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# Regioselective Synthesis of 4-Nitro- or 4-Chloro-Tetrasubstituted Pyrazoles from Hydrazones and β-Halo-β-nitrostyrenes

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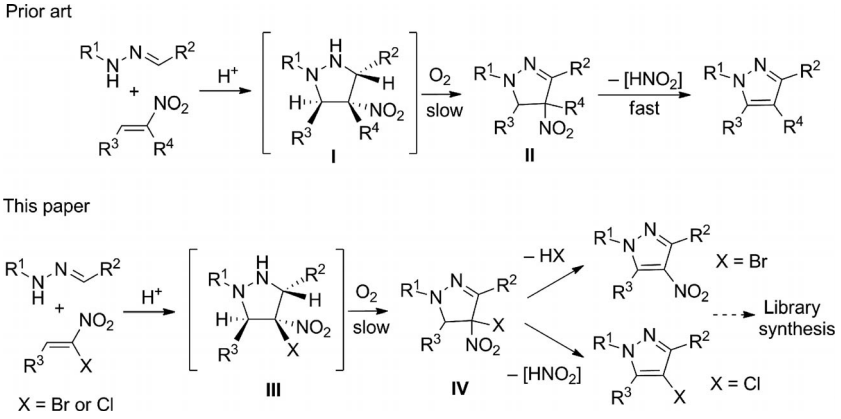
We report an acid-catalyzed cycloaddition reaction of hydrazones with β-bromo- or β-chloro-β-nitrostyrenes for the regioselective synthesis of 4-nitro- or 4-chloro-tetrasubstituted pyrazoles. Arising from a common 4-halo-4-nitropyrazolidine intermediate, the identity of the pyrazole product formed is dependent on the relative leaving group abilities of the halo and nitro substituents.

## Introduction

Substituted pyrazoles are an important class of compounds in the pharmaceutical industry, and they make up the core structures of drugs such as Celebrex®, Viagra®, and Acomplia®, as well as numerous experimental drug candidates.[1] The facile regioselective assembly of substituted pyrazoles from readily available building blocks is always of great interest to medicinal chemists.[2] Synthetic methods that offer multiple points of variation, especially at the late stage of a synthesis, are particularly appealing for the design of libraries and the rapid production of analogs.

Inspired by the pioneering work of Snider[3] and Gomez-Guillen,[4] we have recently demonstrated facile syntheses of substituted pyrazoles from hydrazones and β-nitroalkenes, proceeding via key 4-nitropyrazolidine intermediate **I** (Scheme 1).[5] Slow oxidation of **I** by air followed by fast elimination of $HNO_2$ gives the desired pyrazole products. This versatile method gives easy and regioselective access to a wide range of substituted pyrazoles. However, only a few 4-substituted pyrazoles were prepared in those studies, primarily due to the limited availability of β-substituted β-nitroalkenes. We envisioned that the introduction of an additional leaving group at the C-4 position in key intermediate **IV** might potentially address this issue. In this paper, we report that the reaction of hydrazones with β-halo-β-nitroalkenes, which are easily prepared from the corresponding β-nitroalkenes[6] or by the condensation of aldehydes with bromonitromethane,[7] does indeed give either the 4-nitro-tetrasubstituted pyrazole or the 4-chloro-tetrasubstituted pyrazole regioselectively. Which product is formed appears to depend on the relative leaving-group abilities of the substituents (Br > $NO_2$ > Cl).




Scheme 1. Pyrazole synthesis from hydrazones and nitro olefins.

4-Nitro- and 4-halo-tetrasubstituted pyrazoles are interesting synthetic targets, primarily because the reactive ni-

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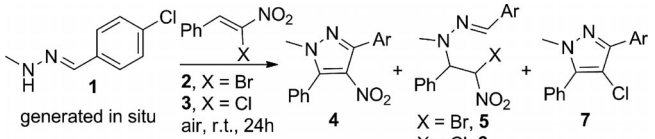
tro[8] and halo[9,10] functional groups offer ample opportunities for further manipulations that would allow the preparation of numerous biologically interesting compounds. Methods that are widely used for the synthesis of these types of molecules often involve nitration and halogenation of 4-unsubstituted-pyrazoles, whose preparation requires multiple steps, most often achieved by the condensation reactions of hydrazines with 1,3-dicarbonyl compounds.[11] Our operationally simple method provides an alternative rapid synthesis of either 4-nitropyrazoles or 4-chloropyrazoles from readily available starting materials. Therefore, we expect this method to become widely used by the synthetic and medicinal chemistry communities.

## Results and Discussion

Our initial experiments were conducted on in-situ-prepared *N*-methylhydrazone **1** with either compound **2** or **3** (Table 1). Methanol, which was the optimal solvent for the cycloaddition reaction of **1** with β-nitrostyrene,[5a] surprisingly gave uncyclized product **5** exclusively with β-bromo-β-nitrostyrene **2** (Table 1, Entry 1). Similarly, with β-chloro-β-nitrostyrene **3**, uncyclized product **6** was the major product (Table 1, Entry 2), along with 4-chloropyrazole **7**, which was formed in 35% yield. Other common solvents such as THF, $Et_2O$, DMF, *i*PrOH, EtOH, $CH_2Cl_2$, EtOAc, and $CH_3CN$ also gave the uncyclized products as the major products. Our previous mechanistic studies showed that a proton played a critical role in the cycloaddition process to form the pyrazole products.[5a,5b] Indeed, when a more acidic alcoholic solvent such as $CF_3CH_2OH$ was used, the formation of uncyclized products **5** or **6** was significantly reduced, and the yields of cyclized pyrazole products **4** and **7** increased (Table 1, Entries 3 and 4). As expected, 4-nitropyrazole **4** was preferably produced from β-bromo-β-nitrostyrene **2** (Table 1, Entry 3), whereas 4-chloropyrazole **7** was the major product with β-chloro-β-nitrostyrene **3** (Table 1, Entry 4). Presumably, relative leaving-group abilities ($Br > NO_2 > Cl$) determined the product outcome. The addition of catalytic amounts of TFA (trifluoroacetic acid) completely suppressed the formation of uncyclized products **5** or **6** (Table 1, Entries 5–8). With β-bromo-β-nitrostyrene **2** (Table 1, Entries 5 and 7), slightly better yields were obtained with MeOH as the solvent. In contrast, with β-chloro-β-nitrostyrene **3** (Table 1, Entries 6 and 8), better yields and ratios of the desired product **7** were obtained with $CF_3CH_2OH$ as the solvent. A dependence of the reaction profile on the combination of solvent and acid used was also observed with other substrates. Therefore, individual reaction optimization could be necessary for new substrates. Interestingly, when too much TFA (10 equiv.; Table 1, Entries 9 and 10) was used, the cycloaddition reaction was suppressed, and both starting materials were recovered. It is worth noting that the isolated uncyclized products **5** or **6** would not cyclize to give the pyrazole products under acidic conditions.

