JOC The Journal of Organic Chemistry

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Regioselective and Guided C−H Activation of 4-Nitropyrazoles

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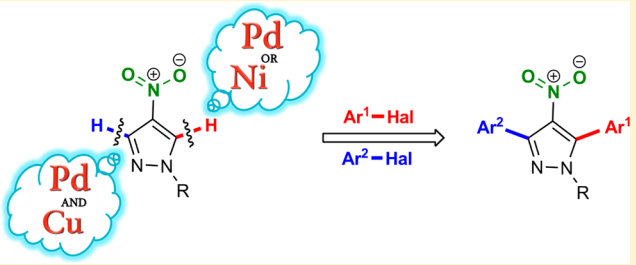
Supporting Information

ABSTRACT: A divergent and regioselective approach to 5-aryl-4-nitro-1*H*-pyrazoles was developed by guided transition-metal-catalyzed arylation of 4-nitro-1*H*-pyrazoles. This method provides a convenient tool for the functionalization of the pharmacologically relevant pyrazole scaffold. The scope and limitations of the methodology were studied.



INTRODUCTION

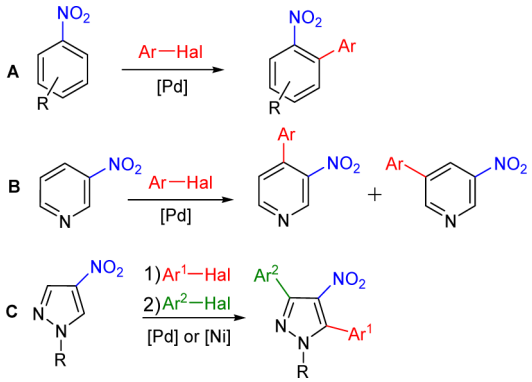
The C−H bond is the most widespread structural fragment in organic chemistry, and its functionalization has been the subject of intensive studies.[1,2] In recent years, transition-metal-catalyzed C−H activation reactions emerged as one of the most important methodologies in modern organic chemistry. The regioselectivity of C−H activation reactions of more complex functionalized substrates containing two or more reactive C−H bonds is an important topic of current research.[1−4] The regioselectivity of such reactions is controlled by the presence of functional groups in the substrate. This includes directing substituents (e.g., carbonyl, cyano),[4] halogen substituents (mostly fluorine or chlorine),[4,5] and ring heteroatoms (namely, sulfur, nitrogen, and oxygen). The use of the nitro group as a regiodirecting substituent in C−H activations has only scarcely been reported to date (Scheme 1).[6] Examples include the Pd-catalyzed *ortho*-arylation of nitrobenzene derivatives.[6a] In a second study, the C−H activation of positions 4 and 5 of 3-nitropyridine was reported.[6b] Surprisingly, the electron-poor position 2 remained unattacked. The result was explained by the assumption that the nitrogen lone pair of the pyridine moiety plays a prominent role in shielding the initial attack of the Pd species to position 2.

In the course of our interest in nitrogen heterocycles,[7] we herein report what are, to the best of our knowledge, the first C−H activation reactions of nitro-substituted pyrazoles.[8] These reactions allow for a convenient synthesis of arylated pyrazoles which are not readily available by other methods.

RESULTS AND DISCUSSION

Our starting point was the synthesis of 4-nitro-1*H*-pyrazoles **3a−f** using two synthetic strategies, as depicted in Scheme 2.

Scheme 1. C−H Activation Reactions of Nitro-Substituted Arenes and Hetarenes[a]



[a]A: ref 6a. B: ref 6b. C: present study.

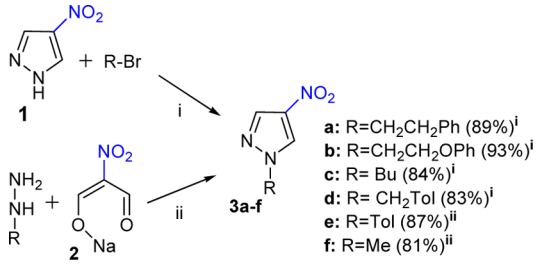
The alkylation of commercially available 4-nitro-1*H*-pyrazole (**1**) in DMF in the presence of K_2CO_3 afforded products **3a−d** in good to excellent yields. The cyclization of commercially available methyl and aryl hydrazine with nitro-malonaldehyde **2** gave products **3e,f** (Scheme 2).

With the desired starting materials **3a−f** in hand, we started to study the direct arylation by C−H activation. Hocek et al.[9] and we[10a] reported the use of a Pd/Cu catalytic system for C−H activation reactions of purine derivatives. At the same time, we also demonstrated that related C−H activations can be conducted by use of Ni catalysts.[10b] Therefore, we decided to

Received: December 18, 2013
Published: March 6, 2014

   dx.doi.org/10.1021/jo4025418 | J. Org. Chem. 2014, 79, 2906−2915

Scheme 2. Synthesis of Nitropyrazoles 3a–f[a]

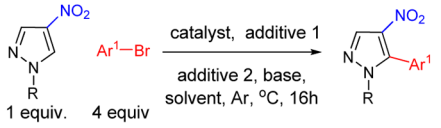


[a]Conditions: (i) DMF, R-Br (1.3 equiv), dry K_2CO_3 (2.3 equiv), 90 °C, 8 h; (ii) DMF, TMSCl, 2 (1.5 equiv), 120 °C, 6 h.

use both catalytic systems to compare their efficiency. In addition, a number of other transition metal catalysts,[1,4] such as Pt, Rh, Ru, Ir, and Fe as well as Cu and Co, were studied.

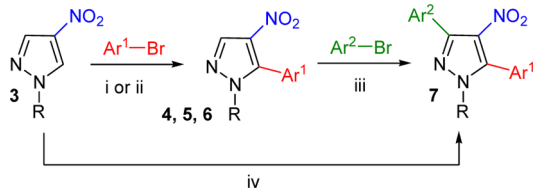
As a model reaction for the optimization of the conditions, we studied the reaction of pyrazole **3e** with tolylbromide. First, the conditions of the Pd/Cu system were optimized (Table 1, entries 1–6). The best yields of product **4d** (up to 83% yield) were obtained (Scheme 3) when an excess of the aryl halide (4 equiv) was employed using $PdCl_2(PPh_3)_2$ (5 mol %) as the catalyst in the presence of CuI (1.2 equiv). The reaction was carried out in the presence of PivOH (0.3 equiv) and K_2CO_3

Table 1. Optimization of the Synthesis of 4d

		Yield % (**4d**)[a]
	1 equiv. Ar1—Br 4 equiv; catalyst, additive 1; additive 2, base, solvent, Ar, °C, 16h	
1	$Pd(OAc)_2$ (5 mol %), Py_3HBF_4 (12 mol %), PivOH (0.3 equiv.), K_2CO_3 (1.3 equiv.), DMF, 120 °C.	traces
2	$Pd(OAc)_2$ (5 mol %), Ag_2CO_3 (1.2 equiv.), PivOH (0.3 equiv.), K_2CO_3 (1.3 equiv.), DMF, 120 °C.	30
3	$Pd(OAc)_2$ (5mol %), CuI (1,2 equiv.), PivOH (0.3 equiv.), K_2CO_3 (1.3 equiv.), DMF, 120 °C.	63
4	$Pd(OAc)_2$ (5 mol %), CuI (1.2 equiv.), PivOH (0.3 equiv.), Cs_2CO_3 (1.3 equiv.), DMF, 120 °C.	60
5	**$PdCl_2(PPh_3)_2$ (5 mol %), CuI (1.2 equiv.), PivOH (0.3 equiv.), K_2CO_3 (1.3 equiv.), DMF, 120 °C.**	**83**
6	$PdCl_2(PPh_3)_2$ (5 mol %), CuI (1.2 equiv.), Ph_3CCO_2H (0.3 equiv.), K_2CO_3 (1.3 equiv.), DMF, 120 °C.	66
7	$PdCl_2(PPh_3)_2$ (5 mol %), CuI (1.2 equiv.), PivOH (0.3 equiv.) K_2CO_3 (1.3 equiv.), Tol, 100 °C.	0
8	$PdCl_2(PPh_3)_2$ (5 mol %), CuI (1.2 equiv.), K_2CO_3 (1.3 equiv.), DMF, 120 °C.	5
9	$NiCl_2$[dppe][b] (5 mol %), CuI (1.2 equiv.), PivOH (0.3 equiv.), K_2CO_3 (1.3 equiv.), DMF, 120 °C.	30
10	$NiCl_2$[dppp][c] (5mol %), CuI (1.2 equiv.), PivOH (0.3 equiv.), K_2CO_3 (1.3 equiv.), DMF, 120 °C.	34
11	$NiCl_2(PPh_3)_2$ (3 mol %), CuI (1.2 equiv.), PivOH (0.3 equiv.), K_2CO_3 (1.3 equiv.), DMF, 120 °C.	37
12	**$NiCl_2(PPh_3)_2$ (5 mol %), CuI (1.2 equiv.), PivOH (0.3 equiv.), K_2CO_3 (1.3 equiv.), DMF, 120 °C.**	**45**
13	$[Ru(p\text{-}cymene)Cl_2]_2$ (5 mol %), CuI (1.2 equiv.), PivOH (0.3 equiv.), K_2CO_3 (1.3 equiv.), DMF, 120 °C.	0
14	$[Rh(cod)Cl]_2$ (5 mol %), CuI (1.2 equiv.), PivOH (0.3 equiv.), K_2CO_3 (1.3 equiv.), DMF, 120 °C.	0

[a]Yields of isolated products. [b]1,2-Bis(diphenylphosphino)ethane nickel(II) chloride. [c]1,3-Bis(dipenylphosphino)propane nickel(II) chloride.

Scheme 3. Synthesis of Products 4–7[a]



[a]Coditions: (i) ArBr (4 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), CuI (1.2 equiv), PivOH (0.3 equiv), K_2CO_3 (1.3 equiv), DMF, under Ar, 120 °C, 6–16 h; (ii) ArBr (4 equiv), $NiCl_2(PPh_3)_2$ (5 mol %), CuI (1.2 equiv), PivOH (0.3 equiv), K_2CO_3 (1.3 equiv), DMF, under Ar, 120 °C, 16 h; (iii) ArBr (4 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), CuI (4 equiv), PivOH (0.3 equiv), K_2CO_3 (1.3 equiv), DMF, under Ar, 120 °C, 16 h; (iv) one-pot, ArBr (6 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), CuI (6 equiv), PivOH (0.3 equiv), K_2CO_3 (1.3 equiv), DMF, under Ar, 120 °C, 16 h.

