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Regioselective Synthesis, NMR, and Crystallographic Analysis of N1-Substituted Pyrazoles

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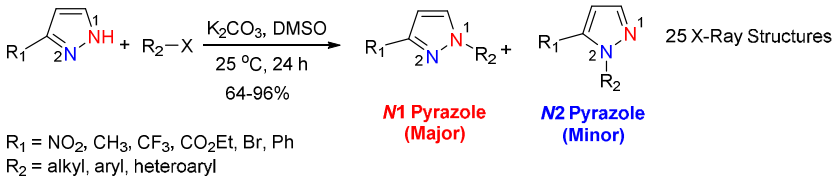


Abstract: A systematic study of the N-substitution reactions of 3-substituted pyrazoles under basic conditions has been undertaken. Regioselective N1-alkylation, -arylation, and -heteroarylation of 3-substituted pyrazoles have been achieved using K_2CO_3-DMSO. The regioselectivity is justified by the DFT calculations at the B3LYP/6-31G**(d) level. A consistent steric effect on chemical shift has been observed for N-alkyl pyrazole analogs. 25 X-ray crystallographic structures have been obtained to confirm the regiochemistry of the major products.

Introduction

Pyrazole derivatives have received increasing attention in chemical,[1] agrochemical,[2] pharmaceutical,[3] and material science.[4] N-Substituted pyrazoles are of particular interest in medicinal chemistry. For example, the non-steroidal anti-inflammatory drugs (NSAID) Celecoxib[5] and Lonazolac[6] as well as CRF1 receptor antagonist GW876008[7] are N-substituted pyrazoles (Figure 1). Recently, N-substituted pyrazoles have been reported to possess inhibitory activities against various biological targets,

such as PDE4,[8] CCR2,[9] c-Met protein kinase,[10] and ALK5.[11] Notably, the aminopyrazole derivative AZD1152 has been clinically evaluated as an anticancer agent.[12]

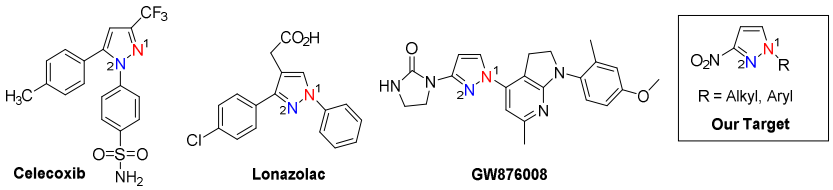
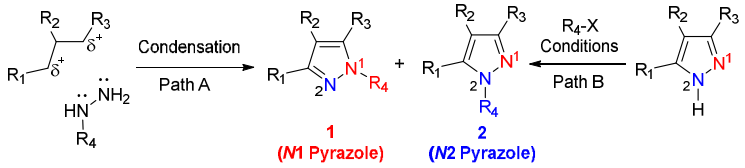


Figure 1. Representative Examples of Medicinally Important N-Substituted Pyrazoles and Our Target

As part of a drug discovery project, we required N1-substituted-3-nitropyrazoles as key intermediates to access 3-aminopyrazoles and other synthetically challenging 3-substituted pyrazoles (Figure 1). N-substituted pyrazoles are commonly prepared via condensation reactions of monosubstituted hydrazines and 1, 3-dielectrophiles (Scheme 1, Path A).[13] However, this approach has major shortcomings: (i) preparation of the intermediates for the condensation reactions can be lengthy and challenging; (ii) requirement for early installation of the N-substituents, which limits the diversity of the N-substitutions on the pyrazole ring; (iii) the pyrazoles obtained from these methods are often a mixture of two regioisomers **1** and **2**; and (iv) the distribution of these two regioisomers is generally unpredictable.

Scheme 1. Methods to Prepare N-Substituted Pyrazoles



As a result of these shortcomings and the difficulty to access 1, 3-dielectrophiles containing a nitro group, we believed the N-substitution reaction of 1*H*-pyrazoles (Scheme 1, Path B) would be a better route to prepare our target than Path A. Path B has been occasionally investigated to prepare N-substituted pyrazoles in the literature. In 2004, Buchwald and colleagues developed diamine ligands for the Ullmann-type reactions for N-arylation of common nitrogen heterocycles with aryl halides.[14] Three unsymmetric 1*H*-pyrazoles were reported, and "the less hindered nitrogen was selectively arylated" to

give the corresponding N1 regioisomers. You and colleagues further modified the procedure by developing ligand-free procedures for several similar Ullmann-type reactions.[15] Only one unsymmetric 1*H*-pyrazole, 3-methylpyrazole, was reported to react with iodobenzene. A mixture of the two regioisomers was observed with the less hindered N1 isomer as the major product (3:1 ratio, 85% yield). The authors agreed with Buchwald that steric hindrance was responsible for the regioselectivity observed.

Pyrazoles, as electron-rich heterocycles, readily participate in nucleophilic substitution reactions. N-Substitution of pyrazoles are usually carried out under basic conditions to prevent quaternization and protonation of pyrazoles by alkyl halides (R_4-X) and X-H.[16,17] However, when secondary halides are employed as electrophiles, elimination and rearrangement of the halides predominate, which explains why current methods are generally limited to primary halides and aromatic halides. Other conditions, such as solvent-free,[16] phase transfer,[18] and microwave irradiation,[19] have been explored to reduce side reactions. However, these protocols require elevated temperatures and give low to moderate yields with low regioselectivity.

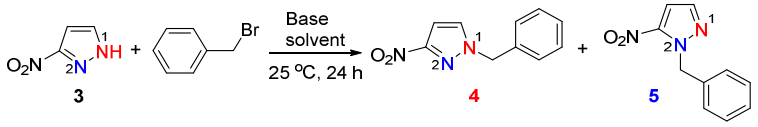
The current literature provides few examples on the N-substitution reactions of pyrazoles, including N-alkylation[20] and N-arylation.[21] Further, thorough regioselectivity studies are non-existent. Therefore, studies of N-substitution reactions of 1*H*-pyrazoles represent a gap in synthetic organic chemistry literature.

Given our need to prepare a series of pyrazole intermediates, we were motivated to develop a simple and robust method for the synthesis of these derivatives in a regiocontrolled fashion. We reasoned that, if the pyrazolate anion could be made nucleophilic enough, facile N-substitution might proceed at low temperature thereby providing both high regioselectivity and yield. To test our hypothesis, the well-known "superbasic media",[22, 23] a mixture of an alkali metal base and DMSO, was employed. As an excellent metal-coordinating solvent, DMSO weakens the electrostatic interactions between metal cations and the anions, thereby making not only alkali metal base more basic, but also the resulting pyrazolate anion more nucleophilic. Our studies toward this end are described herein.