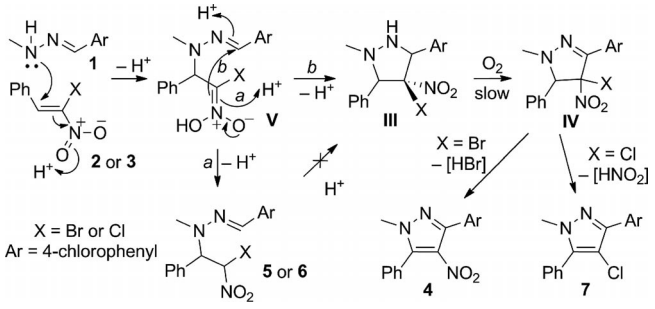
Table 1. Screening of conditions.




| Entry | X | Solvent additives | Yields 4 | 5 or 6 | 7 |
|---|---|---|---|---|---|
| 1 | Br | MeOH | 0% | **5**, 90% | – |
| 2 | Cl | MeOH | – | **6**, 47% | 35% |
| 3 | Br | $CF_3CH_2OH$ | 50% | **5**, 20% | - |
| 4 | Cl | $CF_3CH_2OH$ | 8% | 0% | 57% |
| 5 | Br | MeOH 0.2 equiv. TFA | 82% | 0% | – |
| 6 | Cl | MeOH 0.2 equiv. TFA | 25% | 0% | 45% |
| 7 | Br | $CF_3CH_2OH$ 0.2 equiv. TFA | 75% | 0% | – |
| 8 | Cl | $CF_3CH_2OH$ 0.2 equiv. TFA | 5% | 0% | 55% |
| 9 | Br | $CF_3CH_2OH$ 10 equiv. TFA | little reaction[a] | | |
| 10 | Cl | $CF_3CH_2OH$ 10 equiv. TFA | little reaction[a] | | |

[a] Both starting materials were recovered.

Based on the above observations and on previous mechanistic studies,[5a,5b] plausible reaction pathways are proposed (Scheme 2). Similar to the previously proposed reaction mechanism, the proton-catalyzed stepwise cycloaddition of the hydrazone and the β-halo-β-nitrostyrene generates 4-halo-4-nitropyrazolidine intermediate **III**. A competitive Michael addition process produces **5** or **6** irreversibly. Intermediate **III** undergoes a slow oxidation by air to give intermediate **IV**. Subsequent elimination of either HBr or $HNO_2$, depending on the relative leaving-group ability of the halogen atoms and the nitro group, gives 4-nitropyrazole **4** or 4-chloropyrazole **7**, respectively.

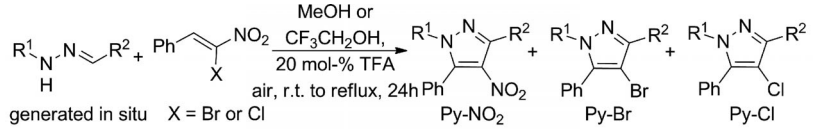


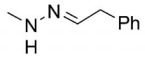
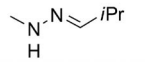
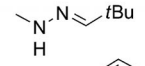
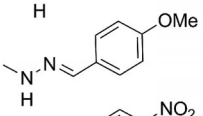
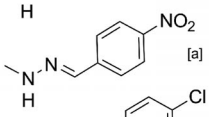
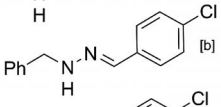
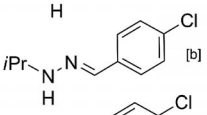
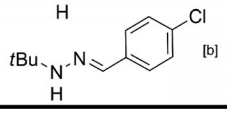

Scheme 2. Plausible reaction pathways.

With a good understanding of the reaction mechanism, we then investigated the reaction scope in terms of other *N*-alkylhydrazones, which were mostly generated in situ.[12]

Table 2. Reaction scope: *N*-alkylhydrazones.




| Entry | Hydrazone | X = Br | X = Cl |
|---|---|---|---|
| | | Conditions; product, yield | Conditions; product, yield |
| 1 |  | MeOH, r.t.<br>**8** (Py-$NO_2$), 41% | $CF_3CH_2OH$, r.t.<br>**9** (Py-Cl),19%; **8** (Py-$NO_2$), 20% |
| 2 |  | $CF_3CH_2OH$, r.t.<br>**10** (Py-$NO_2$), 57% | MeOH, r.t.<br>**11** (Py-Cl), 38%; **10** (Py-$NO_2$), 40% |
| 3 |  | MeOH or $CF_3CH_2OH$<br>r.t. to reflux, no reaction | MeOH or $CF_3CH_2OH$<br>r.t. to reflux, no reaction |
| 4 |  | $CF_3CH_2OH$, r.t.<br>**12** (Py-$NO_2$), 66% | MeOH, r.t.<br>**13** (Py-Cl), 58%; **12** (Py-$NO_2$), 33%<br>$CF_3CH_2OH$, rt<br>**13** (Py-Cl), 62%; **12** (Py-$NO_2$), trace |
| 5 |  [a] | $CF_3CH_2OH$, 70 °C<br>**14** (Py-$NO_2$), 54% | $CF_3CH_2OH$, 50 °C<br>**15** (Py-Cl), 70% |
| 6 |  [b] | MeOH/$H_2O$, r.t.<br>**16** (Py-$NO_2$), 55% | MeOH/$H_2O$, r.t.<br>**17** (Py-Cl), 63% |
| 7 |  [b] | MeOH/$H_2O$, r.t.<br>**18** (Py-$NO_2$), 34% | MeOH/$H_2O$, r.t.<br>**19** (Py-Cl), 41% |
| 8 |  [b] | MeOH or $CF_3CH_2OH$<br>r.t. to reflux, no reaction | MeOH or $CF_3CH_2OH$<br>r.t. to reflux, no reaction |

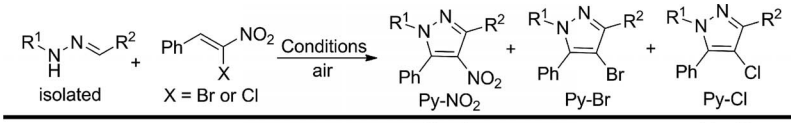
[a] Isolated hydrazone was used. [b] The hydrazine HCl salt was used to form the hydrazone. Water (10 vol-%) was added as co-solvent.

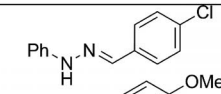
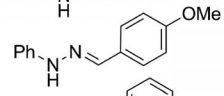
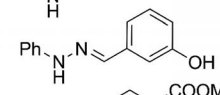
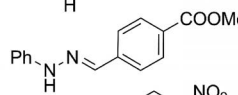
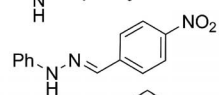
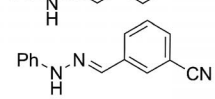
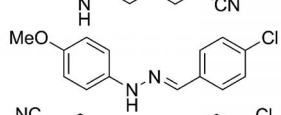
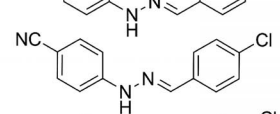
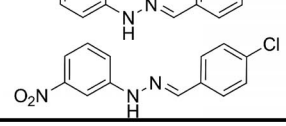
The standard conditions were chosen to be TFA (20 mol-%) as the catalyst in either MeOH or $CF_3CH_2OH$, and the results are listed in Table 2. The general trend held that β-bromo-β-nitrostyrene **2** gave mainly 4-nitropyrazole products, whereas β-chloro-β-nitrostyrene **3** gave mainly 4-chloropyrazole products. Variation of both the aldehyde ($R^2$) and hydrazine ($R^1$) components was studied. The steric effects on both the $R^1$ and the $R^2$ positions were obvious. For example, benzyl (Table 2, Entries 1 and 6) and isopropyl (Table 2, Entries 2 and 7) groups were well tolerated on both positions. However, the presence of a bulky *tert*-butyl group (Table 2, Entries 3 and 8) at either position completely shut down the cycloaddition reaction. Electronic effects were also observed with the $R^2$ substituent (Table 2, Entries 4 and 5). A higher reaction temperature was required in the presence of a strongly electron-withdrawing $R^2$ group such as $NO_2$ (Table 2, Entry 5). As previously observed, changes to the solvent/acid combination could result in altered reaction profiles (Table 2, Entry 4; X = Cl).