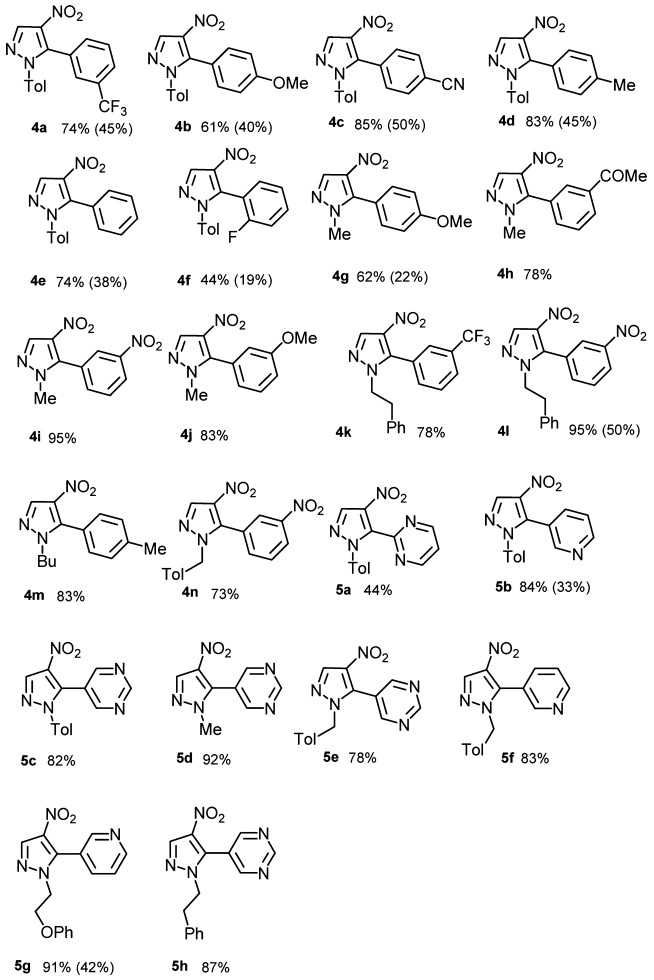
(1.3 equiv) in DMF (120 °C, 16 h) (Table 1, entry 5). It should be mentioned that in the absence of CuI we got an unusual product, namely, corresponding structure **4′**,[11] as a result of the sequential arylation at position 5 of the pyrazole ring and subsequent cleavage of the N–N bond (see structure **4′** in Supporting Information).[11] In the same time, the formation of compound **4″**[11] as a result of directing action of the pyrazole moiety was never observed. The conditions for the Ni/Cu system were optimized, as well (Table 1, entries 9–12). The best conditions, using $NiCl_2(PPh_3)_2$ (5 mol %) as the catalyst under otherwise identical conditions, allowed for the synthesis of **4d** in 45% yield (Table 1, entry 12). To our astonishment, the Ni catalysts proved to be inefficient in the absence of CuI and, in general, were less active than the Pd/Cu system (entries 3 and 5). These results are different from our earlier studies on 1-deazapurine systems.[10b]

With the optimal reaction conditions in hand, we next studied the scope and limitations of our methodology. The reaction of pyrazoles **3a–f** with various aryl halides afforded products **4a–n** and **5a–h** in excellent yields (Scheme 4). In general, aryl bromides gave very good yields, while the corresponding aryl chlorides proved to be unreactive. In the case of aryl iodides, we observed extensive formation of biaryls which could only be suppressed by use of a high excess of the aryl iodide; 4 equiv was enough to increase the overall yields. It is important to note that the syntheses could be performed on gram scale. For instance, compound **4h** was prepared in 10 g amount in 78% yield.

Next, we studied the possibility of introducing aryl groups at position 3. Unfortunately, all of these attempts proved to be unsuccessful (formation of complex mixtures). Besides Ni and Pd, we have tested other additives or catalysts, including salts of Ag, Fe, Ru, Rh, Ir, Co, and Pt. We also tried to change the regioselectivity by variation of the ligands. Trials included S-Phos, X-Phos, PCy_3, $P(tBu)_3$, (2-biphenyl)di-1-adamantylphosphine, *rac*-2-(di-*tert*-butylphosphino)-1,1′-binaphthyl, $(C_6H_5O)_3P$, tris(diethylamino)phosphine, $(C_6F_5)_3P$, $(C_6F_5)_2PhP$; bidantate, 1,2-bis(diphenylphosphino)benzene, 1,2-bis(dicyclohexylphosphino)ethane, dppm, dppe, dppp, dppf, BINAP, DIOP, *rac*-Synphos, (oxidi-2,1-phenylene)-bis-(diphenylphosphine), and XantPhos. Unfortunately, the experiments did not meet success. Finally, we have found that reaction of **3a** and **3d** with 1-bromo-3-nitrobenzene, in the presence of 6.0 (instead of 1.2) equiv of CuI, allowed for the synthesis of 3,5-diaryl-4-nitropyrazoles **7a,b** (Schemes 3 and 5).

dx.doi.org/10.1021/jo4025418 | J. Org. Chem. 2014, 79, 2906–2915

Scheme 4. Structures and Isolated Yields of 5-Aryl-4-nitropyrazoles 4 and 5[a]



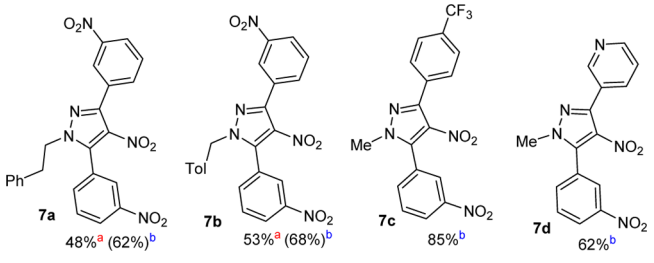
[a]Products were prepared using the Pd/Cu system; yields in parentheses refer to employment of the Ni/Cu system.

The reaction of **4i,l,n** with aryl bromides in the presence of 4.0 equiv of CuI gave rise to products **7a−d** (sequential synthesis).

Although the mechanism of the reactions was not studied, we assume that they proceed by carboxylate-assisted catalyzed C−H bond activation[12] since the addition of the carboxylic acid, namely, pivalic acid, was crucial for the success of the reaction.

The regioselectivity might be explained, following the explanations provided by other authors,[6b] by the assumption that the free electron pair of the imine nitrogen of pyrazole shields position 3 (structure **A** in Scheme 6). Thus, intermediate **B** should be more favorable. Addition of a transition metal (TM) enables the formation of a TM complex with the nitrogen atom of the pyrazole ring despite the shielding effect of the lone pair. In addition, the acidity of the neighboring proton is increased. The ligands as well as the nitro group might bridge the Pd complex and direct the subsequent attack of this species. Thus, we consider species **B**, **C**, **D**, and **E** to be plausible intermediates of this reaction. For instance, it is known that the copper-mediated C−H activation of 1,3-diazoles[4,13] and azines[4,14] proceeds selectively at the α-position with regard to the pyridine-like nitrogen atom. In contrast, under copper-free conditions, the reaction takes place at the β-position, which was explained by the fact that reaction of the corresponding diazoles proceeds via formation of a cuprate (intermediate **E**). This aspect was very well elucidated in a number of recent studies.[3b,13,14] Due to the strong electron-withdrawing effect of the nitro group and its good coordinative nature, the cupration, which follows usually after formation of the Pd species, is directed to position 3 when an excess of copper was used.

Scheme 5. Structures and Yields of 3,5-Diaryl-4-nitropyrazoles 7a−d



[a]Yields refer to one-pot reactions. [b]Yields (in parentheses) refer to consecutive reactions.

Being motivated by recent works of Baran et al.[1c,15] on *innate* and *guided* C−H activation, we decided to turn our attention toward the *innate* protocol developed by this group for a number of heterocycles on the basis of Minisci[16] and borono-Minisci[15d] reactions, using aromatic carboxylic acids and boronic acids, respectively. However, all attempts to develop innate C−H activation reactions of substrates **3** and **4** failed (formation of inseparable mixtures).

The reduction of the nitro group of products **6**, carried out under standard conditions (Pd/C as the catalyst, normal pressure of hydrogen), gave rise to the formation of amines **8a,b** in good yields (Schemes 7 and 8). When the reduction was performed in the presence of formaline, the *N,N*-dimethylamines **10a−c** were obtained.

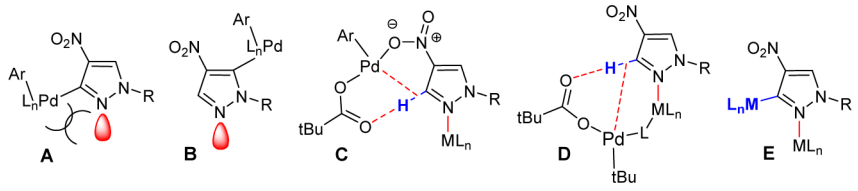
The reaction of pyrazoles **3** with 2-bromobenzaldehydes afforded products **6a−e** (Scheme 9). The hydrogenation of **6a−e** afforded pyrazoloisoquinolines **9a−e** by reduction of the nitro to an amino group and subsequent cyclization. The synthesis of analogues of **6a−e**, containing an ethoxycarbonyl, acyl, or aroyl group, proved to be unsuccessful. Products **9a−e** show a strong fluorescence (see Supporting Information, pictures 1−3).

The structure of the synthesized pyrazoles and derivatives was mainly established by 1D NMR method. The structures of compounds **4h**, **5f**, **7c**, **9c** **10a**, and **4′** were independently confirmed by X-ray single-crystal analyses (Figures 1−5 in Supporting Information).[17]

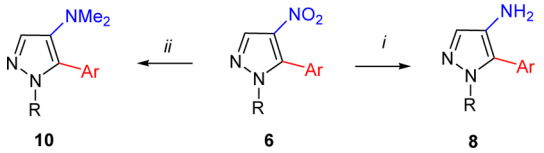
In conclusion, we have studied in detail the transition-metal-catalyzed arylation of 4-nitropyrazoles by two different d-metals, namely, Pd and Ni, using CuI as additive. The use of Pd proved to give better yields than Ni. The reactions proceeded with exclusive C-5 regioselectivity. A mechanistic explanation of this result was proposed. Furthermore, we succeeded to activate the C−H bond at carbon C-3 after arylation of C-5. Our methodology was successfully employed also for the synthesis of pyrazoloisoquinolines. The developed method shows a number of advantages, including high experimental simplicity, catalyst efficiency, functional group compatibility, and low cost of the catalytic system.

dx.doi.org/10.1021/jo4025418 | J. Org. Chem. 2014, 79, 2906−2915

Scheme 6. Proposed Mechanistic Explanation of the Regioselectivity



Scheme 7. Synthesis of Pyrazoles 8 and 10[a]



[a]Conditions: (i) MeOH, H_2, 10% Pd/C, 20 °C, 5 h; (ii) MeOH, H_2, Pd/C (10 mol %), CH_2O in H_2O (37%, 6 equiv), 20 °C, 5 h.

EXPERIMENTAL SECTION

The dry solvents were purchased. Other solvents were purified by distillation. All reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra, the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane), or electrospray ionization (ESI, mass analyzer type was ESI-TOF/MS). For preparative scale chromatography, silica gel 60 (0.063–0.200 mm, 70–230 mesh) was used. The solvents for column chromatography were distilled before use. Conformation of structure of all compounds and assignments was performed using 2D NMR methods such as COSY, HMBC, HSQC, and NOESY.

General Procedure for the Synthesis of 4-Nitropyrazoles by Alkylation. Synthesis of Compounds 3a–d: Corresponding 4-nitro-1*H*-pyrazole (1 equiv) and K_2CO_3 (2.3 equiv) successively were weighed to air and placed in a Schlenk flask, equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and backfilled with argon. The DMF (8 mL for 1 g of 4-nitro-1*H*-pyrazole) and corresponding alkyl bromide (1.3 equiv) were added via a syringe, and the reaction was heated to 90 °C for 8 h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The crude mass was washed with water, which was extracted with chloroform afterward. Finally, the organic phase was dried (Na_2SO_4), filtered, and evaporated to dryness, or (if necessary) the residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired alkylated product.

General Procedure for the Synthesis of 4-Nitropyrazoles by Cyclization. Synthesis of Compounds 3e–f: Corresponding hydrazine (1 equiv) and nitromalonaldehyde (1.5 equiv) were placed in a pressure tube under the flow of dry argon and dissolved in dry DMF (10 mL for 1 g of hydrazine) containing TMSCl (4 mL for 1 g of hydrazine). The mixture was heated at 120 °C for 6 h. Then the solution was evaporated under reduced pressure. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired 4-nitropyrazole.

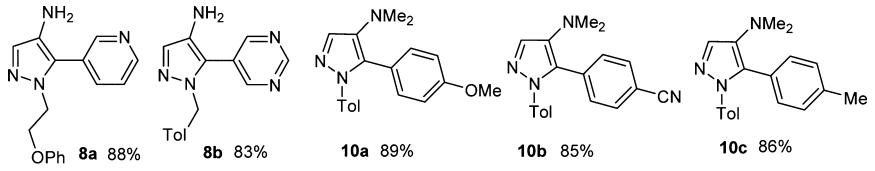
General Procedure for Direct C–H Arylation of 4-Nitropyrazoles. Synthesis of Compounds 4a–n, 4′, 5a–h, and 6a–e: Corresponding 4-nitropyrazole (1 equiv), CuI (1.2 equiv), K_2CO_3 (1.3 equiv), $(CH_3)_3CCO_2H$ (0.3 equiv), and $PdCl_2(PPh_3)_2$ (0.05 equiv) successively were weighed to air and placed in a Schlenk flask, equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and backfilled with argon (three times). The DMF (8 mL for 0.3 g of 4-nitropyrazole) and aryl bromide (4 equiv) were added via a syringe, and the reaction was heated to 120 °C for 6–16 h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired arylated product. Compound **4′** was synthesized following same procedure but without CuI.

