Photochemical Synthesis of Pyrazolines from Tetrazoles in Flow

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Abstract:
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Abstract

Pyrazolines and their pyrazole congeners are important heterocyclic building blocks with numerous applications in the fine chemical industries. However, traditional routes towards these entities are based on multistep syntheses generating substantial amounts of chemical waste. Here we report an alternative approach using UV-light to convert tetrazoles to pyrazolines via a reagent-free photo-click strategy. This route generates nitrile imine dipoles in situ that are trapped with different dipolarophiles rendering a selection of these heterocyclic targets in high chemical yields. A continuous flow method is ultimately realized that generates multi-gram quantities of product in a safe and readily scalable manner thus demonstrating the value of this photochemical approach for future exploitations in industry.

Key words  flow chemistry, photochemistry, pyrazoline, tetrazole, click reaction, drug-like heterocycles

Pyrazolines are a class of pharmaceutically relevant five-membered heterocycles related to aromatic pyrazoles that possess a myriad of beneficial biological properties. Together with their aromatic pyrazole counterparts, these scaffolds feature in numerous drugs, agrochemical agents and their precursors. Synthetically, pyrazolines are predominantly accessed through condensation reactions between hydrazines and enones or their derivatives. A different approach uses the dipolar cycloaddition between alkenes and in situ generated nitrile imines. Typically, nitrile imines are generated from α-halo-hydrazones in the presence of base, however, an alternative albeit underutilized entry to this dipole is available via the photolysis of tetrazoles. This option is potentially attractive as nitrogen gas is formed as the only by-product via a reagent-free reaction that can be performed in the presence of the dipolarophile. As pyrazolines are continuing to be exploited in modern drug discovery programs improved protocols for their efficient and safe generation are in high demand. The adoption of continuous flow reactor technology has streamlined the synthesis of many fine chemical building blocks over the last decades and provided for superior reactions through improved heat and mass transfer. More recently, this trend has witnessed the routine integration of photochemical reactions to provide for potentially more sustainable chemical syntheses. Reactor miniaturization and high spatiotemporal control make continuous photochemical reactions a valuable tool to access a vast variety of chemical structures either facilitated by UV or visible light. Moreover, the uniform irradiation combined with short path lengths typical for flow photoreactors provides for good scalability of continuous photochemical processes. Due to these salient features, we wished to study the continuous photochemical generation of pyrazolines from tetrazole precursors to establish a safe and robust means for the generation of this important heterocyclic scaffold (Scheme 1).

Scheme 1: Photochemical synthesis of pyrazolines from tetrazoles.

To commence we prepared a small set of aryl-tetrazoles following literature-known protocols. The union of in situ generated aryl diazonium salts and phenyl amidine salts thereby rendered the expected adducts (3a-c) in high yields which smoothly underwent oxidative cyclization to the desired tetrazole species. The crystalline nature of tetrazole 4b was exploited to perform single crystal diffraction studies and...
Next, we embarked on developing a continuous flow approach for the photolysis of the tetrazole unit and the concomitant dipolar cycloaddition of the resulting nitrile imine with different dipolarophiles. We opted to use a standardized Vapourtec E-series flow reactor in combination with different light sources. Previous studies from our lab had identified both a medium-pressure Hg-lamp\(^\text{16}\) and a high-power UV-A LED (emitting at 365 nm)\(^\text{17}\) as valuable light sources in a number of related applications. Methyl methacrylate was chosen as model dipolarophile along with acetonitrile as reaction solvent. An adjustable back-pressure regulator (BPR) was set to 2 bar to control the release of stoichiometric amounts of nitrogen gas. The chosen set-up is depicted in Scheme 3 and allowed for quickly screening several variables such as reaction stoichiometry, concentration, and residence time.