Results and Discussion

1. Synthesis. Commercially available 3-nitropyrazole was selected as the first pyrazole to test our hypothesis because the nitro moiety can be readily converted to amines and many other functional groups. Thus, 3-nitropyrazole was treated with benzyl bromide at room temperature in order to examine a variety of bases (Scheme 2 and Table S1). The use of Na_2CO_3, $NaHCO_3$, NaOH, and Et_3N gave 0-10% conversions, and no reaction occurred in the absence of base. Among the bases screened, KOH, K_2CO_3, and Cs_2CO_3 proved to be effective, affording high conversion (>95%) and good regioselectivity (**4**:**5**=10:1). These results could be explained by the fact that DMSO solvates larger alkali metal cations (e.g., K^+ and Cs^+) better than the smaller ones (e.g., Na^+).[24] The nature of the solvent was critical, and DMSO afforded the best results as expected, whereas CH_2Cl_2 and THF were ineffective. For the reaction carried out in K_2CO_3-DMSO, the two regioisomeric products were separable via column chromatography.[25] An X-ray crystallography of the major product unambiguously reveals it is the N1 pyrazole (See Supporting Information). Considering its high efficiency, good regioselectivity, low cost, and non-hygroscopic property, K_2CO_3 was chosen as the base for further experimentation.

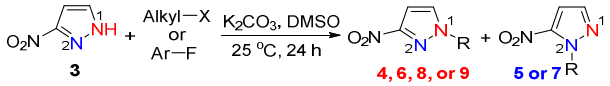
Scheme 2. Optimization of Reaction Conditions for N-Benzylation of 3-Nitropyrazole (See Table S1)

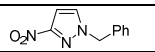
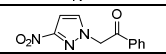
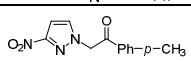
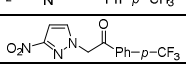
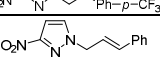
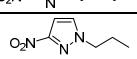
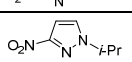
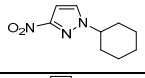
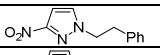
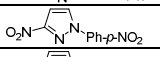
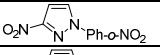
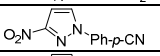
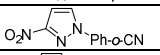
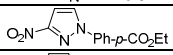
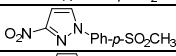
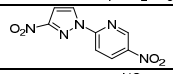
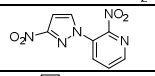
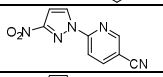
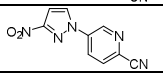
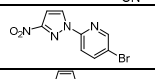
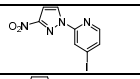
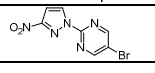


Under the above optimized conditions shown in Scheme 2, the scope of the N-substitution of 3-nitropyrazole was evaluated. A series of alkyl electrophiles were first selected and the results are summarized in Table 1. It appears that the more reactive (Entries 1 vs 2) and the less steric hindered electrophiles (Entries 6 vs 7), the higher the yield and the regioselectivity. In addition, the secondary halide substrates decreased the reaction rates, which suggests that the reactions exhibit S_N2 character in their mechanisms.

It is worth pointing out that bromocyclohexane and phenethyl halides, notorious for their low yields due to elimination under literature reported conditions,[17] afford the alkylated products in moderate

Table 1. Substrate Scope of N-Substitution Reactions of 3-Nitropyrazole[a]



Entry	R-X	*N*1 Isomeric Product		Yield[b] (%) (Ratio 6:7)[c]
1	Bn-Br		**4**	91 (10:1)
2	$BzCH_2$-Br		**6a**	92 (>20:1)
3	*p*-CH_3-$BzCH_2$-Br		**6b**	94 (>20:1)
4	*p*-CF_3-$BzCH_2$-Br		**6c**	91 (>20:1)
5	$PhCH{=}CHCH_2$-Br		**6d**	90 (8:1)
6	Propyl-I		**6e**	84 (7:1)
7	*i*-Propyl-I		**6f**	64 (5:1)
8	Cyclohexyl-Cl		**6g**	<5[d] (n/a[e])
9	Cyclohexyl-Br			67[d] (3:1)
10	Cyclohexyl-I			28[d] (3:1)
11	$PhCH_2CH_2$-Br		**6h**	87 (9:1)
12	*p*-NO_2-Ph-F		**8a**	93 (>99:1)
13	*o*-NO_2-Ph-F		**8b**	92[d] (>99:1)
14	*p*-CN-Ph-F		**8c**	94 (>99:1)
15	*o*-CN-Ph-F		**8d**	92[d] (>99:1)
16	*p*-CO_2Et-Ph-F		**8e**	86 (>99:1)
17	*p*-SO_2CH_3-Ph-F		**8f**	95 (>99:1)
18	5-NO_2-2-F-pyridine		**9a**	96 (>99:1)
19	2-NO_2-3-F-pyridine		**9b**	94 (>99:1)
20	5-CN-2-F-pyridine		**9c**	93 (>99:1)
21	6-CN-3-F-pyridine		**9d**	91 (>99:1)
22	5-Br-2-F-pyridine		**9e**	95 (>99:1)
23	2-F-4-I-pyridine		**9f**	90 (>99:1)
24	5-Br-2-F-pyrimidine		**9g**	94 (>99:1)

[a] Reaction conditions: 3-Nitropyrazole (1.83 mmol), K_2CO_3 (2.20 mmol), electrophile (1.98 mmol), and DMSO (5 mL).

[b] Total isolated yield of N1and N2 regioisomers.

[c] Based on GC/MS analysis of the reaction mixture.

[d] Reaction time was 2 days. Approximate 60% of iodocyclohexane underwent elimination based on NMR studies of the reaction mixture.

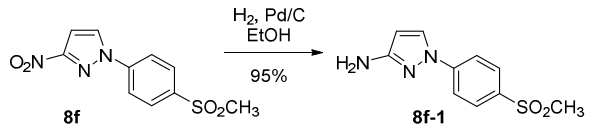
[e] n/a = Not Applicable.

yield and regioselectivity (Entries 9 and 11, respectively). The improved results are likely attributed to the mild reaction conditions employed. The "superbasic media", such as the K_2CO_3-DMSO system in the present study, facilitated the deprotonation of pyrazoles and increased the reactivity of the resulting nucleophile, which allowed the alkylation to occur at room temperature and therefore reduced alkyl halide elimination.

Using the same conditions, aryl fluorides were also successfully employed as electrophiles. Electron-withdrawing groups in the *ortho* or *para* position activated the reactions via an assumed S_NAr mechanism (Entries 12 to 17), whereas substituents in the *meta* position failed to promote any reaction. 1-Chloro-4-fluorobenzene was not reactive enough to yield any product. As for pyridines, the reactions took place more readily although the reaction with 2-fluoropyridine did not occur. Other π-deficient aromatic heterocyclics, such as 5-bromo-2-fluoropyrimidine, underwent an S_NAr reaction at the electron deficient 2-position (Entry 24).

