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

Xiaohu Deng,†[a] Jimmy T. Liang,[a] and Neelakandha S. Mani[a]

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We report an acid-catalyzed cycloaddition reaction of hydrazones with β-halo- 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 HNO2 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-tetra-

Scheme 1. Pyrazole synthesis from hydrazones and nitro olefins.

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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, 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, Et₂O, DMF, iPrOH, EtOH, CH₂Cl₂, EtOAc, and CH₃CN 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 CF₃CH₂OH 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 > NO₂ > 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 CF₃CH₂OH 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.

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 HNO₂, depending on the relative leaving-group ability of the halogen atoms and the nitro group, gives 4-nitropyrazole 4 or 4-chloropyrazole 7, respectively.

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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydrazone</th>
<th>Conditions; product, yield</th>
<th>Conditions; product, yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>MeOH, r.t. 8 (Py-NO₂), 41%</td>
<td>CF₃CH₂OH, r.t. 9 (Py-Cl), 19%, 9 (Py-NO₂), 20%</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>CF₃CH₂OH, r.t. 10 (Py-NO₂), 57%</td>
<td>MeOH, r.t. 11 (Py-Cl), 38%, 10 (Py-NO₂), 40%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>MeOH or CF₃CH₂OH, r.t. to reflux, no reaction</td>
<td>MeOH or CF₃CH₂OH, r.t. to reflux, no reaction</td>
</tr>
<tr>
<td>4</td>
<td>N=N=Ph</td>
<td>CF₃CH₂OH, r.t. 12 (Py-NO₂), 66%</td>
<td>CF₃CH₂OH, r.t. 13 (Py-Cl), 56%, 12 (Py-NO₂), 33%</td>
</tr>
<tr>
<td>5</td>
<td>N=N[OMe]</td>
<td>CF₃CH₂OH, 70 °C 14 (Py-NO₂), 54%</td>
<td>CF₃CH₂OH, 50 °C 15 (Py-Cl), 70%</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>MeOH/H₂O, r.t. 16 (Py-NO₂), 55%</td>
<td>MeOH/H₂O, r.t. 17 (Py-Cl), 63%</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>MeOH/H₂O, r.t. 18 (Py-NO₂), 34%</td>
<td>MeOH/H₂O, r.t. 19 (Py-Cl), 41%</td>
</tr>
<tr>
<td>8</td>
<td>fBu</td>
<td>MeOH or CF₃CH₂OH, r.t. to reflux, no reaction</td>
<td>MeOH or CF₃CH₂OH, r.t. to reflux, no reaction</td>
</tr>
</tbody>
</table>

[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 CF₃CH₂OH, 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 (R²) and hydrazine (R¹) components was studied. The steric effects on both the R¹ and the R² 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 R² substituent (Table 2, Entries 4 and 5). A higher reaction temperature was required in the presence of a strongly electron-withdrawing R² group such as NO₂ (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 R¹ and R² positions. For example, when R² 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 R¹ was an electron-donating group (Table 3, Entry 7), the reaction was favored at room temperature, and with strongly electron-withdrawing R¹ 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 R¹ groups such as CN and NO₂, under more forcing reaction conditions, the reaction mechanism might be different. In these cases, elimination of HNO₂ 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.
Regioselective Synthesis of Tetrasubstituted Pyrazoles

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydrazone</th>
<th>Conditions; product, yield</th>
<th>Conditions; product, yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N-&lt;br&gt;PhN&lt;sub&gt;2&lt;/sub&gt;-&lt;br&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH, r.t., 24 h</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH, r.t., 24 h</td>
</tr>
<tr>
<td>2</td>
<td>N-&lt;br&gt;PhN&lt;sub&gt;2&lt;/sub&gt;-&lt;br&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>MeOH, 50 °C, 24 h</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH, r.t., 48 h</td>
</tr>
<tr>
<td>3</td>
<td>N-&lt;br&gt;PhN&lt;sub&gt;2&lt;/sub&gt;-&lt;br&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH, r.t., 48 h</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH, r.t., 48 h</td>
</tr>
<tr>
<td>4</td>
<td>N-&lt;br&gt;PhN&lt;sub&gt;2&lt;/sub&gt;-&lt;br&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH, r.t., 24 h</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH, r.t., 24 h</td>
</tr>
<tr>
<td>5</td>
<td>N-&lt;br&gt;PhN&lt;sub&gt;2&lt;/sub&gt;-&lt;br&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH, 50 °C, 24 h</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH, 50 °C, 24 h</td>
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<td>6</td>
<td>N-&lt;br&gt;PhN&lt;sub&gt;2&lt;/sub&gt;-&lt;br&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH, r.t., 48 h</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH, 25 °C, 48 h</td>
</tr>
<tr>
<td>7</td>
<td>N-&lt;br&gt;PhN&lt;sub&gt;2&lt;/sub&gt;-&lt;br&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH, r.t., 24 h</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH, r.t., 24 h</td>
</tr>
<tr>
<td>8</td>
<td>N-&lt;br&gt;PhN&lt;sub&gt;2&lt;/sub&gt;-&lt;br&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH, 50 °C, 48 h</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH, 50 °C, 48 h</td>
</tr>
<tr>
<td>9</td>
<td>N-&lt;br&gt;PhN&lt;sub&gt;2&lt;/sub&gt;-&lt;br&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH, 75 °C, 72 h</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH, 75 °C, 72 h</td>
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</tbody>
</table>

