Regioselective Synthesis of 1,3,5-Substituted Pyrazoles from Acetylenic Ketones and Hydrazines

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Received 6 October 2003

Abstract: The synthesis of diversely substituted 1,3,5-substituted pyrazoles from the reaction of acetylenic ketones with substituted hydrazines is reported. The reactions were shown to be highly regioselective regardless of the nature of the substituents in the substrates and afforded essentially single pyrazole isomers in excellent yields.

Key words: pyrazoles, ketones, alkynes, hydrazones, regioselectivity

Compounds incorporating the pyrazole ring system continue to attract considerable interest due to the wide range of biological activities they possess, including analgesic,1 antimicrobial,2 anti-inflammatory,3 hypoglycemic4 and anti-hypertensive5 properties. As part of a drug candidate development program we required the regioselective synthesis of an unsymmetrical 1,3,5 substituted pyrazole derivative of the type \( \text{1} \) (Figure 1).

![Figure 1](image)

Figure 1

Numerous methods for the synthesis of 1,3,5-substituted pyrazoles are known.6 One of the most frequently utilized methods is the reaction of 1,3-dicarbonyl compounds, or equivalent 1,3-bis-electrophilic reagents, with hydrazine derivatives. However, in the case of substituted hydrazines this type of reaction is often reported to result in mixtures of regioisomeric pyrazoles.7 Alternatively, the reaction of substituted hydrazines with \( \alpha,\beta \)-unsaturated ketones has been reported to lead to regioselective formation of pyrazolines which could then be oxidised to the corresponding pyrazoles.8,9 Several other methods for the regioselective synthesis of pyrazoles have also appeared.10–12 It has been known for more than 100 years that hydrazines readily react with acetylenic ketones to afford pyrazoles directly.13–15 However, the regiochemical outcome of this reaction has either not been detailed or it has been reported that mixtures of regioisomers are produced.16–21 Herein we report our own investigations which have shown that substituted pyrazoles can be prepared from acetylenic ketones and substituted hydrazines with high and predictable regioselectivity.

We prepared a range of acetylenic ketones \( \text{2a–l} \) and investigated their reactions with both methylhydrazine and (substituted) phenylhydrazines. Compounds \( \text{2a–l} \) were prepared either via the Pd catalysed carbonylative coupling of phenyl acetylenes with aryl iodides22,23 (Method A) or by the copper catalysed coupling of aryl acid chlorides with phenyl acetylenes24 (Method B) (Scheme 1, Table 1).

A range of solvents was screened for the reaction of \( \text{2a} \) with methylhydrazine and alcohols were found to offer the highest reaction rates as well as the best regioselectivity. Moreover, it was also determined that acid (aq HCl or H\( \text{OAc} \)) or base (NaOMe) catalysis did not influence reaction rate or regioselectivity.

![Scheme 1](image)
Under optimum conditions 2a–l, were reacted with methylhydrazine in ethanol solution at room temperature (Scheme 2, Table 2). The reactions were usually complete within 2–3 hours and afforded one major pyrazole product and one minor pyrazole product. After evaporation of solvent and purification of the crude products by recrystallisation or column chromatography the pyrazoles 3a–l were obtained in good to excellent yields. The major products were assigned as regioisomers 3 based on NOE experiments. In each case, selective irradiation of the N-methyl singlet resulted in an enhancement of the ortho protons of the C-5 aromatic substituent only. In the case of compound 3l conclusive corroboration of the regiochemical assignment was provided by a single-crystal X-ray structure (Figure 2).

The results of Table 2 show that the regioselectivity of the condensation is uniformly high, irrespective of the aryl substituents present in substrates 2. Thus, it is possible to prepare either regioisomeric pyrazole by selection of the appropriate substitution pattern in the acetylenic ketone substrates (entry 1 vs. 2, etc.). Formation of 3a–l as the major product is presumably a result of initial conjugate addition of the more nucleophilic methyl substituted hydrazine nitrogen to the triple bond of the acetylenic ketone system followed by cyclisation of the unsubstituted hydrazine nitrogen onto the carbonyl group in a favoured 5-exo-trig process and dehydration.