The above N1-substituted 3-nitropyrazoles are valuable precursors to various 3-substituted pyrazoles through established reactions. For instance, hydrogenation of **8f** went smoothly to provide 3-aminopyrazole **8f-1** in 95% yield (Scheme 3). Of note, the analogs of **8f-1** have been prepared via either Pd-catalyzed aminations[26] or an S_NAr reaction[21] of 3-amino-1*H*-pyrazoles, but the ratios of N1:N2 products range from 2:1 to 5:1. On the other hand, nitration of N-substituted pyrazoles usually yielded 4-nitropyrazoles.[27,28] Thus, our method represents an efficient alternative route to 3-aminopyrazoles.

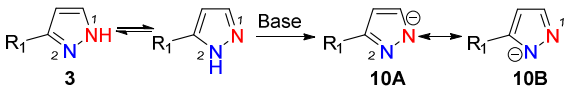
Scheme 3. Reduction of Nitro **8f** to Amine **8f-1**



The regiochemistry of all the products listed in Table 1 was elucidated either by X-ray crystallographic or NMR-nOe studies. Calculations were carried out to explain the regioselectivity. The density functional theory (DFT) calculations at the B3LYP/6-31G**(d) level show that the N1 atom

possesses a higher negative charge than the N2 in **10A** and **10B** (Table 2, entry 1). Therefore, N1 atom is more nucleophilic than N2 and generally the N1 regioisomers are expected to be the major products. When a primary alkyl halide is employed in the substitution step, the regioselectivity increases in order of the bulkiness of the electrophile: α-bromoacetophenones (20:1) > benzyl bromide (10:1) > phenethyl bromide (9:1) > allylic bromide (8:1) > iodopropane (7:1). This trend suggests that the substitution reaction is the rate-determining step and exhibits S_N2 character in the mechanism. For reactions with secondary alkyl halides, the substitution reaction likely proceeds via both S_N1 and S_N2 mechanisms and the products' isomeric ratio N1:N2 decreased. As for N-arylation, the bulky Ar-F provides additional preference of N1 over N2 and only the N1 regioisomers were observed.

Table 2. DFT Calculations at B3LYP/6-31G**(d) Level of 3-Substituted 1*H*-Pyrazolate Anions



3 **10A** **10B**

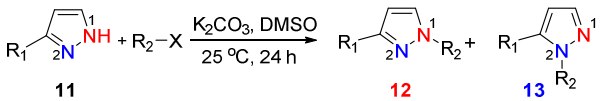
Entry	R_1	Anion	Energy[a]	Charge		
				N1	N2	N1-N2
1	$-NO_2$	**10A**	-430.1817	-0.27	-0.16	-0.11
		10B	-430.1817	-0.28	-0.16	-0.12
		10B-10A	0			
2	$-CO_2Et$	**10A**	-492.8618	-0.26	-0.23	-0.03
		10B	-492.8610	-0.25	-0.18	-0.07
		10B-10A	0.49			
3	$-CF_3$	**10A**	-562.7201	-0.29	-0.17	-0.12
		10B	-562.7207	-0.36	-0.10	-0.26
		10B-10A	-0.34			
4	$-CH_3$	**10A**	-264.9559	-0.41	-0.11	-0.30
		10B	-264.9554	-0.37	-0.15	-0.22
		10B-10A	0.26			

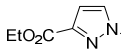
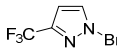
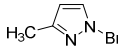
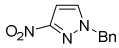
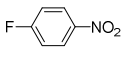
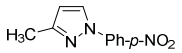
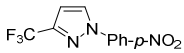
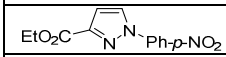
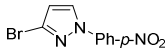
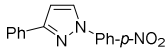
[a] Energies are given in Hartree, and relative energies are in kcal/mol.

Likewise, the calculation results can help to explain the regiochemistry of the N-benzylation of other 3-substituted pyrazoles. For instance, optimization for the 3-CO_2Et pyrazolate anions indicates the N1 and N2 atoms have similar nucleophilicity and therefore the regioselectivity is expected to be low

(Table 2, entry 2), which is consistent with the experimental observations (2:1, Table 3, entry 1). The dramatic change in regioselectivity between the 3-nitro and 3-ester pyrazoles suggests the electronic effect of R_1 plays the major role in regioselectivity when the R_1 groups are similar in size (A-values: -NO_2 = 1.1 vs -CO_2Et = 1.2 kcal/mol). Nonetheless, the steric effect of R_1 does have a great influence on the regioselectivity (Table 3, Entries 2 vs 3). It is noteworthy that the different effect of the methyl and trifluoromethyl groups on the calculated properties of pyrazoles have been discussed in previous papers.[29,30]

Table 3. N-Substitution Reaction of 3-R_1-1*H*-Pyrazole[a]



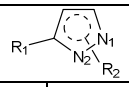
Entry	R_1	R_2-X	N1 Isomeric Product		Yield[b] (%) (12:13)[c]
1	-CO_2Et			12a	92(2:1)
2	-CF_3			12b	92(10:1)
3	-CH_3			12c	95(2:1)[d]
4	-NO_2			4	91(10:1)
5	-CH_3	 (F-Ph-*p*-NO_2)		12d	96(4:1)
6	-CF_3			12e	95(>99:1)
7	-CO_2Et			12f	92(>99:1)
8	-Br			12g	94(>99:1)
9	-Ph			12h	92(>99:1)

[a] Reaction conditions: Pyrazole **11** (1.83 mmol), R_2-X (1.98 mmol), K_2CO_3 (2.20 mmol), and DMSO (5 mL).
[b] Total isolated yield of N1and N2 regioisomers.
[c] Based on GC/MS and NMR studies of the reaction mixture.
[d] Experimental results are consistent with those in ref 16.

2. NMR Studies. By correlating the regiochemistry resolved by X-ray crystallography/nOe with the ^{1}H NMR spectra, it was found that all of the *N*2-CHn proton(s) are more deshielded than the corresponding *N*1-CHn. Moreover, it appears that the bulkier the R_2 group or the R_1, the greater the difference of the chemical shift (δ2-δ1, Table 4) of the *N*-CHn proton(s). This consistent difference could be attributed to a

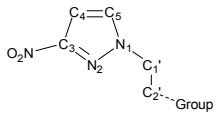
migration of the electron density from the sterically compressed proton(s) in *N*2-CHn to its neighboring atoms. Literature examples indicated that the same phenomena also exist for most of the N-alkyl pyrazoles [16,31,32,33] with few exceptions[31,34] although all of these regioisomers were assigned tentatively due to lack of the X-ray structures. Nonetheless, the data listed in Table 4 show the steric effect on chemical shift and can serve as a supplementary reference for a quick regiochemical assignment of N-alkyl pyrazole analogs.

