, 2H; CH_2), 1.09 (t, *J* 7.4 Hz, 3H; CH_3). ^{13}C NMR (DMSO-d_6): δ_C 157.9, 155.1, 146.1, 145.6, 131.2, 130.6, 129.5, 129.3 (2C), 128.3 (2C), 127.6 (2C), 123.4 (2C), 115.9, 114.3, 72.0, 20.6, 12.2 ppm. ^{15}N NMR: Table 2. MS (EI, 70 eV): *m/z* (%) = 395 (M+2, 35), 393 (M^+, 50), 349 (21), 306 (32), 257 (87), 213 (46), 153 (100), 135 (67), 106 (19), 90 (12). Anal. Calcd for $C_{19}H_{16}BrN_5$ (393.06): C, 57.88; H, 4.09; N, 17.76. Found: C, 57.70; H, 3.90; N, 17.60.

(*E*)-5-Amino-3-methyl-1-(phenyl(*o*-tolylimino)methyl)-1*H*-pyrazole-4-carbonitrile (3k). Pale yellow crystals (CH_3OH/DCM), yield: 0.25 g (80%); mp 213-214 ºC. IR (KBr; ν_{max}, cm^{-1}): 3347-

3257 (NH_2), 3063 (CH aromatic), 2966 (CH aliphatic), 2219 (C≡N), 1653, 1621 (C=N), 1560 (C=C). ^{1}H NMR (DMSO-*d*$_6$): δ_H 8.23 (bs, 2H; NH_2), 7.28 (m, 3H; H-*m,p*), 7.23 (m, 2H; H-*o*), 7.09 (d, *J* 7.1 Hz, 1H; H-6'), 6.90 (ddd, *J* 7.5, 7.5, 1.1 Hz, 1H; H-4'), 6.84 (ddd, *J* 7.3, 7.3, 1.2 Hz, 1H; H-5'), 6.53 (dd, *J* 7.6, 0.9 Hz, 1H; H-3'), 2.17 (s, 3H; Ar-CH_3), 2.05 (s, 3H; pyrazole-CH_3). ^{13}C NMR (DMSO-*d*$_6$): δ_C 157.1 (C-α), 154.9 (C-5), 150.3 (C-3), 145.4 (C-2'), 131.1 (C-*i*), 129.8 (C-6'), 129.4 (C-*p*), 128.7 (2C; C-*o/m*), 128.5 (C-1'), 127.6 (2C; C-*m/o*), 125.8 (C-4'), 123.7 (C-5'), 120.8 C-3'), 114.3 (C≡N), 73.4 (C-4), 18.0 (Ar-CH_3), 12.6 (pyrazole-CH_3). ^{15}N NMR: Table 2. MS (EI, 70 eV): *m/z* (%) = 315 (M^+, 34), 193 (100), 90 (13). Anal. Calcd for $C_{19}H_{17}N_5$ (315.15): C, 72.36; H, 5.43; N, 22.21. Found: C, 72.20; H, 5.30; N, 22.10.

(*E*)-5-Amino-1-(((2',6'-dimethylphenyl)imino)(phenyl)methyl)-3-methyl-1*H*-pyrazole-4-carbonitrile (3l). Pale yellow crystals (CH_3OH/DCM), yield: 0.26 g (81%); mp 275-276 °C. IR (KBr; ν_{max}, cm^{-1}): 3362-3277 (NH_2), 3060 (CH aromatic), 2946 (CH aliphatic), 2213 (C≡N), 1652, 1621 (C=N), 1558 (C=C). ^{1}H NMR (DMSO-*d*$_6$): δ_H 8.16 (bs, 2H; NH_2), 7.33 (tt, *J* 7.3, 2.2 Hz, 1H; H-*p*), 7.26 (dd, *J* 7.7, 7.2 Hz, 2H; H-*m*), 7.18 (d, *J* 7.2 Hz, 2H; H-*o*), 6.90 (d, *J* 7.5 Hz, 2H; H-*m'*), 6.79 (t, *J* 7.5 Hz, 1H; H-*p'*), 2.07 (s, 3H; pyrazole-CH_3), 2.04 (s, 6H; Ar-CH_3). ^{13}C NMR (DMSO-*d*$_6$): δ_C 156.1 (C-α), 155.0 (C-5), 150.2 (C-3), 144.3 (C-*i'*), 131.4 (C-*i)*, 129.2 (C-*p*), 128.2 (2C; C-*o*), 127.7 (2C; C-*m'*), 127.5 (2C; C-*m*), 126.6 (2C; C-*o'*), 123.4 (C-*p'*), 114.3 (C≡N), 73.5 (C-4), 18.3 (Ar-CH_3), 12.6 (pyrazole-CH_3). ^{15}N NMR: Table 2. MS (EI, 70 eV) *m/z* (%) = 329 (M^+, 37), 207 (100), 106 (20). Anal. Calcd for $C_{20}H_{19}N_5$ (329.16): C, 72.93; H, 5.81; N, 21.26. Found: C, 72.80; H, 5.70; N, 21.40.