Next, we investigated the reaction of 2a–l with (substituted) phenylhydrazines (Scheme 3, Table 3). The reactivity of the phenylhydrazines is much lower than that of methylhydrazine and it proved necessary to heat the reactions at reflux in ethanol for 3–4 hours in order to obtain complete conversion of the starting material. Once again, the reactions were found to be highly regioselective in most cases, albeit in the opposite direction (Table 3). As expected, in the case of the phenylhydrazine, it is the unsubstituted nitrogen, which is more nucleophilic. Hence, a parallel series of reactions as mentioned before leads predominantly to regioisomers 5a–r in this case. This was again confirmed by NOE experiments. Thus, irradiation of H-4 provided the position of the ortho protons for both the C-3 and C-5 aryl substituents. Subsequent selective irradiation of these ortho protons showed that only that of the C-5 aryl substituent resulted in an NOE enhancement of the N-aryl ortho protons. As before, rigorous confirmation of this regiochemical assignment was provided by a single-crystal X-ray structure in the case of compound 5c (Figure 3).

Following the above rationalization of our results, we expected significant effects on the regioselectivity of the reaction by introducing substituents in the phenylhydrazine part. Indeed, the reaction of p-methoxyphenylhydrazine

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**Table 1** Preparation of Acetylenic Ketones 2a–l

<table>
<thead>
<tr>
<th>Compound</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Method</th>
<th>Yield (%)</th>
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<td>2b</td>
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<td>OMe</td>
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**Scheme 2**

Synthesis 2004, No. 1, 43–52 © Thieme Stuttgart · New York
with 2e and 2f (entries 13 and 14) resulted in poorer regioselectivity when compared to the reactions with phenylhydrazine (entries 9 and 10). We attribute this to a diminished nucleophilicity differential between the hydrazine nitrogens. Conversely, the reactions of p-nitrophenylhydrazine with 2e and 2f (entries 15 and 16), while being significantly slower (required ca. 20 h at reflux for complete reaction) showed almost complete regioselectivity.

Reaction intermediates could not be detected by HPLC in any of the above cases with the exception of the reaction between p-nitrophenylhydrazine and 2e. By halting the reaction at the appropriate time a transient intermediate could be isolated in 57% yield. On the basis of NMR studies the orange–red solid was identified as the 5-hydroxydihydropyrazole 7 (Figure 4). Upon continued heating at reflux in ethanol, 7 converted to the expected pyrazole 5o in 80% yield. The reactions of 2,4-dinitrophenylhydrazine with 2e and 2f afforded only low yields of the expected pyrazole products 5q and 5r, respectively (Table 3 entries 17 and 18). The major products precipitated from these reactions as highly insoluble red solids, which were identified as the hydrazone adducts 8 and 9. Presumably, the greatly reduced nucleophilicity of the substituted nitrogen of this hydrazine further slows the cyclization of the initial 1,4-addition intermediate to pyrazoles 5q and 5r. In these

![Figure 3](image_url)  
**Figure 3**  
X-ray structure of compound 5c

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Isomer ratio 3:4 before isolation&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Product</th>
<th>Isolated yield (%)</th>
<th>Isomer ratio 3:4 after isolation</th>
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<td>Me</td>
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<td>3a</td>
<td>82</td>
<td>96:4</td>
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<td>Me</td>
<td>H</td>
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<td>H</td>
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<td>3h</td>
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<sup>a</sup> Determined by HPLC analysis.
In summary, we have demonstrated that the reaction of acetylenic ketones with mono-substituted alkyl and arylhydrazines is highly regioselective and leads to 1,3,5-substituted pyrazoles in excellent yields. The regioselectivity of the reactions is not significantly affected by the nature of the substituents in the acetylenic ketones. The ready accessibility of the acetylenic ketone substrates by a variety of routes means that this procedure represents a highly flexible synthesis of diversely substituted 1,3,5-substituted pyrazoles.

All reactions were carried out under an atmosphere of anhyd N₂. Mps (uncorrected) were measured with a Stuart Scientific SMP3 melting point apparatus. NMR Spectra were recorded on a Bruker DPX400 spectrometer. Chemical shifts are reported in ppm referenced to residual protons in the deuterated solvent. Coupling constants (J) are reported in Hz. HMQC and HMBC 2d data sets were used to confirm 13C assignments. IR spectra were recorded on a Thermonicolet Avatar 360 FTIR. Column chromatography was carried out on silica gel (70–230 mesh, E. Merck). Reversed phase HPLC analyses were obtained with a Hewlett Packard 1100 HPLC instrument using a Phenomenex Luna C8 column: A = 0.1% H₃PO₄, B = MeCN; gradient operation 90% A to 10% A in 20 min, 10% A for 5 min; 1.0 mL/min; 40 °C; UV detection at 220 nm.