Less reactive *N*-arylhydrazones were investigated next (Table 3). As a general rule, β-bromo-β-nitrostyrene **2** favored the formation of 4-nitropyrazole products, and β-chloro-β-nitrostyrene **3** favored mainly 4-chloropyrazole products; however, a few exceptions were noted (Table 3, Entries 8 and 9). The electronic effects played out similarly at the $R^1$ and $R^2$ positions. For example, when $R^2$ was an electron-donating group (Table 3, Entries 1–3), the cycloaddition reaction was generally more favored, whereas electron-withdrawing groups (Table 3, Entries 4–6) required more forcing conditions. Similarly, when $R^1$ was an electron-donating group (Table 3, Entry 7), the reaction was favored at room temperature, and with strongly electron-withdrawing $R^1$ groups (Table 3, Entries 8 and 9), higher reaction temperatures were required for the cycloaddition reaction to occur. With β-chloro-β-nitrostyrene **3**, good yields of the expected 4-chloropyrazole products were obtained. However, in the case of β-bromo-β-nitrostyrene **2**, instead of the usual 4-nitropyrazole products, 4-bromopyrazole product **38** (Table 3, Entry 8) and 4-*unsubstituted*-pyrazole product **39** (Table 3, Entry 9) were the major products isolated. One possible explanation is that in the presence of strongly electron-withdrawing $R^1$ groups such as CN and $NO_2$, under more forcing reaction conditions, the reaction mechanism might be different. In these cases, elimination of $HNO_2$ from 4-halo-4-nitropyrazolidine intermediate **III** might be favored (Scheme 3). Subsequent air oxidation gave 4-bromopyrazole **38**. The formation of 4-unsubstituted pyrazole derivative **40** most probably comes from a subsequent acid-mediated hydrodebromination process at elevated temperature.

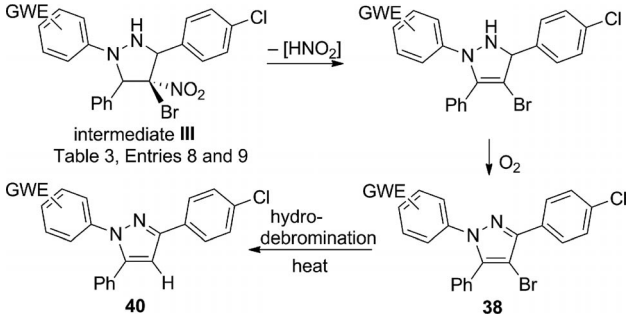
  

Table 3. Reaction scope: *N*-arylhydrazones.




| Entry | Hydrazone | X = Br<br>Conditions; product, yield | X = Cl<br>Conditions; product, yield |
|---|---|---|---|
| 1 |  | $CF_3CH_2OH$, r.t., 24 h<br>**20** (Py-$NO_2$), 58%; **21** (Py-Br), 15% | $CF_3CH_2OH$, r.t., 24 h<br>**22** (Py-Cl), 74% |
| 2 |  | MeOH, 50 °C, 24 h<br>**23** (Py-$NO_2$), 32% | $CF_3CH_2OH$, r.t., 48 h<br>**24** (Py-Cl), 68% |
| 3 |  | $CF_3CH_2OH$, r.t., 48 h<br>**25** (Py-$NO_2$), 58%; **26** (Py-Br), 25% | $CF_3CH_2OH$, r.t., 48 h<br>**27** (Py-Cl), 62% |
| 4 |  | $CF_3CH_2OH$, r.t., 24 h<br>**28** (Py-$NO_2$), 30% | $CF_3CH_2OH$, r.t., 24 h<br>**29** (Py-Cl), 67% |
| 5[a] |  | $CF_3CH_2OH$, 50 °C, 24 h<br>**30** (Py-$NO_2$), 16%; **31** (Py-Br), 25% | $CF_3CH_2OH$, 75 °C, 24 h<br>**32** (Py-Cl), 59% |
| 6[a] |  | $CF_3CH_2OH$, r.t., 48 h<br>**33** (Py-$NO_2$), 23%; **34** (Py-Br), 14% | $CF_3CH_2OH$, r.t., 48 h<br>**35** (Py-Cl), 31% |
| 7 |  | $CF_3CH_2OH$, r.t., 24 h<br>**36** (Py-$NO_2$), 63% | $CF_3CH_2OH$, r.t., 24 h<br>**37** (Py-Cl), 72% |
| 8 |  | $CF_3CH_2OH$, 50 °C, 48 h<br>**38** (Py-Br), 45% | $CF_3CH_2OH$, 75 °C, 24 h<br>**39** (Py-Cl), 45% |
| 9 |  | $CF_3CH_2OH$, 75°C, 72 h<br>**40** (Py-H), 41% | $CF_3CH_2OH$, 75 °C, 73 h<br>**41** (Py-Cl), 85% |

[a] 10 equiv. of TFA were used.




Scheme 3. Proposed mechanism for the formation of compounds **38** and **40**.

## Conclusions

We have developed a facile, regioselective synthesis of 4-nitro- or 4-chloro-tetrasubstituted pyrazoles from hydrazones and β-halo-β-nitrostyrenes. This cycloaddition reaction is believed to go via key 4-halo-4-nitropyrazolidine intermediate **III**. The regioselective formation of either a 4-nitro- or a 4-chloro-tetrasubstituted pyrazole product is mainly determined by the relative leaving group ability of the halogen and nitro substituents.

## Experimental Section

**General:** $^1H$ and $^{13}C$ NMR spectra were recorded with a 600 MHz spectrometer. Flash column chromatography was performed using Merck silica gel 60. HRMS (ESI) was performed with a microTOF apparatus. All reagents and solvents were purchased from commercial sources and were used without further purification.

**Representative Procedure A:** 4-Chlorobenzaldehyde (84 mg, 0.6 mmol, 1.2 equiv.) was dissolved in MeOH (2 mL), and then methylhydrazine (28 mg, 0.6 mmol, 1.2 equiv.) was added. After the mixture had been stirred at room temperature for 1 h, HPLC analysis showed that the methylhydrazone had been formed. TFA (8 μL, 0.1 mmol, 0.2 equiv.) and β-bromo-β-nitrostyrene **2** (114 mg, 0.5 mmol, 1.0 equiv.) were added sequentially, and the reaction solution was stirred open to air at room temperature for 1 d. The solvent was evaporated, and the residue was purified by flash column chromatography with EtOAc/hexanes as eluent to give compound **4** (128 mg, 0.41 mmol, 82%).

**Representative Procedure B:** A mixture of β-bromo-β-nitrostyrene **2** (114 mg, 0.5 mmol, 1.0 equiv.) and *N*-(4-chlorobenzylidene)-*N*′-phenylhydrazine (138 mg, 0.6 mmol, 1.2 equiv.) was dissolved in $CF_3CH_2OH$ (2 mL), and then TFA (8 μL, 0.1 mmol, 0.2 equiv.) was added. The reaction mixture was stirred at room temperature open to air for 1 d. The solvent was evaporated, and the residue was purified by flash column chromatography with EtOAc/hexanes as eluent to give compounds **20** (108 mg, 0.29 mmol, 58%) and **21** (30 mg, 0.075 mmol, 15%).

**3-(4-Chlorophenyl)-1-methyl-4-nitro-5-phenyl-1*H*-pyrazole (4):** The title compound was isolated in 82% yield (128 mg; Table 1, entry 5). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.66–7.62 (m, 2 H), 7.58–7.54 (m, 3 H), 7.46–7.42 (m, 4 H), 3.80–3.65 (s, 3 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 146.2, 143.2, 135.3, 130.5, 130.4, 129.6, 129.0, 128.9, 128.5, 127.0, 38.0 (one overlapping carbon peak) ppm. HRMS (ESI): calcd. for $C_{16}H_{13}ClN_3O_2$ $[M + H]^+$ 314.0691; found 314.0676.

