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Synthesis and Characterization of 3-Methyl-1-(4-(trifluoromethyl)phenyl)indeno [1,2-c]pyrazol-4(1*H*)-one

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Abstract: Pyrazoles have potential applications in the agrochemical and medicinal chemistry industries as pesticides, anti-inflammatory medications, and antitumor drugs. Fluorinated fused-ring pyrazoles may also possess medicinally useful properties. Herein, we report the acid-catalyzed synthesis of a new tricyclic, trifluoromethylated indenopyrazole, 3-methyl-1-(4-(trifluoromethyl)phenyl)indeno[1,2-c]pyrazol-4(1*H*)-one, from 2-acetyl-1,3-indanedione and 4-trifluoromethylphenylhydrazine. This isomeric pyrazole was obtained in yields ranging from 4–24%. NMR spectroscopic characterization and elemental analysis support the structural assignment, identity, and purity of the product.

Keywords: indenopyrazole; 2-acetyl-1,3-indanedione; 4-trifluoromethylphenylhydrazine

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1. Introduction

While the preparation of heteroaromatic species such as pyrazoles is well documented, the synthesis and bioactivity studies of fused-ring pyrazoles remain a vibrant area of research with many compounds of this type finding use in the treatment of diseases [1–8]. In addition, fluorine substitution has been extensively investigated in drug research for its ability to enhance biological activity and increase chemical or metabolic stability [9–11].

Triketones also possess useful medicinal properties, such as antibiotic activity [12]. Fused-ring triketones, such as 2-acetyl-1,3-indanedione, serve as a useful scaffold upon which highly functionalized, tricyclic *N*-aryl pyrazoles may be built [3,13]. Earlier efforts showed that the acid-catalyzed condensation of 2-trifluoroacetyl-1,3-indanedione (**A**) with phenylhydrazine provided the 3-trifluoromethyl fused-ring pyrazole **B** as the sole regioisomer in 70% yield. See Figure 1 [3].

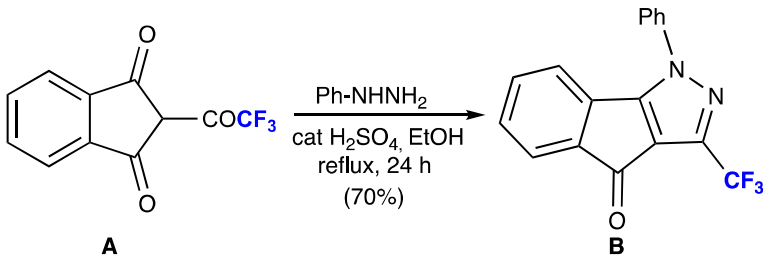


Figure 1. 3-trifluoromethylindenopyrazole synthesis.

The product regiochemistry of the reaction depicted above is noteworthy, given that many investigations of pyrazole product formation have shown that conventional and microwave-mediated condensations between 1,3-diketones and hydrazines typically yield two regioisomers as shown in Figure 2, often in unequal proportions [13,14].

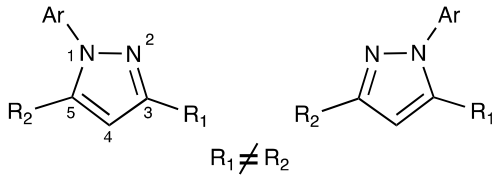


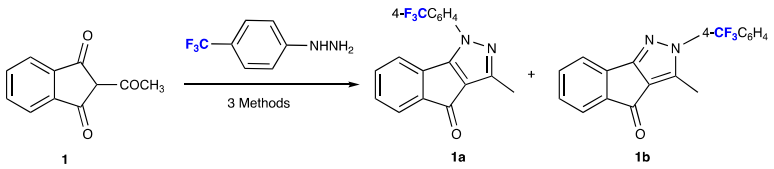
Figure 2. Pyrazole Regioisomers.

It is surmised that a combination of steric and electronic factors conspires to affect the pyrazole product distribution [15]. In the case of compound **A**, the greater electrophilic character of the trifluoroacetyl group relative to the topologically constrained indanedione ring system carbonyl likely contributes to the initial nucleophilic attack by the hydrazine, which ultimately leads to the observed regiochemistry of compound **B**.