Initial experiments compared the UV-A LED (75 W input power) with the medium-pressure Hg-lamp (85 W input power) that was used in combination with a low-pass filter to exclude wavelengths above 400 nm. A stream of compressed air was directed into the flow module to regulate the temperature to ca. 28 °C. Inside the reactor unit a tubular flow coil (10 mL, PFA) was fitted around the light source. The release of nitrogen gas bubbles after the BPR indicated photolytic cleavage of the tetrazole and formation of the anticipated pyrazoline (6) in case of the medium-pressure Hg-lamp. Interestingly, the UV-A LED did not generate the pyrazoline product (table 1, entry 1) and the tetrazole substrate was recovered in almost quantitative yield indicating that light with wavelengths of 280-320 nm is critical for the photolysis step.\(^\text{18}\) Going forward, the medium-pressure Hg-lamp was further exploited in combination with the filter. As outlined in table 1, substrate concentrations up to 100 mM were tolerated and only a small excess of the dipolarophile of 1.2 equiv. was needed. Degassing of the solvent did not provide any advantages indicating that residual oxygen is not detrimental under photochemical conditions. Furthermore, it was found that the residence time could be reduced from 20 min to 10 min, whereas shorter residence times of 5 min did not lead to full consumption of the tetrazole (entries 3-5). As expected, no product formed in the absence of UV-light (entry 6). Notably, the high concentration together with a short residence time of 10 minutes would provide for good reaction throughput in view of reaction scale-up.

### Table 1: Optimization study for model pyrazoline formation.

<table>
<thead>
<tr>
<th>entry</th>
<th>lamp</th>
<th>conc. 4a (mM)</th>
<th>equiv. 5</th>
<th>t&lt;sub&gt;res&lt;/sub&gt; (min)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LED</td>
<td>50</td>
<td>1</td>
<td>2.0</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>Hg-lamp(^a)</td>
<td>50</td>
<td>1</td>
<td>2.0</td>
<td>65%</td>
</tr>
<tr>
<td>3</td>
<td>Hg-lamp(^a)</td>
<td>100</td>
<td>1.2</td>
<td>20 min</td>
<td>73%</td>
</tr>
<tr>
<td>4</td>
<td>Hg-lamp(^a)</td>
<td>100</td>
<td>1.2</td>
<td>10 min</td>
<td>79%</td>
</tr>
<tr>
<td>5</td>
<td>Hg-lamp(^a)</td>
<td>100</td>
<td>1.2</td>
<td>5 min</td>
<td>50%(^b)</td>
</tr>
<tr>
<td>6</td>
<td>none</td>
<td>100</td>
<td>1.2</td>
<td>10 min</td>
<td>0%</td>
</tr>
</tbody>
</table>

\(^a\) filter used to exclude >400 nm light; \(^b\) ca. 45% of remaining substrate 4a.

The optimized reaction conditions (entry 4) were then applied to the preparation of pyrazolines 6a-c and confirmed that all three tetrazoles underwent this tandem dipolar cycloaddition process smoothly (Figure 1). The desired pyrazolines were formed as single regioisomers in accordance with previous reports.\(^4\) Replacing methyl methacrylate with maleimide and N-cyclohexylmaleimide afforded the desired bicyclic pyrazolines 6d-f in excellent yields. Next, acrylonitrile and fumaronitrile were trialed as alternative dipolarophiles. It was established that acrylonitrile forms the expected pyrazoline product in good yield (6g ca. 80% crude product by 'H-NMR), however, aerobic oxidation was found to be rapid yielding the nitrile containing pyrazole product 7 after chromatographic purification. Similarly, fumaronitrile generated the anticipated dicyano pyrazoline 6h, but after purification by silica gel chromatography the isomeric cyanopyrazole (8) was obtained as single regioisomer indicating elimination of HCN on contact with silica. Interestingly, these findings highlight a simple approach to access either of the regioisomeric forms (7 and 8) of these nitrile-substituted pyrazoles. Lastly, cyclohexenone was successfully used as dipolarophile together with tetrazole 4a rendering the desired adduct 6i in high yield after chromatographic purification. However, this compound

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**Scheme 2:** Synthesis of aryl-tetrazole substrates and X-ray crystallographic studies.

**Scheme 3:** Flow photolysis set-up towards pyrazolines 6.
underwent slow oxidation to the corresponding bicyclic pyrazole \(9\) in CDCl\(_3\), which could be suppressed by using d\(6\)-DMSO during NMR analysis.