**(*E*)-1-(2-Bromo-2-nitro-1-phenylethyl)-2-(4-chlorobenzylidene)-1-methylhydrazine (5):** The title compound was isolated in 90% yield (178 mg; Table 1, Entry 1). $^1$H NMR (600 MHz, $CDCl_3$) (two sets of peaks): $\delta$ = 7.55–7.48 (m, 2 H), 7.38–7.28 (m, 7 H), 7.22–7.20 and 7.15–7.11 (s, 1 H), 6.91–6.86 and 6.85–6.80 (d, $J$ = 10.0 Hz, 1 H), 4.95–4.90 and 4.79–4.74 (d, $J$ = 10.0 Hz, 1 H), 2.88–2.85 and 2.77–2.73 (d, $J$ = 0.9 Hz, 3 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 134.7, 134.6, 133.7, 133.6, 133.2, 133.1, 133.08, 133.05, 129.5, 129.2, 128.95, 128.89, 128.8, 128.7, 128.5, 128.1, 127.1, 127.0, 81.0, 78.9, 74.2, 73.5, 38.1, 37.5 ppm. HRMS (ESI): calcd. for $C_{16}H_{16}BrClN_3O_2$ $[M + H]^+$ 396.0109; found 396.0096.

**(*E*)-1-(2-Chloro-2-nitro-1-phenylethyl)-2-(4-chlorobenzylidene)-1-methylhydrazine (6):** The title compound was isolated in 47% yield (82 mg; Table 1, Entry 2). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.53–7.47 (m, 2 H), 7.38–7.29 (m, 7 H), 7.16–7.12 (s, 1 H), 6.82–6.77 (d, $J$ = 9.9 Hz, 1 H), 4.95–4.80 (d, $J$ = 9.9 Hz, 1 H), 2.85–2.68 (d, $J$ = 0.9 Hz, 3 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 134.6, 133.7, 133.3, 133.0, 129.2, 128.84, 128.80, 128.6, 127.2, 90.1, 73.9, 37.4 ppm. HRMS (ESI): calcd. for $C_{16}H_{16}Cl_2N_3O_2$ $[M + H]^+$ 352.0614; found 352.0601.

**4-Chloro-3-(4-chlorophenyl)-1-methyl-5-phenyl-1*H*-pyrazole (7):** The title compound was isolated in 35% yield (53 mg; Table 1, Entry 2). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.92–7.88 (m, 2 H), 7.55–7.43 (m, 5 H), 7.42–7.38 (m, 2 H), 3.83 (s, 3 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 145.3, 141.4, 133.9, 130.5, 129.7, 129.3, 128.8, 128.6, 128.5, 128.0, 106.5, 38.2 ppm. HRMS (ESI): calcd. for $C_{16}H_{13}Cl_2N_2$ $[M + H]^+$ 303.0450; found 303.0453.

**3-Benzyl-1-methyl-4-nitro-5-phenyl-1*H*-pyrazole (8):** The title compound was isolated in 41% yield (60 mg; Table 2, Entry 1). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.54–7.48 (m, 3 H), 7.42–7.37 (m, 2 H), 7.37–7.33 (m, 2 H), 7.33–7.28 (m, 2 H), 7.25–7.21 (m, 1 H), 4.37–4.33 (s, 2 H), 3.69–3.65 (s, 3 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 148.2, 142.8, 137.8, 130.2, 129.5, 129.1, 128.8, 128.4, 127.4, 126.6, 37.7, 33.5 (one overlapping carbon peak) ppm. HRMS (ESI): calcd. for $C_{17}H_{16}N_3O_2$ $[M + H]^+$ 294.1237; found 294.1234.

**3-Benzyl-4-chloro-1-methyl-5-phenyl-1*H*-pyrazole (9):** The title compound was isolated in 19% yield (26 mg; Table 2, Entry 1). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.51–7.46 (m, 2 H), 7.46–7.42 (m, 1 H), 7.42–7.38 (m, 2 H), 7.38–7.34 (m, 2 H), 7.32–7.28 (m, 2 H), 7.23–7.18 (m, 1 H), 4.11–3.96 (s, 2 H), 3.83–3.67 (s, 3 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 147.5, 140.0, 138.9, 129.6, 129.0, 128.8, 128.7, 128.4, 128.3, 126.2, 107.6, 38.0, 32.4 ppm. HRMS (ESI): calcd. for $C_{17}H_{16}ClN_2$ $[M + H]^+$ 283.0997; found 283.0998.

**3-Isopropyl-1-methyl-4-nitro-5-phenyl-1*H*-pyrazole (10):** The title compound was isolated in 57% yield (70 mg; Table 2, Entry 2). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.55–7.49 (m, 3 H), 7.39–7.34 (m, 2 H), 3.65 (s, 3 H), 3.70–3.62 (dt, $J$ = 14.0, 7.0 Hz, 1 H), 1.39–1.33 (d, $J$ = 6.9 Hz, 6 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 154.6, 142.7, 130.0, 129.5, 128.7, 127.7, 37.6, 27.0, 21.3 (one overlapping carbon peak) ppm. HRMS (ESI): calcd. for $C_{13}H_{16}N_3O_2$ $[M + H]^+$ 246.1237; found 246.1225.

**4-Chloro-3-isopropyl-1-methyl-5-phenyl-1*H*-pyrazole (11):** The title compound was isolated in 38% yield (44 mg; Table 2, Entry 2). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.51–7.47 (m, 2 H), 7.46–7.40 (m, 3 H), 3.81–3.73 (s, 3 H), 3.16–3.04 (dt, $J$ = 14.0, 7.0 Hz, 1 H), 1.41–1.30 (d, $J$ = 7.0 Hz, 6 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 153.5, 139.9, 129.6, 128.9, 128.6, 128.5, 106.3, 37.9, 26.4, 21.4 ppm. HRMS (ESI): calcd. for $C_{13}H_{16}ClN_2$ $[M + H]^+$ 235.0997; found 235.0994.

**3-(4-Methoxyphenyl)-1-methyl-4-nitro-5-phenyl-1*H*-pyrazole (12):** The title compound was isolated in 66% yield (102 mg; Table 2, Entry 4). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.67–7.63 (m, 2 H), 7.57–7.53 (ddd, $J$ = 3.6, 2.4, 1.0 Hz, 3 H), 7.47–7.42 (m, 2 H), 7.01–6.96 (m, 2 H), 3.88–3.85 (s, 3 H), 3.75–3.73 (s, 3 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 160.4, 147.1, 142.9, 130.5, 130.2, 129.6, 128.9, 127.3, 122.8, 113.7, 55.3, 37.8 ppm. HRMS (ESI): calcd. for $C_{17}H_{16}N_3O_3$ $[M + H]^+$ 310.1186; found 310.1175.

**4-Chloro-3-(4-methoxyphenyl)-1-methyl-5-phenyl-1*H*-pyrazole (13):** The title compound was isolated in 58% yield (86 mg; Table 2, Entry 4). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.90–7.85 (m, 2 H), 7.55–7.50 (m, 2 H), 7.49–7.43 (m, 3 H), 7.01–6.95 (m, 2 H), 3.86–3.84 (s, 3 H), 3.84–3.82 (s, 3 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 159.5, 146.3, 141.0, 129.7, 129.2, 128.7, 128.6, 128.3, 124.5, 113.8, 106.1, 55.3, 38.1 ppm. HRMS (ESI): calcd. for $C_{17}H_{16}ClN_2O$ $[M + H]^+$ 299.0946; found 299.0942.