General Procedure for One-Pot Double C–H Arylation of 4-Nitropyrazoles. Synthesis of Compounds 7a,b: Corresponding 4-nitropyrazole (1 equiv), CuI (6 equiv), K_2CO_3 (1.3 equiv), $(CH_3)_3CCO_2H$ (0.3 equiv), and $PdCl_2(PPh_3)_2$ (0.05 equiv) successively were weighed to air and placed in a Schlenk flask, equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and backfilled with argon (three times). The DMF (8 mL for 0.3 g of 4-nitropyrazole) and aryl bromide (6 equiv) were added via a syringe, and the reaction was heated to 120 °C for 6–16 h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired arylated product.

General Procedure for C–H Arylation of the Third Position of 4-Nitropyrazoles. Synthesis of Compounds 7a–d: Corresponding 4-nitro-5-arylpyrazole (1 equiv), CuI (4 equiv), K_2CO_3 (1.3 equiv), $(CH_3)_3CCO_2H$ (0.3 equiv), and $PdCl_2(PPh_3)_2$ (0.05 equiv) successively were weighed to air and placed in a Schlenk flask, equipped with a magnetic stir bar, which then was capped with a rubber septum. The reaction vessel was evacuated and backfilled with argon (three times). The DMF (8 mL for 0.3 g of 4-nitropyrazole) and aryl bromide (4 equiv) were added via a syringe, and the reaction was heated to 120 °C for 16 h. Upon completion, the reaction was cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired arylated product.

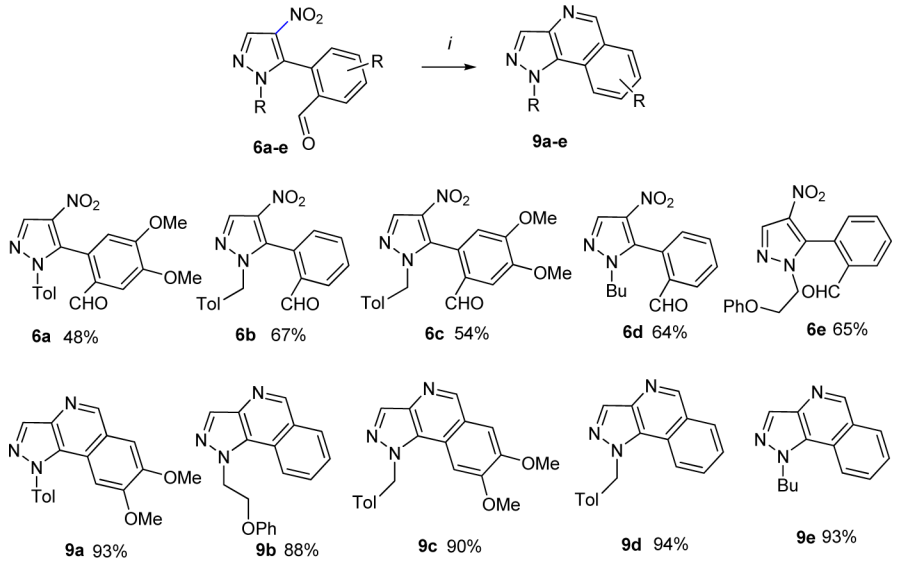
General Procedure for Reduction of 4-Nitropyrazoles. Synthesis of Compounds 8a,b and 9a–e: To a Schlenk flask equipped with a magnetic stir bar and filled with corresponding 4-nitro-5-arylpyrazole (1 equiv) was added 10% Pd/C (0.1 equiv). The flask was fitted with a rubber septum and then held under vacuum for 3 min, after that, it was filled with MeOH (25 mL for 0.3 g of 4-nitropyrazole) and hydrogen. Holding under vacuum was repeated one more time, and after sequential filling with hydrogen, the reaction mixture was stirred for 5 h under H_2 atmosphere. After the reaction was stopped, the mixture was filtered through a Celite pad, and the filtrate was evaporated to dryness or (if necessary) was purified by

Scheme 8. Structures and Yields of Pyrazoles 8a,b and 10a–c



dx.doi.org/10.1021/jo4025418 | J. Org. Chem. 2014, 79, 2906–2915

Scheme 9. Structures and Yields of Pyrazoles 6a−e and 9a−e[a]



[a]Conditions: (i) MeOH, H_2, 10% Pd/C, 20 °C, 5 h.

column chromatography typically using heptane/ethyl acetate mixtures to provide the desired product.

General Procedure for Reduction of 4-Nitropyrazoles with Formaldehyde. Synthesis of Compounds 10a−c: To a Schlenk flask equipped with a magnetic stir bar and filled with corresponding 4-nitro-5-arylpyrazole (1 equiv) was added 10% Pd/C (0.1 equiv). The flask was fitted with a rubber septum and then held under vacuum for 3 min, after that, it was filled with MeOH (25 mL for 0.3 g of 4-nitropyrazole), formaldehyde solution (6 equiv, 37 wt % in H_2O, contains 10−15% methanol as stabilizer), and hydrogen. Holding under vacuum was repeated one more time, and after sequential filling with hydrogen, the reaction mixture was stirred for 4−6 h under H_2 atmosphere. After the reaction was stopped, the mixture was filtered through Celite pad and filtrate was evaporated to dryness or (if necessary) was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired product.

*4-Nitro-1-phenethyl-1H-pyrazole (**3a**):* White solid (0.193 g, 89%), mp 130−130 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ = 3.14 (d, 2H, ^3J = 7.2 Hz, CH_2), 4.43 (d, 2H, ^3J = 7.0 Hz, CH_2), 7.14−7.31 (m, 5H, CH_{Ar}), 8.25 (s, 1H, pyrazole), 8.75 (s, 1H, pyrazole); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 35.1, 53.4 (CH_2), 126.6, 128.4, 128.6, 130.4 (CH), 134.6 (C), 135.5 (CH), 137.5 (C).

*4-Nitro-1-(2-phenoxyethyl)-1H-pyrazole (**3b**):* White solid (0.216 g, 93%), mp 127−128 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ = 4.15 (d, 2H, ^3J = 5.3 Hz, CH_2), 4.34 (d, 2H, ^3J = 5.3 Hz, CH_2), 6.64−6.71 (m, 3H, CH_{Ar}), 6.98−7.05 (m, 2H, CH_{Ar}), 8.03 (s, 1H, pyrazole), 8.71 (s, 1H, pyrazole); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 52.0, 65.4 (CH_2), 114.5, 121.0, 131.0 (CH), 134.9 (C), 135.7 (CH), 157.8 (C).

*1-Butyl-4-nitro-1H-pyrazole (**3c**):* Brown solid (0.142 g, 84%), mp 92−93 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ = 0.88 (t, 3H, ^3J = 7.4 Hz, $CH_2CH_2CH_2CH_3$), 1.18−1.27 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.72−1.84 (m, 2H, $CH_2CH_2CH_2CH_3$), 4.17 (t, 2H, ^3J = 7.2 Hz, $CH_2CH_2CH_2CH_3$), 8.24 (s, 1H, pyrazole), 8.90 (s, 1H, pyrazole); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 13.2 (Me), 18.9, 31.1, 52.0 (CH_2), 130.3(CH), 134.7 (C), 135.4 (CH).

*1-(4-Methylbenzyl)-4-nitro-1H-pyrazole (**3d**):* White solid (0.180 g, 87%), mp 112−113 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ = 2.27 (s, 3H, Me), 5.34 (s, 2H, CH_2), 7.14−7.25 (m, 4H, CH_{Ar}), 8.25 (s, 1H, pyrazole), 9.00 (s, 1H, pyrazole); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 20.6 (Me), 55.6 (CH_2), 128.0, 129.2, 130.3 (CH), 132.2, 132.7, 135.0 (C), 135.8, 137.5 (CH).

*4-Nitro-1-p-tolyl-1H-pyrazole (**3e**):* Brown solid (0.176 g, 87%), mp 98−99 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ = 2.35 (s, 3H, Me), 7.34 (d, 2H, ^3J = 8.4 Hz, CH_{Ar}), 7.81 (d, 2H, ^3J = 8.4 Hz, CH_{Ar}), 8.50 (s, 1H, pyrazole), 9.56 (s, 1H, pyrazole); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 20.5 (Me), 119.3, 127.7, 130.0 (CH), 136.1 (C), 136.7 (CH), 137.9 (C).

*1-Methyl-4-nitro-1H-pyrazole (**3f**):* Yellow solid (0.102 g, 81%), mp 96−97 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ = 3.91 (s, 3H, Me), 8.22 (s, 1H, pyrazole), 8.83 (s, 1H, pyrazole); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 39.6 (Me), 130.9 (CH), 134.8 (C), 135.4 (CH).

*5-(3-(Trifluoromethyl)phenyl)-4-nitro-1-p-tolyl-1H-pyrazole (**4a**):* Brown oil (0.256 g, 74%^{Pd}, 0.156g, 45%^{Ni}); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.32 (s, 3H, Me), 7.04 (d, 2H, ^3J = 8.5 Hz, CH_{Ar}), 7.12 (d, 2H, ^3J = 8.5 Hz, CH_{Ar}), 7.49−7.56 (m, 3H, CH_{Ar}), 7.66−7.70 (m, 1H, CH_{Ar}), 8.38 (s, 1H, pyrazole); ^{19}F NMR (282 MHz, $CDCl_3$) δ = −62.9; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 21 (Me), 123.4 (q, ^1J = 262 Hz, CF_3), 126.7 (q, ^3J = 4 Hz, $CHCCF_3$), 127.5 (q, ^3J = 4 Hz, $CHCCF_3$), 129.0, 129.8, 130.0, 130.9 (CH), 131.0 (q, ^2J = 33 Hz, CCF_3), 133.8 (CH), 134.0, 135.5 (C), 137.3 (CH), 139.1, 139.5 (C); MS (GC, 70 eV) m/z (%) = 347 (M^+, 100), 300(16), 346(14), 262 (11), 91 (25), 65 (14); HRMS (EI) calcd for $C_{17}H_{12}N_3O_2F_3$ (M^+) 347.08761, found 347.08784; IR (ATR, cm^{-1}) ν = 3043 (w), 1556 (w), 1505 (s), 1391 (s), 1311(s), 1266 (m), 1124 (s), 1073 (s), 1024 (m), 904 (m), 868 (w), 830 (s), 699 (s), 646 (m), 529 (m).

*5-(4-Methoxyphenyl)-4-nitro-1-p-tolyl-1H-pyrazole (**4b**):* Brown oil (0.188 g, 61%^{Pd}, 0.123g, 40%^{Ni}); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.32 (s, 3H, Me), 3.81 (s, 3H, OMe), 6.86−6.89 (m, 2H, CH_{Ar}), 7.05−7.12 (m, 4H, CH_{Ar}), 7.20−7.23 (m, 2H, CH_{Ar}), 8.35 (s, 1H, pyrazole); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ = 21.1 (Me), 55.3 (OMe), 114 (CH), 118.3 (C), 125.1, 129.9, 131.9 (CH), 133.2, 136.2 (C), 137.4 (CH), 138.8, 140.8, 160.8 (C); MS (GC, 70 eV) m/z (%) = 309 (M^+, 100), 224 (11), 91 (21), 65 (14); HRMS (ESI) calcd for $C_{17}H_{16}N_3O_3$ (M + H) 310.11862, found 310.11868; IR (ATR, cm^{-1}) ν = 3021 (w), 1611 (m), 1558 (w), 1506 (s), 1455 (m), 1392 (s), 1324 (s), 1291 (m), 1250 (m), 1176 (s), 1113 (w), 1026 (m), 1014 (m), 954 (m), 862 (w), 842 (s), 821 (s), 762 (s), 713 (w), 615 (m), 595 (m).