Correspondingly, a non-fluorinated analog of compound **A**, 2-acetyl-1,3-indanedione (compound **1**), was selected to examine whether the pyrazole isomeric product selectivity would be similar to that observed in the 3-trifluoromethyl indenopyrazole synthesis. Compound **1** contains the 2-$COCH_3$ group, which is sterically slightly smaller than the -$COCF_3$ group, but because the methyl group is an inductive electron donor, the carbonyl would have a smaller partial positive charge and perhaps not be as prone to nucleophilic attack by the arylhydrazine. It was thus anticipated that the condensation of 2-acetyl-1,3-indanedione with 4-trifluoromethylphenylhydrazine would yield a mixture of pyrazole isomeric products.

2. Results

The regioisomeric pyrazoles 3-methyl-1-(4-(trifluoromethyl)phenyl)indeno[1,2-c]pyrazol-4(1*H*)-one (**1a**) and 3-methyl-2-(4-(trifluoromethyl)phenyl)indeno[1,2-c]pyrazol-4(2*H*)-one (**1b**) were prepared according to Scheme 1. Three runs were conducted to compare conventional reflux, microwave, and microwave-sonication methods for effectiveness.



Run	Methods	% Yield	% Yield
1	Conventional	4	36
2	μ-wave	6	24
3	μ-wave/sonication	24	50

Scheme 1. Synthesis of 3-methyl-1-(4-(trifluoromethyl)phenyl)indeno[1,2-c]pyrazol-4(1*H*)-one (**1a**) and 3-methyl-2-(4-(trifluoromethyl)phenyl)indeno[1,2-c]pyrazol-4(2*H*)-one (**1b**).

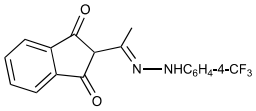
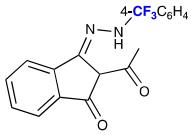
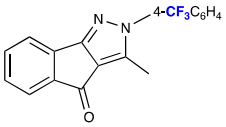
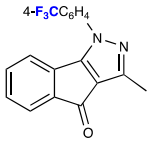
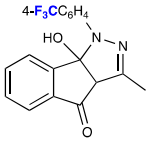
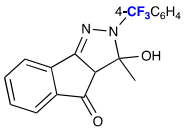
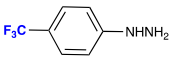
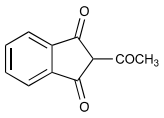
Compound **1a** was satisfactorily characterized by ^{1}H and ^{13}C nuclear magnetic resonance, mass spectrometry, and elemental analysis. All preparative methods and characterization data are reported in the experimental section. ^{1}H and ^{13}C NMR spectra, as well as the EI mass spectrum, are available as Supplemental Materials. The preparation, isolation, and characterization of **1b** were reported previously, but the characterization data for **1b** are provided in ref. [16] and in the experimental section [16].

3. Discussion

3.1. Synthesis and Purification

As indicated earlier, three runs of the reaction in Scheme 1 were conducted. The details for each run are provided in the experimental section. Run 1, a conventional reflux conducted in ethanol, was analyzed by thin-layer chromatography to assess reaction completion after 48 h. Table 1 provides R_f values for the crude reaction mixture eluted with CH_2Cl_2 and 30:70 *v:v* EtOAc:Hexane.

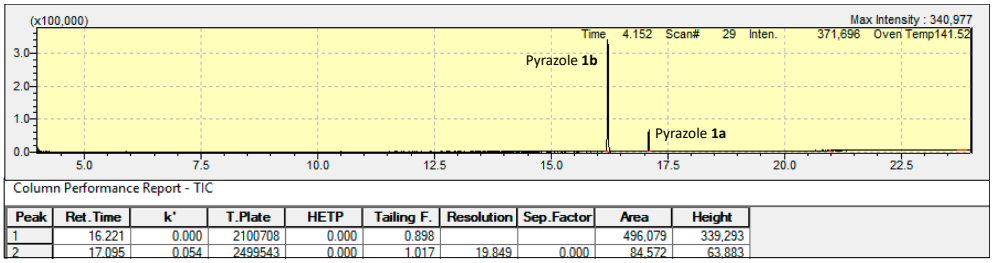
Table 1. Measured TLC R_f values for conventional run 1 crude reaction mixture.