**1-Methyl-4-nitro-3-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole (14):** The title compound was isolated in 54% yield (87 mg; Table 2, Entry 5). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.35–8.28 (m, 2 H), 7.92–7.84 (m, 2 H), 7.63–7.53 (m, 3 H), 7.50–7.40 (m, 2 H), 3.83–3.74 (s, 3 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 148.1, 145.0, 143.6, 137.0, 130.6, 130.2, 129.6, 129.0, 126.6, 123.4, 38.2 (one overlapping carbon peak) ppm. HRMS (ESI): calcd. for $C_{16}H_{13}N_4O_4$ $[M + H]^+$ 325.0931; found 325.0931.

**4-Chloro-1-methyl-3-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole (15):** The title compound was isolated in 70% yield (109 mg; Table 2, Entry 5). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.31–8.27 (m, 2 H), 8.20–8.15 (m, 2 H), 7.58–7.49 (m, 3 H), 7.49–7.44 (m, 2 H), 3.99–3.81 (s, 3 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 147.1, 143.9, 141.9, 138.4, 129.7, 129.6, 128.9, 127.6, 127.5, 123.7, 107.4, 38.5 ppm. HRMS (ESI): calcd. for $C_{16}H_{13}ClN_3O_2$ $[M + H]^+$ 314.0691; found 314.0684.

**1-Benzyl-3-(4-chlorophenyl)-4-nitro-5-phenyl-1*H*-pyrazole (16):** The title compound was isolated in 55% yield (107 mg; Table 2, Entry 6). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.69–7.65 (m, 2 H), 7.56–7.51 (m, 1 H), 7.51–7.46 (m, 2 H), 7.44–7.41 (m, 2 H), 7.33–7.26 (m, 5 H), 5.21–5.13 (s, 2 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 146.3, 143.3, 135.4, 135.1, 130.6, 130.4, 129.7, 129.0, 128.8, 128.8, 128.5, 128.3, 127.5, 127.5, 126.9, 54.3 ppm. HRMS (ESI): calcd. for $C_{22}H_{17}ClN_3O_2$ $[M + H]^+$ 390.1004; found 390.0993.

**1-Benzyl-4-chloro-3-(4-chlorophenyl)-5-phenyl-1*H*-pyrazole (17):** The title compound was isolated in 63% yield (119 mg; Table 2, Entry 6). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.97–7.91 (m, 2 H), 7.48–7.39 (m, 5 H), 7.35–7.30 (m, 2 H), 7.29–7.22 (m, 3 H), 7.09–7.03 (dd, $J$ = 7.8, 1.6 Hz, 2 H), 5.34–5.19 (s, 2 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 145.7, 141.7, 136.7, 134.0, 130.4, 129.9, 129.5, 128.8, 128.7, 128.6, 128.6, 128.0, 127.8, 127.0, 107.1, 54.3 ppm. HRMS (ESI): calcd. for $C_{22}H_{17}Cl_2N_2$ $[M + H]^+$ 379.0763; found 379.0759.

**3-(4-Chlorophenyl)-1-isopropyl-4-nitro-5-phenyl-1*H*-pyrazole (18):** The title compound was isolated in 34% yield (58 mg; Table 2, Entry 7). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.69–7.65 (m, 2 H), 7.59–7.53 (m, 3 H), 7.45–7.39 (m, 4 H), 4.38–4.25 (sept, $J$ = 6.6 Hz, 1 H), 1.52–1.45 (d, $J$ = 6.6 Hz, 6 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 146.0, 142.1, 135.2, 130.9, 130.6, 130.2, 129.5, 129.1,

128.9, 128.4, 127.3, 51.6, 22.4 ppm. HRMS (ESI): calcd. for $C_{18}H_{17}ClN_3O_2$ [M + H]$^+$ 342.1004; found 342.1006.

**4-Chloro-3-(4-chlorophenyl)-1-isopropyl-5-phenyl-1*H*-pyrazole (19):** The title compound was isolated in 41% yield (67 mg; Table 2, Entry 7). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.96–7.90 (m, 2 H), 7.57–7.46 (m, 3 H), 7.45–7.38 (m, 4 H), 4.52–4.36 (sept, $J$ = 6.6 Hz, 1 H), 1.56–1.54 (s, 2 H), 1.51–1.45 (d, $J$ = 6.6 Hz, 6 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 145.0, 140.4, 133.7, 130.9, 129.9, 129.2, 128.8, 128.6, 128.5, 128.4, 106.1 ppm. HRMS (ESI): calcd. for $C_{18}H_{17}Cl_2N_2$ [M + H]$^+$ 331.0763; found 331.0765.

**3-(4-Chlorophenyl)-4-nitro-1,5-diphenyl-1*H*-pyrazole (20):** The title compound was isolated in 58% yield (108 mg; Table 3, Entry 1). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.74–7.69 (m, 2 H), 7.49–7.42 (m, 3 H), 7.42–7.37 (m, 2 H), 7.37–7.29 (m, 5 H), 7.28–7.21 (m, 2 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 146.9, 142.4, 138.3, 135.5, 131.7, 130.5, 130.2, 130.2, 129.1, 128.8, 128.7, 128.6, 128.6, 126.8, 125.3 ppm. HRMS (ESI): calcd. for $C_{21}H_{15}ClN_3O_2$ [M + H]$^+$ 376.0847; found 376.0834.

**4-Bromo-3-(4-chlorophenyl)-1,5-diphenyl-1*H*-pyrazole (21):** The title compound was isolated in 15% yield (30 mg; Table 3, Entry 1). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.01–7.95 (m, 2 H), 7.46–7.41 (m, 2 H), 7.40–7.35 (m, 3 H), 7.35–7.25 (m, 7 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 148.6, 142.3, 139.7, 134.4, 130.5, 130.2, 129.3, 129.1, 128.9, 128.8, 128.6, 128.5, 127.7, 124.8, 94.8 ppm. HRMS (ESI): calcd. for $C_{21}H_{15}BrClN_2$ [M + H]$^+$ 409.0102; found 409.0082.

**4-Chloro-3-(4-chlorophenyl)-1,5-diphenyl-1*H*-pyrazole (22):** The title compound was isolated in 74% yield (135 mg; Table 3, Entry 1). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.02–7.97 (m, 2 H), 7.46–7.42 (m, 2 H), 7.39–7.36 (m, 3 H), 7.34–7.27 (m, 7 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 146.9, 140.5, 139.6, 134.3, 130.1, 129.9, 129.0, 128.9, 128.8, 128.6, 128.5, 128.1, 127.7, 124.8, 108.8 ppm. HRMS (ESI): calcd. for $C_{21}H_{15}Cl_2N_2$ [M + H]$^+$ 365.0607; found 365.0593.

**3-(4-Methoxyphenyl)-4-nitro-1,5-diphenyl-1*H*-pyrazole (23):** The title compound was isolated in 32% yield (59 mg; Table 3, Entry 2). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.74–7.69 (m, 2 H), 7.46–7.41 (m, 1 H), 7.41–7.37 (m, 2 H), 7.36–7.33 (m, 2 H), 7.33–7.28 (m, 3 H), 7.28–7.23 (m, 2 H), 7.02–6.97 (m, 2 H), 3.96–3.73 (s, 3 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 160.5, 147.7, 142.1, 138.5, 132.0, 131.7, 130.4, 130.2, 130.0, 129.0, 128.6, 128.6, 127.1, 125.3, 122.5, 113.8, 55.3 ppm. HRMS (ESI): calcd. for $C_{22}H_{18}N_3O_3$ [M + H]$^+$ 372.1343; found 372.1325.

**4-Chloro-3-(4-methoxyphenyl)-1,5-diphenyl-1*H*-pyrazole (24):** The title compound was isolated in 68% yield (122 mg; Table 3, Entry 2). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.01–7.95 (m, 2 H), 7.40–7.35 (m, 3 H), 7.35–7.31 (m, 2 H), 7.30–7.25 (m, 4 H), 7.03–6.97 (m, 2 H), 3.97–3.73 (s, 3 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 159.8, 147.9, 140.2, 139.9, 130.0, 129.0, 128.9, 128.8, 128.5, 128.5, 127.4, 124.8, 124.2, 113.9, 108.6, 55.3 ppm. HRMS (ESI): calcd. for $C_{22}H_{18}ClN_2O$ [M + H]$^+$ 361.1102; found 361.1097.