**stable pyrazolines:**

\[
\begin{align*}
\text{Ph} &- \text{N} - \text{CO}_2\text{Me} & \text{Ph} &- \text{N} - \text{OCF}_3 \\
6a, 79\% & & 6b, 74\% \\
\text{Ph} &- \text{N} - \text{Me} & \text{Ph} &- \text{N} - \text{O} \\
6c, 68\% & & 6d, 81\% \\
\text{Ph} &- \text{N} - \text{OCF}_3 & \text{Ph} &- \text{N} - \text{O} \\
6e, 77\% & & 6f, 74\%
\end{align*}
\]

**unstable pyrazolines:**

\[
\begin{align*}
\text{Ph} &- \text{N} - \text{CN} & \text{Ph} &- \text{N} - \text{CN} \\
6g & & 7, 70\% \\
\text{Ph} &- \text{N} - \text{HCN} & \text{Ph} &- \text{N} - \text{HCN} \\
\text{SiO}_2 & & \text{H} & - \text{H}^+ \\
6h & & 8, 78\% \\
\text{Ph} &- \text{N} - \text{CN} & \text{Ph} &- \text{N} - \text{CN} \\
6i, 80\% & & \text{Ph} &- \text{N} - \text{CONH}_2 \\
\text{Ph} &- \text{N} - \text{CN} & \text{Ph} &- \text{N} - \text{CONH}_2 \\
9, 89\%
\end{align*}
\]

**Figure 1:** Summary of substrate scope and reactivity of products (scale: 1-2 mmol).

A final part of this study concerned the scalability of the flow process in view of generating gram quantities of product. The reaction between tetrazole \(4a\) and maleimide under optimized conditions (table 1, entry 4) was chosen for this test. A stock solution containing both reactants was prepared and processed through the photo-reactor under steady state conditions for a period of 2 h. Throughout this process formation of nitrogen gas was observed after the backpressure regulator indicating steady release of this gaseous by-product. The resulting product solution was concentrated under reduced pressure and subsequently cooled to 5 °C to initiate precipitation of the target product. After filtration and drying pyrazoline \(6d\) was obtained as a beige solid in 80% yield equating to a productivity of 1.6 g/h. Moreover, this material allowed for the generation of single crystals and verification of the anticipated connectivity of this product by means of single crystal X-ray diffraction. As depicted in Figure 2, the imide moiety thereby facilitates H-bonding between two molecules in the solid state.

**Figure 2:** Crystal structure of \(6d\) displaying strong intermolecular H-bonding (CCDC-2221468).

In conclusion, we report a continuous photochemical click reaction converting arylated tetrazoles into various pyrazolines and pyrazoles. Using a medium-pressure Hg-lamp as light source combined with a low-pass filter to exclude wavelengths above 400 nm, these targets are generated in high yields (68-81%) in only 10 minutes residence time. The flow process is robust and tolerates concentrations of 100 mM which lends itself to generating gram quantities of products (throughput 6 mmol/h). The release of nitrogen gas that is formed along with the highly reactive nitrile imine dipole is achieved safely and steadily using a backpressure regulator. Overall, this reagent-free flow process is attractive as it provides a sustainable entry to medicinally relevant pyrazoline building blocks and their pyrazole congeners in a highly efficient and scalable manner.

The experimental section has no title; please leave this line here.

Solvents were purchased from Sigma–Aldrich and Fisher Scientific and used without further purification. Substrates and reagents were purchased from Alfa Aesar, Fisher Scientific, Fluorochem or Sigma–Aldrich and used as received. \(^1\)H NMR spectra were recorded with 400 and 500 MHz instruments and are reported relative to residual solvent: CDCl\(_3\) (\(\delta = 7.26\) ppm) and d\(6\)-DMSO (\(\delta = 2.50\) ppm). \(^13\)C NMR spectra were recorded with the same instruments (100 and 125 MHz) and again are reported relative to CHCl\(_3\) (\(\delta = 77.16\) ppm) and d\(6\)-DMSO (\(\delta = 39.52\) ppm). Data reported for \(^1\)H NMR are as follows: chemical shift (\(\delta/\text{ppm}\)) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = heptet, m = multiplet. Data for \(^13\)C{\(^1\)H} NMR are reported in terms of chemical shift (\(\delta/\text{ppm}\)) and multiplicity (C, CH, CH\(_2\), or CH\(_3\)). COSY, HSQC and HMBC, experiments were used in the structural assignment. IR spectra were recorded with a Bruker Platinum spectrophotometer (near, ATR sampling) with the intensities of the characteristic signals being reported as weak (w, <20% of the tallest signal), medium (m, 21–70% of the tallest signal), or strong (s, >71% of the tallest signal). High-resolution mass spectrometry (HRMS) was performed using the indicated techniques with a micromass LCT.
orthogonal time-of-flight mass spectrometer with leucine-enkephalin (Tyr-Gly-Gly-Phe-Leu) as an internal lock mass. For UV/Vis measurements, a Shimadzu UV-1800 UV spectrophotometer was used. Continuous-flow experiments were performed with a Vapourtec E-Series system equipped with a UV150 photoreactor in combination with a high-power LED emitting light at 365 nm wavelength and a medium-pressure Hg-lamp (combined with a low-pass filter).