[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 13C 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<sub>3</sub>CH<sub>2</sub>OH (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%).
NMR (600 MHz, CDCl3): δ = 7.51–7.47 (m, 2 H), 7.46–7.40 (m, 3 H), 7.31–7.33 (s, 3 H), 3.16–3.04 (dt, J = 14.0, 4.0 Hz, 1 H), 2.38–2.33 (s, 3 H) ppm. HRMS (ESI): calcd. for C13H13ClN2 [M + H]+ 235.0997; found 235.0994.

3-(4-Methoxyphenyl)-1-methyl-4-nitro-5-phenyl-1H-pyrazole (12): The title compound was isolated in 66% yield (102 mg; Table 2, Entry 4). 1H NMR (600 MHz, CDCl3): δ = 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. 13C NMR (151 MHz, CDCl3): δ = 153.5, 139.9, 129.6, 128.6, 128.5, 106.3, 37.9, 26.4, 21.4 ppm. HRMS (ESI): calcd. for C17H16N4O2 [M + H]+ 310.1186; found 310.1175.

4-Chloro-3-(4-methoxyphenyl)-1-methyl-5-phenyl-1H-pyrazole (13): The title compound was isolated in 58% yield (86 mg; Table 2, Entry 4). 1H NMR (600 MHz, CDCl3): δ = 7.70–7.85 (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. 13C NMR (151 MHz, CDCl3): δ = 159.5, 146.3, 141.0, 129.7, 128.7, 128.6, 128.3, 124.5, 113.8, 106.1, 53.3, 38.1 ppm. HRMS (ESI): calcd. for C17H16N4O2 [M + H]+ 299.0946; found 299.0942.

1-Methyl-4-nitro-3-(4-nitrophenyl)-5-phenyl-1H-pyrazole (14): The title compound was isolated in 54% yield (87 mg; Table 2, Entry 5). 1H NMR (600 MHz, CDCl3): δ = 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. 13C NMR (151 MHz, CDCl3): δ = 148.1, 145.0, 143.6, 137.0, 130.6, 129.3, 129.0, 126.3, 124.3, 38.2 (one overlapping carbon peak) ppm. HRMS (ESI): calcd. for C16H15N3O3 [M + H]+ 325.0931; found 325.0931.

4-Chloro-1-methyl-3-(4-nitrophenyl)-5-phenyl-1H-pyrazole (15): The title compound was isolated in 70% yield (109 mg; Table 2, Entry 5). 1H NMR (600 MHz, CDCl3): δ = 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. 13C NMR (151 MHz, CDCl3): δ = 147.1, 143.9, 141.9, 138.4, 129.7, 126.9, 126.8, 126.7, 125.7, 107.4, 38.5 ppm. HRMS (ESI): calcd. for C16H15N3O3 [M + H]+ 325.0931; found 325.0931.

1-Benzyl-3-(4-chloro-5-phenyl)-4-nitro-1H-pyrazole (16): The title compound was isolated in 55% yield (107 mg; Table 2, Entry 6). 1H NMR (600 MHz, CDCl3): δ = 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. 13C NMR (151 MHz, CDCl3): δ = 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 C22H17ClN2O2 [M + H]+ 390.1004; found 390.0993.

1-Benzyl-4-chloro-3-(4-chloro-5-phenyl)-1H-pyrazole (17): The title compound was isolated in 63% yield (119 mg; Table 2, Entry 6). 1H NMR (600 MHz, CDCl3): δ = 7.79–7.71 (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), 5.34–5.15 (s, 2 H) ppm. 13C NMR (151 MHz, CDCl3): δ = 145.7, 141.7, 136.7, 134.0, 130.4, 129.9, 129.5, 128.8, 128.7, 128.6, 128.6, 128.0, 127.0, 107.1, 54.3 ppm. HRMS (ESI): calcd. for C22H17ClN2O2 [M + H]+ 379.0763; found 379.0759.