Entry	Possible Intermediate & Pyrazole Structures	R_f (CH_2Cl_2)	R_f (EtOAc/Hexane)	Relative Spot Size/ Color (1 = Largest; 6 = Smallest)
1/2		0.94	0.97	2/Orange
	or			
1/2		0.81	0.85	4/Yellow-orange
3		0.46	0.75	1/Pale brown
4		0.36	0.58	3/Pale brown
5/6		0.16	0.46	5/Pale brown
	or			
5/6		0.08	0.38	6/Pale brown
	Reactants			
7		0.06	0.15	Not present
8		0.28	0.66	Not present

As Table 1 shows, the crude reaction mixture contains multiple intermediate and product species formed during the reaction while the starting materials were fully depleted. Based on the spot color on the developed TLC plate, the medium-intensity orange and intense yellow-orange compounds (entries 1/2) were assessed to be regioisomeric arylhydrazone intermediates. This color range and intensity are consistent with the arylhydrazone intermediates reported previously. [15] Entry 3, which we assessed to be the major pyrazole isomer (**1b**), was by far the largest diameter spot but more brownish in appearance. Entry 4, the minor pyrazole (**1a**) was much less intense but had a similar brown appearance. Entries 5/6, assessed to be the regioisomeric pyrazol-ols, were the smallest spots and the least intense with a slight brown coloration.

Following the TLC analysis of Run 1, the solvent was removed under reduced pressure. After workup, the crude product mixture (0.484 g, 71% mass balance) was subjected to the first chromatographic separation, which provided three major fractions containing mixtures of compounds 1/2, 3/4, and 5/6, respectively. Each major fraction was then combined, concentrated to dryness, and weighed: compounds 1/2 (0.122g, 18% yield), the pyrazole

isomers (compounds 3/4) (0.320 g, 47% yield), and compounds 5/6 (0.020 g, 3% yield). No further attempts were made to isolate the intermediates 1, 2, 5, and 6. The fraction containing the pyrazole isomers was then analyzed by gas chromatography (Figure 3). Based on the areas of the two eluent peaks, **1b** constituted 85.4% of the pyrazole isomeric mixture (0.273 g), while **1a** comprised 14.6% of the pyrazole mixture (0.047 g). From these data, a **1b**:**1a** ratio of 5.9:1 was determined.



Peak	Ret.Time	k'	T.Plate	HETP	Tailing F.	Resolution	Sep.Factor	Area	Height
1	16.221	0.000	2100708	0.000	0.898			496,079	339,293
2	17.095	0.054	2499543	0.000	1.017	19.849	0.000	84,572	63,883

Figure 3. Gas Chromatograph of Pyrazole Isomer Mixture.

To isolate the individual pyrazoles, a second column chromatographic separation was undertaken using a 10–30% gradient elution of EtOAc/hexane. The second column afforded the pyrazole isomers in two separate fractions: **1b**—0.270 g; **1a**—0.046 g. Each pyrazole isomer was then recrystallized twice from hot ethanol to give pyrazole **1b** (0.236 g, 36%) and pyrazole **1a** (0.026 g, 4%) for an overall moderate yield of 40% with a final **1b**:**1a** ratio of 9:1. The unsatisfactory yield of **1a** was thus attributed, in part, to the necessity of performing two chromatographic separations and mechanical loss from two recrystallizations to achieve isomeric purity.

To examine whether a microwave-mediated process would change the product distribution, run 2 was conducted in ethanol at 80 °C for a period of 1 h on the variable power mode. The overall yield was only 30%, possibly a result of the lowered reactant concentration compared to run 1 and the brief reaction time (1 h). However, the **1b**:**1a** ratio was determined to be 4:1, a slight decrease from the initial 5.9:1 ratio found for run 1. At present, it is unclear whether the microwave-mediated process contributed to the change in product distribution. The use of tandem radial chromatography afforded satisfactory separation of the hydrazone intermediates (compounds 1 and 2) as the major fractions (0.205 g combined mass), pyrazole isomers **1a** (0.020 g), and **1b** (0.078 g) as well as the pyrazol-ol intermediates (0.033 g). The pyrazole isomers did not require further purification by recrystallization, thus minimizing mechanical product loss.