**3-(4-Nitro-1,5-diphenyl-1*H*-pyrazol-3-yl)phenol (25):** The title compound was isolated in 58% yield (103 mg; Table 3, Entry 3). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.45–7.40 (m, 1 H), 7.40–7.35 (m, 2 H), 7.35–7.32 (m, 2 H), 7.32–7.27 (m, 5 H), 7.27–7.23 (m, 2 H), 7.22–7.19 (dd, $J$ = 3.0, 1.4 Hz, 1 H), 6.91–6.86 (dt, $J$ = 6.5, 2.7 Hz, 1 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 155.7, 147.6, 142.2, 138.3, 131.9, 131.3, 130.2, 130.1, 129.6, 129.1, 128.7, 128.6, 126.8, 125.4, 121.3, 116.7, 116.0 ppm. HRMS (ESI): calcd. for $C_{21}H_{16}N_3O_3$ [M + H]$^+$ 358.1186; found 358.1190.

**3-(4-Bromo-1,5-diphenyl-1*H*-pyrazol-3-yl)phenol (26):** The title compound was isolated in 25% yield (49 mg; Table 3, Entry 3). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.62–7.57 (dt, $J$ = 7.7, 1.2 Hz, 1 H), 7.50–7.46 (dd, $J$ = 2.6, 1.5 Hz, 1 H), 7.40–7.36 (m, 3 H), 7.35–7.30 (m, 3 H), 7.30–7.24 (m, 5 H), 6.90–6.82 (ddd, $J$ = 8.2, 2.7, 1.0 Hz, 1 H), 5.44–5.30 (s, 1 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 155.6, 149.3, 142.2, 139.7, 133.3, 130.2, 129.6, 129.0, 128.9, 128.8, 128.5, 127.7, 124.8, 120.5, 115.6, 114.9, 94.9 ppm. HRMS (ESI): calcd. for $C_{21}H_{16}BrN_2O$ [M + H]$^+$ 391.0441; found 391.0426.

**3-(4-Chloro-1,5-diphenyl-1*H*-pyrazol-3-yl)phenol (27):** The title compound was isolated in 62% yield (107 mg; Table 3, Entry 3). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.61–7.56 (dt, $J$ = 7.7, 1.3 Hz, 1 H), 7.51–7.48 (d, $J$ = 2.2 Hz, 1 H), 7.40–7.34 (m, 3 H), 7.33–7.30 (m, 2 H), 7.30–7.24 (m, 6 H), 6.85–6.80 (ddd, $J$ = 8.2, 2.6, 0.9 Hz, 1 H), 5.89–4.46 (br. s, 1 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 155.8, 147.9, 140.5, 139.6, 132.7, 130.0, 129.7, 129.0, 128.9, 128.5, 128.2, 127.7, 124.9, 120.1, 115.7, 114.6, 109.0 ppm. HRMS (ESI): calcd. for $C_{21}H_{16}ClN_2O$ [M + H]$^+$ 347.0946; found 347.0943.

**Methyl 4-(4-Nitro-1,5-diphenyl-1*H*-pyrazol-3-yl)benzoate (28):** The title compound was isolated in 30% yield (60 mg; Table 3, Entry 4). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.17–8.13 (m, 2 H), 7.87–7.82 (m, 2 H), 7.49–7.43 (m, 1 H), 7.43–7.38 (ddd, $J$ = 8.3, 7.1, 0.9 Hz, 2 H), 7.38–7.30 (m, 5 H), 7.29–7.24 (m, 2 H), 4.01–3.83 (s, 3 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 166.7, 147.0, 142.4, 138.3, 134.7, 131.9, 130.8, 130.3, 130.2, 129.6, 129.1, 129.1, 128.9, 128.6, 126.7, 125.3, 52.3 ppm. HRMS (ESI): calcd. for $C_{23}H_{18}N_3O_4$ [M + H]$^+$ 400.1292; found 400.1287.

**Methyl 4-(4-Chloro-1,5-diphenyl-1*H*-pyrazol-3-yl)benzoate (29):** The title compound was isolated in 67% yield (130 mg; Table 3, Entry 4). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.18–8.11 (m, 4 H), 7.43–7.36 (m, 3 H), 7.35–7.27 (m, 7 H), 3.95–3.92 (s, 3 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 166.9, 146.9, 140.7, 139.6, 136.0, 129.9, 129.7, 129.7, 129.1, 129.0, 128.6, 128.0, 127.8, 127.3, 124.8, 109.2, 52.1 ppm. HRMS (ESI): calcd. for $C_{23}H_{18}ClN_2O_2$ [M + H]$^+$ 389.1051; found 389.1043.

**4-Nitro-3-(4-nitrophenyl)-1,5-diphenyl-1*H*-pyrazole (30):** The title compound was isolated in 16% yield (31 mg; Table 3, Entry 5). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.37–8.31 (m, 2 H), 7.99–7.94 (m, 2 H), 7.49–7.44 (m, 1 H), 7.44–7.38 (m, 2 H), 7.38–7.31 (m, 5 H), 7.29–7.25 (m, 2 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 148.3, 145.8, 142.8, 138.2, 136.7, 130.4, 130.3, 130.2, 129.2, 129.1, 128.7, 126.5, 125.3, 123.5 (one overlapping carbon peak) ppm. HRMS (ESI): calcd. for $C_{21}H_{15}N_4O_4$ [M + H]$^+$ 387.1088; found 387.1084.

**4-Bromo-3-(4-nitrophenyl)-1,5-diphenyl-1*H*-pyrazole (31):** The title compound was isolated in 25% yield (52 mg; Table 3, Entry 5). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.35–8.30 (m, 2 H), 8.29–8.24 (m, 2 H), 7.43–7.38 (m, 3 H), 7.36–7.31 (m, 5 H), 7.30–7.27 (m, 2 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 147.5, 147.2, 142.9, 139.5, 138.4, 130.2, 129.3, 129.0, 128.6, 128.5, 128.4, 128.1, 124.8, 123.6, 95.2 ppm. HRMS (ESI): calcd. for $C_{21}H_{15}BrN_3O_2$ [M + H]$^+$ 420.0342; found 420.0326.

**4-Chloro-3-(4-nitrophenyl)-1,5-diphenyl-1*H*-pyrazole (32):** The title compound was isolated in 59% yield (110 mg; Table 3, Entry 5). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.35–8.30 (m, 2 H), 8.30–8.25 (m, 2 H), 7.43–7.37 (m, 3 H), 7.36–7.26 (m, 7 H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ = 147.5, 145.6, 141.1, 139.5, 138.0, 129.9, 129.3, 129.0, 128.7, 128.1, 128.0, 127.8, 124.8, 123.7, 109.5 ppm. HRMS (ESI): calcd. for $C_{21}H_{15}ClN_3O_2$ [M + H]$^+$ 376.0847; found 376.0840.