*4-(4-Nitro-1-p-tolyl-1H-pyrazol-5-yl)benzonitrile (**4c**):* Brown oil (0.258 g, 85%^{Pd}, 0.152g, 50%^{Ni}); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.33 (s, 3H, Me), 7.01 (d, 2H, ^3J = 8.3 Hz, CH_{Ar}), 7.12 (d, 2H, ^3J = 8.3 Hz, CH_{Ar}), 7.42 (d, 2H, ^3J = 8.6 Hz, CH_{Ar}), 7.64 (d, 2H, ^3J = 8.6 Hz, CH_{Ar}), 8.35 (s, 1H, pyrazole); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ = 21 (Me), 113.8, 117.8 (C), 125.1, 127.8, 129.9, 131.2, 132.0, 132.8 (CH), 134.0, 135.3 (C), 137.3 (CH), 138.6, 139.6, 143.4 (C); MS (GC, 70 eV) m/z (%) = 304 (M^+, 100), 303(13), 257 (16), 219 (10) 91 (35), 65 (20); HRMS (ESI) calcd for $C_{17}H_{13}N_4O_2$ (M + H) 305.1033, found 305.10312; IR (ATR, cm^{-1}) ν = 3042 (w), 1557 (w), 1508 (s),

dx.doi.org/10.1021/jo4025418 | J. Org. Chem. 2014, 79, 2906−2915

1455 (m), 1390 (s), 1322 (s), 1200 (w), 1179 (w), 1112 (w) 1007 (w), 955 (m), 909 (m), 820 (s), 728 (s), 649 (m), 630 (w), 595 (m), 552 (s).

*4-Nitro-1,5-di-p-tolyl-1H-pyrazole (**4d**):* Brown oil (0.246 g, 83%^{Pd}, 0.131g, 45%^{Ni}); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.33 (s, 3H, Me), 2.37 (s, 3H, Me), 7.09 (m, 4H, CH_{Ar}), 7.17 (s, 4H, CH_{Ar}), 8.36 (s, 1H, pyrazole); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ = 21.1, 21.5 (Me), 123.4 (C), 125.1, 128.5, 129.2, 130.2, 130.4 (CH), 133.7, 136.2 (C), 137.4 (CH), 138.8, 140.3, 141.0 (C); MS (GC, 70 eV) *m*/*z* (%) = 293 (M^+, 100), 249 (11), 246 (15), 209(13), 208 (21), 91 (39), 89 (11), 65 (28); HRMS (ESI) calcd for $C_{17}H_{16}N_3O_2$ (M + H) 294.1237, found 294.12351; IR (ATR, cm^{-1}) ν = 3041 (w), 1557 (w), 1505 (s), 1388 (s), 1321 (s), 1178 (w), 1112 (w), 1020 (w), 945 (w), 875 (w) 827 (s), 763 (s), 698 (m), 629 (w), 592 (m).

*4-Nitro-5-phenyl-1-p-tolyl-1H-pyrazole (**4e**):* Brown oil (0.206 g, 74%^{Pd}, 0.106g, 38%^{Ni}); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.32 (s, 3H, Me), 7.04−7.11 (m, 4H, CH_{Ar}), 7.27−7.31 (m, 2H, CH_{Ar}), 7.34−7.43 (m, 3H, CH_{Ar}), 8.37 (s, 1H, pyrazole); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ = 21.1 (Me), 125.1 (CH), 126.6 (C), 128.5, 129.6, 130.0, 130.4 (CH), 136.1 (C), 137.4 (CH), 138.9, 140.8 (C); MS (GC, 70 eV) *m*/*z* (%) = 279 (M^+, 100), 279 (100), 235 (11), 232 (16), 194 (14), 91 (34), 89 (11), 65 (23); HRMS (ESI) calcd for $C_{16}H_{14}N_3O_2$ (M + H) 280.10805, found 280.10789; IR (ATR, cm^{-1}) ν = 3056 (w), 1606 (w), 1556 (w), 1504 (s), 1446 (m), 1386 (s), 1322 (s), 1184 (m), 1116 (w), 1069 (w), 1034 (w), 1007 (w), 949 (m), 915 (m), 861 (m) 821 (s), 754 (s), 709 (m), 690 (s), 646 (m), 594 (m), 528 (s).

*5-(2-Fluorophenyl)-4-nitro-1-p-tolyl-1H-pyrazole (**4f**):* Brown oil (0.130 g, 44%^{Pd}, 0.056g, 19%^{Ni}); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.29 (s, 3H, Me), 7.16−7.22 (m, 4H, CH_{Ar}), 7.23−7.35 (m, 2H, CH_{Ar}), 7.46−7.59 (m, 2H, CH_{Ar}), 8.69 (s, 1H, pyrazole); ^{19}F NMR (282 MHz, DMSO-d_6) δ = −112.7 (CF); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ = 20.5 (Me), 114.6 (d, *J* = 14 Hz, C), 115.7 (d, *J* = 24 Hz, CH), 124.6 (d, *J* = 3 Hz, CH), 125.0, 129.6, 132.2 (CH), 133.0 (d, *J* = 8 Hz, CH), 134.7 (d, *J* = 79 Hz, CF), 135.5 (C), 137.2 (CH), 139.1, 157.6, 160.9 (C); MS (GC, 70 eV) *m*/*z* (%) = 297 (M^+, 100), 132 (17), 91 (66), 65 (44); HRMS (ESI) calcd for $C_{16}H_{12}N_3O_2F$ (M + H) 298.09863, found 298.09895; IR (ATR, cm^{-1}) ν = 2923 (w), 1711 (w), 1623 (w), 1559 (w), 1507 (s), 1460 (m), 1392 (s), 1324 (s), 1265 (w), 1224 (m), 1178 (w), 1109 (w), 1035 (w), 957 (w), 866 (w), 815 (s), 757 (s), 710 (w), 646 (w), 595 (w), 550 (w).

*5-(4-Methoxyphenyl)-1-methyl-4-nitro-1H-pyrazole (**4g**):* Brown solid (0.144 g, 62%^{Pd}, 0.051g, 22%^{Ni}), mp 67−68 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 3.70 (s, 3H, NMe), 3.85 (s, 3H, OMe), 7.09 (d, 2H, ^3J = 8.6 Hz, CH_{Ar}), 7.50 (d, 2H, ^3J = 8.6 Hz, CH_{Ar}), 8.35 (s, 1H, pyrazole); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 37.9 (NMe), 55.3 (OMe), 114.0 (CH), 118.1 (C), 131.6 (CH), 132.2 (C), 136.0 (CH), 141.1, 160.5 (C); MS (GC, 70 eV) *m*/*z* (%) = 233 (M^+, 100), 148 (25), 133 (28), 101 (15); HRMS (ESI) calcd for $C_{11}H_{12}N_3O_3$ (M + H) 234.08732, found 234.08738; IR (ATR, cm^{-1}) ν = 2837 (w), 1609 (m), 1575 (w), 1505 (s), 1459 (m), 1440 (m), 1391 (s), 1321 (s), 1297 (m), 1259 (s), 1175 (s), 1111 (m), 1034 (m), 970 (m), 945 (w), 867 (m), 834 (s), 798 (m), 762 (s), 696 (w), 642 (m), 615 (m), 586 (s), 530 (m).

*1-(3-(1-Methyl-4-nitro-1H-pyrazol-5-yl)phenyl)ethanone (**4h**):* Brown solid (0.198 g, 78%^{Pd}), mp 109−111 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.63 (s, 3H, C(O)Me), 3.71 (s, 3H, Me), 7.70−7.75 (m, 1H, CH_{Ar}), 7.83−7.87 (m, 1H, CH_{Ar}), 8.12−8.17 (m, 2H, CH_{Ar}), 8.41 (s, 1H, pyrazole); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 26.8, 38.0 (Me), 127.1 (C), 129.1, 129.7, 129.8 (CH), 132.6 (C), 134.5, 136.0 (CH), 137.0, 140.3, 197.4 (C); MS (GC, 70 eV) *m*/*z* (%) = 245 (M^+, 37), 230 (100), 43 (42); HRMS (EI) calcd for $C_{12}H_{11}N_3O_3$ (M^+) 245.07949, found 245.07931; IR (ATR, cm^{-1}) ν = 3064 (w), 1678 (s), 1605 (m), 1552 (w), 1483 (s), 1423 (m), 1392 (s), 1220 (s), 1169 (m), 1037 (w), 962 (w), 944 (w), 860 (m), 828 (s), 802 (s), 761 (s), 693 (m), 588 (m).

*1-Methyl-4-nitro-5-(3-nitrophenyl)-1H-pyrazole (**4i**):* Brown solid (0.235 g, 95%^{Pd}), mp 126−128 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 3.73 (s, 3H, Me), 7.85−7.95 (m, 1H, CH_{Ar}), 8.05−8.09 (m, 1H, CH_{Ar}), 8.41−8.45 (m, 2H, CH_{Ar}, pyrazole), 8.53−8.54 (m, 1H, CH_{Ar}); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 38.1 (Me), 125.0, 125.2 (CH), 128.2 (C), 130.2 (CH), 132.4 (C), 135.9, 136.7 (CH), 138.8, 147.8, 162.3 (C); MS (GC, 70 eV) *m*/*z* (%) = 248 (M^+, 100), 163 (26), 117 (52); HRMS (EI) calcd for $C_{10}H_8N_4O_4$ (M^+) 248.05401, found 248.05381; IR (ATR, cm^{-1}) ν = 3068 (w), 1673 (w), 1526 (m), 1505 (m), 1472 (m), 1388 (m), 1349 (s), 1322 (m), 1239 (m) 1172 (w), 1087 (m), 979 (w), 919 (w), 826 (m), 758 (m), 726 (m), 694 (m), 675 (m), 640 (m), 592 (w).

*5-(3-Methoxyphenyl)-1-methyl-4-nitro-1H-pyrazole (**4j**):* Yellow oil (0.193 g, 83%^{Pd}); ^{1}H NMR (250 MHz, $CDCl_3$) δ = 3.73 (s, 3H, NMe), 3.84 (s, 3H, OMe), 6.89−6.95 (m, 2H, CH_{Ar}), 7.05−7.09 (m, 1H, CH_{Ar}), 7.44 (t, 1H, ^3J = 7.5 Hz, CH_{Ar}), 8.17 (s, 1H, pyrazole); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ = 38.0 (NMe), 55.4 (OMe), 115.3, 115.9, 121.7 (CH), 127.7 (C), 130.0, 136.3 (CH), 141.3, 159.7 (C); MS (GC, 70 eV) *m*/*z* (%) = 233 (M^+, 100), 148 (30), 133 (30), 115 (30), 95 (76); HRMS (EI) calcd for $C_{11}H_{11}N_3O_3$ (M^+) 233.07949, found 233.07921; IR (ATR, cm^{-1}) ν = 2923 (w), 1582 (w), 1555 (w), 1499 (m), 1465 (m), 1390 (m), 1348 (m), 1323 (s), 1285 (m), 1257 (m), 1208 (m), 1168 (m), 1044 (m), 1021 (m), 975 (w), 824 (s), 786 (m), 761 (m), 737 (m), 691 (m), 640 (w).

*5-(3-(Trifluoromethyl)phenyl)-4-nitro-1-phenethyl-1H-pyrazole (**4k**):* Yellow oil (0.281 g, 78%^{Pd}); ^{1}H NMR (250 MHz, DMSO-d_6) δ = 3.04 (d, 2H, ^3J = 6.3 Hz, CH_2), 4.14 (d, 2H, ^3J = 6.3 Hz, CH_2), 6.81−6.85 (m, 2H, CH_{Ar}), 7.17−7.22 (m, 3H, CH_{Ar}), 7.34−7.38 (m, 2H, CH_{Ar}), 7.67 (t, 1H, ^3J = 7.9 Hz, CH_{Ar}), 7.88 (d, 1H, ^3J = 8.0 Hz, CH_{Ar}), 8.52 (s, 1H, pyrazole); ^{19}F NMR (282 MHz, DMSO-d_6) δ = −61.0 (CF_3); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 34.9, 51.3 (CH_2), 123.7 (q, ^1J = 272 Hz, CF_3), 126.4 (q, ^3J = 4 Hz, CH), 126.7 (CH), 126.8 (q, ^3J = 4 Hz, CH), 127.3 (C), 128.5 (CH), 129.0 (q, ^2J = 32 Hz, CCF_3), 129.6 (CH), 132.5 (C), 133.8, 136.5 (CH), 137.4, 140.1 (C); MS (GC, 70 eV) *m*/*z* (%) = 361 (M^+, 1), 104 (100), 91 (24); HRMS (ESI) calcd for $C_{18}H_{15}N_3O_2F_3$ (M + H) 362.11109, found 362.11081; IR (ATR, cm^{-1}) ν = 1558 (w), 1506 (s), 1462 (m), 1399 (m), 1309 (s), 1245 (m), 1163 (s), 1123 (s), 1096 (m), 1074 (s), 1028 (m), 932 (w), 902 (m), 869 (m), 829 (s), 809 (m), 758 (s), 700 (s), 645 (w), 593 (m), 558 (m).