**Acetylenic Ketones 2a–h, Method A; Typical Procedure**

To a Parr autoclave was charged iodobenzene (2.8 g, 13.5 mmol), 4-ethynyltoluene (2.06 mL, 16.2 mmol), palladium acetate (151 mg, 0.675 mmol), diphenylphosphino ferrocene (278 mg, 0.675 mmol) and Et₃N (9.4 mL, 67.5 mmol) in THF (11 mL). The autoclave was evacuated with nitrogen gas (× 3), flushed with carbon monoxide (× 3) and heated to 80 °C. After 24 h, the autoclave was cooled, opened, and the contents were filtered through a plug of silica gel. The filtrate was concentrated and the residue was purified by flash chromatography to afford the title compounds 5a–j in 50–98% yields.

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**Table 3 Preparation of Substituted 1,3,5-Triarylpyrazoles 5 from Acetylenic Ketones 2 and Arylhydrazines**

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<tr>
<th>Entry</th>
<th>R¹</th>
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<th>Product</th>
<th>Isolated yield (%)</th>
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* Determined by HPLC analysis.

---

Figure 4

B = MeCN; gradient operation 90% A to 10% A in 20 min, 10% A for 5 min; 1.0 mL/min; 40 °C; UV detection at 220 nm.

Acetylenic Ketones 2a–h, Method A; Typical Procedure

To a Parr autoclave was charged iodobenzene (2.8 g, 13.5 mmol), 4-ethynyltoluene (2.06 mL, 16.2 mmol), palladium acetate (151 mg, 0.675 mmol), diphenylphosphino ferrocene (278 mg, 0.675 mmol) and Et₃N (9.4 mL, 67.5 mmol) in THF (11 mL). The autoclave was evacuated with nitrogen gas (× 3), flushed with carbon monoxide (× 3) and heated to 80 °C. After 24 h, the autoclave was cooled, opened, and the contents were filtered through a plug of silica gel. The filtrate was concentrated and the residue was purified by flash chromatography to afford the title compounds 5a–j in 50–98% yields.
2) and left under a pressure of 42 atm of carbon monoxide for 14 h at 70 °C. The autoclave was evacuated, flushed with nitrogen (3), the THF was removed under vacuum and the residue dispersed between isopropyl acetate (20 mL) and H₂O (40 mL). The aq phase was extracted with isopropyl acetate (20 mL) and the combined organic phases were washed with aq HCl (1.0 M; 30 mL), sat. brine (20 mL), dried (Na₂SO₄) and concentrated under vacuum. The residual oil was purified by flash column chromatography (4% EtOAc in hexanes) to afford 3-(4-methylphenyl)-1-phenyl-2-propyn-1-one (2a).

Yield: 2.59 g (85%); pale orange solid; mp 67–68 °C.

IR (Nujol): 2198, 1627, 1600, 1507, 1449, 1315, 1207 cm⁻¹.

¹H NMR (CDCl₃): δ = 8.40 (m, 1 H, H-1d), 7.38 (m, 2 H, H-3b), 7.25 (m, 1 H, H-1d), 7.20 (m, 2 H, H-1c), 6.84 (m, 2 H, H-3c), 2.04 (s, 3 H, CH₃).

¹³C NMR (CDCl₃): δ = 177.2 (C-1), 141.0 (C-3d), 137.5 (C-1a), 133.6 (C-1d), 133.0 (C-3b), 129.5 (C-3c), 129.3 (C-1c), 117.3 (C-3a), 93.0 (C-2), 87.4 (C-3), 21.2 (CH₃).


1-(4-Methylphenyl)-3-phenyl-2-propyn-1-one (2b)

Brown solid; mp 70–71 °C.

IR (Nujol): 2201, 1635, 1601, 1487, 1285, 1208, 1168 cm⁻¹.

¹H NMR (CDCl₃): δ = 8.36 (m, 2 H, H-1b), 7.42 (m, 2 H, H-3b), 6.97–7.08 (m, 5 H, H-3c, H-1d, H-1c), 2.08 (s, 3 H, CH₃).

¹³C NMR (CDCl₃): δ = 176.9 (C-1), 144.7 (C-1d), 135.3 (C-1a), 132.9 (C-3b), 130.2 (C-1d), 129.7 (C-1b), 129.3 (C-1c), 128.5 (C-3c), 120.5 (C-3a), 91.8 (C-2), 87.6 (C-3), 21.3 (CH₃).

Anal. Calcd for C₁₂H₁₀O: C, 82.74; H, 5.49. Found: C, 82.73; H, 5.51.

3-(4-Chlorophenyl)-1-phenyl-2-propyn-1-one (2c)

Cream needles; mp 107–108 °C.

IR (Nujol): 2201, 1652, 1301, 1207 cm⁻¹.