Table 4. ^{1}H NMR Chemical Shift (δ) in $CDCl_3$ of Representative N1- and N2-Alkyl Pyrazoles

		**N1 Pyrazole**		**N2 Pyrazole**		
R_1	**R_2**	**Compound**	**δ1**	**Compound**	**δ2**	**δ2-δ1**
NO_2	*i*-Propyl	**6f**	4.58	**7f**	5.44	0.86
	Cyclohexyl	**6g**	4.19	**7g**	5.03	0.84
	Bn	**4**	5.37	**5**	5.79	0.42
CO_2Et	Bn	**12a**	5.39	**13a**	5.78	0.39
CF_3		**12b**	5.35	**13b**	5.43	0.08
CH_3		**12c**[16]	5.24	**13c**[16]	5.29	0.05

3. X-Ray Crystallographic Analysis. To confirm the regiochemistry of the above N1-substituted pyrazoles, X-ray crystallographic structures of 25 products were obtained at 100 K. In Tables S2 and S3 are gathered the selected geometry data. For example purposes, a short version of Table S2 is included here (Table 5), and the ORTEP plot of compound **8a** is shown in Figure 2. Compound **8a** crystallizes into an orthorhombic crystal system.

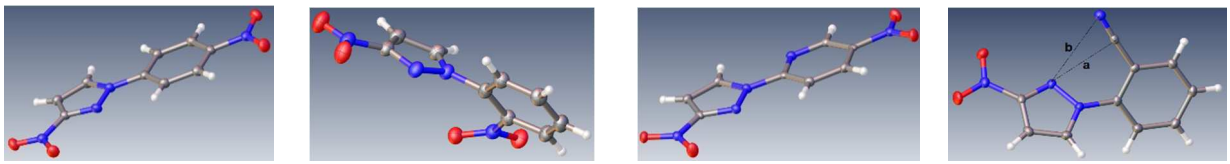
Table 5. Selected Bond Lengths (Å) and Angles (°) of 3-Nitropyrazoles



Compound		N1-N2	N2-C3	C3-C4	C4-C5	C5-N1	N2-N1-C1'-C2'
1*H*-Pyrazole[a]		1.344 (5)	1.325 (5)	1.391 (7)	1.364 (6)	1.345 (4)	n/a
	8a	1.355 (2)	1.324 (3)	1.394 (3)	1.361 (3)	1.369 (3)	-0.9 (3)
	8b	1.352 (2)	1.327 (2)	1.394 (3)	1.362 (3)	1.364 (2)	42.4 (2)
	9a	1.354 (4)	1.327 (5)	1.402 (5)	1.361 (5)	1.370 (4)	−1.4 (5)
	9g	1.353 (2)	1.319 (2)	1.403 (3)	1.364 (3)	1.375 (2)	16.4 (2)

[a] Data are taken from ref 35 and 36.

In light of the data in Tables S2 and S3, some key points are worth mentioning. For the N1-aryl analogs, moving the substituents from *para/meta* to *ortho* position leads to an increase of the dihedral angle (N2-N1-C1'-C2') from 0.8-16.4° to ca. 40°, i.e., the pyrazole and the aryl rings are no longer coplanar (e.g., Figure 2, **8b** vs **8a**). In the N1-pyridyl analogs, the nitrogen in the pyridyl ring is *anti* to the N2 atom in the pyrazole ring presumably due to their electronic repulsion (e.g., **9a**). The same repulsive effect could be used to explain why the *o*-NO_2 group is also preferred to be *anti* to the N2 atom in compound **8b**. On the contrary, the linear geometry of the *o*-CN group permits a possible attraction between the nitrile group and the N2 atom in the pyrazole, resulting in a close contact between these two moieties (**8d**, a = 2.84 Å; b = 3.30 Å).



8a **8b** **9a** **8d**

Figure 2. Representative X-Ray Structures of Pyrazoles: **8a**, **8b**, **9a**, and **8d**

Conclusions

In conclusion, a simple and regioselective reaction protocol has been established to functionalize the pyrazole rings at the N1 position in good to excellent yields. The resulting functionalized pyrazoles are useful in synthesis, e.g., N1-substituted 3-nitropyrazoles can be employed to prepare the analogs of GW876008 (Figure 1). Our method also allows chemists to readily access other pyrazoles which are difficult to prepare via traditional cycloaddition procedures (e.g., *N*-cycloalkylpyrazole **6g**). DFT calculations at the B3LYP/6-31G**(d) level are helpful to explain the electronic effect of the C3 substituents plays an important role in the regiochemistry. Furthermore, a quick method for determining product distribution by ^{1}H NMR for 3-substituted pyrazoles has been developed. Lastly, the obtained X-ray crystal structures of the 25 new products will serve as a reliable source for theoretical studies of pyrazole.

The construction of functionalized heterocycles constitutes one of the most fundamental and important endeavors in chemical synthesis. We believe this work will find reasonable application among synthetic, medicinal, and physical organic chemists.

Experimental Section

General Methods. Reactions were run using commercially available starting materials and anhydrous solvents without further purification unless otherwise stated. Melting points (°C) are uncorrected. High-resolution mass spectra (HRMS) were obtained by using electrospray ionization (ESI) in the positive mode.

Theoretical Calculations. All the DFT calculations were carried out at the B3LYP/6-31G**(d) level using Gaussian09.[37] Charge is set to -1, and Spin to Singlet.

X-Ray Crystallography. A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a diffractometer ($Cu_{K\alpha}$ radiation, λ=1.54178 Å), and equipped with a nitrogen flow apparatus. The collection method involved 1.0° scans in ω at 30°,

55°, 80°, and 115° in *2θ*. Data integration down to 0.84 Å resolution was carried out with reflection spot size optimization. Absorption corrections were made. The structure was solved by the direct methods procedure and refined by least-squares methods again F^2. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms.

General Procedure for the N-Substitution Reaction of 3-nitropyrazole with Alkyl, Aryl and Heteroaryl Electrophiles. 3-Nitropyrazole (207 mg, 1.83 mmol, 1.0 equiv), potassium carbonate (303.6 mg, 2.20 mmol, 1.2 equiv), electrophile (1.98 mmol, 1.1 equiv), and a stirring bar were placed in a vial. At 0 °C, 5 mL of DMSO was added. The resulting mixture was slowly warmed to room temperature and stirred at this temperature for 24 h. The reaction was quenched with iced water (10 mL). The resulting mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and evaporated to give the crude product, which was purified via column chromatography (silica gel, eluting with 0-100% of EtOAc in hexane) to provide the desired product. All the compounds shown in Tables 1 and 3 were prepared according to this procedure.

1-Benzyl-3-nitro-1*H*-pyrazole (4). Obtained as a white solid (308 mg, 83%), which was recrystallized from a mixture of EA and hexanes as fine colorless needles of m. p. 63-64 °C. The x-ray structure of this compound was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28-7.41 (m, 6H), 6.90 (d, J = 2.4 Hz, 1H), 5.37 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 155.7, 134.3, 132.3, 129.1, 128.8, 128.1, 103.4, 57.5; HRMS (ESI+) calcd for $C_{10}H_9N_3O_2$ ($[M+H]^+$) 204.0773; found 204.0777.

2-Benzyl-3-nitro-1*H*-pyrazole (5). Obtained as a colorless oil (15 mg, 4%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58 (d, J = 2.5 Hz, 1H), 7.26-7.33 (m, 6H), 7.08 (d, J = 2.5 Hz, 1H), 5.79 (s, 2H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 145.5, 138.2, 135.2, 128.8, 128.4, 127.7, 107.2, 56.4; HRMS (ESI+) calcd for $C_{10}H_9N_3O_2$ ($[M+H]^+$) 204.0773; found 204.0771.