*4-Nitro-5-(3-nitrophenyl)-1-phenethyl-1H-pyrazol (**4l**):* Brown oil (0.321 g, 95%^{Pd}, 0.169g, 50%^{Ni}); ^{1}H NMR (300 MHz, DMSO) δ = 3.13 (t, 2H, ^3J = 6.1 Hz, CH_2), 4.16 (t, 2H, ^3J = 6.1 Hz, CH_2), 6.73−6.78 (m, 2H, CH_{Ar}), 6.95−6.99 (m, 1H, CH_{Ar}), 7.15−7.28 (m, 3H, CH_{Ar}), 7.51 (t, 1H, ^3J = 8.0 Hz, CH_{Ar}), 7.62 (t, 1H, ^4J = 1.4 Hz, CH_{Ar}), 8.26−8.31 (m, 2H, CH_{Ar}, pyrazole); ^{13}C NMR (75.5 MHz, DMSO) δ = 35.9, 51.9 (CH_2), 124.8, 127.4 (CH), 127.9 (C), 128.6, 128.9, 129.6, 135.5 (CH), 136.7 (C), 136.8 (CH), 139.6, 148.0 (C); MS (GC, 70 eV) *m*/*z* (%) = 338 (M^+, 1), 104 (100), 91(29); HRMS (ESI) calcd for $C_{17}H_{14}N_4O_4$ (M + H) 339.109, found 339.109; IR (ATR, cm^{-1}) ν = 2923 (w), 1559 (w), 1525 (s), 1499 (s), 1455 (m), 1398 (s), 1346 (s), 1322 (s), 1254 (m), 1178 (m), 1098 (w), 1077 (w), 1030 (w), 978 (w), 904 (w), 871 (m), 825 (s), 736 (s), 697 (s), 647 (m), 560 (m).

*1-Butyl-4-nitro-5-p-tolyl-1H-pyrazole (**4m**):* Yellow solid (0.215 g, 83%^{Pd}), mp 163−164 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 0.73 (t, 3H, ^3J = 7.7 Hz, $CH_2CH_2CH_2CH_3$), 1.05−1.17 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.59−1.68 (m, 2H, $CH_2CH_2CH_2CH_3$), 2.41 (s, 3H, Me), 3.93 (t, 3H, ^3J = 6.7 Hz, $CH_2CH_2CH_2CH_3$), 7.35−7.42 (m, 4H, CH_{Ar}), 8.38 (s, 1H, pyrazole); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 13.2 (Me), 18.7 (CH_2), 21.0 (Me), 30.9, 49.4 (CH_2), 123.5 (C), 129.2, 129.6 (CH), 132.2 (C), 136.17 (CH), 139.8, 141.3 (C); MS (GC, 70 eV) *m*/*z* (%) = 270 (M^+, 17), 227 (100); HRMS (ESI) calcd for $C_{14}H_{18}N_3O_2$ (M + H) 260.13935, found 260.13948; IR (ATR, cm^{-1}) ν = 3126 (w), 2953 (w), 2232 (m), 1555 (w), 1500 (s), 14960 (m), 1396 (s), 1320 (s), 1251 (m), 1195 (m), 1113 (w), 1027 (w), 983 (w), 880 (w), 846 (s), 763 (s), 685 (w), 595 (w), 569 (m), 548 (s).

*1-(4-Methylbenzyl)-4-nitro-5-(3-nitrophenyl)-1H-pyrazole (**4n**):* Yellow solid (0.246 g, 73%^{Pd}), mp 157−158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.30 (s, 3H, NMe), 5.13 (s, 2H, CH_2), 6.86 (d, 2H, ^3J = 7.9 Hz, CH_{Ar}), 7.08 (d, 2H, ^3J = 7.9 Hz, CH_{Ar}), 7.56−7.60 (m, 1H, CH_{Ar}), 7.67 (t, 1H, ^3J = 8.0 Hz, CH_{Ar}), 8.08−8.10 (m, 1H, CH_{Ar}), 8.26 (s, 1H, pyrazole), 8.36−8.40 (m, 1H, CH_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ = 21.1 (Me), 54.8 (CH_2), 125.0, 125.1, 127.3 (CH),

dx.doi.org/10.1021/jo4025418 | J. Org. Chem. 2014, 79, 2906−2915

128.3 (C), 129.7, 129.9 (CH), 131.5, 133.9 (C), 135.9, 136.5 (CH), 138.7, 148.1 (C); MS (GC, 70 eV) m/z (%) = 338 (M^+, 1), 105 (100); HRMS (EI) calcd for $C_{17}H_{14}N_4O_4$ (M^+) 338.10096, found 338.10021; IR (ATR, cm^{-1}) ν = 3117 (w), 2919 (w), 1620 (w), 1565 (w), 1530 (s), 1498 (s), 1477 (s), 1453 (m), 1400 (s), 1344 (s), 1322 (s), 1247 (m), 1184 (m), 1085 (w), 1035 (w), 1006 (w), 900 (m), 871 (m), 829 (s), 773 (s), 740 (s), 696 (m), 680 (m), 651 (w), 607 (m), 534 (w).

*(Z)-3-(p-Tolylamino)-2-nitro-3-p-tolylacrylonitrile (**4′**):* Yellow solid (0.067 g, 23%^{Pd}), mp 171−173 °C; ^{1}H NMR (300 MHz, DMSO) δ = 2.19 (s, 3H, Me), 2.27 (s, 3H, Me), 6.95−7.04 (m, 4H, CH_{Ar}), 7.19 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.35 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 12.07 (s, 1H, NH); ^{13}C NMR (62.9 MHz, DMSO) δ = 20.4, 20.9 (Me), 104.1, 114.0 (C), 126.0, 126.1 (CH), 127.2 (C), 128.5, 129.1, 129.2 (CH), 134.5, 136.8, 141.0 (C); MS (GC, 70 eV) m/z (%) = 293 (M^+, 100); HRMS (ESI) calcd for $C_{17}H_{16}N_3O_2$ (M + H) 294.1237, found 293.12375; IR (ATR, cm^{-1}) ν = 3208 (w), 2920 (w), 2217 (w), 1707 (w), 1590 (m), 1559 (s), 1506 (s), 1426 (m), 1362 (m), 1324 (w), 1274 (s), 1195 (s), 1159 (s), 1111 (m), 1020 (m), 955 (w), 818 (s), 765 (m), 719 (m), 700 (m), 665 (w), 572 (w).

*2-(4-Nitro-1-p-tolyl-1H-pyrazol-5-yl)pyrimidine (**5a**):* Yellow solid (0.123 g, 44%^{Pd}), mp 204−206 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.28 (s, 3H, Me), 7.15−7.23 (m, 4H, CH_{Ar}), 7.65 (t, 1H, ^3J = 4.9 Hz, CH_{Ar}), 8.69 (s, 1H, pyrazole), 8.96 (d, 2H, ^3J = 4.9 Hz, pyrimidine); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ =20.5 (Me), 122.0, 124.3, 129.8 (CH), 134.2, 135.6 (C), 136.7 (CH), 138.2, 139.1, 155.8 (C), 158.1 (CH); MS (GC, 70 eV) m/z (%) = 281 (M^+, 50), 264 (77), 234 (100), 91 (41); HRMS (EI) calcd for $C_{14}H_{11}N_5O_2$ (M^+) 281.09073, found 281.09078; IR (ATR, cm^{-1}) ν = 1558 (w), 1512 (s), 1465 (m), 1394 (s), 1324 (s), 1288 (m), 1218 (w), 1176 (w), 1099 (w), 1042 (w), 988 (w), 960 (m), 868 (w), 818 (s), 758 (m), 732 (w), 709 (m), 667 (w), 650 (w), 625 (m), 596 (m), 534 (m).

*3-(4-Nitro-1-p-tolyl-1H-pyrazol-5-yl)pyridine (**5b**):* Brown oil (0.235 g, 84%^{Pd}, 0.092g, 33%^{Ni}); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.32 (s, 3H, Me), 7.04 (d, 2H, ^3J = 8.5 Hz, CH_{Ar}), 7.12 (d, 2H, ^3J = 8.5 Hz, CH_{Ar}),7.32−7.36 (m, 1H, pyridine), 7.67−7.71 (m, 1H, pyridine), 8.39 (s, 1H, pyrazole) 8.47 (s, 1H, pyridine), 8.64 (d, 1H, pyridine); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ = 21.1 (Me), 123.2, 125.3, 130.0 (CH), 134.4, 135.5 (C), 137.5 (CH), 137.6 (C), 138.1 (CH), 139.6 (C), 150.5, 150.7 (CH); MS (GC, 70 eV) m/z (%) = 280 (M^+, 100), 280 (100), 279 (70), 236 (16), 234 (14), 233 (52), 232 (17), 220 (11), 195 (11), 91 (33), 65 (26); HRMS (ESI) calcd for $C_{15}H_{13}N_4O_2$ (M + H) 281.1033, found 281.1033; IR (ATR, cm^{-1}) ν = 3054 (w), 1599 (w), 1549 (w), 1494 (s), 1471 (m), 1392 (s), 1318 (s), 1192 (m), 1179 (w), 1110 (w), 1031 (m), 1005 (w), 955 (m), 920 (w), 861 (m) 824 (s), 761 (s), 706 (s), 620 (m), 533 (s).

*5-(4-Nitro-1-p-tolyl-1H-pyrazol-5-yl)pyrimidine (**5c**):* Brown oil (0.230 g, 82%^{Pd}); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.35 (s, 3H, Me), 7.05 (d, 2H, ^3J = 8.5 Hz, CH_{Ar}), 7.17 (d, 2H, ^3J = 8.5 Hz, CH_{Ar}), 8.42 (s, 1H, pyrazole), 8.68 (s, 2H, pyrimidine), 9.22 (s, 1H, pyrimidine); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 21.2 (Me), 122.1 (C), 125.5, 130.3 (CH), 134.4, 134.7, 135.0 (C), 137.6 (CH), 140.3 (C), 157.8, 159.1 (CH); MS (GC, 70 eV) m/z (%) = 281 (M^+, 100), 280 (16), 264 (26), 237 (22), 235 (13), 234 (68), 221 (12), 207 (18), 91 (49), 65 (33); HRMS (EI) calcd for $C_{14}H_{11}N_5O_2$ (M^+) 281.09073, found 281.09048; IR (ATR, cm^{-1}) ν = 3046 (w), 1598 (w), 1556 (m), 1495 (s), 1463 (m), 1396 (s), 1320 (s), 1286 (m), 1212 (m), 1165 (w), 1111 (w), 1039 (w), 1002 (w), 957 (m), 918 (w), 862 (w) 825 (s), 762 (s), 743 (w), 723 (s), 628 (s), 539 (m).

*5-(1-Methyl-4-nitro-1H-pyrazol-5-yl)pyrimidine (**5d**):* Brown solid (0.188 g, 92%^{Pd}), mp 177−179 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 3.82 (s, 3H, Me), 8.47 (s, 1H, pyrazole), 9.11 (s, 2H, pyrimidine), 9.37 (s, 1H, pyrimidine); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 38.3 (Me), 122.0 (C), 128.6, 131.4 (CH), 131.9, 135.4 (C), 136.1, 157.8, 159.1 (CH); MS (GC, 70 eV) m/z (%) = 205 (M^+, 100), 175 (27), 161 (25), 134 (42), 120 (31), 1075 (34), 79 (27), 62 (78); HRMS (EI) calcd for $C_8H_7N_5O_2$ (M^+) 205.05943, found 205.05932; IR (ATR, cm^{-1}) ν = 2961 (w), 1713 (w), 1674 (w), 1598 (w), 1556 (m), 1496 (m), 1471 (m), 1392 (s), 1320 (s), 1248 (m), 1193 (m), 1154 (m), 1119 (m), 1052 (w), 999 (w), 972 (m), 920 (m), 878 (m), 828 (m), 761 (m), 716 (s), 694 (m), 641 (m), 628 (m), 594 (m), 539 (s).