¹H NMR (CDCl₃): δ = 8.34 (m, 2 H, H-3b), 7.24 (m, 1 H, H-1d), 7.19 (m, 2 H, H-3b), 7.03 (m, 2 H, H-3c), 6.93 (m, 2 H, H-3b).

¹³C NMR (CDCl₃): δ = 176.9 (C-1), 137.2 (C-3d), 136.7 (C-1a), 134.1 (C-3e), 133.8 (C-1d), 129.5 (C-3b), 128.9 (C-1b), 128.6 (C-1c), 118.7 (C-3a), 90.8 (C-2), 88.0 (C-3).

Anal. Calcd for C₁₁H₈ClO: C, 74.85; H, 3.77; Cl, 16.23. Found: C, 74.60; H, 3.79; Cl, 16.72.

1-(4-Methoxyphenyl)-3-phenyl-2-propyn-1-one (2d)

Cream needles; mp 107–108 °C.

IR (Nujol): 2198, 1628, 1600, 1377, 1308, 1260, 1160 cm⁻¹.

¹H NMR (CDCl₃): δ = 8.43 (m, 2 H, H-1b), 7.41 (m, 2 H, H-3b), 7.23 (m, 3 H, H-3c, H-1d), 6.62 (m, 2 H, H-3c), 3.24 (s, 3 H, CH₃).

¹³C NMR (CDCl₃): δ = 177.2 (C-1), 161.7 (C-1d), 137.6 (C-1a), 135.1 (C-1b), 133.5 (C-3b), 129.5 (C-1c), 128.5 (C-1d), 114.4 (C-3c), 121.2 (C-3a), 93.5 (C-3), 87.4 (C-2), 54.6 (C-3e).


1-(4-Methoxyphenyl)-3-phenyl-2-propyn-1-one (2h)

Cream solid; mp 100–101 °C.

IR (Nujol): 2188, 1626, 1598, 1316, 1254, 1168, 1031 cm⁻¹.

¹H NMR (CDCl₃): δ = 8.40 (m, 2 H, H-3b), 7.45 (m, 2 H, H-1b), 7.08 (m, 1 H, H-1d), 7.2 (m, 2 H, H-1c), 6.75 (m, 2 H, H-3c), 3.38 (s, 3 H, H-1e).

¹³C NMR (CDCl₃): δ = 175.9 (C-1), 164.4 (C-1d), 132.8 (C-3c), 131.9 (C-3b), 130.9 (C-3a), 130.2 (C-3d), 128.5 (C-1b), 120.7 (C-1a), 113.9 (C-1c), 91.5 (C-3), 87.6 (C-2), 54.8 (C-1e).


Acetylenic Ketones 2i-L, Method B; Typical Procedure

Phenylacetylene (2.44 g, 23.9 mmol), nitrobenzyl chloride (5.32 g, 28.7 mmol), copper(I) iodide (455 mg, 2.39 mmol) and Et₃N (16.8 mL, 0.12 mol) were dissolved in THF (25 mL) and the mixture heatted at 60 °C for 5 h. H₂O (50 mL) was added causing the product to precipitate and the solid was removed by filtration and washed with H₂O (50 mL). The solid was dispersed between EtOAc (30 mL) and H₂O (30 mL). The EtOAc layer was washed with sat. brine (20 mL), dried (Na₂SO₄) and concentrated in vacuo to give a residue. The solid was recrystallized from EtOAc to afford 1-(4-nitrophenyl)-3-phenyl-2-propyn-1-one (2i).

Pale yellow solid; mp 163–164 °C.

IR (Nujol): 2203, 1634, 1591, 1376, 1342, 1311, 1286, 1211 cm⁻¹.

¹H NMR (CDCl₃): δ = 8.29 (m, 2 H, H-1c), 7.67 (m, 2 H, H-1b), 7.25 (m, 1 H, H-1d), 7.19 (m, 2 H, H-3c), 6.94 (m, 2 H, H-3b).

¹³C NMR (CDCl₃): δ = 176.7 (C-1), 148.2 (C-1d), 136.9 (C-3a), 134.2 (C-3d), 133.1 (C-1b), 129.5 (C-3b), 128.7 (C-3c), 126.0 (C-1a), 123.3 (C-1c), 89.9 (C-2), 88.9 (C-3).

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Anal. Calcd for C_{15}H_{9}NO_{3}: C, 71.71; H, 3.61; N, 5.58. Found: C, 71.48; H, 3.58; N, 5.46.

1-Phenyl-3-(4-nitrophenyl)-2-propyn-1-one (2j)
Pale yellow solid; mp 148–150 °C.
IR (Nujol): 1521, 1322, 1312, 1132, 1086 cm⁻¹.