(*E*)-5-Amino-1-(((4'-chlorophenyl)imino)(phenyl)methyl)-3-methyl-1*H*-pyrazole-4-carbonitrile (3m). Pale yellow crystals (CH_3OH/DCM), yield: 0.25 g (76%); mp 257-258 °C. IR (KBr; ν_{max}, cm^{-1}): 3357-3257 (NH_2), 3100 (CH aromatic), 2930 (CH aliphatic), 2223 (C≡N), 1642, 1614 (C=N), 1559 (C=C). ^{1}H-NMR (DMSO-*d*$_6$): δ_H 8.19 (bs, 2H; NH_2), 7.31 (m, 3H; H-*m,p*), 7.26 (dd, *J* 7.7, 1.7 Hz, 2H; H-*o*), 7.20 (d, *J* 8.6 Hz.2H; H-*m'*), 6.79 (d, *J* 8.6 Hz, 2H; H-*o'*), 2.05 (s, 3H; pyrazole-CH_3). ^{13}C-NMR (DMSO-*d*$_6$): δ_C 158.0 (C-α), 154.8 (C-5), 150.5 (C-3), 145.6 (C-*i'*), 130.7 (C-*i)*, 129.5 (C-*p*), 129.2 (2C; C-*o*), 128.3 (2C; C-*m'*), 127.74 (C-*i*), 127.68 (2C; C-*m*), 123.5 (2C; C-*o'*), 114.3 (C≡N), 73.3 (C-4), 12.6 (CH_3). ^{15}N NMR: Table 2. MS (EI, 70 eV): *m/z* (%) = 336 (M^+, 8), 335 (M^+, 30), 301 (22), 300 (18), 225 (100), 150 (24), 124 (22), 110 (24). Anal. Calcd for $C_{18}H_{14}ClN_5$ (335.09): C, 64.38; H, 4.20; N, 20.86. Found: C, 64.20; H, 4.00; N, 20.70.

(*E*)-5-Amino-3-methyl-1-(((4'-nitrophenyl)imino)(phenyl)methyl)-1*H*-pyrazole-4-carbonitrile (3n). Pale yellow crystals (CH_3OH/DCM), yield: 0.26 g (76%); mp 279-280 °C. IR (KBr; ν_{max}, cm^{-1}): 3394-3294 (NH_2), 3067 (CH aromatic), 2924 (CH aliphatic), 2212 (C≡N), 1659, 1602 (C=N), 1557 (C=C). ^{1}H NMR (DMSO-*d*$_6$): δ_H 8.18 (bs, 2H; NH_2), 8.05 (d, *J* 8.8 Hz, 2H; H-*m'*), 7.31 (m, 5H; H-*o,m,p*), 7.03 (d, *J* 8.9 Hz, 2H; H-*o'*), 2.07 (s, 3H; CH_3). ^{13}C NMR (DMSO-*d*$_6$): δ_C 157.8 (C-α), 154.9 (C-5), 153.3 (C-*p'*), 151.0 (C-3), 143.2 (C-*i'*), 130.5 (C-*i*), 129.8 (C-*p*), 129.2 (2C), 127.7 (2C; C-*m,o*), 124.2 (2C; C-*m'*), 122.6 (2C; C-*o'),* 114.2 (C≡N), 73.4 (C-4), 12.6 (CH_3). ^{15}N NMR: Table 2. MS (EI, 70 eV): *m/z* (%) = 346 (61, M^+), 306 (32), 224 (92), 153 (100), 136 (65), 106 (18). Anal. Calcd for $C_{18}H_{14}N_6O_2$ (346.12): C, 62.42; H, 4.07; N, 24.27. Found: C, 62.30; H, 4.20; N, 24.10.

(*E*)-5-Amino-1-(((4'-bromophenyl)imino)(phenyl)methyl)-3-methyl-1*H*-pyrazole-4-carbonitrile (3o). Pale yellow crystals (CH_3OH/DCM), yield: 0.29 g (75%); mp 250-251 ºC. IR (KBr; ν_{max}, cm^{-1}): 3370-3272 (NH_2), 3100 (CH aromatic), 2925 (CH aliphatic), 2219 (C≡N), 1642, 1614 (C=N), 1558 (C=C). ^{1}H NMR (DMSO-d_6): δ_H 8.19 (bs, 2H; NH_2), 7.32 (m, 5H; H-*m,p,m'*), 7.26 (dd, *J* 7.8, 1.7 Hz, 2H; H-*o*), 6.79 (d, *J* 8.6 Hz, 2H; H-*o'*), 2.05 (s, 3H; CH_3). ^{13}C NMR (DMSO-d_6): δ_C 158.0 (C-α), 154.8 (C-5), 150.5 (C-3), 146.0 (C-*i'*), 131.2 (2C; C-*m*), 130.7 (C-*i*), 129.5 (C-*p*), 129.2 (2C; C-*o*), 127.7 (2C; C-*m'*), 123.9 (C-*o'*), 115.9 (C-*p'*), 114.3 (C≡N), 73.3 (C-4), 12.6 (CH_3). ^{15}N NMR: Table 2. MS (EI, 70 eV): *m/z* (%) = 381 (M+2, 34), 379 (M^+, 36), 259 (100), 106 (14). 88 (9). Anal. Calcd for $C_{18}H_{14}BrN_5$ (379.04): C, 56.86; H, 3.71; N, 18.42. Found: C, 56.70; H, 3.70; N, 18.30.

Conclusions

N-Arylbenzamidrazones reacted with 2-(ethoxymethylene)malononitriles to furnish the corresponding pyrazoles. The regiochemistry of the products requires that the process begin with attack by the remote nitrogen of the benzamidrazone, on the methylenemalononitrile in conjugate fashion.

Acknowledgements

The NMR spectrometer at Florida Institute of Technology was purchased with the assistance of the National Science Foundation (CHE 03-42251).

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