*5-(1-(4-Methylbenzyl)-4-nitro-1H-pyrazol-5-yl)pyrimidine (**5e**):* Yellow solid (0.230 g, 78%^{Pd}), mp 106−108 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ = 2.25 (s, 3H, Me), 5.31 (s, 2H, CH_2), 6.90 (d, 2H, ^3J = 8.3 Hz, CH_{Ar}), 7.09 (d, 2H, ^3J = 8.3 Hz, CH_{Ar}), 8.54 (s, 1H, pyrimidine), 8.94 (s, 2H, pyrimidine), 9.33 (s, 1H, pyrazole); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 20.6 (Me), 53.9 (CH_2), 122.0 (C), 127.2, 129.2 (CH), 132.2, 134.0, 135.6 (C), 136.5 (CH), 137.3 (C), 157.5, 159.2 (CH); MS (GC, 70 eV) m/z (%) = 295 (M^+, 78), 105 (100), 77 (28); HRMS (EI) calcd for $C_{15}H_{13}N_5O_2$ (M^+) 295.10638, found 295.10704; IR (ATR, cm^{-1}) ν = 3128 (w), 1599 (w), 1549 (m), 1514 (m), 1470 (m), 1441 (w), 1399 (s), 1354 (m), 1324 (m), 1260 (m), 1187 (m), 1009 (w), 1055 (w), 987 (w), 913 (w), 870 (m), 824 (m), 772 (m), 757 (s), 722 (s), 629 (m), 612 (s), 538 (m).

*3-(1-(4-Methylbenzyl)-4-nitro-1H-pyrazol-5-yl)pyridine (**5f**):* Yellow solid (0.244 g, 83%^{Pd}), mp 113−115 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.24 (s, 3H, Me), 5.21 (s, 2H, CH_2), 6.87 (d, 2H, ^3J = 8.1 Hz, CH_{Ar}), 7.08 (d, 2H, ^3J = 8.1 Hz, CH_{Ar}), 7.54−7.58 (m, 1H, CH_{Ar}), 7.92−7.96 (m, 1H, CH_{Ar}), 8.50 (s, 1H, pyrazole), 8.65−8.73 (m, 2H, CH_{Ar}); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 20.6 (Me), 53.5 (CH_2), 123.5, 127.1, 129.1 (CH), 132.4, 133.4 (C), 136.5 (CH), 137.2 (C), 137.7 (CH), 138.6 (C), 149.8, 151.0 (CH); MS (GC, 70 eV) m/z (%) = 294 (M^+, 84), 105 (100); HRMS (EI) calcd for $C_{16}H_{14}N_4O_2$ (M^+) 294.11113, found 294.11093; IR (ATR, cm^{-1}) ν = 2918 (w), 1602 (w), 1573 (w), 1552 (w), 1498 (s), 1466 (m), 1400 (s), 1355 (w), 1324 (s), 1258 (m); 1190 (m), 1101 (w), 1029 (m), 996 (m), 873 (w), 839 (m), 813 (m), 798 (s), 763 (m), 708 (m), 614 (m).

*3-(4-Nitro-1-(2-phenoxyethyl)-1H-pyrazol-5-yl)pyridine (**5g**):* Dark brown oil (0.282 g, 91%^{Pd}, 0.130g, 42%^{Ni}); ^{1}H NMR (250 MHz, DMSO-d_6) δ = 4.32 (br. s, 4H, 2xCH_2), 6.81−6.94 (m, 3H, CH_{Ar}), 7.21−7.27 (m, 2H, CH_{Ar}), 7.55−7.66 (m, 2H, CH_{Ar}), 8.13 (br. s, 1H, CH_{Ar}), 8.51 (s, 1H, pyrazole); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 49.4, 65.3 (CH_2), 114.2, 120.9, 128.5, 128.7, 129.4 (CH), 131.3 (C), 131.4, 131.9 (CH), 133.1 (C), 136.7 (CH), 157.5 (C); MS (GC, 70 eV) m/z (%) = 310 (M^+, 22), 217 (51), 170 (16), 120 (100), 77 (66); HRMS (EI) calcd for $C_{16}H_{14}N_4O_3$ (M^+) 310.10604, found 310.10655; IR (ATR, cm^{-1}) ν = 3076 (w), 1598 (w), 1552 (w), 1496 (s), 1405 (m), 1361 8w), 1321 (m), 1272 (w), 1248 (m), 1178 (w), 1151 (w), 1082 (w), 1048 (w), 1011 (w), 995 (w), 906 (w), 830 (m), 753 (s), 708 (m), 693 (s), 615 (m), 539 (w).

*5-(4-Nitro-1-phenethyl-1H-pyrazol-5-yl)pyrimidine (**5h**):* Yellow oil (0.256 g, 87%^{Pd}); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 3.05 (d, 2H, ^3J = 7.0 Hz, CH_2), 4.25 (d, 2H, ^3J = 7.0 Hz, CH_2), 6.86−6.89 (m, 2H, CH_{Ar}), 7.18−7.23 (m, 3H, CH_{Ar}), 8.47 (s, 2H, pyrimidine), 8.57 (s, 1H, pyrazole), 9.29 (s, 1H, pyrimidine); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 35.1, 51.6 (CH_2), 121.6 (C), 126.8, 128.6 (CH), 133.2, 135.8 (C), 136.7 (CH), 137.3 (C), 157.2, 159.0 (CH); MS (GC, 70 eV) m/z (%) = 295 (M^+, 1), 104 (100), 91 (45); HRMS (ESI) calcd for $C_{15}H_{14}N_5O_2$ (M + H) 296.1142, found 296.11452; IR (ATR, cm^{-1}) ν = 2929 (w), 2223 (m), 1599 (w), 1550 (m), 1499 (s), 1465 (m), 1399 (s), 1322 (s), 1263 (m), 1178 (m), 1077 (w), 1031 (w), 974 (w), 915 (w), 867 (w), 826 (s), 748 (m), 724 (m), 701 (s), 627 (m), 561 (w).

*4,5-Dimethoxy-2-(4-nitro-1-p-tolyl-1H-pyrazol-5-yl)benzaldehyde (**6a**):* Brown oil (0.176 g, 48%^{Pd}); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.31 (s, 3H, Me), 3.82 (s, 3H, OMe), 3.97 (s, 3H, OMe), 6.72 (s, 1H, CH_{Ar}), 7.02−7.10 (m, 4H, CH_{Ar}), 7.41 (s, 1H, CH_{Ar}), 8.41 (s, 1H, pyrazole), 9.66 (s, 1H, COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ = 21.1 (Me), 56.2 (OMe), 56.4 (OMe), 111.3, 113.5 (CH), 122.7 (C), 124.7 (CH), 128.5 (C), 129.8 (CH), 135.7 (C), 137.2 (CH), 137.9, 139.3, 150.6, 153.4 (C), 188.1 (CH); MS (GC, 70 eV) m/z (%) = 367 (M^+, 16), 367 (16), 350 (12), 322 (34), 321 (100), 319(28), 309 (12), 308 (15), 306 (15), 305 (13), 277 (13), 254 (11), 91 (22), 65 (17); HRMS (ESI) calcd for $C_{19}H_{18}N_3O_5$ (M + H) 368.1241, found 368.12386; IR (ATR, cm^{-1}) ν = 3010 (w), 1683 (m), 1592 (w), 1557 (w), 1505 (s), 1456 (m), 1394 (s), 1316 (s), 1281 (s), 1221 (m), 1163 (m), 1118 (s), 1016 (s), 976 (w), 875 (m) 817 (s), 785 (m), 763 (w), 746 (m), 716 (w), 629 (w), 584 (w).

dx.doi.org/10.1021/jo4025418 | J. Org. Chem. 2014, 79, 2906−2915

*2-(1-(4-Methylbenzyl)-4-nitro-1H-pyrazol-5-yl)benzaldehyde (**6b**):* Yellow oil (0.215 g, 67%^{Pd}); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.22 (s, 3H, Me), 5.05−5.06 (m, 2H, CH_2), 6.81 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.03 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.51−7.54 (m, 1H, CH_{Ar}), 7.81−7.84 (m, 2H, CH_{Ar}), 8.06−8.09 (m, 1H, CH_{Ar}), 8.47 (s, 1H, pyrazole), 9.73 (s, 1H, CHO); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 20.6 (Me), 53.7 (CH_2), 126.6 (C), 127.5, 128.9, 131.1, 131.3 (CH), 132.1 (C), 132.2 (CH), 133.6 (C), 134.1 (CH), 134.4 (C), 136.1 (CH), 137.2, 139.4 (C), 191.4 (CHO); MS (GC, 70 eV) *m*/*z* (%) = 321 (M^+, 100), 77 (18); HRMS (ESI) calcd for $C_{18}H_{15}N_3O_3$ (M + H) 322.11862, found 322.11825; IR (ATR, cm^{-1}) ν = 3129 (w), 1706 (s), 1564 (m), 1497 (s), 1459 (m), 1399 (s), 1350 (m), 1321 (s), 1295 (m), 1268 (m), 1244 (m), 1195 (m), 1133 (w), 1042 (w), 1021 (w), 922 (w), 879 (w), 831 (s), 811 (m), 781 (s), 762 (s), 732 (m), 667 (m), 602 (m), 534 (m).

*2-(1-(4-Methylbenzyl)-4-nitro-1H-pyrazol-5-yl)-4,5-dimethoxybenzaldehyde (**6c**):* Yellow solid (0.205 g, 54%^{Pd}), mp 68−69 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.28 (s, 3H, Me), 3.82 (s, 3H, OMe), 3.90 (s, 3H, OMe), 5.34 (s, 2H, CH_2), 7.16−7.24 (m, 4H, CH_{Ar}), 7.32 (d, 2H, ^4J = 3.9 Hz, CH_{Ar}), 8.25 (s, 1H, CH_{Ar}), 9.0 (s, 1H, pyrazole), 10.07 (s, 1H, CHO); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 20.7 (Me), 55.6 (CH_2), 55.7, 56.5 (OMe), 110.5, 116.0 (CH), 119.3, 125.7 (C), 128.0, 129.2, 130.4 (CH), 132.7 (C), 135.8 (CH), 137.5, 148.6, 154.5 (C), 190.2 (CHO); MS (GC, 70 eV) *m*/*z* (%) = 381 (M^+, 58), 335 (34), 105 (100); HRMS (EI) calcd for $C_{20}H_{19}N_3O_5$ (M^+) 381.13192, found 381.13183; IR (ATR, cm^{-1}) ν = 1667 (m), 1584 (m), 1504 (s), 1470 (m), 1444 (m), 1385 (m), 1340 (w), 1311 (w), 1269 (s), 1217 (m), 1154 (s), 1041 (m), 1014 (m), 979 (m), 866 (s), 811 (s), 756 (m), 737 (s), 654 (m), 588 (s), 555 (m).

*2-(1-Butyl-4-nitro-1H-pyrazol-5-yl)benzaldehyde (**6d**):* Dark brown oil (0.174 g, 64%^{Pd}); ^{1}H NMR (250 MHz, DMSO-d_6) δ = 0.70 (t, 3H, ^3J = 7.2 Hz, $CH_2CH_2CH_2CH_3$), 1.05−1.17 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.53−1.64 (m, 2H, $CH_2CH_2CH_2CH_3$), 3.78−3.85 (m, 2H, $CH_2CH_2CH_2CH_3$), 7.61−7.64 (m, 1H, CH_{Ar}), 7.86−7.90 (m, 2H, CH_{Ar}), 8.15−8.18 (m, 1H, CH_{Ar}), 8.44 (s, 1H, pyrazole), 9.92 (s, 1H, CHO); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 13.1 (Me), 18.7, 30.6, 49.5 (CH_2), 126.6 (C), 131.2, 131.4 (CH), 132.2 (C), 132.7 (CH), 133.0 (C), 134.3 (CH), 134.5 (C), 136.0 (CH), 139.3 (C), 192.0 (CHO); MS (GC, 70 eV) *m*/*z* (%) = 273 (M^+, 1), 227 (100), 183 (18), 171 (55), 129 (29), 115 (23), 102 (26); HRMS (EI) calcd for $C_{14}H_{15}O_3N_3$ (M^+) 273.11079, found 273.11081; IR (ATR, cm^{-1}) ν = 3391 (w), 2958 (w), 1703 (m), 1599 (w), 1558 (w), 1500 (s), 1461 (m), 1401 (s9, 1321 (s), 1271 (m), 1242 (m), 1197 (m), 1023 (w), 845 (w), 826 (s), 758 (s), 605 (w).