3-(4-Chlorophenyl)-1-methyl-4-nitro-5-phenyl-1H-pyrazole (18): The title compound was isolated in 34% yield (58 mg; Table 2, Entry 7). 1H NMR (600 MHz, CDCl3): δ = 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. 13C NMR (151 MHz, CDCl3): δ = 146.0, 142.1, 135.2, 130.9, 130.6, 130.2, 129.5, 129.1, 128.9, 128.7, 128.6, 128.5, 128.4, 128.2, 128.2, 128.1, 127.0, 126.9, 126.8, 126.5, 126.4, 126.3, 125.7, 125.7, 124.5, 124.4, 37.9 ppm. HRMS (ESI): calcd. for C13H13ClN2 [M + H]+ 235.0997; found 235.0994.
3-(4-Chloro-3-(4-chlorophenyl)-1H-pyrazole-3-yl)phenol (26): The title compound was isolated in 25% yield (49 mg; Table 3, Entry 3). 

\[ \text{H NMR (600 MHz, CDCl}_3\]: } \delta = 7.62-7.57 (dd, 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 (dd, J = 8.2, 2.7, 1.0 Hz, 1 H), 5.44-5.30 (s, 1 H) ppm. 

\[ ^{13}C \text{ NMR (151 MHz, CDCl}_3\]: } \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$_{15}$BrN$_2$O$_2$ [M + H$^+$]: 391.0441; found 391.0426.

3-(4-Chloro-1H-pyrazol-3-yl)phenol (27): The title compound was isolated in 62% yield (107 mg; Table 3, Entry 3). 

\[ \text{H NMR (600 MHz, CDCl}_3\]: } \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, 0.6, 0.9 Hz, 1 H), 5.89-4.46 (br s, 1 H) ppm. 

\[ ^{13}C \text{ NMR (151 MHz, CDCl}_3\]: } \delta = 155.8, 147.9, 140.5, 139.6, 132.7, 130.0, 129.9, 128.9, 128.5, 127.7, 124.9, 120.1, 115.7, 114.6, 109.0 ppm. HRMS (ESI): calcd. for C$_{21}$H$_{15}$BrN$_2$O$_2$ [M + H$^+$]$: 347.0946; found 347.0943.

Methyl 4-(4-Nitro-1H-pyrazol-3-yl)phenyl-1H-pyrazole (28): The title compound was isolated in 30% yield (60 mg; Table 3, Entry 4). 

\[ \text{H NMR (600 MHz, CDCl}_3\]: } \delta = 8.17–8.11 (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. 

\[ ^{13}C \text{ NMR (151 MHz, CDCl}_3\]: } \delta = 166.7, 147.0, 142.4, 138.3, 134.7, 131.9, 130.8, 130.3, 129.6, 129.1, 129.9, 128.6, 127.8, 127.3, 124.8, 109.2, 52.1 ppm. HRMS (ESI): calcd. for C$_{21}$H$_{15}$N$_3$O$_2$ [M + H$^+$]: 398.1071; found 398.1043.

4-Nitro-1H-pyrazole (29): The title compound was isolated in 16% yield (31 mg; Table 3, Entry 5). 

\[ \text{H NMR (600 MHz, CDCl}_3\]: } \delta = 8.37–8.31 (m, 2 H), 7.99–7.94 (m, 4 H), 7.49–7.44 (m, 1 H), 7.44–7.38 (m, 2 H), 7.38–7.29 (m, 2 H), 4.01–3.83 (s, 3 H) ppm. 

\[ ^{13}C \text{ NMR (151 MHz, CDCl}_3\]: } \delta = 148.3, 145.8, 142.8, 136.7, 130.4, 130.3, 129.0, 128.6, 128.6, 128.1, 127.1, 125.2, 113.8, 55.3 ppm. HRMS (ESI): calcd. for C$_{21}$H$_{15}$N$_3$O$_2$ [M + H$^+$]: 398.1071; found 398.1043.

4-Nitro-1H-pyrazole (30): The title compound was isolated in 16% yield (31 mg; Table 3, Entry 5). 

\[ \text{H NMR (600 MHz, CDCl}_3\]: } \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), 3.95–3.92 (s, 3 H) ppm. 

\[ ^{13}C \text{ NMR (151 MHz, CDCl}_3\]: } \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, 123.6, 95.2 ppm. HRMS (ESI): calcd. for C$_{21}$H$_{15}$N$_3$O$_2$ [M + H$^+$]: 397.1088; found 387.1084.