For run 3, the microwave reaction time was extended to 2 h on the variable power mode and the volume of ethanol lowered to one-third of that used in run 2. Following μ-wave irradiation at 80 °C, the sample was sonicated at 60 °C for an additional hour. Tandem radial chromatography was employed to isolate the isomeric pyrazole products in a pure form (74% yield). Additional fractions collected were the hydrazone intermediates (compounds 1 and 2 (0.032 g combined mass)) and the pyrazol-ol intermediates 5 and 6 (0.015 g combined mass). It is clear from the small quantities of the intermediates remaining that the microwave-sonication method was more effective than either the conventional reflux or the 1 h microwave-only method in the formation of these fused-ring pyrazoles. These modifications led to a 2.47-fold increase in the product yield over that obtained in run 2. Additionally notable was the reduction in the **1b**:**1a** ratio to 2.1:1.

Improvements observed in the overall yield of compound **1a** appear to be due in part to modifications in the μ-wave reaction conditions, the continuation of the reaction under sonication conditions, and the radial chromatographic method used to isolate the pyrazole products. These improvements point to the value of combining μ-wave irradiative and sonication methods to mediate the preparation of pyrazoles. Future studies are warranted to expand the scope of arylhydrazine and other bifunctional nucleophile condensations with 2-acetyl-1,3-indanedione.

3.2. Spectral Characterization

With the target compound **1a** isolated, key resonances in the ^{1}H, ^{13}C, and ^{19}F NMR spectra were used to establish product identity. Figure 4 shows the chemical shift assignments for **1a** and **1b** that support the product structures. See Supplementary Materials.

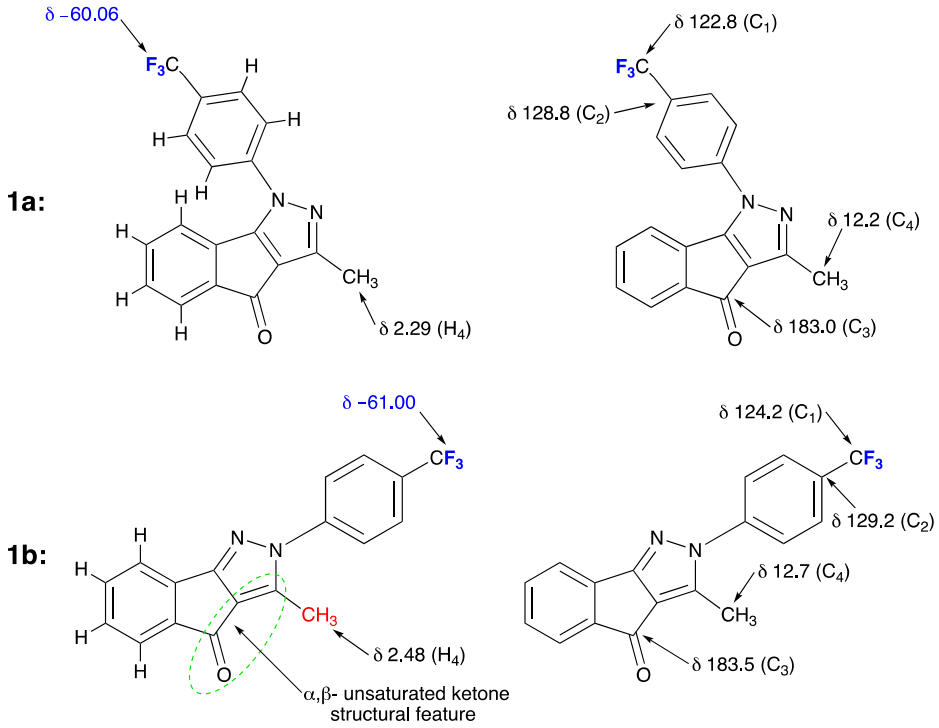


Figure 4. Key ^{19}F, ^{1}H, and ^{13}C NMR assignments for compounds **1a** and **1b**.