Procedures for preparation of tetrazoles 4a-c\textsuperscript{14}

To a solution of concentrated HCl (3 mL, 12 M) at 0 °C was added the desired aniline (12 mmol) under stirring. After 5 minutes a solution of NaN\textsubscript{3} (12 mmol in 4 mL water) was added slowly and the suspension was stirred for another 10 minutes before a solution of NaBF\textsubscript{4} (20 mmol in 4 mL water) was added. After 10 minutes stirring the solid diazonium product (2) was isolated by filtration, washed with dilute NaBF\textsubscript{4} solution (ca. 5% w/v) and dried under vacuum.

To a suspension of benzamidine hydrochloride (1, 1 equiv., 0.4 M) and K\textsubscript{2}CO\textsubscript{3} (3 equiv.) in MeCN/water (50/50) was added the diazonium tetrafluoroborate salt (2, 1 equiv.) at 0 °C. After 5 hours stirring at ambient temperature, the aryl imino-triazine adduct (3) was isolated as a yellow solid by filtration, washed with water and dried under reduced pressure.

A suspension of molecular iodine (1.2 equiv.) and KI (1.5 equiv.) was prepared in DMF (0.2 M) and stirred for 10 minutes at room temperature. Solid K\textsubscript{2}CO\textsubscript{3} (3 equiv.) and the desired aryl imino-triazine adduct (3) were added before the resulting mixture was heated to 100 °C for 1 hour. After cooling to ambient temperature, the reaction mixture was quenched by addition of aqueous Na\textsubscript{2}SO\textsubscript{4} followed by extractive work-up with EtOAc and aqueous brine. Purification was achieved by silica gel chromatography using EtOAC/cyclohexane (3:7) as eluent giving the tetrazole products 4 as yellow oils or off-white solids.

2-(4-Isopropylphenyl)-5-phenyl-2H-tetrazole, 4a:
Yellow oil, 85% (3.4 g, 12.8 mmol).
IR (neat): 3035 (w), 2926 (w), 1529 (m), 1465 (s), 1449 (s), 1362 (m), 1014 (s), 995 (m), 776 (s), 732 (s), 694 (s) cm\textsuperscript{-1}.
\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta = 8.42 - 8.13 \) (m, 2H), 7.61 - 7.56 (m, 3H), 7.49 (d, J = 7.7 Hz, 1H), 7.36 (d, J = 7.7 Hz, 2H), 1.97 (s, 4H).
\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \( \delta = 165.0 \) (C), 136.1 (C), 135.4 (2C), 131.6 (CH), 131.4 (CH), 129.8 (2CH), 129.2 (2CH), 127.1 (2CH) 127.0 (C), 17.2 (2CH).
HRMS (ESI\textsuperscript{+}): m/z [M+H]\textsuperscript{+} calcd for C\textsubscript{25}H\textsubscript{22}N\textsubscript{4}O\textsubscript{2}: 371.1291; found: 371.1292.

Procedures for pyrazolines and pyrazoles

A homogeneous solution containing the desired tetrazole (4a-c, 1 equiv.) and the dipolarophile (1.2 equiv.) was prepared in MeCN (100 mM) and passed through the UV150 photoreactor of a Vapourtec E-series system equipped with a medium-pressure Hg-lamp (85% input power, low-pass filter) and a flow coil (10 mL, PFA, residence time 10 min). Temperature control was provided via a stream of compressed air (ca. 28 °C internal reactor temperature). The exiting reaction mixture passed a BF\textsubscript{3}Et\textsubscript{2}O set to 25 bar before being collected in a flask. Evaporation of the solvent was followed by silica gel chromatography (eluent EtOAc/cyclohexane (10:90 to 20:80) to render the desired pyrazoline (6a-f, 6i) and pyrazole (7) products after final evaporation of all volatiles.