*2-(4-Nitro-1-(2-phenoxyethyl)-1H-pyrazol-5-yl)benzaldehyde (**6e**):* Yellow solid (0.219 g, 65%^{Pd}), mp 98−100 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ = 4.21−4.28 (m, 4H, 2xCH_2), 6.75−6.78 (m, 2H, CH_{Ar}), 6.87−6.93 (m, 1H, CH_{Ar}), 7.19−7.26 (m, 2H, CH_{Ar}), 7.64−7.67 (m, 1H, CH_{Ar}), 7.81−7.91 (m, 2H, CH_{Ar}), 9.51 (s, 1H, pyrazole), 9.89 (s, 1H, CHO); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 49.4, 65.2 (CH_2), 114.2, 121.0 (CH), 127.0 (C), 129.4, 131.1, 131.4, 131.6 (CH), 133.4 (C), 134.1 (CH), 136.5 (CH), 140.0, 157.6 (C), 191.7 (CHO); MS (GC, 70 eV) *m*/*z* (%) = 337 (M^+, 1), 231 (100), 146 (65), 120 (43), 75 (63); HRMS (ESI) calcd for $C_{18}H_{15}N_3O_4$ (M + H) 338.11353, found 338.11364; IR (ATR, cm^{-1}) ν = 1713 (w), 1600 (w), 1553 (w), 1497 (s), 1475 (m), 1394 (m), 1320 (s), 1234 (s), 1159 (m), 1079 (m), 1045 (m), 1002 (m), 897 (w), 869 (m), 823 (s), 795 (m), 748 (s), 683 (m), 610 (m), 577 (m), 533 (m).

*4-Nitro-3,5-bis(3-nitrophenyl)-1-phenethyl-1H-pyrazole (**7a**):* Yellow solid (0.220 g, 48%$^{one\text{-}pot}$, 0.284 g, 62%^{consecutive}), mp 148−150 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 3.18 (t, 2H, ^3J = 6.4 Hz, CH_2), 4.21 (t, 2H, ^3J = 6.4 Hz, CH_2), 6.80−6.84 (m, 2H, CH_{Ar}), 7.07−7.11 (m, 1H, CH_{Ar}), 7.19−7.32 (m, 3H, CH_{Ar}), 7.56 (t, 1H, ^3J = 8.0 Hz, CH_{Ar}), 7.69 (t, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.74 (t, 1H, ^4J = 1.7 Hz, CH_{Ar}), 8.06−8.10 (m, 2H, CH_{Ar}), 8.30−8.38 (m, 1H, CH_{Ar}); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ = 34.9, 51.2 (CH_2), 123.2, 123.5, 123.8, 124.1, 126.5 (CH), 127.1 (C), 127.6, 128.0, 128.3, 128.8 (CH), 131.0 (C), 134.4, 134.5 (CH), 135.6, 140.6, 144.7, 147.1, 147.2 (C); MS (GC, 70 eV) *m*/*z* (%) = 459 (M^+, 1), 104 (100); HRMS (EI) calcd for $C_{23}H_{17}N_5O_6$ (M^+) 459.11733, found 459.11773; IR (ATR, cm^{-1}) ν = 2923 (w), 1525 (s), 1499 (s), 1477 (m), 1455 (m), 1398 (s), 1346 (s), 1322 (s), 1254 (m), 1178 (m), 1098 (w), 1077 (w), 1030 (w), 978 (w), 931 (w), 904 (w), 871 (m), 825 (s), 736 (s), 697 (s), 676 (s), 647 (m), 607 (w), 560 (m).

*1-(4-Methylbenzyl)-4-nitro-3,5-bis(3-nitrophenyl)-1H-pyrazole (**7b**):* Yellow solid (0.243 g, 53%$^{one\text{-}pot}$, 0.312 g, 68%^{consecutive}), mp 131−132 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 2.31 (s, 3H, NMe), 5.18 (s, 2H, CH_2), 6.90 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.09 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.59−7.74 (m, 3H, CH_{Ar}), 8.04−8.14 (m, 2H, CH_{Ar}), 8.31−8.44 (m, 2H, CH_{Ar}), 8.62−8.64 (m, 1H, CH_{Ar}); ^{13}C NMR, due to bed solubility in DMSO-d_6, it was not possible to measure; MS (GC, 70 eV) *m*/*z* (%) = 459 (M^+, 62), 105 (100); HRMS (EI) calcd for $C_{23}H_{17}N_5O_6$ (M^+) 459.11733, found 459.11682; IR (ATR, cm^{-1}) ν = 3086 (w), 2922 (s), 2852 (w), 1620 (w), 1524 (s), 1454 (m), 1345 (s), 1244 (w), 1201 (w), 1097 (m), 1041 (w), 909 (m), 870 (w), 842 (m), 808 (m), 736 (s), 677 (s), 570 (w).

*3-(4-(Trifluoromethyl)phenyl)-1-methyl-4-nitro-5-(3-nitrophenyl)-1H-pyrazole (**7c**):* White solid (0.333 g, 85%^{consecutive}), mp 202−204 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.81 (s, 3H, Me), 7.71−7.77 (m, 2H, CH_{Ar}), 7.78−7.93 (m, 4H, CH_{Ar}), 8.35−8.36 (m, 1H, CH_{Ar}), 8.44 (dt, 1H, ^3J = 7.1 Hz, ^4J = 2.5 Hz, CH_{Ar}); ^{19}F NMR (282 MHz, $CDCl_3$) δ = −62.8 (CF_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ = 38.3 (Me), 124.0 (q, ^1J = 272 Hz, CF_3), 124.9 (CH), 125.2 (C), 125.2, 125.3, 125.4 (CH), 128.6 (C), 129.6, 130.2 (CH), 131.4 (q, ^2J = 33 Hz, CH), 133.6 (C), 135.7 (CH), 140.6, 146.3, 148.4 (C); MS (GC, 70 eV) *m*/*z* (%) = 392 (M^+, 100), 373 (16), 316 (14), 174 (28), 163 (40), 117 (40); HRMS (EI) calcd for $C_{17}H_{11}N_4O_4F_3$ (M^+) 392.07269, found 392.07271; IR (ATR, cm^{-1}) ν = 3087 (w), 1525 (m), 1505 (m), 1451 (m), 1350 (s), 1321 (s), 1239 (m), 1191 (w), 1166 (m), 1108 (s), 1063 (s), 1013 (m), 964 (w), 916 (m), 877 (w), 849 (s), 815 (m), 800 (m), 769 (w), 731 (s), 697 (s), 678 (m), 656 (m), 647 (m), 595 (m).

*3-(1-Methyl-4-nitro-5-(3-nitrophenyl)-1H-pyrazol-3-yl)pyridine (**7d**):* Brown solid (0.201 g, 62%^{consecutive}), mp 202−204 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.77 (s, 3H, NMe), 7.57−7.63 (m, 1H, CH_{Ar}), 7.74−7.76 (m, 2H, CH_{Ar}), 7.96−7.99 (m, 1H, CH_{Ar}), 8.25−8.31 (m, 2H, CH_{Ar}), 8.38−8.42 (m, 1H, CH_{Ar}), 8.54 (t, 1H, ^4J = 1.9 Hz, CH_{Ar}); ^{13}C NMR, due to bed solubility in DMSO-d_6, it was not possible to measure; MS (GC, 70 eV) *m*/*z* (%) = 325 (M^+, 100), 163 (23), 117 (25); HRMS (EI) calcd for $C_{15}H_{11}N_5O_4$ (M^+) 325.0811, found 325.08113; IR (ATR, cm^{-1}) ν = 3098 (w), 2929 (w), 1620 (w), 1524 (s), 1503 (m), 1454 (m), 1379 (w), 1346 (s), 1235 (m), 1087 (m), 1002 (w), 901 (m), 840 (m), 799 (m), 768 (w), 737 (s), 720 (m), 696 (s), 673 (m), 646 (m).

*1-(2-Phenoxyethyl)-5-(pyridin-3-yl)-1H-pyrazol-4-amine (**8a**):* Brown oil (0.246 g, 88%); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.99−3.14 (br. s, 2H, NH_2), 4.21−4.35 (m, 4H, 2xCH_2), 6.66−6.70 (m, 2H, CH_{Ar}), 6.82−6.88 (m, 1H, CH_{Ar}), 7.12−7.19 (m, 3H, CH_{Ar}), 7.34−7.39 (m, 1H, CH_{Ar}), 7.74−7.77 (m, 1H, CH_{Ar}); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 49.1, 66.6 (CH_2), 114.4, 121.2, 123.8 (CH), 125.9, 127.6, 128.2 (C), 129.5, 131.3, 137.4, 149.3, 150.4 (CH) 158.1 (C); MS (GC, 70 eV) *m*/*z* (%) = 280 (M^+, 100), 173 (34), 160 (81), 105 (28), 77 (30); HRMS (EI) calcd for $C_{16}H_{16}N_4O$ (M^+) 280.13186, found 280.13186; IR (ATR, cm^{-1}) ν = 3321 (w), 2929 (w), 1666 (w), 1597 (m), 1494 (m), 1460 (w), 1411 (m), 1370 (m), 1291 (w), 1238 (s), 1172 (m), 1081 (w), 1054 (m), 1003 (w), 959 (w), 903 (w), 814 (m), 789 (w), 753 (s), 711 (s), 690 (s), 618 (m).

*1-(4-Methylbenzyl)-5-(pyrimidin-5-yl)-1H-pyrazol-4-amine (**8b**):* Brown oil (0.220 g, 83%); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.19 (br. s, 5H, NH_2, Me), 5.08 (s, 2H, CH_2), 6.74 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 6.95 (d, 2H, ^3J = 8.0 Hz, CH_{Ar}), 7.17 (s, 1H, pyrazole), 8.52 (s, 2H, pyrimidine), 9.08 (s, 1H, pyrimidine); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ = 21.0 (Me), 54.1 (CH_2), 123.7, 124.6 (C), 126.5 (CH) 129.1, 129.5, 131.0 (CH), 133.8, 137.7 (C), 156.9 (CH), 158.0 (C); MS (GC, 70 eV) *m*/*z* (%) = 265 (M^+, 87), 105 (100); HRMS (EI) calcd for $C_{15}H_{15}N_5$ (M^+) 265.13220, found 265.13228; IR (ATR, cm^{-1}) ν = 2922 (w), 1682 (w), 1545 (m), 1515 (m), 1406 (s), 1315 (m), 1187 (m), 1119 (w), 1038 (w), 998 (m), 912 (w), 793 (s), 752 (m), 724 (s), 657 (m), 627 (s).

dx.doi.org/10.1021/jo4025418 | J. Org. Chem. 2014, 79, 2906−2915

*7,8-Dimethoxy-1-p-tolyl-1H-pyrazolo[4,3-c]isoquinoline (**9a**):* Gray solid (0.297 g, 93%), mp 180−182 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.46 (s, 3H, Me), 3.51 (s, 3H, OMe), 3.92 (s, 3H, OMe), 6.83 (s, 1H, CH_{Ar}), 7.48 (d, 2H, ^3J = 8.1 Hz, CH_{Ar}), 7.54(d, 2H, ^3J = 8.1 Hz, CH_{Ar}), 7.73 (s, 1H, CH_{Ar}), 8.45 (s, 1H, pyrazole), 8.95 (s, 1H, Py); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 20.8 (Me), 55.0, 55.7 (OMe), 100.8, 108.6 (CH), 117.6, 122.7 (C), 126.9, 127.9 (CH), 129.8 (C), 135.3 (CH), 135.9, 138.1, 138.9 (C), 147.9 (CH), 149.3, 151.8 (C); MS (GC, 70 eV) *m*/*z* (%) = 319 (M^+, 100); HRMS (EI) calcd for $C_{19}H_{17}N_3O_2$ (M^+) 319.13153, found 319.13144; IR (ATR, cm^{-1}) ν = 2905 (w), 1622 (w), 1518 (w), 1492 (s), 1455 (m), 1437 (m), 1385 (m), 1295 (w), 1258 (s), 1205 (m), 1174 (m), 1137 (s), 1084 (m), 944 (m), 925 (m), 865 (m), 824 (s), 796 (s), 713 (m), 664 (w), 630 (w), 573 (m), 563 (m).