1H NMR (C_{6}D_{6}): δ = 8.28 (m, 2 H, H-1b), 7.68 (m, 2 H, H-3c), 7.13–7.29 (m, 3 H, H-1c–H-1d), 6.97 (m, 2 H, H-3b).

13C NMR (C_{6}D_{6}): δ = 176.1 (C-1), 148.2 (C-3d), 136.8 (C-1a), 134.2 (C-1d), 133.1 (C-3b), 132.1 (C-3a), 129.5 (C-1b), 128.7 (C-1c), 123.3 (C-3c), 91.8 (C-2), 88.9 (C-3).

Anal. Calcd for C_{17}H_{16}N_{2}: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.07; H, 6.51; N, 11.30.

1-Methyl-3-(4-nitrophenyl)-5-phenylpyrazole (3c)
Yellow solid; mp 148–150 °C.
IR (Nujol): 1521, 1322, 1312, 1132, 1086 cm⁻¹.

1H NMR (C_{6}D_{6}): δ = 8.10 (m, 2 H, H-1b), 7.82 (m, 2 H, H-3c), 7.31–7.21 (m, 5 H, H-5b–H-5d), 6.47 (s, 1 H, H-4), 3.48 (s, 3 H, NCH_{3}).

1C NMR (C_{6}D_{6}): δ = 148.0 (C-3b), 147.1 (C-3), 139.7 (C-3a), 130.4 (C-1a), 128.7 (C-5b), 128.6 (C-5c), 124.0 (C-3b), 104.0 (C-4), 37.2 (NCH_{3}).

Anal. Calcd for C_{17}H_{16}N_{2}O: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.69; H, 4.70; N, 14.97.

1-Methyl-3-phenyl-5-(4-nitrophenyl)pyrazole (3d)
Cream solid; mp 131–134 °C.
IR (Nujol): 1511, 1191, 1087, 1075 cm⁻¹.

1H NMR (C_{6}D_{6}): δ = 8.18 (m, 2 H, H-1b), 7.93 (m, 2 H, H-3c), 7.42 (m, 2 H, H-3c), 7.27 (m, 1 H, H-3d), 6.89 (m, 2 H, H-5b), 6.54 (s, 1 H, H-4), 3.40 (s, 3 H, NCH_{3}).

1C NMR (C_{6}D_{6}): δ = 150.7 (C-3), 147.3 (C-5d), 142.4 (C-5), 136.3 (C-5a), 133.6 (C-3a), 128.9 (H-5b), 128.7 (H-3c), 128.0 (C-3d), 125.7 (C-3b), 126.3 (C-5c), 104.0 (C-4), 37.3 (C-1a).

Anal. Calcd for C_{16}H_{13}ClN_{2}O: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.52; H, 4.62; N, 14.74.

1-Methyl-3-(4-chlorophenyl)-5-phenylpyrazole (3e)
White solid; mp 131–132 °C.
IR (Nujol): 1511, 1191, 1086, 1011 cm⁻¹.

1H NMR (C_{6}D_{6}): δ = 7.93 (m, 2 H, H-3c), 7.32 (m, 2 H, H-3b), 7.20–7.25 (m, 5 H, 5-Ph), 6.52 (s, 1 H, H-4), 3.48 (s, 3 H, N-CH_{3}).

1C NMR (C_{6}D_{6}): δ = 149.2 (C-3)–144.8 (C-5), 133.2 (C-3d), 132.7 (C-3a), 130.9 (C-5a), 128.9 (C-3c), 128.7 (C-5b), 128.6 (C-5c), 128.3 (C-5d), 126.9 (C-3b), 103.1 (C-4), 37.0 (N-CH_{3}).

Anal. Calcd for C_{16}H_{13}ClN_{2}C: 71.51; H, 4.88; Cl, 13.19; N, 10.42. Found: C, 71.19; H, 4.86; Cl, 13.21; N, 10.22.

1-Methyl-3-phenyl-5-(4-iodophenyl)pyrazole (3f)
Cream solid; mp 58–60 °C.
IR (Nujol): 1601, 1479, 1364, 1291, 1188, 1087 cm⁻¹.

1H NMR (C_{6}D_{6}): δ = 8.21 (m, 2 H, H-1b), 7.41 (m, 2 H, H-3c), 7.24 (m, 1 H, H-3d), 7.17 (m, 2 H, H-5c), 6.91 (m, 2 H, H-5b), 6.56 (s, 1 H, H-4), 3.42 (s, 3 H, NCH_{3}).