Methyl 1-(4-isopropylphenyl)-5-methyl-3-phenyl-4,5-dihydro-1H-pyrazole-5-carboxylate, 6a:
Yellow oil 79% (2.5 g, 7.5 mmol).
IR (neat): 2956 (m), 2869 (w), 1735 (s), 1666 (w), 1610 (m), 1497 (s), 1447 (m), 1384 (s), 1257 (s), 1203 (s), 1121 (s), 1089 (s), 826 (s), 756 (s), 690 (s), 530 (m) cm\textsuperscript{-1}.
\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta = 7.73 - 7.69 \) (m, 2H), 7.40 (d, J = 8.1, 6.6 Hz, 2H), 7.36 - 7.32 (m, 1H), 7.14 (d, J = 8.7 Hz, 2H), 7.06 (d, J = 8.7 Hz, 2H), 3.78 (s, 2H), 3.70 (d, J = 16.6 Hz, 1H), 3.29 (d, J = 16.6 Hz, 1H), 2.87 (hept, J = 6.9 Hz, 1H), 1.64 (s, 3H), 1.25 (d, J = 6.9 Hz, 6H).
\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \( \delta = 174.4 \) (C), 144.6 (C), 141.3 (C), 140.8 (C), 130.5 (2CH), 124.8 (2CH + CH), 125.6 (2CH), 117.6 (2CH), 119.4 (2CH), 72.9 (2CH), 71.9 (2CH), 35.9 (CH), 144.7 (s), 143.3 (CH), 24.1 (2CH), 21.0 (CH).
HRMS (ESI\textsuperscript{+}): m/z [M+H]\textsuperscript{+} calcd for C\textsubscript{25}H\textsubscript{22}N\textsubscript{2}O\textsubscript{2}: 373.1911; found: 373.1909.

Methyl 5-methyl-3-phenyl-1-(4-(trifluoromethoxy)phenyl)-4,5-dihydro-1H-pyrazole-5-carboxylate, 6b:
Yellow oil 74% (1.4 g, 3.7 mmol).
IR (neat): 2954 (w), 1739 (s), 1609 (w), 1509 (s), 1391 (w), 1253 (s), 1206 (s), 1162 (s), 1124 (m), 806 (w), 692 (w) cm\textsuperscript{-1}.
\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta = 7.71 - 7.66 \) (m, 2H), 7.42 - 7.33 (m, 2H), 7.05 - 7.14 (m, 4H), 3.76 (s, 3H), 3.71 (d, J = 16.8 Hz, 1H), 3.30 (d, J = 16.8 Hz, 1H), 1.64 (s, 3H).
\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \( \delta = 173.6 \) (C), 145.9 (C), 142.4 (C), 142.0 (C), 131.9 (C), 129.0 (CH), 128.6 (2CH), 125.8 (2CH), 122.0 (2CH), 120.6 (CF\textsubscript{3}), \( q = 254.5 \) Hz, 142.3 (CH), 69.0 (C), 53.1 (CH), 48.3 (CH), 21.1 (CH).
\textsuperscript{15}F NMR (376 MHz, CDCl\textsubscript{3}): \( \delta = -58.3 \) (s).
HRMS (ESI\textsuperscript{+}): m/z [M+H]\textsuperscript{+} calcd for C\textsubscript{25}H\textsubscript{22}F\textsubscript{2}N\textsubscript{2}O\textsubscript{2}: 379.1264; found: 379.1263.

Methyl 1-(2,6-dimethylphenyl)-5-methyl-3-phenyl-4,5-dihydro-1H-pyrazole-5-carboxylate, 6c:
Yellow oil 68% (1.1 g, 3.4 mmol).
IR (neat): 2950 (m), 1732 (s), 1586 (m), 1445 (s), 1365 (m), 1260 (m), 1201 (m), 1065 (m), 759 (s), 693 (s) cm\textsuperscript{-1}.
**1H NMR (CDCl₃, 400 MHz):** δ = 7.67 – 7.63 (m, 2H), 7.36 (dd, J = 8.3, 6.6 Hz, 2H), 7.32 – 7.26 (m, 1H), 7.03 (m, 3H), 3.92 (d, J = 16.8 Hz, 1H), 3.68 (s, 3H), 3.19 (d, J = 16.8 Hz, 1H), 2.19 (brd, 6H)*, 1.42 (s, 6H).