**3-(4-Nitro-1,5-diphenyl-1*H*-pyrazol-3-yl)benzonitrile (33):** The title compound was isolated in 23% yield (42 mg; Table 3, Entry 6). $^1$H

NMR (600 MHz, $CDCl_3$): $\delta$ = 8.12–8.09 (t, $J$ = 1.7 Hz, 1 H), 8.03–7.99 (dt, $J$ = 7.9, 1.5 Hz, 1 H), 7.78–7.73 (dt, $J$ = 7.8, 1.4 Hz, 1 H), 7.61–7.57 (t, $J$ = 7.8 Hz, 1 H), 7.49–7.43 (m, 1 H), 7.44–7.39 (m, 2 H), 7.38–7.30 (m, 5 H), 7.29–7.22 (m, 2 H) ppm. $^{13}C$ NMR (151 MHz, $CDCl_3$): $\delta$ = 145.9, 142.7, 138.2, 133.6, 132.8, 132.7, 131.8, 131.6, 130.3, 130.2, 129.2, 129.1, 129.0, 128.7, 126.5, 125.3, 118.3, 112.7 ppm. HRMS (ESI): calcd. for $C_{22}H_{15}N_4O_2$ $[M + H]^+$ 367.1190; found 367.1177.

**3-(4-Bromo-1,5-diphenyl-1*H*-pyrazol-3-yl)benzonitrile (34):** The title compound was isolated in 14% yield (28 mg; Table 3, Entry 6). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ = 8.38–8.34 (td, $J$ = 1.7, 0.6 Hz, 1 H), 8.33–8.27 (ddd, $J$ = 7.9, 1.8, 1.2 Hz, 1 H), 7.71–7.66 (dt, $J$ = 7.7, 1.4 Hz, 1 H), 7.60–7.55 (td, $J$ = 7.8, 0.6 Hz, 1 H), 7.43–7.38 (m, 3 H), 7.35–7.26 (m, 7 H) ppm. $^{13}C$ NMR (151 MHz, $CDCl_3$): $\delta$ = 147.4, 142.6, 139.5, 133.4, 132.0, 131.7, 131.4, 130.1, 129.3, 129.2, 129.0, 128.6, 128.5, 127.9, 124.8, 118.7, 112.7, 94.7 ppm. HRMS (ESI): calcd. for $C_{22}H_{15}BrN_3$ $[M + H]^+$ 400.0444; found 400.0444.

**3-(4-Chloro-1,5-diphenyl-1*H*-pyrazol-3-yl)benzonitrile (35):** The title compound was isolated in 31% yield (55 mg; Table 3, Entry 6). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ = 8.40–8.36 (t, $J$ = 1.7 Hz, 1 H), 8.33–8.29 (dt, $J$ = 7.9, 1.5 Hz, 1 H), 7.71–7.64 (dt, $J$ = 7.5, 1.4 Hz, 1 H), 7.61–7.53 (t, $J$ = 7.8 Hz, 1 H), 7.43–7.36 (m, 3 H), 7.36–7.27 (m, 7 H) ppm. $^{13}C$ NMR (151 MHz, $CDCl_3$): $\delta$ = 145.8, 140.9, 139.5, 133.0, 131.6, 131.6, 131.0, 129.9, 129.3, 129.2, 129.0, 128.6, 128.0, 127.9, 124.8, 118.7, 112.8, 108.9 ppm. HRMS (ESI): calcd. for $C_{22}H_{15}ClN_3$ $[M + H]^+$ 356.0949; found 356.0947.

**3-(4-Chlorophenyl)-1-(4-methoxyphenyl)-4-nitro-5-phenyl-1*H*-pyrazole (36):** The title compound was isolated in 63% yield (127 mg; Table 3, Entry 7). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ = 7.72–7.67 (m, 2 H), 7.48–7.36 (m, 5 H), 7.36–7.31 (m, 2 H), 7.18–7.12 (m, 2 H), 6.83–6.78 (m, 2 H), 3.84–3.66 (s, 3 H) ppm. $^{13}C$ NMR (151 MHz, $CDCl_3$): $\delta$ = 159.6, 146.6, 142.3, 135.4, 131.4, 131.3, 130.5, 130.2, 130.0, 128.8, 128.6, 128.5, 126.9, 126.7, 114.2, 55.5 ppm. HRMS (ESI): calcd. for $C_{22}H_{17}ClN_3O_3$ $[M + H]^+$ 406.0953; found 406.0966.

**4-Chloro-3-(4-chlorophenyl)-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrazole (37):** The title compound was isolated in 72% yield (141 mg; Table 3, Entry 7). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ = 8.01–7.96 (m, 2 H), 7.45–7.40 (m, 2 H), 7.40–7.35 (m, 3 H), 7.34–7.29 (m, 2 H), 7.22–7.17 (m, 2 H), 6.85–6.80 (m, 2 H), 3.80–3.77 (s, 3 H) ppm. $^{13}C$ NMR (151 MHz, $CDCl_3$): $\delta$ = 159.0, 146.6, 140.5, 134.2, 132.9, 130.2, 129.9, 128.9, 128.8, 128.6, 128.5, 128.2, 126.3, 114.1, 108.3, 55.5 ppm. HRMS (ESI): calcd. for $C_{22}H_{17}Cl_2N_2O$ $[M + H]^+$ 395.0712; found 395.0702.

**4-[4-Bromo-3-(4-chlorophenyl)-5-phenyl-1*H*-pyrazol-1-yl]benzonitrile (38):** The title compound was isolated in 45% yield (97 mg; Table 3, Entry 8). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ = 8.01–7.93 (m, 2 H), 7.62–7.56 (m, 2 H), 7.51–7.43 (m, 5 H), 7.43–7.38 (m, 2 H), 7.35–7.30 (m, 2 H) ppm. $^{13}C$ NMR (151 MHz, $CDCl_3$): $\delta$ = 149.7, 142.8, 142.5, 134.9, 132.9, 130.0, 129.8, 129.8, 129.2, 129.0, 128.7, 128.4, 124.4, 118.0, 110.9, 96.6 ppm. HRMS (ESI): calcd. for $C_{22}H_{14}BrClN_3$ $[M + H]^+$ 434.0054; found 434.0046.

**4-[4-Chloro-3-(4-chlorophenyl)-5-phenyl-1*H*-pyrazol-1-yl]benzonitrile (39):** The title compound was isolated in 45% yield (87 mg; Table 3, Entry 8). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ = 8.01–7.96 (m, 2 H), 7.62–7.58 (m, 2 H), 7.50–7.44 (m, 5 H), 7.43–7.39 (m, 2 H), 7.35–7.30 (dd, $J$ = 7.7, 1.8 Hz, 2 H) ppm. $^{13}C$ NMR (151 MHz, $CDCl_3$): $\delta$ = 148.2, 142.8, 140.8, 134.9, 132.9, 129.8, 129.8, 129.5, 129.1, 128.9, 128.8, 127.6, 124.4, 118.1, 110.9, 110.5 ppm. HRMS (ESI): calcd. for $C_{22}H_{14}Cl_2N_3$ $[M + H]^+$ 390.0559; found 390.0551.

**3-(4-Chlorophenyl)-1-(3-nitrophenyl)-5-phenyl-1*H*-pyrazole (40):** The title compound was isolated in 41% yield (76 mg; Table 3, Entry 9). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ = 8.33–8.29 (t, $J$ = 2.2 Hz, 1 H), 8.16–8.11 (ddd, $J$ = 8.2, 2.2, 1.0 Hz, 1 H), 7.88–7.82 (m, 2 H), 7.63–7.59 (ddd, $J$ = 8.0, 2.1, 1.0 Hz, 1 H), 7.50–7.44 (m, 1 H), 7.44–7.35 (m, 5 H), 7.31–7.27 (m, 2 H), 6.83–6.81 (s, 1 H) ppm. $^{13}C$ NMR (151 MHz, $CDCl_3$): $\delta$ = 151.8, 148.5, 145.0, 140.9, 134.3, 131.0, 130.1, 129.8, 129.6, 129.1, 128.95, 128.94, 128.8, 127.1, 121.7, 119.7, 106.3 ppm. HRMS (ESI): calcd. for $C_{21}H_{15}ClN_3O_2$ $[M + H]^+$ 376.0847; found 376.0829.