1C NMR (C_{6}D_{6}): δ = 150.4 (C-3)–144.7 (C-5), 137.9 (C-5d), 134.4 (C-3a), 129.3 (C-5c), 128.8 (C-5b), 128.7 (C-3c), 128.3 (C-3d), 127.5 (C-5a), 125.7 (C-3b), 103.0 (C-4), 37.0 (N-CH_{3}), 20.9 (CH_{3}).

Anal. Calcd for C_{17}H_{16}I_{2}N_{2}O: C, 48.49; H, 6.55; N, 11.24.

1-Methyl-3-(4-methylphenyl)-5-phenylpyrazole (3g)
Pale yellow solid; mp 172–174 °C.
IR (Nujol): 1601, 1513, 1491, 1345, 1259, 1117 cm⁻¹.
1H NMR (CD$_3$)$_2$NO: δ = 8.22 (m, 2 H, H-3c), 8.08 (m, 2 H, H-3b), 7.41 (m, 2 H, H-5b), 7.03 (m, 2 H, H-5c), 6.86 (s, 1 H, H-4), 3.73 (s, 3 H, N-CH$_3$), 3.64 (s, 3 H, O-CH$_3$).

13C NMR (CD$_3$)$_2$NO: δ = 159.9 (C-5d), 150.3 (C-3), 144.6 (C-5), 141.3 (C-3a), 132.0 (C-5c), 128.7 (C-3d), 125.7 (C-3b), 123.4 (9) (C-5a), 114.1 (C-5c), 102.4 (C-4), 54.6 (O-CH$_3$), 37.0 (N-CH$_3$).

Anal. Calcd for C$_{17}$H$_{16}$N$_2$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.16; H, 6.11; N, 10.70.

1-Methyl-3-(4-methoxyphenyl)-5-phenylpyrazole (3l)
Yellow solid; mp 127–128 °C.

IR (Nujol): 1667, 1603, 1593, 1549, 1224 cm$^{-1}$.

Cream solid; mp 59–61 °C.

1-Methyl-3-phenyl-5-(4-methoxyphenyl)pyrazole (3k)

Yellow solid; mp 111–112 °C.

1-Methyl-3-(4-fluorophenyl)-5-phenylpyrazole (3j)

Pale yellow solid; mp 111–112 °C.

1-Methyl-3-(4-fluorophenyl)-5-phenylpyrazole (3j)

Pale yellow solid; mp 111–112 °C.

1-Methyl-3-(4-methoxyphenyl)-5-phenylpyrazole (3l)

Pale yellow solid; mp 127–128 °C.

1-Methyl-3-(4-methylphenyl)-5-phenylpyrazole (3m)

Pink solid; mp 132–133 °C.

1-Methyl-3-phenyl-5-(4-nitrophenyl)pyrazole (5c)

Chromatography (1% EtOAc in hexane) to afford 1,5-diphenyl-3,5-disubstituted 1-arylpiprazoles 5a–r; Typical Procedure

To a solution of 2a (193 mg, 0.88 mmol) in EtOH (2 mL) at r.t. under nitrogen was added phenylhydrazine (0.12 mL, 1.23 mmol). The solution was heated at reflux for 3–4 h and the EtOH was removed in vacuo. The residual orange oil was purified by column chromatography (1% EtOAc in hexane) to afford 1,5-diphenyl-3-(4-phenyl)-pyrazolyl (5a).

Yield: 223 mg (82%); off white solid; mp 127–128 °C.

IR (Nujol): 1531, 1321, 1201 cm$^{-1}$.

1H NMR (CD$_3$)$_2$NO: δ = 8.22 (m, 2 H, H-3b), 7.47 (m, 2 H, H-1b), 7.22–7.30 (m, 4 H, H-3c, H-3d), 6.84 (s, 1 H, H-4), 2.27 (s, 3 H, CH$_3$).

1,3-Diphenyl-5-(4-methylphenyl)pyrazole (5b)

Anal. Calcd for C$_{22}$H$_{18}$N$_2$: C, 85.13; H, 5.87; N, 9.03. Found: C, 84.89; H, 5.87; N, 9.03.

1,3-Diphenyl-5-(4-methylphenyl)pyrazole (5b)

Off white solid; mp 116–117 °C.

IR (Nujol): 1593, 1494, 1175, 1074 cm$^{-1}$.

1H NMR (CD$_3$)$_2$NO: δ = 8.13 (m, 2 H, H-3b), 7.35 (m, 2 H, H-1b), 7.26 (m, 2 H, H-1c), 7.14 (m, 1 H, H-1d), 7.07 (m, 2 H, H-5b), 6.83–6.93 (m, 3 H, 3c-3d, H-3d), 6.79 (m, 2 H, H-5c), 6.71 (s, 1 H, H-4), 1.97 (s, 3 H, CH$_3$).