The ^{19}F nuclear magnetic resonances observed for **1a** and **1b** at −60.06 and −61.00 ppm, respectively, are consistent with a -CF_3 group attached to an aromatic ring, which generally varies from −60–−64 ppm [17]. That there is only a modest ^{19}F chemical shift variation between the pyrazole isomers is also consistent with the fact that the electronic environments the CF_3 groups encounter are very similar. Evidence in the ^{13}C NMR of aromatic trifluoromethyl group presence for **1a** was confirmed by **C**F_3 (C_1) resonance centered at 122.8 ppm, which appeared as a quartet with a $^{1}J_{C\text{-}F}$ = 285 Hz, as well as a **C**-CF_3 (C_2) resonance centered at 128.8 ppm, which appeared as a quartet with a $^{2}J_{C\text{-}F}$ = 32 Hz. For **1b**, the **C**F_3 (C_1) resonance centered at 124.2 ppm appeared as a quartet with a $^{1}J_{C\text{-}F}$ = 272 Hz, as well as a **C**-CF_3 (C_2) resonance centered at 129.2 ppm, which appeared as a quartet with a $^{2}J_{C\text{-}F}$ = 32 Hz. The carbonyl carbon (C_3) chemical shifts at 183.0 ppm (**1a**) and 183.5 ppm (**1b**) are consistent with a ketone conjugated with an aromatic ring. The pyrazolic C**H**$_3$ (H_4) singlet at 2.29 ppm for **1a** is slightly upfield relative to the C**H**$_3$ (H_4) singlet for **1b** at 2.48 ppm. The downfield shift of **1b**'s H_4 proton signal may be due in part to the extended conjugation and, therefore, deshielding imparted by the α,β unsaturated ketone structural feature circled in green in Figure 4. This extended conjugation may also influence the C_4 carbon resonance of **1b** (12.7 ppm), which is downfield relative to **1a**'s C_4 carbon resonance at 12.2 ppm. These chemical shift differences, while small, provide a rationale for the regioisomeric pyrazole assignments.

4. Materials and Methods

4.1. Instrumentation

IR spectra were collected on a Thermo Scientific Nicolet iS5 FT-IR spectrometer (iD5 ATR) with a resolution of 2 cm^{-1}. NMR spectra were collected on a Bruker Avance 300 NMR spectrometer operating at 300.13 MHz for ^{1}H, 282.40 MHz for ^{19}F, and 75.47 MHz for ^{13}C

with d^6-DMSO as solvent. Hexafluorobenzene served as an internal standard for ^{19}F NMR chemical shifts. Mass spectral data were collected on a Shimadzu QP 2010S GC-MS instrument. Melting points were obtained on an SRS Digimelt MPA160 apparatus and are uncorrected. Reaction temperatures were maintained using a J-Kem® 410 temperature controller. Microwave reactions were carried out in a CEM Discover® microwave reactor using the variable power mode. Sonications were performed using a Branson 1800 sonicator operating at 40 Hz. Combustion analysis was conducted by Atlantic Microlab, Inc., Norcross, GA, USA.

4.2. Chemicals

All chemicals were obtained from Sigma-Aldrich and used as purchased unless otherwise indicated. Thin layer chromatography was accomplished on precut SiO_2 plates, using both CH_2Cl_2 and a 30:70 mixture of EtOAc/Hexane (*v*:*v*) as the eluting solvent or solvent mixture. Column chromatography was accomplished using a 130–270 mesh silica gel (Sigma-Aldrich, St. Louis, MO, USA) in a 2″ diameter Kontes glass column. Radial chromatography was accomplished on a Chromatotron™ (Harrison Research, Palo Alto, CA, USA) using 4 mm silica gel/gypsum plates (Analtech, Newark, DE, USA). A gradient elution (20–60% EtOAc/Hexane (*v*:*v*)) was employed for radial chromatographic separations.