Bromo-4-(4-nitro-1H-pyrazol-3-yl)phenyl-1H-pyrazole (31): The title compound was isolated in 25% yield (52 mg; Table 3, Entry 5). 

\[ \text{H NMR (600 MHz, CDCl}_3\]: } \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. 

\[ ^{13}C \text{ NMR (151 MHz, CDCl}_3\]: } \delta = 147.5, 145.6, 144.1, 139.5, 138.0, 130.2, 129.9, 129.3, 129.0, 128.7, 128.1, 123.8, 123.6, 95.2 ppm. HRMS (ESI): calcd. for C$_{21}$H$_{15}$BrN$_2$O$_2$ [M + H$^+$]: 420.0324; found 420.0326.

3-Chloro-3-(4-nitro-1H-pyrazol-3-yl)phenol (32): The title compound was isolated in 59% yield (110 mg; Table 3, Entry 5). 

\[ \text{H NMR (600 MHz, CDCl}_3\]: } \delta = 8.35–8.30 (m, 2 H), 8.29–8.24 (m, 2 H), 7.43–7.37 (m, 3 H), 7.36–7.26 (m, 7 H) ppm. 

\[ ^{13}C \text{ NMR (151 MHz, CDCl}_3\]: } \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, 109.5 ppm. HRMS (ESI): calcd. for C$_{21}$H$_{15}$ClN$_2$O$_2$ [M + H$^+$]: 376.0847; found 376.0840.
The title compound was isolated in 41% yield (76 mg; Table 3, Entry 7).\(^1\)\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta = 7.22–7.17 (m, 2 \text{ H}), 6.85–6.80 (m, 2 \text{ H}), 3.80–3.77 (s, 3 \text{ H}) \text{ ppm.} \) Table 3, Entry 8).\(^1\)H NMR (600 MHz, CDCl\(_3\)): The title compound was isolated in 45% yield (87 mg; 4-\{4-Chloro-3-(4-chlorophenyl)-5-phenyl-1-\}pyrazol-3-yl\}benzonitrile (34): The title compound was isolated in 31% yield (55 mg; Table 3, Entry 6).\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta = 7.9, 1.5 \text{ Hz, 1 H), 7.71–7.64 (dt, } J = 7.5, 1.4 \text{ Hz, 1 H), 7.61–7.53 (t, } J = 7.8 \text{ Hz, 1 H), 7.43–7.36 (m, 3 \text{ H), 7.36–7.27 (m, 7 \text{ H}) ppm.} \) \(^13\)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\(_{15}\)ClN\(_3\) [M + H\(^+\)]\(^+\) 356.0949; found 356.0947. \(1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta = 8.38–8.34 (d, } J = 1.7, 0.6 \text{ Hz, 1 H), 8.33–8.27 (ddd, } J = 7.9, 1.8, 1.2 \text{ Hz, 1 H), 7.71–7.66 (dt, } J = 7.7, 1.4 \text{ Hz, 1 H), 7.60–7.55 (td, } J = 7.8, 0.6 \text{ Hz, 1 H), 7.43–7.38 (m, 3 \text{ H), 7.35–7.26 (m, 7 \text{ H}) ppm.} \) \(^13\)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, 129.1, 129.0, 128.7, 126.5, 125.3, 118.3, 112.7 ppm. HRMS (ESI): calcd. for C\(_{22}\)H\(_{15}\)O\(_2\) [M + H\(^+\)]\(^+\) 367.1190; found 376.1177.

4-Chloro-3-(4-chlorophenyl)-1-(3-nitrophenyl)-5-phenyl-1H-pyrrole (40): The title compound was isolated in 85% yield (173 mg; Table 3, Entry 9).\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta = 8.12–8.09 (t, } J = 2.2 \text{ Hz, 1 H), 8.16–8.11 (dd, } J = 8.2, 2.2, 1.1 \text{ Hz, 1 H), 8.04–7.98 (m, 2 \text{ H), 7.59–7.54 (ddd, } J = 8.1, 2.2, 1.0 \text{ Hz, 1 H), 7.59–7.42 (m, 6 \text{ H), 7.37–7.31 (m, 2 \text{ H}) ppm.} \) \(^13\)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, 121.9, 121.8, 128.9, 127.5, 122.0, 119.3, 110.2 ppm. HRMS (ESI): calcd. for C\(_{21}\)H\(_{15}\)ClN\(_3\)O\(_2\) [M + H\(^+\)]\(^+\) 410.0458; found 410.0449.

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

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Regioselective Synthesis of Tetrasubstituted Pyrazoles


[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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