13C NMR (CD$_3$)$_2$NO: δ = 152.2 (C-3), 144.1 (C-5), 140.8 (C-1a), 137.5 (C-3d), 131.2 (C-5a), 129.5 (C-3c), 128.9 (C-5c), 128.6 (C-5d), 128.4 (C-1c), 127.6 (C-5b), 126.9 (C-1d), 126.0 (C-3b), 125.3 (C-1b), 105.5 (C-4), 21.1 (CH$_3$).

Anal. Calcd for C$_{22}$H$_{16}$N$_2$: C, 85.13; H, 5.85; N, 9.03. Found: C, 84.89; H, 5.87; N, 9.03.

1,3-Diphenyl-5-(4-methylphenyl)pyrazole (5b)

Pale yellow solid; mp 139–140 °C.

IR (Nujol): 1595, 1546, 1517, 1496, 1339, 1290, 1172 cm$^{-1}$.

1H NMR (CD$_3$)$_2$NO: δ = 8.10 (m, 2 H, H-3b), 7.62 (m, 2 H, H-5c), 7.30 (m, 2 H, H-3c), 7.18 (m, 1 H, H-3d), 7.13 (m, 2 H, H-1b), 6.97 (m, 1 H, H-1d), 6.93 (m, 2 H, H-1c), 6.79 (m, 2 H, H-5b), 6.58 (s, 1 H, H-4).

13C NMR (CD$_3$)$_2$NO: δ = 152.4 (C-3), 147.2 (C-5d), 141.9 (C-5), 140.0 (C-1a), 136.5 (C-5a), 133.1 (C-3a), 129.0, 128.95, 128.94, 128.93, 128.4 (C-3d), 127.7 (C-1d), 126.0 (C-3b), 125.2 (C-1b), 123.5 (C-5c), 106.4 (C-4).
Anal. Calcd for C_{21}H_{15}ClN_{2}: C, 76.24; H, 4.57; Cl, 10.72; N, 8.47.

1,1-Diphenyl-3-(4-chlorophenyl)pyrazole (5e)
Cream solid; mp 104–105 °C.
IR (Nujol): 1603, 1548, 1487, 1352, 1090 cm⁻¹.
1 H NMR (C₆D₆): δ = 8.12 (m, 2 H, H-2b), 7.30 (m, 2 H, H-3c), 7.23 (m, 2 H, H-1b), 7.17 (m, 1 H, H-3d), 6.96–6.87 (m, 5 H, H-1c, H-1d, H-5c), 6.82 (m, 2 H, H-8b), 6.59 (s, 1 H, H-4).
13 C NMR (C₆D₆): δ = 152.1 (C-3), 142.9 (C-5), 140.8 (C-1a), 134.2 (C-5d), 133.6 (C-3a), 130.1 (C-5b), 129.4 (C-5a), 128.9 (C-3c), 128.8 (C-3c), 128.7 (C-1c), 128.2 (C-3d), 127.2 (C-1d), 126.0 (C-3b), 125.2 (C-1b), 105.4 (C-4).
Anal. Calcd for C_{21}H_{15}ClN_{2}: C, 76.24; H, 4.57; Cl, 10.72; N, 8.47.

1,5-Diphenyl-3-(4-fluorophenyl)pyrazole (5f)
Cream solid; mp 146–147 °C.
IR (Nujol): 1600, 1520, 1372, 1352, 1090 cm⁻¹.
1 H NMR (C₆D₆): δ = 8.26 (m, 2 H, H-3b), 7.42 (m, 2 H, H-3c), 7.38 (m, 2 H, H-1b), 7.29 (m, 1 H, H-1d), 7.1–6.97 (m, 5 H, H-1c, H-1d, H-5b), 6.72 (s, 1 H, H-4), 6.72 (m, 2 H, H-3c).
13 C NMR (C₆D₆): δ = 161.9 (d, J = 248.5 Hz, C-5d), 152.1 (C-3), 143.1 (C-5), 140.4 (C-1a), 133.7 (C-1a), 130.7 (d, J = 8.1 Hz, C-5b), 128.3 (C-3c), 128.1 (C-3d), 127.1 (C-1c), 125.2 (C-1b), 115.4 (d, J = 21.6 Hz, C-5c), 105.4 (C-4).
Anal. Calcd for C_{16}H_{16}F_{3}N_{3}: C, 80.24; H, 4.81; F, 6.04; N, 8.91.
Found: C, 80.12; H, 4.83; F, 5.97; N, 8.98.