*4.3. Methods for the Preparation and Isolation of 3-Methyl-1-(4-(trifluoromethyl)phenyl)indeno[1,2-c]pyrazol-4(1H)-one (**1a**)*

4.3.1. Run 1

A 50 mL round-bottom flask equipped with a magnetic stirrer was charged with 25 mL ethanol, 2-acetyl-1,3-indanedione (2 mmol), and 4-trifluoromethylphenylhydrazine (2 mmol). Then, 1 drop of concentrated sulfuric acid was added while stirring. A reflux condenser was affixed, and the reaction mixture was refluxed at 78 °C for 48 h. The resulting solution was analyzed by TLC, evaporated to dryness under reduced pressure and the solid residue was neutralized with 15 mL of saturated Na_2CO_3. This solution was extracted with 3 × 5 mL of CH_2Cl_2, and the organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure to obtain 0.484 g (71% mass balance) of solid products and intermediates. The pyrazole mixture was purified by column chromatography (2× columns): 1st column using CH_2Cl_2 as the mobile phase, followed by a 2nd column using a gradient elution of 10–30% ethyl acetate/hexane.

3-methyl-1-(4-(trifluoromethyl)phenyl)indeno[1,2-c]pyrazol-4(1*H*)-one (**1a**) This compound was obtained as golden-brown crystals (ethanol), 0.026 g (4% yield), m.p. 154–156 °C. FT-IR (ATR): 1708 cm^{-1} (C=O), 1321 cm^{-1} (Ar-CF_3). NMR: ^1H δ 2.29 (3H, s), 7.26 (1H, d, $^3J_{H\text{-}H}$ =7.50 Hz), 7.35–7.59 (3H, m), 7.91–7.98 (4H, m). ^{13}C δ 12.2, 120.6, 122.6, 122.8 (CF_3, q, $^1J_{C\text{-}F}$ = 285 Hz), 124.1, 124.6, 125.1, 128.8 (C-CF_3, q, $^2J_{C\text{-}F}$ = 32 Hz), 130.5, 131.8, 133.7, 134.4, 135.5, 139.9, 141.3, 146.7, 157.1, 183.0. ^{19}F δ −60.06 (s, 3F). MS: *m*/*z* 328 (100%, M^+), 327 (40%, M − H^+), 259 (5%, M − CF_3^+). Analysis calculated for $C_{18}H_{11}F_3N_2O$: C, 65.85, H, 3.38, N, 8.53. Found: C, 65.96, H, 3.43, N, 8.46 (See Supplementary Materials).

3-methyl-2-(4-(trifluoromethyl)phenyl)indeno[1,2-c]pyrazol-4(2*H*)-one (**1b**) This compound was obtained as brown crystals (ethanol), 0.236 g (36% yield), m.p. 149–152 °C. Physical and spectroscopic data for this compound were previously reported in the literature. [16] FT-IR (ATR): 1705 cm^{-1} (C=O), 1318 cm^{-1} (Ar-CF_3). NMR: ^1H δ 2.48 (3H, s), 7.20–7.59 (4H, m), 7.69–7.98 (4H, m). ^{13}C δ 12.7, 121.1, 123.1, 124.1, 124.2 (CF_3, q, $^1J_{C\text{-}F}$ = 272 Hz), 124.6, 125.5, 127.0, 127.5, 127.6, 129.2 (C-CF_3, q, $^2J_{C\text{-}F}$ = 32 Hz), 130.9, 132.3, 134.2, 140.3, 147.2, 157.6, 183.5. ^{19}F δ −61.00 (s, 3F). MS: *m*/*z* 328 (50%, M^+), 327 (100%, M − H^+), 259 (15%, M − CF_3^+). Analysis calculated for $C_{18}H_{11}F_3N_2O$: C, 65.85, H, 3.38, N, 8.53. Found: C, 66.08, H, 3.42, N, 8.33 (See Supplementary Materials).

4.3.2. Run 2

A 30 mL microwave vial equipped with a magnetic stirrer was charged with 12 mL ethanol, 2-acetyl-1,3-indanedione (1 mmol), and 4-trifluoromethylphenylhydrazine (1 mmol).

Then, 1 drop of concentrated sulfuric acid was added while stirring. The vial was capped, placed in the microwave reactor, and irradiated for 1 h at 80 °C using the variable power setting. The resulting solution was evaporated to dryness under reduced pressure and the solid residue (mass 0.340 g, 92% mass balance) was neutralized with 15 mL of saturated Na_2CO_3. This solution was extracted with 3 × 5 mL of CH_2Cl_2, and the organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the pyrazole mixture was purified by tandem radial chromatography (10–30% ethyl acetate/hexane). Fractions collected, in order of elution, were compounds 1/2 (0.205 g), 1b (0.078 g), 1a (0.020 g), and compounds 5/6 (0.033 g).