2-(3-Nitro-1*H*-pyrazol-1-yl)-1-phenylethan-1-one (6a). Obtained as a white solid (391 mg, 92%), which was recrystallized from a mixture of EA and hexanes as colorless needles of m. p. 118-120 °C. The x-ray structure of this compound was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47 (d, J = 6.0

Hz, 2H), 7.55-7.69 (m, 4H), 7.00 (d, J = 0.1 Hz, 1H), 5.72 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 190.6, 156.1, 134.7, 134.3, 133.7, 129.2, 128.0, 103.5, 58.9; HRMS (ESI+) calcd for $C_{11}H_{10}N_3O_3$ ($[M+H]^+$) 232.0722; found 232.0725.

2-(3-Nitro-1*H*-pyrazol-1-yl)-1-(p-tolyl)ethan-1-one (6b). Obtained as a light yellow solid (422 mg, 94%), which was recrystallized from a mixture of EA and hexanes as white needles of m. p. 165-166 °C. The x-ray structure of this compound was obtained. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.02 (d, J = 2.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 2.4 Hz, 1H), 6.05 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 191.7, 155.2, 144.8, 135.8, 131.5, 129.4, 128.1, 102.9, 59.1, 21.2; HRMS (ESI+) calcd for $C_{12}H_{12}N_3O_3$ ($[M+H]^+$) 246.0879; found 246.0878.

2-(3-Nitro-1*H*-pyrazol-1-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-one (6c). Obtained as a light yellow solid (498 mg, 91%), which was recrystallized from a mixture of EA and hexanes as white needles of m. p. 120-121 °C. The x-ray structure of this compound was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, J = 7.5 Hz, 2H), 7.80 (d, J = 7.5 Hz, 2H), 7.61(d, J = 1.0 Hz, 1H), 7.00 (d, J = 1.0 Hz, 1H), 5.76 (s, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 189.9, 156.3, 136.4, 135.7 (q, J = 33.1 Hz), 134.3, 128.5, 126.3 (q, J = 3.8 Hz), 123.3 (q, J = 272.6 Hz), 103.7, 59.0; ^{19}F NMR ($CDCl_3$, 470 MHz) δ -63.4 (s); HRMS (ESI+) calcd for $C_{12}H_9F_3N_3O_3$ ($[M+H]^+$) 300.0596; found 300.0594.

1-Cinnamyl-3-nitro-1*H*-pyrazole (6d). Obtained as a light yellow solid (337 mg, 80%), which was recrystallized from a mixture of EA and hexanes as colorless needles of m. p. 71-72 °C. The x-ray structure of this compound was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54 (d, J = 0.1 Hz, 1H), 7.26-7.37 (m, 5H), 6.91 (d, J = 0.1 Hz, 1H), 6.68 (d, J = 15.6 Hz, 1H), 6.30-6.39 (m, 1H), 4.96-4.50 (m, 1H),; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 155.8, 136.0, 135.3, 131.6, 128.8, 128.7, 126.8, 121.3 103.3, 55.8; HRMS (ESI+) calcd for $C_{12}H_{12}N_3O_2$ ($[M+H]^+$) 230.0930; found 230.0931.

2-Cinnamyl-3-nitro-1*H*-pyrazole (7d). Obtained as a colorless oil (42 mg, 10%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (d, J = 2.0 Hz, 1H), 7.26-7.37 (m, 5H), 7.09 (d, J = 2.0 Hz, 1H), 6.63 (d, J =

16.0 Hz, 1H), 6.35 (dd, *J* = 16.0, 6.5 Hz, 1H), 5.37 (d, *J* = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 145.6, 138.2, 135.8, 134.8, 128.6, 128.3, 126.7, 122.2, 106.9, 55.1; HRMS (ESI+) calcd for $C_{12}H_{12}N_3O_2$ ($[M+H]^+$) 230.0930; found 230.0934.

3-Nitro-1-propyl-1*H*-pyrazole (6e). Obtained as a colorless oil (181 mg, 64%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47 (d, *J* = 1.8 Hz, 1H), 6.90 (d, *J* = 1.8 Hz, 1H), 4.18 (t, *J* = 6.9 Hz, 2H), 1.92-2.00 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 155.7, 132.0, 102.8, 55.5, 23.5, 10.9; HRMS (ESI+) calcd for $C_6H_{10}N_3O_2$ ($[M+H]^+$) 156.0773; found 156.0771.

3-Nitro-1-propyl-1*H*-pyrazole (7e). A less polar mixture of **6e** and **7e** (**6e**:**7e** = 7:1) was obtained as a colorless oil (56 mg, 20%). By comparing the spectra of the mixture with those of the pure **6e**, the peaks which belong to **7e** can be identified. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.50 (d, *J* = 2.0 Hz, 1H), 7.05 (d, *J* = 2.0 Hz, 1H), 4.56 (t, *J* = 7.5 Hz, 2H), 1.93-1.98 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 137.7, 131.6, 106.7, 54.7, 23.4, 10.9.

1-Isopropyl-3-nitro-1*H*-pyrazole (6f). Obtained as a white solid (144 mg, 51%), which was recrystallized from a mixture of EA and hexanes as fine colorless needles of m. p. 63−64 °C. The x-ray structure of this compound was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.56 (d, *J* = 2.1 Hz, 1H), 6.90 (d, *J* = 2.1 Hz, 1H), 4.59-4.64 (m, 1H), 1.58 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 155.4, 129.4, 102.7, 56.0, 22.6; HRMS (ESI+) calcd for $C_6H_{10}N_3O_2$ ($[M+H]^+$) 156.0773; found 156.0777.

2-Isopropyl-3-nitro-1*H*-pyrazole (7f). A less polar mixture of **7f** and **6f** (**7f:6f** = 1:10) was obtained as a colorless oil (37 mg, 11%). By comparing the spectra of the mixture with those of the pure **6f**, the peaks which belong to **7f** can be identified. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.51 (d, *J* = 2.0 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 5.44 (Septet, *J* = 6.5 Hz, 1H), 1.53 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 145.4, 137.6, 106.7, 53.8, 22.3.

1-Cyclohexyl-3-nitro-1*H*-pyrazole (6g). Obtained as a colorless oil (171 mg, 48%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.49 (d, *J* = 2.5 Hz, 1H), 6.88 (d, *J* = 2.5 Hz, 1H), 4.16-4.22 (tt, *J* = 12.0, 4.0 Hz, 1H), 2.18-2.21 (m, 2H), 1.91-1.95 (m, 2H), 1.72-1.79 (m, 2H), 1.39-1.48 (m, 2H), 1.24-1.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 155.3, 129.4, 102.5, 63.1, 33.1, 25.1, 25.0; HRMS (ESI+) calcd for

$C_9H_{14}N_3O_2$ ([M+H]$^+$) 196.1086; found 196.1089.