**13C NMR (CDCl₃, 100 MHz):** δ = 173.3 (C), 145.5 (C), 140.2 (C), 138.2 (2C, broad)*, 132.9 (C), 129.1 (2CH, broad)*, 128.5 (2CH), 128.2 (CH), 127.1 (CH), 125.4 (CH), 70.9 (C), 52.4 (CH), 46.1 (CH), 22.1 (CH₂), 20.2 (CH₃)*, 18.7 (CH₃)*. The signals denoted with * appear broadened due to restricted rotation around the sterically congested C-N bond.

HRMS (ESI+): m/z [M+H]+ calc'd for C₃₇H₆₂N₄O₂: 323.1754; found: 323.1755.

1-(4-Isopropylphenyl)-3-phenyl-3a,6a-dihydroyropyrole[3,4-c]pyrazole-4,6(1H,5f)-dione, 6d:

Yellow solid, 81% (3.2 g, 9.6 mmol).

IR (neat): 3255 (broad), 2959 (m), 2869 (w), 1784 (s), 1610 (w), 1514 (s), 1381 (m), 1342 (m), 1207 (m), 1192 (m), 827 (m), 736 (m) cm⁻¹.

**1H NMR (CDCl₃, 400 MHz):** δ = 8.43 (s, 1H), 7.99 (d, J = 7.1 Hz, 2H), 7.46 (d, J = 8.7 Hz, 1H), 7.44 – 7.36 (m, 3H), 7.20 (d, J = 8.6 Hz, 2H), 5.11 (d, J = 10.9 Hz, 1H), 4.85 (d, J = 8.6 Hz, 1H), 2.87 (hept, J = 6.9 Hz, 1H), 1.23 (d, J = 7.0 Hz, 6H).

**13C NMR (CDCl₃, 100 MHz):** δ = 172.6 (C), 171.5 (C), 142.3 (C), 142.1 (C), 130.3 (C), 129.4 (CH), 128.6 (2CH), 127.1 (2CH), 127.0 (2CH), 114.4 (2CH), 69.9 (CH), 54.6 (CH), 33.4 (2CH), 24.1 (CH₃), 21.0 (CH₃).


Crystal data (CCDC-2221468): P2₁/c; a 17.3845(5) b 6.2983(2) c 15.8490(3); α = 90°, β = 103.57(2)°, γ = 90°.

3-Phenyl-1-(4-trifluoromethyl)phenyl]-3a,6a-dihydroyropyrole[3,4-c]pyrazole-4,6(1H,5f)-dione, 6e:

Beige solid, 77% (1.1 g, 3.1 mmol).

IR (neat): 3203 (m), 3086 (w), 1774 (w), 1706 (s), 1508 (s), 1256 (s), 1200 (s), 1169 (m), 1090 (m), 1016 (m), 843 (m), 805 (m), 767 (m), 687 (m), 622 (m) cm⁻¹.

**1H NMR (d=DMSO, 400 MHz):** δ = 11.87 (br s, 1H), 8.04 – 7.90 (m, 2H), 7.52 – 7.46 (m, 2H), 7.45 – 7.39 (m, 3H), 7.31 (d, J = 8.7 Hz, 2H), 5.33 (d, J = 10.7 Hz, 1H), 5.13 (d, J = 10.7 Hz, 1H).

**13C NMR (d=DMSO, 100 MHz):** δ = 175.4 (C), 174.2 (C), 145.5 (C), 144.0 (C), 142.3 (C, q. J = 2 Hz), 130.8 (C), 129.9 (CH), 128.9 (2CH), 127.5 (2CH), 122.5 (2CH), 120.7 (2CH), 115.2 (CH), 67.0 (CH), 55.6 (CH).

**19F NMR (d=DMSO, 376 MHz):** δ = -57.2 (s).

HRMS (ESI+): m/z [M+H]+ calc'd for C₃₇H₆₂F₄N₄O₂: 376.0904; found: 376.0903.

5-Cyclopentyl-1-(4-isopropylphenyl)-3-phenyl-3a,6a-dihydroyropyrole[3,4-c]pyrazole-4,6(1H,5f)-dione, 6f:

Beige solid, 74% (1.2 g, 2.9 mmol).

IR (neat): 2957 (m), 2870 (w), 1703 (s), 1610 (m), 1513 (s), 1446 (w), 1369 (s), 1220 (m), 1158 (m), 891 (m), 735 (s), 690 (s) cm⁻¹.