3-methyl-1-(4-(trifluoromethyl)phenyl)indeno[1,2-c]pyrazol-4(1*H*)-one (**1a**) This compound was obtained as golden-brown crystals, 0.020 g (6% yield). Physical and spectroscopic data for this compound are consistent with that reported in run 1.

3-methyl-2-(4-(trifluoromethyl)phenyl)indeno[1,2-c]pyrazol-4(2*H*)-one (**1b**) This compound was obtained as brown crystals, 0.078 g (24% yield). Physical and spectroscopic data for this compound are consistent with that reported in the literature [16].

4.3.3. Run 3

A 10 mL microwave vial equipped with a magnetic stirrer was charged with 4 mL of ethanol, 2-acetyl-1,3-indanedione (0.5 mmol), and 4-trifluoromethylphenylhydrazine (0.5 mmol). Then, 1 drop of concentrated sulfuric acid was added while stirring. The vial was capped, placed in the microwave reactor, and irradiated for 2 h at 80 °C using the variable power setting. Following irradiation, the sample was sonicated at 60 °C for an additional hour. The resulting solution was evaporated to dryness under reduced pressure, and the solid residue (mass 0.178 g, 96% mass balance) was neutralized with 15 mL of saturated Na_2CO_3. This solution was extracted with 3 × 5 mL of CH_2Cl_2, and the organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the pyrazole mixture was purified by tandem radial chromatography (10–30% ethyl acetate/hexane). Fractions collected, in order of elution, were compounds 1/2 (0.032 g), 1b (0.087 g), 1a (0.042 g), and compounds 5/6 (0.015 g).

3-methyl-1-(4-(trifluoromethyl)phenyl)indeno[1,2-c]pyrazol-4(1*H*)-one (**1a**) This compound was obtained as golden-brown crystals, 0.042 g (24% yield). Physical and spectroscopic data for this compound are consistent with that reported in run 1.

3-methyl-2-(4-(trifluoromethyl)phenyl)indeno[1,2-c]pyrazol-4(2*H*)-one (**1b**) This compound was obtained as brown crystals, 0.087 g (50% yield). Physical and spectroscopic data for this compound are consistent with that reported in the literature [16].

Supplementary Materials: Figure S1: ^{1}H NMR of 3-methyl-1-(4-(trifluoromethyl)phenyl)indeno[1,2-c]pyrazol-4(1*H*)-one; Figure S2: ^{13}C NMR of 3-methyl-1-(4-(trifluoromethyl)phenyl)indeno[1,2-c]pyrazol-4(1*H*)-one; Figure S3: Mass spectrum (EI) for 3-methyl-1-(4-(trifluoromethyl)phenyl)indeno[1,2-c]pyrazol-4(1*H*)-one. Figure S4: Mass spectrum (EI) for 3-methyl-2-(4-(trifluoromethyl)phenyl)indeno[1,2-c]pyrazol-4(2*H*)-one.