2-Cyclohexyl-3-nitro-1*H*-pyrazole (7g). Obtained as a colorless oil (68 mg, 19%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.51 (d, *J* = 2.5 Hz, 1H), 7.03 (d, *J* = 2.5 Hz, 1H), 5.00-5.06 (m, 1H), 2.05-2.07 (m, 2H), 1.87-1.95 (m, 3H), 1.74-1.76 (m, 1H), 1.42-1.50 (m, 2H), 1.24-1.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 145.5, 137.5, 106.6, 61.0, 32.8, 25.5, 25.2; HRMS (ESI+) calcd for $C_9H_{14}N_3O_2$ ([M+H]$^+$) 196.1086; found 196.1085.

3-Nitro-1-phenethyl-1*H*-pyrazole (6h). Obtained as a white solid (312 mg, 78%), which was recrystallized from a mixture of EA and hexanes as colorless rods of m. p. 100−101 °C. The x-ray structure of this compound was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 7.18-7.31 (m, 4H), 7.09 (dd, *J* = 6.0, 1.5 Hz, 2H), 6.78 (d, *J* = 2.4 Hz, 1H), 4.43 (t, *J* = 7.8 Hz, 2H), 3.21 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) *δ* 155.8, 136.8, 132.5, 128.8, 128.6, 127.1, 102.6, 55.3, 36.4; HRMS (ESI+) calcd for $C_{11}H_{12}N_3O_2$ ([M+H]$^+$) 218.0930; found 218.0928.

3-Nitro-2-phenethyl-1*H*-pyrazole (7h). Obtained as a colorless oil (35 mg, 9%). ^{1}H NMR ($CDCl_3$, 500 MHz) *δ* 7.51 (d, *J* = 2.0 Hz, 1H), 7.24-7.31 (m, 3H), 7.16-7.18 (m, 2H), 7.02 (d, *J* = 2.0 Hz, 1H), 4.83 (t, *J* = 7.5 Hz, 2H), 3.16 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) *δ* 145.8, 138.0, 138.9, 128.8, 128.7, 127.0, 106.7, 54.2, 36.6; HRMS (ESI+) calcd for $C_{11}H_{12}N_3O_2$ ([M+H]$^+$) 218.0930; found 218.0934.

3-Nitro-1-(4-nitrophenyl)-1*H*-pyrazole (8a). Obtained as a white solid (400 mg, 93%), which was recrystallized from a mixture of EA and hexanes as colorless crystals of m. p. 164−165 °C. The X-ray crystallographic data for this compound are provided in the Supporting Information. ^{1}H NMR (DMSO-d_6, 300 MHz) *δ* 8.99 (d, *J* = 2.7 Hz, 1H), 8.43 (d, *J* = 8.7 Hz, 2H), 8.22 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 2.7 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75.5 MHz) *δ* 157.6, 146.8, 143.0, 133.2, 125.8, 120.4, 105.8; HRMS (ESI+) calcd for $C_9H_7N_4O_4$ ([M+H]$^+$) 235.0467; found 235.0466.

3-Nitro-1-(2-nitrophenyl)-1*H*-pyrazole (8b). Obtained as a white solid (395 mg, 92%), which

was recrystallized from a mixture of EA and hexanes as white crytals of m. p. 101−102 °C. The X-ray crystallographic data for this compound are provided in the Supporting Information. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 (dd, J = 7.8, 1.2 Hz, 1H), 7.66-7.84 (m, 4H), 7.11 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 157.6, 144.6, 134.1, 133.8, 132.4, 131.0, 128.1, 125.8, 104.2; HRMS (ESI+) calcd for $C_9H_7N_4O_4$ ($[M+H]^+$) 235.0467; found 235.0468.

4-(3-Nitro-1*H*-pyrazol-1-yl)benzonitrile (8c). Obtained as a white solid (370 mg, 94%), which was recrystallized from a mixture of EA and hexanes as fine colorless grain-like crystals of m. p. 203−204 °C. The x-ray structure of this compound was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (d, J = 2.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 2.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 157.0, 141.3, 134.1, 132.5, 119.9, 118.0, 110.7, 105.2; HRMS (ESI+) calcd for $C_{10}H_7N_4O_2$ ($[M+H]^+$) 215.0569; found 215.0566.

2-(3-Nitro-1*H*-pyrazol-1-yl)benzonitrile (8d). Obtained as a white solid (370 mg, 92%), which was recrystallized from a mixture of EA and hexanes as fine colorless grain-like crystals of m. p. 133−134 °C. The X-ray crystallographic data for this compound are provided in the Supporting Information. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.70 (d, J = 2.7 Hz, 1H), 8.15 (d, J = 7.5 Hz, 1H), 7.93-8.00 (m, 2H), 7.74-7.80 (m, 1H), 7.44 (d, J = 2.7 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 157.0, 140.0, 135.2, 134.8, 134.7, 130.0, 125.7, 115.7, 106.8, 104.4; HRMS (ESI+) calcd for $C_{10}H_7N_4O_2$ ($[M+H]^+$) 215.0569; found 215.0567.

Ethyl 4-(3-nitro-1*H*-pyrazol-1-yl)benzoate (8e). Obtained as a light yellow solid (412 mg, 86%), which was recrystallized from a mixture of EA and hexanes as colorless short needles of m. p. 159−160 °C. The x-ray structure of this compound was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20 (d, J = 8.7 Hz, 2H), 8.09 (d, J = 2.7 Hz, 1H), 7.85 (d, J = 8.7 Hz, 2H), 7.14 (d, J = 2.7 Hz, 1H), 4.42 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 165.2, 157.3, 141.9, 132.7, 131.2, 129.6, 119.7, 105.4, 61.4, 14.5; HRMS (ESI+) calcd for $C_{12}H_{12}N_3O_4$ ($[M+H]^+$) 262.0828; found

262.0830.

1-[4-(Methylsulfonyl)phenyl]-3-nitro-1*H*-pyrazole (8f). Obtained as a light yellow solid (466 mg, 95%), which was recrystallized from a mixture of EA and hexanes as rectangular crystals of m. p. 192−193 °C. The x-ray structure of this compound was obtained. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.96 (d, J = 2.7 Hz, 1H), 8.23 (d, J = 8.7 Hz, 2H), 8.15 (d, J = 8.7 Hz, 2H), 7.44 (d, J = 2.7 Hz, 1H), 3.32 (s, 3H); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 157.5, 144.4, 142.1, 133.0, 129.4, 120.3, 105.6, 43.8; HRMS (ESI+) calcd for $C_{10}H_{10}N_3O_4S$([M+H]$^+$) 268.0392; found 268.0391.