1,5-Diphenyl-3-(4-methoxyphenyl)pyrazole (5f)
White solid; mp 140–141 °C.
IR (Nujol): 1610, 1502, 1252, 1179, 1028 cm⁻¹.
1 H NMR (C₆D₆): δ = 8.21 (m, 2 H, H-3b), 7.48 (m, 2 H, H-1b), 7.11 (m, 2 H, H-1c), 7.03 (m, 4 H, H-1c, H-5c), 6.98 (m, 1 H, H-1d), 6.81 (s, 1 H, H-4), 3.43 (s, 3 H, OCH₃).
13 C NMR (C₆D₆): δ = 160.0 (C-3d), 152.1 (C-3), 144.1 (C-5), 140.8 (C-1a), 131.3 (C-5a), 128.9 (C-5c), 128.6 (C-3c), 128.4 (C-5d), 127.3 (C-3b), 126.8 (C-1d), 126.5 (C-3a), 125.2 (C-1b), 114.3 (C-3c), 105.2 (C-4), 54.6 (OCH₃).
Anal. Calcd for C_{21}H_{15}O₃N: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.04; H, 4.85; F, 5.97; N, 8.98.

1,5-Diphenyl-3-(4-methoxypyrazole) (5f)
Yellow oil.
IR (Nujol): 1614, 1520, 1297, 1251 cm⁻¹.
1 H NMR (C₆D₆): δ = 8.29 (m, 2 H, H-3b), 7.51 (m, 2 H, H-1b), 7.42 (m, 2 H, H-3c), 7.29 (m, 2 H, H-3d), 7.20 (m, 2 H, H-5b), 7.08 (m, 2 H, H-1c), 7.02 (m, 1 H, H-1d), 6.84 (s, 1 H, H-4), 6.71 (m, 2 H, H-5c), 3.31 (s, 3 H, OCH₃).
13 C NMR (C₆D₆): δ = 159.8 (C-5d), 152.0 (C-4), 144.1 (C-5), 140.9 (C-1a), 130.2 (C-5b), 128.8 (C-3c), 128.6 (C-1c), 127.9 (C-3d), 126.9 (C-1d), 126.0 (C-3b), 125.3 (C-1b), 114.0 (C-5c), 105.1 (C-4), 54.6 (OCH₃).
1-(4-Methoxyphenyl)-3-phenyl-5-(4-fluorophenyl)pyrazole (5n)

Pale brown solid; mp 131–134 °C.

1-(4-Methoxyphenyl)-3-(4-fluorophenyl)-5-phenylpyrazole (5o)

Red solid; mp 134–136 °C.

1-(2,4-Dinitrophenyl)-3-(4-fluorophenyl)-5-phenylpyrazole (5p)

Pale yellow solid; mp 125–126 °C.

1-Phenyl-3-(4-fluorophenyl)-2-propyn-1-one-2,4-dinitrophenylhydrazone (9)

Red solid; mp 239–242 °C.

1-Phenyl-3-(4-fluorophenyl)-2-propyn-1-one-2,4-dinitrophenylhydrazone (8)

Red solid; mp 250–252 °C.
IR (Nujol): 3260, 2187, 1611, 1591, 1517, 1499 cm⁻¹.

$^1$H NMR (CD$_2$Cl$_2$): $\delta$ = 12.16 (s, 1 H, NH), 9.06 (m, 1 H, H-1f), 8.31 (m, 3 H, H-1c, H-3b), 7.75 (m, 2 H, H-5b), 7.40–7.47 (m, 3 H, H-5c, H-5d), 7.12 (m, 2 H, H-3c).

$^{13}$C NMR (C$_6$D$_6$): $\delta$ = 161.5 (d, $J$ = 212.5 Hz, C-3d), 143.9 (C-1b), 138.7 (C-1e), 135.6 (C-1a), 132.6 (C-5b), 130.8 (C-5d), 130.0 (C-1d), 128.9 (d, $J$ = 8.1 Hz, C-3b), 123.3 (C-1f), 120.2 (C-5a), 117.1 (C-1c), 115.8 (d, $J$ = 21 Hz, C-3c), 106.6 (C-5), 78.2 (C-4).

Anal. Calcd for C$_{21}$H$_{13}$FN$_4$O$_4$: C, 62.38; H, 3.24; F, 4.70; N, 13.86.

Found: C, 62.16; H, 3.12; F, 4.72; N, 13.75.

Acknowledgment

We wish to thank Ms. Jennifer Chilenski for the X-ray crystallographic data and Mr Paul Byway for the HRMS data.

References