**4-Chloro-3-(4-chlorophenyl)-1-(3-nitrophenyl)-5-phenyl-1*H*-pyrazole (41):** The title compound was isolated in 85% yield (173 mg; Table 3, Entry 9). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ = 8.27–8.23 (t, $J$ = 2.2 Hz, 1 H), 8.16–8.10 (ddd, $J$ = 8.2, 2.2, 1.1 Hz, 1 H), 8.04–7.98 (m, 2 H), 7.59–7.54 (ddd, $J$ = 8.1, 2.2, 1.0 Hz, 1 H), 7.50–7.42 (m, 6 H), 7.37–7.31 (m, 2 H) ppm. $^{13}C$ NMR (151 MHz, $CDCl_3$): $\delta$ = 148.5, 148.0, 140.9, 140.5, 134.9, 129.9, 129.8, 129.7, 129.6, 129.5, 129.1, 128.9, 128.8, 127.5, 122.0, 119.3, 110.2 ppm. HRMS (ESI): calcd. for $C_{21}H_{14}Cl_2N_3O_2$ $[M + H]^+$ 410.0458; found 410.0449.

**Supporting Information** (see footnote on the first page of this article): $^1H$ and $^{13}C$ NMR spectra of compounds **4**–**41**.

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[1] J. Elguero, P. Goya, N. Jagerovic, A. M. S. Silva, "Pyrazoles as Drugs: Facts and Fantasies", in *Targets in Heterocyclic Systems* (Eds.: O. A. Attanasi, D. Spinelli), Royal Society of Chemistry, Cambridge, **2002**, vol. 6, p. 52.

[2] a) J. Elguero, in *Comprehensive Heterocyclic Chemistry* (Eds.: A. R. Karitzyky, C. W. Ress), Pergamon, Oxford, **1984**, vol. 5, p. 167; b) J. Elguero, in *Comprehensive Heterocyclic Chemistry II* (Eds.: A. R. Karitzyky, C. W. Ress), Pergamon, Oxford, **1996**, vol. 3, p. 1; c) K. Makino, H. S. Kim, Y. Kurasawa, *J. Heterocycl. Chem.* **1998**, *35*, 489 and references cited therein.

[3] B. B. Snider, R. S. E. Conn, S. Sealfon, *J. Org. Chem.* **1979**, *44*, 218.

[4] a) M. Gomez-Guillen, J. L. Conde-Jimenez, *Carbohydr. Res.* **1988**, *180*, 1; b) M. Gomez-Guillen, F. Hans-Hans, J. M. Lassaletta-Simon, M. E. Martin-Zamora, *Carbohydr. Res.* **1989**, *189*, 349.

[5] a) X. Deng, N. S. Mani, *Org. Lett.* **2006**, *8*, 3505; b) X. Deng, N. S. Mani, *J. Org. Chem.* **2008**, *73*, 2412; c) X. Deng, N. S. Mani, *Org. Lett.* **2008**, *10*, 1307; d) J. T. Liang, X. Deng, N. S. Mani, *Org. Process Res. Dev.* **2011**, *15*, 876.

[6] a) M. Ganesh, I. N. N. Namboothiri, *Tetrahedron* **2007**, *63*, 11973; b) L. V. Romashov, Y. A. Khomutova, V. M. Danilenko, S. L. Ioffe, A. V. Lesiv, *Synthesis* **2010**, 407.

[7] a) D. Dauzonne, P. Demerseman, *Synthesis* **1990**, 66; b) D. I. Aleksiev, S. M. Ivanova, *Russ. J. Org. Chem.* **1993**, *29*, 2226.

[8] a) H. W. Hamilton, D. F. Ortwine, D. F. Worth, J. A. Bristol, *J. Med. Chem.* **1987**, *30*, 91; b) J. K. Chakrabarti, T. M. Hotten, I. A. Pullar, N. C. Tye, *J. Med. Chem.* **1989**, *32*, 2573; c) S. Manfredini, R. Bazzanini, P. G. Baraldi, M. Guarneri, D. Simoni, M. E. Marongiu, A. Pani, P. La Colla, E. Tramontano, *J. Med. Chem.* **1992**, *35*, 917; d) E. J. Barreiro, C. A. Camara, H. Verli, L. Brazil-Mas, N. G. Castro, W. M. Cintra, Y. Aracava, C. R. Rodrigues, C. A. M. Fraga, *J. Med. Chem.* **2003**, *46*, 1144; e) E. J. Hanan, B. K. Chan, A. A. Estrada, D. G. Shore, J. P. Lyssikatos, *Synlett* **2010**, *18*, 2759; f) S. Wang, R. Beck, A. Burd, T. Blench, F. Marlin, T. Ayele, S. Buxton, C. Dagostin, M. Malic, R. Joshi, *J. Med. Chem.* **2010**, *53*, 1473; g) Y. Takahashi, S. Hibi, Y. Hoshino, K. Kikuchi, K. Shin, K. Murata-Tai, M. Fujisawa, M. Ino, H. Shibata, M. Yonaga, *J. Med. Chem.* **2012**, *55*, 5255; h) D. J. Rawson, S. Ballard, C.

  

Barber, L. Barker, K. Beaumont, M. Bunnage, S. Cole, M. Corless, S. Denton, D. Ellis, *Bioorg. Med. Chem.* **2012**, *20*, 498.
[9] a) K. M. Khan, G. M. Maharvi, M. I. Choudhary, P. S. Attaur-Rahman, *J. Heterocycl. Chem.* **2005**, *42*, 1085; b) M. Nayak, S. Batra, *Adv. Synth. Catal.* **2010**, *352*, 3431; c) M. Kienle, A. J. Wagner, C. Dunst, P. Knochel, *Chem. Asian J.* **2011**, *6*, 517; d) I. L. Dalinger, I. A. Vatsadze, T. K. Shkineva, G. P. Popova, S. A. Shevelev, *Synthesis* **2012**, 2058; e) M. Nayak, N. Rastogi, J. Batra, *Eur. J. Org. Chem.* **2012**, *7*, 1360.
[10] a) S. R. Stauffer, Y. Huang, C. J. Coletta, R. Tedesco, J. A. Katzenellenbogen, *Bioorg. Med. Chem.* **2001**, *9*, 141; b) A. S. Paulson, J. Eskildsen, P. Vedso, M. Begtrup, *J. Org. Chem.* **2002**, *67*, 3904; c) J. Yin, M. P. Rainka, X. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1162; d) S. K. Meegalla, D. Doller, D. Sha, R. Soll, N. Wisnewski, G. M. Silver, D. Dhanoa, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4949; e) S. Guillou, O. Nesmes, M. S. Ermolenko, Y. L. Janin, *Tetrahedron* **2009**, *65*, 3529.
[11] a) Q. Sha, Y. Wei, *Synthesis* **2013**, *45*, 413; b) S. R. Graham, P. J. Brown, J. G. Ford, *Org. Process Res. Dev.* **2010**, *14*, 242; c) M. G. Saulnier, D. B. Frennesson, M. D. Wittman, K. Zimmermann, U. Velaparthi, D. R. Langley, C. Struzynski, X. Sang, J. Carboni, A. Li, A. Greer, Z. Yang, P. Balimane, M. Gottardis, R. Attar, D. Vyas, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1702; d) A. A. Zabierek, K. M. Konrad, A. M. Haidle, *Tetrahedron Lett.* **2008**, *49*, 2996; e) Z. Zhao, Z. Wang, *Synth. Commun.* **2007**, *37*, 137; f) J. W. A. M. Janssen, H. J. Koeners, C. G. Kruse, C. L. Habraken, *J. Org. Chem.* **1973**, *38*, 1777.
[12] No difference was observed in the behavior of the reactions with in situ prepared or isolated hydrazone. The choice of one or the other was made primarily on the basis of operational convenience.

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