5-Nitro-2-(3-nitro-1*H*-pyrazol-1-yl)pyridine (9a). Obtained as a light yellow solid (412 mg, 96%), which was recrystallized from a mixture of EA and hexanes as colorless needles of m. p. 173−174 °C. The X-ray crystallographic data for this compound are provided in the Supporting Information. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.34 (d, J = 2.4 Hz, 1H), 8.70-8.75 (m, 2H), 8.31 (d, J = 9.0 Hz, 1H), 7.16 (d, J = 3.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 157.8, 152.2, 144.8, 143.7, 135.9, 132.0, 113.3, 105.6; HRMS (ESI+) calcd for $C_8H_6N_5O_4$ ([M+H]$^+$) 236.0420; found 236.0418.

2-Nitro-3-(3-nitro-1*H*-pyrazol-1-yl)pyridine (9b). Obtained as a white solid (404 mg, 94%), which was recrystallized from a mixture of EA and hexanes as colorless crystals of m. p. 130−131 °C. The x-ray structure of this compound was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.70 (d, J = 4.5 Hz, 1H), 8.22 (d, J = 7.8 Hz, 1H), 7.82-7.84 (m, 2H), 7.15-7.16 (m, 1H); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 157.7, 151.4, 149.6, 137.9, 136.2, 130.1, 127.5, 105.2; HRMS (ESI+) calcd for $C_8H_6N_5O_4$ ([M+H]$^+$) 236.0420; found 236.0418.

6-(3-Nitro-1*H*-pyrazol-1-yl)nicotinonitrile (9c). Obtained as a light yellow solid (368 mg, 93%), which was recrystallized from a mixture of EA and hexanes as fine colorless needles of m. p. 185−186 °C. The x-ray structure of this compound was obtained.^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78 (d, J = 2.1 Hz, 1H), 8.71 (d, J = 2.7 Hz, 1H), 8.77 (d, J = 8.7 Hz, 1H), 8.20 (dd, J = 8.7, 2.1 Hz, 1H), 7.14 (d, J = 2.7 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 158.0, 152.9, 151.6, 144.4, 132.2, 116.7, 113.4, 109.0,

105.8; HRMS (ESI+) calcd for $C_9H_6N_5O_2$ ($[M+H]^+$) 216.0521; found 216.0520.

5-(3-Nitro-1*H*-pyrazol-1-yl)picolinonitrile (9d). Obtained as a white solid (358 mg, 91%), which was recrystallized from a mixture of EA and hexanes as colorless crystals of m. p. 147−148 °C. The x-ray structure of this compound was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.16 (s, 1H), 8.35 (dd, J = 9.3, 3.0 Hz, 1H), 8.15 (d, J = 2.4 Hz, 1H), 7.91 (d, J = 9.3 Hz, 1H), 7.23 (d, J = 2.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 157.8, 142.4, 137.3, 133.5, 131.6, 130.2, 128.2, 117.2, 105.7; HRMS (ESI+) calcd for $C_9H_6N_5O_2$ ($[M+H]^+$) 216.0521; found 216.0523.

5-Bromo-2-(3-nitro-1*H*-pyrazol-1-yl)pyridine (9e). Obtained as a light yellow solid (466 mg, 95%), which was recrystallized from a mixture of EA and hexanes as white needles of m. p. 210−211 °C. The x-ray structure of this compound was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.62 (d, J = 1.5 Hz, 1H), 8.53 (s, 1H), 8.03 (d, J = 0.9 Hz, 2H), 7.10 (d, J = 1.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 156.9, 149.2, 148.3, 142.6, 130.9, 119.3, 114.6, 104.9; HRMS (ESI+) calcd for $C_8H_6BrN_4O_2$ ($[M+H]^+$) 268.9674; found 268.9673.

4-Iodo-2-(3-nitro-1*H*-pyrazol-1-yl)pyridine (9f). Obtained as a light yellow solid (522 mg, 90%), which was recrystallized from a mixture of EA and hexanes as colorless rod-like crystals of m. p. 238−239 °C. The x-ray structure of this compound was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.63 (s, 1H), 8.52 (d, J = 0.9 Hz, 1H), 8.12 (d, J = 6.3 Hz, 1H), 7.72 (d, J = 6.3 Hz, 1H), 7.09 (d, J = 0.9 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 157.0, 149.0, 132.7, 131.1, 126.3, 121.3, 109.5, 104.8; HRMS (ESI+) calcd for $C_8H_6IN_4O_2$ ($[M+H]^+$) 316.9535; found 316.9534.

5-Bromo-2-(3-nitro-1*H*-pyrazol-1-yl)pyrimidine (9g). Obtained as a light yellow solid (464 mg, 94%), which was recrystallized from a mixture of EA and hexanes as colorless crystals of m. p. 224−225 °C. The x-ray structure of this compound was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.88 (s, 2H), 8.65 (d, J = 2.7 Hz, 1H), 7.12 (d, J = 2.7 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 160.5, 158.1, 153.3, 133.6, 119.2, 105.4; HRMS (ESI+) calcd for $C_7H_5BrN_5O_2$ ($[M+H]^+$) 269.9627; found 269.9624.

1-(4-(Methylsulfonyl)phenyl)-1H-pyrazol-3-amine (8f-1). A mixture of **8f** (20 mg, 0.075 mmol), Pd/C (10 wt%, 2 mg), and 5 mL ethanol was stirred under hydrogen balloon at 25 °C for 20 h. The resulting mixture was filtrated through celite. The filtrate was concentrated to give a light yellow solid, which was purified via column chromatography (silica gel, eluting with 0-100% of EtOAc in hexane) to provide **8f-1** (17 mg, 95%) as a white solid. m. p. 185-186 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96 (d, J = 9.0 Hz, 1H), 7.78 (d, J = 2.5 Hz, 1H), 7.74 (d, J = 9.0 Hz, 1H), 7.78 (d, J = 2.5 Hz, 1H), 5.94 (d, J = 2.5 Hz, 1H), 3.93 (bs, 2H), 3.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 156.8, 143.8, 135.8, 129.1, 128.0, 117.2, 98.4, 44.7; HRMS (ESI+) calcd for $C_{10}H_{12}N_3O_2S([M+H]^+)$ 238.0650; found 238.0651.

Ethyl 1-benzyl-1H-pyrazole-3-carboxylate (12a). Obtained as a white solid (257 mg, 61%), which was recrystallized from a mixture of EA and hexanes as colorless crystals of m. p. 44.5-45.5 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.22-7.36 (m, 6H), 6.82 (d, J = 2.5 Hz, 1H), 5.39 (s, 2H), 4.40 (q, J = 7.0 Hz, 2H), 1.39 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 162.4, 143.6, 135.5, 130.5, 128.9, 128.4, 127.9, 109.5, 60.9, 56.8, 14.4; HRMS (ESI+) calcd for $C_{13}H_{15}N_2O_2$ ($[M+H]^+$) 231.1134; found 231.1136.

Ethyl 1-benzyl-1H-pyrazole-5-carboxylate (13a). Obtained as a colorless oil (76 mg, 18%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54 (d, J = 2.0 Hz, 1H), 7.22-7.31 (m, 5H), 6.87 (d, J = 2.0 Hz, 1H), 5.78 (s, 2H), 4.30 (q, J = 7.0 Hz, 2H), 1.32 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 159.7, 138.4, 137.2, 132.2, 128.2, 127.6, 127.5, 111.7, 61.0, 54.9, 14.2; HRMS (ESI+) calcd for $C_{13}H_{15}N_2O_2$ ($[M+H]^+$) 231.1134; found 231.1137.