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References

1. Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. From 2000 to Mid-2010: A Fruitful Decade for the Synthesis of Pyrazoles. *Chem. Rev.* **2011**, *111*, 6984–7034. [CrossRef] [PubMed]
2. Sloop, J.; Holder, C.; Henary, M. Selective Incorporation of Fluorine in Pyrazoles. *Eur. J. Org. Chem.* **2015**, *16*, 3405–3422. [CrossRef]
3. Sloop, J.; Bumgardner, C.; Loehle, W.D. Synthesis of Fluorinated Heterocycles. *J. Fluor. Chem.* **2002**, *118*, 135–147. [CrossRef]
4. Wu, M.; Wang, R.; Chen, F.; Chen, W.; Zhou, Z.; Yi, W. Synthesis of Indenopyrazole Frameworks via Cascade C–H Functionalization/[3 + 2] Dipolar Cycloaddition/Aromatization Rearrangement Reactions. *Org. Lett.* **2020**, *22*, 7152–7157. [CrossRef] [PubMed]
5. Aggarwal, R.; Kumar, S. 5-Aminopyrazole as precursor in design and synthesis of fused pyrazoloazines. *Beilstein J. Org. Chem.* **2018**, *14*, 203–242. [CrossRef] [PubMed]
6. Abdelhamid, I.; Hawass, M.; Sanad, S.; Elwahy, A. Synthesis of various pyrazole-fused heterocyclic systems using pyrazole-4-carbaldehydes as versatile precursors. *Arkivoc* **2021**, *ix*, 42–72. [CrossRef]
7. Nugiel, D.; Vidwans, A.; Etzkorn, A.; Rossi, R.; Benfield, P.; Burton, C.; Cox, S.; Doleniak, D.; Seitz, S. Synthesis and Evaluation of Indenopyrazoles as Cyclin-Dependent Kinase Inhibitors. 2. Probing the Indeno Ring Substituent Pattern. *J. Med. Chem.* **2002**, *45*, 5224–5232. [CrossRef] [PubMed]
8. Minegishi, H.; Fukashiro, S.; Ban, H.S.; Nakamura, H. Discovery of Indenopyrazoles as a New Class of Hypoxia Inducible Factor (HIF)-1 Inhibitors. *ACS Med. Chem. Lett.* **2013**, *4*, 297–301. [CrossRef] [PubMed]
9. Mykhailiuk, P. Fluorinated Pyrazoles: From Synthesis to Applications. *Chem. Rev.* **2021**, *121*, 1670–1715. [CrossRef] [PubMed]
10. Gillis, E.; Eastman, K.; Hill, M.; Donnelly, D.; Meanwell, N. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315–8359. [CrossRef] [PubMed]
11. Penning, T.; Talley, J.; Bertenshaw, S.; Carter, J.; Collins, P.; Docter, S.; Graneto, M.; Lee, L.; Malecha, J.; Miyashiro, J.; et al. Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: Identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1h-pyrazol-1-yl]benzenesulfonamide (sc-58635, celecoxib). *J. Med. Chem.* **1997**, *40*, 1347–1365. [CrossRef] [PubMed]
12. van Klink, J.W.; Larsen, L.; Perry, N.; Weavers, R.; Cook, G.; Bremer, P.; MacKenzie, A.; Kirikae, T. Triketones active against antibiotic-resistant bacteria: Synthesis, structure-activity relationships, and mode of action. *Bioorganic Med. Chem.* **2005**, *13*, 6651–6662. [CrossRef] [PubMed]
13. Sloop, J.; Boyle, P.; Fountain, A.W.; Gomez, C.; Jackson, J.; Pearman, W.; Schmidt, R.; Weyand, J. Novel Fluorinated Indanone, Tetralone and Naphthone Derivatives: Synthesis and Unique Structural Features. *Appl. Sci.* **2012**, *2*, 61–99. [CrossRef]
14. Sloop, J.; Jackson, J.; Schmidt, R. Microwave-Mediated Pyrazole Fluorinations Using Selectfluor®. *Heteroat. Chem.* **2009**, *20*, 341–345. [CrossRef]
15. Sloop, J.; Lechner, B.; Washington, G.; Bumgardner, C.; Loehle, W.; Creasy, W. Pyrazole Formation: Examination of Kinetics and Mechanistic Pathways. *Int. J. Chem. Kinet.* **2008**, *40*, 370–383. [CrossRef]
16. Boyle, P.; Breaud, D.; Churley, M.; Coppock, P., Jr.; Encarnacion-Thomas, E.; Fernandes, C.; Fountain, A.; Gomez, C.; Guzman, A.; Jackson, J.; et al. Synthesis and Structural Features of Indanone, Tetralone and Naphthone Derivatives: Selective Fluorination and Condensation Products, Chapter 2. In *Current Perspectives on Chemical Sciences, Volume 2*; Sutar, H., Ed.; Book Publisher International: London, UK, 2020; 16p. [CrossRef]
17. Dolbier, W. *Guide to Fluorine NMR For Organic Chemists*; John Wiley and Sons, Inc.: Hoboken, NJ, USA, 2009.