**1H NMR (CDCl₃, 400 MHz):** δ = 8.05 (d, J = 7.0 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.47 – 7.33 (m, 3H), 7.21 (d, J = 8.8 Hz, 2H), 5.08 (d, J = 11.0 Hz, 1H), 4.80 (d, J = 11.0 Hz, 1H), 4.48 (p, J = 8.3 Hz, 1H), 2.88 (hept, J = 6.9 Hz, 1H), 2.01 – 1.78 (m, 5H), 1.59 – 1.54 (m, 2H), 1.23 (d, J = 7.0 Hz, 6H).

**13C NMR (CDCl₃, 100 MHz):** δ = 172.8 (C), 171.9 (C), 142.7 (C), 142.4 (C), 142.0 (C), 130.6 (C), 129.3 (CH), 1285 (2CH), 1271.2 (2CH), 1270.7 (2CH), 114.4 (2CH), 65.5 (CH), 53.2 (CH), 52.5 (CH), 33.4 (CH), 28.8 (CH₂), 28.7 (CH₂), 25.3 (CH₃) 25.3 (CH₃), 24.1 (CH₃), 24.1 (CH₃).

HRMS (ESI+): m/z [M+H]+ calc for C_{22}H_{24}N_{4}O: 331.1805; found: 331.1812.

Funding Information
This research has been supported by Science Foundation Ireland (12/RCC275, P2 and 18/R1/5702), the Royal Society of Chemistry (Research Enablement Grant; E20-2998) and the School of Chemistry through provision of a Sir Walter Harley scholarship to MDF.

Acknowledgment
We gratefully to Dr Julia Bruno and Dr Andrew D. Phillips for solving the crystal structures reported in this paper as well as Dr Jimmy Muldoon and Dr Yannick Ortin for assistance with MS and NMR experiments.

Supporting Information
YES (this text will be updated with links prior to publication)

Primary Data
NO.

Conflict of Interest
The authors declare no conflict of interest.

References


(13) [Donnelly, K.; Baumann, M. J. Flow Chem. 2021, 11, 223.]

(14) [Ramanathan, M.; Wang, Y.-H.; Liu, S.-T. Org. Lett. 2015, 17, 5886.]

(15) [CCDC 2221466, CCDC 2221467 and CCDC 2221468 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via forums.ccdc.cam.ac.uk/structures.]


(18) [Oligomerisation of the dipolarophile was observed when using the high-power LED emitting at 365 nm.]
Supporting Information

Photochemical Synthesis of Pyrazolines from Tetrazoles in Flow

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2. X-ray crystallography details \hspace{1cm} SI-3

3. Copies of NMR spectra \hspace{1cm} SI-5
1. Details on light sources used in this study

Emission spectrum of UV-LED emitting at 365 nm (tuneable 50-100 W input power)

Emission Spectra of Medium-Pressure Hg Lamp (tuneable 75-150 W input power)
2. X-ray crystallography details

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<tr>
<td>CCDC deposition no.</td>
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### Crystal Data

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<tr>
<td><strong>Formula</strong></td>
<td>C₁₉H₁₇N₃</td>
<td>C₁₄H₁₀F₁₃N₄O</td>
<td>C₃₀H₁₉N₃O₂</td>
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<tr>
<td><strong>Formula Weight</strong></td>
<td>287.35</td>
<td>306.25</td>
<td>333.38</td>
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<td><strong>Crystal System</strong></td>
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<td><strong>Space group</strong></td>
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<td>P2₁/n (No. 14)</td>
<td>P2₁/c (No. 14)</td>
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<tr>
<td>a, b, c [Å]</td>
<td>11.4268(2)</td>
<td>11.5500(2)</td>
<td>6.2983(2)</td>
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<tr>
<td>alpha, beta, gamma [°]</td>
<td>98.826(2)</td>
<td>93.383(2)</td>
<td>100.537(2)</td>
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<tr>
<td>V [Å³]</td>
<td>1510.24(6)</td>
<td>2647.34(10)</td>
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<td>Z</td>
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<tr>
<td>D(calc) [g/cm³]</td>
<td>1.264</td>
<td>1.537</td>
<td>1.298</td>
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<tr>
<td>Mu(CuKα) [%/mm]</td>
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<td>1.135</td>
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<td>F(000)</td>
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<td>1248</td>
<td>704</td>
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<td>Crystal Size [mm]</td>
<td>0.09 x 0.10 x 0.38</td>
<td>0.09 x 0.25 x 0.34</td>
<td>0.02 x 0.03 x 0.14</td>
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### Data Collection