1-Benzyl-3-(trifluoromethyl)-1H-pyrazole (12b). Obtained as a colorless oil (294 mg, 71%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31-7.37 (m, 4H), 7.21-7.24 (m, 2H), 6.52 (d, J = 2.5 Hz, 1H), 5.33 (s, 2H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 142.4 (q, J = 38.1 Hz), 135.5, 130.6, 129.0, 128.6, 128.0, 121.4 (q, J = 268.3 Hz), 104.9, 56.6; ^{19}F NMR ($CDCl_3$, 470 MHz) δ -61.8 (s); HRMS (ESI+) calcd for $C_{11}H_{10}F_3N_2$

([M+H]$^+$) 227.0796; found 227.0794.

1-Benzyl-5-(trifluoromethyl)-1H-pyrazole (13b). A more polar mixture of **12b** and **13b** (**12b**:**13b** = 1.8:1) was obtained as a colorless oil (87 mg, 21%). By comparing the spectra of the mixture with those of the pure **12b**, the peaks which belong to **13b** can be identified. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (d, J = 1.5 Hz, 1H), 7.23-7.37 (m, 3H), 7.20-7.21 (m, 2H), 6.65 (d, J = 1.5 Hz, 1H), 5.43 (s, 2H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 138.9, 135.7, 132.0 (q, J = 39.1 Hz), 128.7, 128.1, 127.4, 120.2 (q, J = 268.3 Hz), 107.8, 54.7; ^{19}F NMR ($CDCl_3$, 470 MHz) δ -59.0 (s); HRMS (ESI+) calcd for $C_{11}H_{10}F_3N_2$ ([M+H]$^+$) 227.0796; found 227.0798.

3-Methyl-1-(4-nitrophenyl)-1*H*-pyrazole (12d). Obtained as a white solid (237 mg, 64%), which was recrystallized from a mixture of EA and hexanes as colorless crystals of m. p. 161−162 °C. The x-ray structure of this compound was obtained. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.31 (d, J = 9.5 Hz, 2H), 7.92 (d, J = 2.5 Hz, 1H), 7.82 (d, J = 9.5 Hz, 2H), 6.34 (d, J = 2.5 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 152.6, 144.9, 144.4, 127.6, 125.4, 118.0, 109.6, 13.8; HRMS (ESI+) calcd for $C_{10}H_{10}N_3O_2$ ([M+H]$^+$) 204.0776; found 204.0773.

5-Methyl-1-(4-nitrophenyl)-1*H*-pyrazole (13d). A more polar mixture of **12d** and **13d** (**12d**:**13d** = 1:1.5) was obtained as a white solid (120 mg, 32%). By comparing the spectra of the mixture with those of the pure **12d**, the peaks which belong to **13d** can be identified. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.36 (d, J = 7.0 Hz, 2H), 7.71 (d, J = 7.0 Hz, 2H), 7.64 (d, J = 1.5 Hz, 1H), 6.28 (d, J = 1.5 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 146.1, 145.0, 141.4, 139.1, 124.7, 124.1, 109.0, 13.1; HRMS (ESI+) calcd for $C_{10}H_{10}N_3O_2$ ([M+H]$^+$) 204.0776; found 204.0778.

1-(4-Nitrophenyl)-3-(trifluoromethyl)-1*H*-pyrazole (12e). Obtained as a white solid (447 mg, 95%), which was recrystallized from a mixture of EA and hexanes as colorless crystals of m. p. 111−112 °C. The x-ray structure of this compound was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.34 (d, J = 10.2 Hz, 2H), 8.11 (d, J = 2.4 Hz, 1H), 7.91 (d, J = 10.2 Hz, 2H), 6.82 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$,

75.5 MHz) δ 146.5, 145.6 (q, J = 39.2 Hz), 143.5, 128.7, 125.5, 120.8 (q, J = 268.8 Hz), 119.6, 107.4; ^{19}F NMR ($CDCl_3$, 470 MHz) δ -62.6 (s); HRMS (ESI+) calcd for $C_{10}H_7F_3N_3O_2$ ($[M+H]^+$) 258.0490; found 258.0494.

Ethyl 1-(4-nitrophenyl)-1*H*-pyrazole-3-carboxylate (12f). Obtained as a white solid (439 mg, 92%), which was recrystallized from a mixture of EA and hexanes as colorless crystals of m. p. 158-160 °C. The x-ray structure of this compound was obtained. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.37 (d, J = 9.0 Hz, 2H), 8.06 (d, J = 2.7 Hz, 1H), 7.98 (d, J = 9.0 Hz, 2H), 7.07 (d, J = 2.7 Hz, 1H), 4.47 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125.5 MHz) δ 161.7, 146.8, 146.4, 143.8, 128.6, 125.4, 119.8, 111.5, 61.5, 14.3; HRMS (ESI+) calcd for $C_{12}H_{12}N_3O_4$ ($[M+H]^+$) 262.0828; found 262.0825.

3-Bromo-1-(4-nitrophenyl)-1H-pyrazole (12g). Obtained as a white solid (459 mg, 94%), which was recrystallized from a mixture of EA and hexanes as colorless crystals of m. p. 145-146 °C. The x-ray structure of this compound was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.33 (d, J = 8.7 Hz, 2H), 7.93 (d, J = 2.1 Hz, 1H), 7.85 (d, J = 8.7 Hz, 2H), 6.58 (d, J = 2.1 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 145.8, 143.5, 130.5, 128.8, 125.4, 118.4, 112.3; HRMS (ESI+) calcd for $C_9H_7BrN_3O_2$ ($[M+H]^+$) 267.9722; found 267.9720.

1-(4-Nitrophenyl)-3-phenyl-1H-pyrazole (12h). Obtained as a white solid (446 mg, 92%), which was recrystallized from a mixture of EA and hexanes as colorless crystals of m. p. 168-169 °C. The x-ray structure of this compound was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.35 (d, J = 9.0 Hz, 2H), 8.06 (d, J = 2.4 Hz, 1H), 7.91-7.97 (m, 3H), 7.26-7.48 (m, 2H), 6.87 (d, J = 2.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 153.5, 144.6, 143.9, 131.9, 130.5, 128.8, 128.6, 125.7, 125.4, 118.2, 107.0; HRMS (ESI+) calcd for $C_{15}H_{12}N_3O_2$ ($[M+H]^+$) 266.0930; found 266.0927.

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Supporting Information Available: Tables S1-S3, the DFT optimized geometries and energies for anions **10A** and **10B**, copies of ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra for all new compounds, crystallographic data for **8a**, **8b**, **9a**, and **8d**, and the CIF files of the 25 compounds can be found in the supporting information. This material is available free of charge via the Internet at http://pubs.acs.org.

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