*1-(2-Phenoxyethyl)-1H-pyrazolo[4,3-c]isoquinoline (**9b**)L.* Yellow solid (0.254 g, 88%), mp 117−119 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 4.51 (t, 2H, ^3J = 5.3 Hz, CH_2), 5.24 (t, 2H, ^3J = 5.3 Hz, CH_2), 6.68−6.72 (m, 2H, CH_{Ar}), 6.82−6.88 (m, 1H, CH_{Ar}), 7.13−7.20 (m, 1H, CH_{Ar}), 7.78−7.83 (m, 1H, CH_{Ar}), 7.93−7.99 (m, 1H, CH_{Ar}), 8.29−8.32 (m, 1H, CH_{Ar}), 8.37 (s, 1H, pyrazole), 9.07 (s, 1H, Py); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 51.5, 66.8 (CH_2), 114.2, 120.8, 122.0 (CH), 122.6, 126.8 (C), 127.3 (CH), 128.1 (C), 129.3, 129.4, 130.8, 134.2 (CH), 136.3 (C), 149.4 (CH), 157.9 (C); MS (GC, 70 eV) *m*/*z* (%) = 289 (M^+, 24), 196 (26), 182 (31), 169 (100), 128 (51), 77 (47); HRMS (ESI) calcd for $C_{18}H_{16}N_3O$ (M + H) 290.12879, found 290.1288; IR (ATR, cm^{-1}) ν = 3033 (w), 1622 (w), 1588 (m), 1531 (w), 1496 (m), 1445 (m), 1416 (m), 1350 (w), 1286 (m), 1241 (s), 1133 (w), 1061 (m), 1021 (w), 950 (m), 906 (m), 827 (m), 789 (m), 741 (s), 686 (s), 592 (m), 574 (s).

*1-(4-Methylbenzyl)-7,8-dimethoxy-1H-pyrazolo[4,3-c]isoquinoline (**9c**):* Gray solid (0.300 g, 90%), mp 168−170 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 2.27 (s, 3H, Me), 3.77 (s, 3H, OMe), 4.00 (s, 3H, OMe), 5.96 (s, 2H, CH_2), 6.97 (d, 2H, ^3J = 8.1 Hz, CH_{Ar}), 7.08 (d, 2H, ^3J = 8.1 Hz, CH_{Ar}), 7.28 (s, 1H, CH_{Ar}), 7.38 (s, 1H, CH_{Ar}), 8.34 (s, 1H, pyrazole), 8.87 (s, 1H, Py); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 21.0 (Me), 56.0 (OMe), 56.1 (CH_2), 56.3 (OMe), 101.9, 108.2 (CH), 118.8, 122.7 (C), 125.7, 128.4 (CH), 128.5 (C), 129.8, 132.0 (CH), 132.1 (C), 133.8 (CH), 133.9, 135.9, 137.7 (C), 147.4 (CH), 149.4, 152.8 (C); MS (GC, 70 eV) *m*/*z* (%) = 333 (M^+, 100), 105 (72); HRMS (EI) calcd for $C_{20}H_{19}N_3O_2$ (M^+) 333.14718, found 333.14682; IR (ATR, cm^{-1}) ν = 2920 (w), 1622 (w), 1582 (w), 1495 (m), 1436 (m), 1405 (m), 1265 (m), 1191 (m), 1154 (s), 1117 (s), 1072 (m), 1016 (m), 926 (m), 850 (m), 803 (m), 783 (m), 753 (m), 719 (s), 693 (s), 575 (m), 538 (s).

*1-(4-Methylbenzyl)-1H-pyrazolo[4,3-c]isoquinoline (**9d**):* Light yellow solid (0.256 g, 94%), mp 163−164 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.18 (s, 3H, Me), 6.06 (s, 2H, CH_2), 6.98 (d, 2H, ^3J = 8.4 Hz, CH_{Ar}), 7.07 (d, 2H, ^3J = 8.4 Hz, CH_{Ar}), 7.69−7.75 (m, 1H, CH_{Ar}), 7.80−7.86 (m, 1H, CH_{Ar}), 8.25−8.32 (m, 2H, CH_{Ar}), 8.43 (s, 1H, pyrazole), 9.08 (s, 1H, Py); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ = 20.5 (Me), 55.1 (CH_2), 121.5 (CH), 122.2 (C), 126.1 (CH), 126.7 (C), 127.2, 129.3, 131.1, 134.0 (CH), 134.1, 136.6, 136.7 (C), 149.5 (CH); MS (GC, 70 eV) *m*/*z* (%) = 273 (M^+, 75), 105 (100); HRMS (ESI) calcd for $C_{18}H_{16}N_3$ (M + H) 274.13387, found 274.13397; IR (ATR, cm^{-1}) ν = 3129 (w), 1621 (w), 1531 (w), 1512 (w), 1474 (w), 1415 (m), 1349 (m), 1309 (m), 1179 (w), 11052 (w), 1063 (m), 1019 (w), 994 (w), 952 (w), 927 (w), 889 (m), 836 (m), 793 (s), 759 (s), 734 (m), 698 (m), 615 (w), 578 (s).

*1-Butyl-1H-pyrazolo[4,3-c]isoquinoline (**9e**):* Yellow solid (0.209 g, 93%), mp 137−139 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 0.98 (t, 3H, ^3J = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 1.39−1.54 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.93−2.05 (m, 2H, $CH_2CH_2CH_2CH_3$), 4.80 (t, 2H, ^3J = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 7.69−7.76 (m, 1H, CH_{Ar}), 7.87−7.93 (m, 1H, CH_{Ar}), 8.15−8.18 (m, 1H, CH_{Ar}), 8.26−8.30 (m, 2H, pyrazole, CH_{Ar}), 9.03 (s, 1H, Py); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ = 13.7 (Me), 19.9, 31.9, 52.8 (CH_2), 121.1 (CH), 123.5 (C), 127.1, 129.8, 131.3, 133.6 (CH), 136.1, 147.6, 149.0 (C); MS (GC, 70 eV) *m*/*z* (%) = 225 (M^+, 20), 182 (100), 169 (35), 128 (28); HRMS (EI) calcd for $C_{14}H_{15}N_3$ (M^+) 225.12605, found 225.12597; IR (ATR, cm^{-1}) ν = 2955 (w), 2930 (w), 2205 (w), 2063 (m), 1958 (m), 1463 (m), 1412 (m), 1346 (m), 1313 (w), 1275 (m), 1232 (w), 1086 (w), 1053 (m), 978 (m), 930 (m), 875 (m), 859 (m), 781 (s), 743 (s), 700 (s), 596 (w), 569 (s).

*5-(4-Methoxyphenyl)-N,N-dimethyl-1-p-tolyl-1H-pyrazol-4-amine (**10a**):* Orange oil (0.273 g, 89%); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.30 (s, 3H, Me), 2.56 (s, 6H, NMe_2), 3.80 (s, 3H, OMe), 6.84 (d, 2H, ^3J = 8.5 Hz, CH_{Ar}), 7.06 (br. s, 4H, CH_{Ar}), 7.20 (d, 2H, ^3J = 8.5 Hz, CH_{Ar}), 7.51 (s, 1H, pyrazole); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ = 21.0 (Me), 44.7 (NMe_2), 55.2 (OMe), 113.8 (CH), 123.0 (C), 124.8, 129.2 (CH) 131.2 (C), 131.2 (CH), 131.6, 136.6, 136.9, 138.1, 159.2 (C); MS (GC, 70 eV) *m*/*z* (%) = 307 (M^+, 100), 307 (100), 306 (10), 224 (40), 146 (13), 132 (19), 91 (18), 65 (13); HRMS (ESI) calcd for $C_{16}H_{15}N_3O_2$ (M + H) 308.17600, found 308.17655; IR (ATR, cm^{-1}) ν = 3011 (w), 1614 (w), 1565 (w), 1513 (s), 1456 (m), 1384 (m), 1287 (w), 1245 (s), 1176 (m), 1086 (w), 1035 (m), 962 (s), 926 (w), 813 (s), 740 (w) 661 (m), 631 (m), 576 (m), 528 (m).

*4-(4-(Dimethylamino)-1-p-tolyl-1H-pyrazol-5-yl)benzonitrile (**10b**):* Orange oil (0.257 g, 85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.33 (s, 3H, Me), 2.56 (s, 6H, NMe_2), 7.02 (d, 2H, ^3J = 8.3 Hz, CH_{Ar}), 7.10 (d, 2H, ^3J = 8.3 Hz, CH_{Ar}), 7.42 (d, 2H, ^3J = 8.3 Hz, CH_{Ar}), 7.56 (d, 2H, ^3J = 8.3 Hz, CH_{Ar}), 7.57 (s, 1H, pyrazole); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 21.1 (Me), 44.9 (NMe_2), 111.2, 118.6 (C), 125.1, 129.6 (CH), 130.0 (C), 130.2, 131.8, 132.0 (CH), 135.2, 137,6. 138,1 (C); MS (GC, 70 eV) *m*/*z* (%) = 302 (M^+, 100), 303 (23), 302 (100), 301 (13), 276 (11), 260 (10), 219 (34), 146 (12), 132 (20), 91 (25), 65 (14); HRMS (ESI) calcd for $C_{19}H_{19}N_4$ (M + H) 303.1610, found 303.16064; IR (ATR, cm^{-1}) ν = 2942 (w), 2777 (w), 1558 (w), 1513 (s), 1452 (w), 1411 (w), 1382 (m), 1312 (w), 1232 (w), 1180 (w), 1149 (w), 1086 (w), 1031 (w), 1015 (w), 961 (m), 926 (w), 818 (s), 771 (w), 729 (w), 700 (w), 660 (w), 629 (w), 593 (w), 573 (w).

*N,N-Dimethyl-1,5-di-p-tolyl-1H-pyrazol-4-amine (**10c**):* Orange oil (0.250 g, 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.30 (s, 3H, Me), 2.33 (s, 3H, Me), 2.56 (s, 6H, NMe_2), 6.99−7.21 (m, 8H, CH_{Ar}), 7.49 (s, 1H, pyrazole); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ = 21.0 (Me), 21.3 (Me), 44.8 (NMe_2), 124.8 (CH), 127.7 (C), 129.0, 129.2, 129.9, 131.2 (CH) 131.7, 136.6, 136.7, 138.0, 138.1 (C); MS (GC, 70 eV) *m*/*z* (%) = 291 (M^+, 100), 291 (100), 290 (10), 276 (11), 208 (36), 146 (11), 132 (20), 91 (19), 65 (11); HRMS (ESI) calcd for $C_{19}H_{22}N_3$ (M + H) 292.17355, found 292.18126; IR (ATR, cm^{-1}) ν = 2946 (w), 1558 (w), 1515 (m), 1556 (w), 1420 (w), 1382 (m), 1327 (s), 1271 (w), 1230 (w), 1175 (m), 1148 (m), 1121 (s), 1095 (m), 1073 (m), 1031 (m), 971 (m), 926 (m), 908 (m), 810 (s), 717 (m), 702 (m), 694 (m), 658 (m), 582 (m).

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org. X-ray crystallographic data (excluding structure factors) for the structure **4h**, **5f**, **7c**, **9c** **10a**, and **4′** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. 949372-949376 and 977379 can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk, or via www.ccdc.cam.ac.uk/data_request/cif.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support by the DAAD (scholarship for A.G.) and by the State of Mecklenburg-Vorpommern is gratefully acknowledged. We are grateful to Satenik Mkrtchyan for the preparation of the Supporting Information, and to Enamine Ltd. Company (Ukraine) for support.

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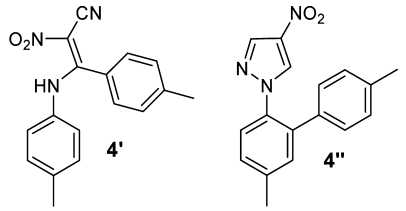
(11) After we conducted arylation of pyrazole **3e** without CuI, we detected the compound **4′** instead of expected **4″**. The substance **4′** was isolated by preparative column chromatography, and its structure was unambiguously corroborated by X-ray analysis (for details, see Supporting Information).



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(17) X-ray crystallographic data (excluding structure factors) for the structure **4h**, **5f**, **7c**, **9c** **10a** and **4′** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. 949372-949376 and 977379 can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk, or via www.ccdc.cam.ac.uk/data_request/cif.