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<tr>
<td><strong>Temperature (K)</strong></td>
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<td>150</td>
<td>101</td>
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<tr>
<td><strong>Radiation [ Ångstrom]</strong></td>
<td>CuKα 1.54184</td>
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<tr>
<td><strong>Theta Min-Max [°]</strong></td>
<td>2.9, 76.6</td>
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<td>2.6, 76.4</td>
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<tr>
<td><strong>Dataset</strong></td>
<td>-11: 10 ; -14: 14 ; -19:</td>
<td>-9: 9 ; -13: 10 ; -34:</td>
<td>-21: 21 ; -7: 7 ; -19:</td>
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<tr>
<td><strong>Tot., Uniq. Data, R(int)</strong></td>
<td>37116, 6312, 0.017</td>
<td>13853, 13853, 0.0432</td>
<td>24997, 3561, 0.060</td>
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<tr>
<td><strong>Observed Data [I&gt;0.0 σ(I)]</strong></td>
<td>5975</td>
<td>8845</td>
<td>2763</td>
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### Refinement

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<td>13853, 398</td>
<td>3561, 228</td>
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<tr>
<td><strong>R, wR2, S</strong></td>
<td>0.0328, 0.0897, 1.06</td>
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<td>0.0456, 0.1282, 1.02</td>
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<td><strong>Min. and Max. Resd. Dens. [e/ Å³]</strong></td>
<td>-0.19, 0.32</td>
<td>-0.33, 0.34</td>
<td>-0.22, 0.26</td>
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</tbody>
</table>

**Table 1.** Crystallographic Data and Refinement Details for 050, 053 and 054.
EXPERIMENTAL METHODS

SCXRD data for all compounds were collected using an Oxford Diffraction Supernova diffractometer equipped with Atlas detector and Oxford cryosystem to control of temperature as well as CuKα radiation (wavelength of $\lambda = 1.54184$ Å). X-ray measurements were made and images integrated using CrysAlisPro software. Crystal structures were solved by direct methods and refined by least-square using SHELX technique integrated in OLEX2 software, and anisotropic displacement parameters for non-hydrogen atoms were applied. Hydrogen atoms were placed at calculated positions and treated using a riding model with isotropic displacement parameters set at 1.2Ueq of the attached atom.

REFERENCES


3. Copies of NMR spectra

2-(4-Isopropylphenyl)-5-phenyl-2H-tetrazole, 4a:
5-Phenyl-2-(4-(trifluoromethoxy)phenyl)-2H-tetrazole, 4b:
2-(2,6-Dimethylphenyl)-5-phenyl-2H-tetrazole, 4c:

![NMR spectra](attachment:image1.png)
Methyl 1-(4-isopropylphenyl)-5-methyl-3-phenyl-4,5-dihydro-1H-pyrazole-5-carboxylate, 6a:
Methyl 5-methyl-3-phenyl-1-(4-(trifluoromethoxy)phenyl)-4,5-dihydro-1H-pyrazole-5-carboxylate, 6b:
Methyl 1-(2,6-dimethylphenyl)-5-methyl-3-phenyl-4,5-dihydro-1H-pyrazole-5-carboxylate, 6c:
1-(4-Isopropylphenyl)-3-phenyl-3a,6a-dihydropyrrolo[3,4-c]pyrazole-4,6(1H,5H)-dione, 6d:
3-Phenyl-1-(4-(trifluoromethoxy)phenyl)-3a,6a-dihydropyrrolo[3,4-c]pyrazole-4,6(1H,5H)-dione, 6e:
5-Cyclopentyl-1-(4-isopropylphenyl)-3-phenyl-3a,6a-dihydropyrrolo-[3,4-c]pyrazole-4,6(1H,5H)-dione, 6f:
1-(4-Isopropylphenyl)-3-phenyl-1,3a,4,5,6,7a-hexahydro-7H-indazol-7-one, 6i:
1-(4-Isopropylphenyl)-3-phenyl-1H-pyrazole-5-carbonitrile, 7:
1-(4-Isopropylphenyl)-3-phenyl-1H-pyrazole-4-carbonitrile, 8:
1-(4-Isopropylphenyl)-3-phenyl-1,4,5,6-tetrahydro-7H-indazol-7-one, 9: