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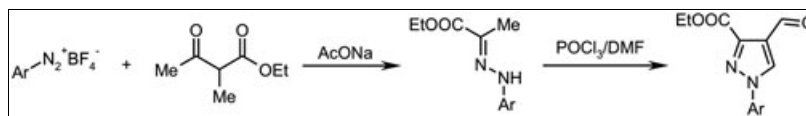
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A new simple and convenient method of synthesis of ethyl 1-aryl-4-formyl-1*H*-pyrazole-3-carboxylates from aromatic amines *via* diazonium salts has been developed. Hydrolysis and hydrazinolysis of these compounds has been investigated.

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INTRODUCTION

Pyrazoles are widely explored heterocyclic compounds [1]. A lot of these compounds display different types of physiological activity [2] and therefore are of interest for biological screening [3]. For example, this class of compounds has been previously reported to be selective cyclooxygenase-2 (COX-2) inhibitors [4], CB₁ receptor antagonists [5], anticancer [6], antibacterial [7], antimalarial agents [8]. For biological screening, the possibility of modification of the lead molecule is very desirable. The introduction of reactive functional groups into the pharmacophore-containing scaffold is the simplest way for such modification [9].

There are a lot of methods for preparing of pyrazole ring. As rule the compound possesses N-N single, double, or triple bonds are using. In such way, pyrazoles can be obtained by cyclization reactions of unsaturated carbonyl- or 1,3-dicarbonyl compounds with hydrazine derivatives [10,11], cyclization of hydrazones, and semicarbazones of methyl ketones in Vilsmeier–Haack reaction [12]. Other examples of synthesis of pyrazole derivatives are using aliphatic diazocompounds in cycloaddition reaction [13]. In the most cases, starting hydrazine derivatives are noncommercial product and must be prepared. A lot them are toxic, explosive, and unstable at room temperature. So, development of new methods for preparation of pyrazole ring is actual task.

Here, we present a simple and convenient method for the synthesis of ethyl 3-formyl-1-aryl-1*H*-pyrazole-4-carboxylates from aromatic amines *via* diazonium salts. Aromatic amines are commercial available product and easy can be transformed into diazonium salts and used without isolation. Azocoupling of diazonium salts **1** with ethyl 2-methyl-3-oxobutanoate **2** in the presence of AcONa afforded the corresponding arylhydrazones **3** in a moderate yield.

RESULTS AND DISCUSSION

Cyclization of hydrazones of methyl ketones is widely reported in literature [12]. However, in all cases,

nonfunctional pyrazolecarbaldehydes were prepared except [12f,g]. Treatment **3a–m** with three equivalents of Vilsmeier–Haack complex affords pyrazoles (Scheme 1). Reaction proceeded at 70°C. After completion of the reactions, the resulting mixtures were poured into water, extracted with ethyl acetate. The organic layers were washed with water, dried over anhydrous sodium sulfate, and concentrated to give crude products. The pure compounds **4** were obtained by recrystallization.

Both electron-donating and electron-withdrawing substituents are tolerated; giving the corresponding products that can be isolated in pure state in yields 55–96%.

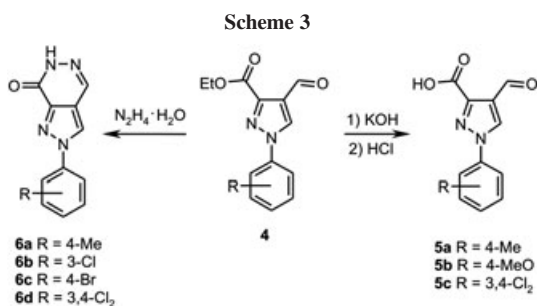
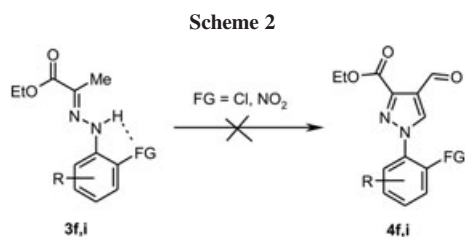
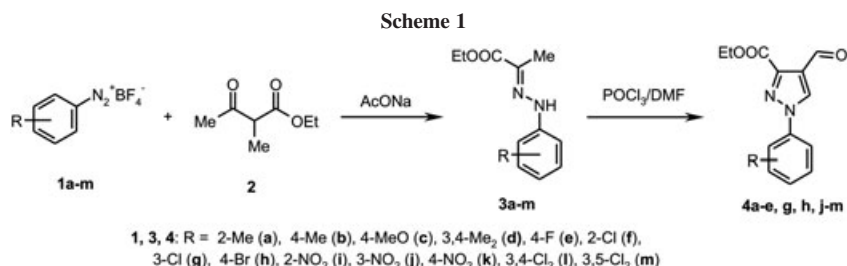
In the case of compound **3f,i** possessing functional groups in ortho-position compounds **4** are not formed. It can be explained by formation of hydrogen bond that deactivated NH-group (Scheme 2). Methyl group do not form hydrogen bond and compound **3a** undergo formylation and cyclization normally.

Aromatic or heteroaromatic compounds possessing two carbonyl groups in the ortho-positions are versatile building blocks for the synthesis of condensed heterocycles such as fused [c]furans [14], [c]thiophenes [15], [c]pyrroles [16], and [d]oxazines [17]. We have also studied some properties of the compounds **4**. It was established, that in 0.2*M* potassium hydroxide solution, EtOH/H₂O (1:1.5) pyrazoles **4** are converted to the corresponding acids **5a–c** (Scheme 3). Hydrazinolysis of this compounds leads to the anelation pyridazine ring (compounds **6a–d**).

In conclusion, we have described a simple and highly efficient method for the synthesis of 1-aryl-4-formyl-1*H*-pyrazole-3-carboxylates from various aromatic amines. The mild conditions, the simple experimental protocol, and high yields are the major advantages of this procedure.

EXPERIMENTAL

¹H-NMR and ¹³C-NMR spectra were recorded on a Varian Mercury 400 (400 MHz for ¹H) or Varian Gemini (200 MHz for ¹H, 50 MHz for ¹³C). The ¹H and ¹³C chemical shifts are reported



in parts per million (ppm) relative to deuterated solvent as an internal reference.

General procedure for the synthesis of ethyl 2-(2-arylhydrazinylidene)propanoates (3a–m). A solution of the ethyl 2-methyl-3-oxo-butyrate **2** (1.44 g, 10 mmol) and sodium acetate trihydrate (2.04 g, 15 mmol) in ethanol (30 mL) was cooled in an ice bath to 0–5°C. To the solution, while being stirred, arenediazonium tetrafluoroborate **1** (10 mmol) was added slowly. The reaction mixture was stirred for 4 h at 0°C. The ethanol was evaporated to half-volume, and mixture was poured into 50 g of ice-water mixture. The precipitated solid was collected and recrystallized from ethanol.

Ethyl 2-[2-(2-methylphenyl)hydrazinylidene]propanoate (3a). Yield: 1.50 g (68%); mp 75°C. ¹H-NMR (CDCl₃, 200 MHz) δ: 1.39 (t, *J* = 7.1 Hz, 3H, CH₃CH₂), 2.12 (s, 3H, CH₃), 2.26 (s, 3H, CH₃), 4.32 (q, *J* = 7.1 Hz, 2H, CH₂), 6.90 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.11 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.23 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.53 (br s, 1H, NH), 7.60 (d, *J* = 7.6 Hz, 1H, Ar-H); ¹³C-NMR (CDCl₃, 50 MHz) δ: 10.1, 14.3, 16.8, 61.2, 114.0, 121.4, 121.7, 127.4, 130.4, 133.2, 143.1, 165.2. Anal. Calcd. for C₁₂H₁₆N₂O₂: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.26; H, 7.18; N, 12.57.

Ethyl 2-[2-(4-methylphenyl)hydrazinylidene]propanoate (3b). Yield: 1.48 g (67%); mp 87°C. ¹H-NMR (CDCl₃, 200 MHz) δ: 1.37 (t, *J* = 7.2 Hz, 3H, CH₃CH₂), 2.09 (s, 3H, CH₃), 2.29 (s, 3H,

CH₃), 4.31 (q, *J* = 7.2 Hz, 2H, CH₂), 7.10 (br s, 4H, Ar-H), 7.71 (br s, 1H, NH); ¹³C-NMR (CDCl₃, 50 MHz) δ: 10.2, 14.3, 20.7, 61.1, 113.9 (2C), 122.5, 129.7 (2C), 131.7, 140.9, 165.3. Anal. Calcd. for C₁₂H₁₆N₂O₂: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.58; H, 7.23; N, 12.85.

Ethyl 2-[2-(4-methoxyphenyl)hydrazinylidene]propanoate (3c). Yield: 1.56 g (66%); mp 71°C. ¹H-NMR (CDCl₃, 200 MHz) δ: 1.37 (t, *J* = 7.2 Hz, 3H, CH₃CH₂), 2.08 (s, 3H, CH₃), 3.78 (s, 3H, CH₃O), 4.30 (q, *J* = 7.2 Hz, 2H, CH₂), 6.85 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.15 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.69 (br s, 1H, NH); ¹³C-NMR (CDCl₃, 50 MHz) δ: 10.2, 14.3, 55.5, 61.1, 114.6 (2C), 115.2 (2C), 131.3, 137.2, 155.0, 165.3. Anal. Calcd. for C₁₂H₁₆N₂O₃: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.16; H, 6.68; N, 11.98.

Ethyl 2-[2-(3,4-dimethylphenyl)hydrazinylidene]propanoate (3d). Yield: 1.48 g (63%); mp 67°C. ¹H-NMR (CDCl₃, 200 MHz) δ: 1.38 (t, *J* = 7.1 Hz, 3H, CH₃CH₂), 2.09 (s, 3H, CH₃), 2.28 (s, 3H, CH₃), 2.33 (s, 3H, CH₃), 4.31 (q, *J* = 7.1 Hz, 2H, CH₂), 6.87 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.03 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H, Ar-H), 7.15 (d, *J* = 2.4 Hz, 1H, Ar-H), 7.72 (br s, 1H, NH); ¹³C-NMR (CDCl₃, 50 MHz) δ: 10.2, 14.3, 20.5, 21.2, 61.0, 112.1, 118.6, 123.8, 129.2, 132.0, 139.8, 144.4, 165.3. Anal. Calcd. for C₁₃H₁₈N₂O₂: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.42; H, 7.63; N, 11.85.

Ethyl 2-[2-(4-fluorophenyl)hydrazinylidene]propanoate (3e). Yield: 1.79 g (80%); mp 81°C. ¹H-NMR (CDCl₃, 200 MHz) δ: 1.37 (t, *J* = 7.1 Hz, 3H, CH₃CH₂), 2.09 (s, 3H, CH₃), 4.31 (q, *J* = 7.1 Hz, 2H, CH₂), 6.99 (t, *J* = 8.8 Hz, 2H, Ar-H), 7.16 (dd, *J* = 8.8 Hz, 4.6 Hz, 2H, Ar-H), 7.76 (br s, 1H, NH); ¹³C-NMR (CDCl₃, 50 MHz) δ: 10.3, 14.3, 61.2, 115.1 (d, *J*_{C-F} = 8.0 Hz, 2C), 115.9 (d, *J*_{C-F} = 23.0 Hz, 2C), 132.5, 139.5, 158.3 (d, *J*_{C-F} = 238.6 Hz, 1C), 165.2. Anal. Calcd. for C₁₁H₁₃FN₂O₂: C, 58.92; H, 5.84; N, 12.49. Found: C, 58.69; H, 5.68; N, 12.58.

Ethyl 2-[2-(2-chlorophenyl)hydrazinylidene]propanoate (3f). Yield: 2.12 g (88%); mp 100°C. ¹H-NMR (CDCl₃, 200 MHz) δ: 1.38 (t, *J* = 7.1 Hz, 3H, CH₃CH₂), 2.15 (s, 3H, CH₃), 4.33 (q, *J* = 7.2 Hz, 2H, CH₂), 6.89 (dt, *J* = 8.0 Hz, 1.4 Hz, 1H, Ar-H), 7.22–7.31 (m, 2H, Ar-H), 7.68 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.09 (br s, 1H, NH); ¹³C-NMR (CDCl₃, 50 MHz) δ: 10.4, 14.3, 61.3, 115.2, 118.4, 121.9, 128.0, 129.0, 135.1, 139.1, 164.9. Anal. Calcd. for C₁₁H₁₃ClN₂O₂: C, 54.89; H, 5.44; N, 11.64. Found: C, 54.69; H, 5.62; N, 11.58.

Ethyl 2-[2-(3-chlorophenyl)hydrazinylidene]propanoate (3g). Yield: 1.95 g (81%); mp 59°C. ¹H-NMR (CDCl₃, 200 MHz) δ: 1.38 (t, *J* = 7.2 Hz, 3H, CH₃CH₂), 2.11 (s, 3H, CH₃), 4.32 (q, *J* = 7.2 Hz, 2H, CH₂), 6.92 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.03 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.20 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.25 (s, 1H, Ar-H), 7.74 (br s, 1H, NH); ¹³C-NMR (CDCl₃, 50 MHz) δ: 10.4, 14.3, 61.4, 112.1, 114.1, 121.9, 130.3, 133.7, 135.1, 144.4, 165.0. Anal. Calcd. for C₁₁H₁₃ClN₂O₂: C, 54.89; H, 5.44; N, 11.64. Found: C, 54.73; H, 5.33; N, 11.69.

Ethyl 2-[2-(4-bromophenyl)hydrazinylidene]propanoate (3h).

Yield: 2.22 g (78%); mp 154°C. ¹H-NMR (CDCl₃, 200 MHz) δ: 1.37 (t, *J* = 7.1 Hz, 3H, CH₃CH₂), 2.09 (s, 3H, CH₃), 4.31 (q, *J* = 7.1 Hz, 2H, CH₂), 7.08 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.38 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.76 (br s, 1H, NH); ¹³C-NMR (CDCl₃, 50 MHz) δ: 10.4, 14.3, 61.3, 115.6 (2C), 126.2, 132.1 (2C), 133.3, 142.3, 165.0. Anal. Calcd. for C₁₁H₁₃BrN₂O₂: C, 46.33; H, 4.60; N, 9.82. Found: C, 46.54; H, 4.51; N, 9.96.

Ethyl 2-[2-(2-nitrophenyl)hydrazinylidene]propanoate (3i).

Yield: 1.68 g (67%); mp 110°C. ¹H-NMR (CDCl₃, 200 MHz) δ: 1.39 (t, *J* = 7.1 Hz, 3H, CH₃CH₂), 2.25 (s, 3H, CH₃), 2.39 (q, *J* = 7.1 Hz, 2H, CH₂), 6.94–7.01 (m, 1H, Ar-H), 7.54–7.62 (m, 1H, Ar-H), 7.98–8.04 (m, 1H, Ar-H), 8.17 (d, *J* = 8.4 Hz, 1H, Ar-H), 10.95 (br s, 1H, NH); ¹³C-NMR (CDCl₃, 50 MHz) δ: 11.7, 14.3, 61.7, 116.8, 120.3, 125.8, 132.7, 136.3, 139.2, 140.6, 162.5. Anal. Calcd. for C₁₁H₁₃N₃O₄: C, 52.59; H, 5.22; N, 16.72. Found: C, 52.27; H, 5.29; N, 16.58.

Ethyl 2-[2-(3-nitrophenyl)hydrazinylidene]propanoate (3j).

Yield: 1.63 g (65%); mp 143°C. ¹H-NMR (CDCl₃, 200 MHz) δ: 1.40 (t, *J* = 7.2 Hz, 3H, CH₃CH₂), 2.17 (s, 3H, CH₃), 4.34 (q, *J* = 7.2 Hz, 2H, CH₂), 7.43 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.58 (ddd, *J* = 8.0 Hz, 2.0 Hz, 1.0 Hz, 1H, Ar-H), 7.77 (ddd, *J* = 8.0 Hz, 2.0 Hz, 1.0 Hz, 1H, Ar-H), 8.01 (t, *J* = 2.0 Hz, 1H, Ar-H), 8.13 (br s, 1H, NH); ¹³C-NMR (CDCl₃, 50 MHz) δ: 10.7, 14.3, 61.6, 108.7, 116.2, 119.7, 130.1, 135.2, 144.5, 149.0, 164.8. Anal. Calcd. for C₁₁H₁₃N₃O₄: C, 52.59; H, 5.22; N, 16.72. Found: C, 52.70; H, 5.31; N, 16.83.

Ethyl 2-[2-(4-nitrophenyl)hydrazinylidene]propanoate (3k).

Yield: 1.81 g (72%); mp 171°C. ¹H-NMR (CDCl₃, 200 MHz) δ: 1.40 (t, *J* = 7.0 Hz, 3H, CH₃CH₂), 2.18 (s, 3H, CH₃), 4.35 (q, *J* = 7.0 Hz, 2H, CH₂), 7.27 (d, *J* = 9.2 Hz, 2H, Ar-H), 8.06 (br s, 1H, NH), 8.21 (d, *J* = 9.2 Hz, 2H, Ar-H); ¹³C-NMR (CDCl₃, 50 MHz) δ: 10.8, 14.3, 61.7, 112.7, 113.4 (2C), 125.9 (2C), 136.9, 148.3, 164.5. Anal. Calcd. for C₁₁H₁₃N₃O₄: C, 52.59; H, 5.22; N, 16.72. Found: C, 52.74; H, 5.34; N, 16.55.

Ethyl 2-[2-(3,4-dichlorophenyl)hydrazinylidene]propanoate (3l).

Yield: 1.68 g (61%); mp 125°C. ¹H-NMR (CDCl₃, 200 MHz) δ: 1.38 (t, *J* = 7.1 Hz, 3H, CH₃CH₂), 2.10 (s, 3H, CH₃), 4.32 (q, *J* = 7.1 Hz, 2H, CH₂), 7.01 (dd, *J* = 8.8 Hz, 2.5 Hz, 1H, Ar-H), 7.32 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.34 (d, *J* = 2.5 Hz, 1H, Ar-H), 7.75 (br s, 1H, NH); ¹³C-NMR (CDCl₃, 50 MHz) δ: 10.5, 14.3, 61.5, 113.4, 115.6, 124.7, 130.8, 133.2, 134.3, 142.8, 164.8. Anal. Calcd. for C₁₁H₁₂Cl₂N₂O₂: C, 48.02; H, 4.40; N, 10.18. Found: C, 47.87; H, 4.29; N, 10.08.

Ethyl 2-[2-(3,5-dichlorophenyl)hydrazinylidene]propanoate (3m).

Yield: 1.84 g (67%); mp 115°C. ¹H-NMR (CDCl₃, 200 MHz) δ: 1.39 (t, *J* = 7.1 Hz, 3H, CH₃CH₂), 2.10 (s, 3H, CH₃), 4.33 (q, *J* = 7.1 Hz, 2H, CH₂), 6.93 (s, 1H, Ar-H), 7.10 (s, 2H, Ar-H), 7.73 (br s, 1H, NH); ¹³C-NMR (CDCl₃, 50 MHz) δ: 10.6, 14.3, 61.6, 111.8, 112.5 (2C), 121.7 (2C), 135.7, 145.0, 164.7. Anal. Calcd. for C₁₁H₁₂Cl₂N₂O₂: C, 48.02; H, 4.40; N, 10.18. Found: C, 48.23; H, 4.27; N, 10.30.

General procedure for the synthesis of ethyl 1-aryl-4-formyl-1*H*-pyrazole-3-carboxylates (4a–m). The Vilsmeier–Haack reagent was prepared by adding of 1.4 mL (15 mmol) POCl₃ to 1.5 mL DMF at 0°C in a round-bottomed flask in an ice-cold condition (0–5°C) under constant stirring. Appropriate ethyl 2-(2-arylhydrazinylidene)propanoates **3a–m** (5 mmol) in 5 mL DMF were added to the Vilsmeier–Haack reagent and stirred for further an hour, and the reaction mixture was kept on a water bath at 70°C for 4 h. After the reaction, the mixture was poured into 20 g of crushed ice

under constant manual stirring. After neutralization with K₂CO₃ solution, ethyl acetate (30 mL) was added. The organic phase was separated and the aqueous phase extracted with AcOEt (2 × 30 mL). The combined organic solutions were washed with water (30 mL) and brine (30 mL), dried, and concentrated. The product was isolated by recrystallization from ethanol.

Ethyl 4-formyl-1-(2-methylphenyl)-1*H*-pyrazole-3-carboxylate (4a).

Yield: 0.94 g (73%); mp 99°C. ¹H-NMR (CDCl₃, 200 MHz) δ: 1.45 (t, *J* = 7.1 Hz, 3H, CH₃CH₂), 2.24 (s, 3H, CH₃), 4.51 (q, *J* = 7.1 Hz, 2H, CH₂), 7.30–7.42 (m, 4H, Ar-H), 8.18 (s, 1H, CH_{pyr}), 10.50 (s, 1H, CHO); ¹³C-NMR (CDCl₃, 50 MHz) δ: 14.3, 17.7, 61.8, 124.9, 126.1, 126.8, 129.9, 131.4, 133.6, 133.9, 138.4, 143.9, 161.4, 186.6. Anal. Calcd. for C₁₄H₁₄N₂O₃: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.93; H, 5.54; N, 10.67.

Ethyl 4-formyl-1-(4-methylphenyl)-1*H*-pyrazole-3-carboxylate (4b).

Yield: 1.05 g (81%); mp 112°C. ¹H-NMR (CDCl₃, 200 MHz) δ: 1.47 (t, *J* = 7.1 Hz, 3H, CH₃CH₂), 2.41 (s, 3H, CH₃), 4.52 (q, *J* = 7.1 Hz, 2H, CH₂), 7.30 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.64 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.46 (s, 1H, CH_{pyr}), 10.46 (s, 1H, CHO); ¹³C-NMR (CDCl₃, 50 MHz) δ: 14.3, 21.0, 61.8, 120.2 (2C), 125.5, 129.9, 130.1 (2C), 136.3, 138.8, 144.1, 161.3, 186.5. Anal. Calcd. for C₁₄H₁₄N₂O₃: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.01; H, 5.32; N, 10.70.

Ethyl 4-formyl-1-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate (4c).

Yield: 0.88 g (64%); mp 94°C. ¹H-NMR (CDCl₃, 200 MHz) δ: 1.47 (t, *J* = 7.1 Hz, 3H, CH₃CH₂), 3.86 (s, 3H, CH₃), 4.52 (q, *J* = 7.1 Hz, 2H, CH₂), 7.00 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.65 (d, *J* = 9.0 Hz, 2H, Ar-H), 8.40 (s, 1H, CH_{pyr}), 10.46 (s, 1H, CHO); ¹³C-NMR (CDCl₃, 50 MHz) δ: 14.3, 55.6, 61.8, 114.7 (2C), 121.9 (2C), 125.4, 129.9, 132.1, 144.0, 159.8, 161.4, 186.5. Anal. Calcd. for C₁₄H₁₄N₂O₄: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.08; H, 5.31; N, 10.36.

Ethyl 1-(3,4-dimethylphenyl)-4-formyl-1*H*-pyrazole-3-carboxylate (4d).

Yield: 1.20 g (88%); mp 97°C. ¹H-NMR (CDCl₃, 200 MHz) δ: 1.47 (t, *J* = 7.1 Hz, 3H, CH₃CH₂), 2.31 (s, 3H, CH₃), 2.33 (s, 3H, CH₃), 4.52 (q, *J* = 7.1 Hz, 2H, CH₂), 7.23 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.43 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H, Ar-H), 7.55 (d, *J* = 2.4 Hz, 1H, Ar-H), 8.44 (s, 1H, CH_{pyr}), 10.45 (s, 1H, CHO); ¹³C-NMR (CDCl₃, 50 MHz) δ: 14.3, 19.4, 19.8, 61.8, 117.5, 121.4, 125.4, 129.9, 130.5, 136.5, 137.5, 138.3, 144.0, 161.4, 186.5. Anal. Calcd. for C₁₅H₁₆N₂O₃: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.38; H, 5.75; N, 10.36.

Ethyl 1-(4-fluorophenyl)-4-formyl-1*H*-pyrazole-3-carboxylate (4e).

Yield: 0.90 g (69%); mp 84°C. ¹H-NMR (DMSO-*d*₆, 400 MHz) δ: 1.43 (t, *J* = 7.2 Hz, 3H, CH₃), 4.43 (q, *J* = 7.2 Hz, 2H, CH₂), 7.21 (t, *J* = 8.8 Hz, 2H, Ar-H), 8.04 (dd, *J*_{HH} = 8.8 Hz, *J*_{HF} = 4.8 Hz, 2H, Ar-H), 9.19 (s, 1H, CH_{pyr}), 10.31 (s, 1H, CHO); ¹³C-NMR (CDCl₃, 50 MHz) δ: 14.3, 62.0, 116.6 (d, *J*_{C-F} = 23.0 Hz, 2C), 122.4 (d, *J*_{C-F} = 8.7 Hz, 2C), 125.7, 130.2, 136.7, 144.4, 161.2, 162.3 (d, *J*_{C-F} = 248.4 Hz, 1C) 186.4. Anal. Calcd. for C₁₃H₁₁FN₂O₃: C, 59.54; H, 4.23; N, 10.68. Found: C, 59.79; H, 4.41; N, 10.47.

Ethyl 1-(3-chlorophenyl)-4-formyl-1*H*-pyrazole-3-carboxylate (4g).

Yield: 0.82 g (59%); mp 94°C. ¹H-NMR (DMSO-*d*₆, 400 MHz) δ: 1.43 (t, *J* = 7.2, 3H, CH₃), 4.44 (q, *J* = 7.2, 2H, CH₂), 7.44 (d, *J* = 8.4, 1H, Ar-H), 7.55 (t, *J* = 8.4, 1H, Ar-H), 8.00 (d, *J* = 8.4, 1H, Ar-H), 8.10 (s, 1H, Ar-H), 9.30 (s, 1H, CH_{pyr}), 10.31 (s, 1H, CHO); ¹³C-NMR (CDCl₃, 50 MHz) δ: 14.3, 62.1, 118.1, 120.8, 125.8, 128.8, 130.1, 130.7, 135.7, 139.4, 144.6, 161.2, 186.3. Anal. Calcd. for C₁₃H₁₁ClN₂O₃: C, 56.03; H, 3.98; N, 10.05. Found: C, 55.87; H, 4.09; N, 10.23.

Ethyl 1-(4-bromophenyl)-4-formyl-1H-pyrazole-3-carboxylate (4h). Yield: 1.37 g (85%); mp 148°C. ¹H-NMR (CDCl₃, 200 MHz) δ: 1.47 (t, *J* = 7.1 Hz, 3H, CH₃), 4.52 (q, *J* = 7.2 Hz, 2H, CH₂), 7.65 (s, 4H, Ar-H), 8.50 (s, 1H, CH_{pyr}), 10.49 (s, 1H, CHO); ¹³C-NMR (CDCl₃, 50 MHz) δ: 14.3, 62.0, 121.7 (2C), 122.4, 125.8, 129.9, 132.8 (2C), 137.5, 144.5, 161.1, 186.3. Anal. Calcd. for C₁₃H₁₁BrN₂O₃: C, 48.32; H, 3.43; N, 8.67. Found: C, 48.09; H, 3.35; N, 8.89.

Ethyl 4-formyl-1-(3-nitrophenyl)-1H-pyrazole-3-carboxylate (4j). Yield: 1.20 g (83%); mp 165°C. ¹H-NMR (DMSO-*d*₆, 200 MHz): δ = 1.37 (t, *J* = 7.1 Hz, 3H, CH₃), 4.41 (q, *J* = 7.1 Hz, 2H, CH₂), 7.81 (t, *J* = 8.0 Hz, 1H, Ar-H), 8.24 (dd, *J* = 8.0 Hz, 1.4 Hz, 1H, Ar-H), 8.39 (dd, *J* = 8.0 Hz, 1.4 Hz, 1H, Ar-H), 8.68 (d, *J* = 1.4 Hz, 1H, Ar-H), 9.40 (s, 1H, CH_{pyr}), 10.25 (s, 1H, CHO); ¹³C-NMR (DMSO-*d*₆, 50 MHz): δ = 14.1, 61.6, 114.5, 122.7, 125.3, 125.6, 131.3, 132.4, 138.9, 144.2, 148.4, 160.6, 185.8. Anal. Calcd. for C₁₃H₁₁N₃O₅: C, 53.98; H, 3.83; N, 14.53. Found: C, 53.80; H, 3.72; N, 14.71.

Ethyl 4-formyl-1-(4-nitrophenyl)-1H-pyrazole-3-carboxylate (4k). Yield: 1.07 g (74%); mp 146°C. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ = 1.44 (t, *J* = 7.2 Hz, 3H, CH₃), 4.45 (q, *J* = 7.2 Hz, 2H, CH₂), 8.32 (d, *J* = 9.2 Hz, 2H, Ar-H), 8.38 (d, *J* = 9.2 Hz, 2H, Ar-H), 9.45 (s, 1H, CH_{pyr}), 10.32 (s, 1H, CHO); ¹³C-NMR (DMSO-*d*₆, 50 MHz): δ = 14.1, 61.7, 120.3 (2C), 125.3 (2C), 125.5, 132.5, 142.5, 144.7, 146.4, 160.6, 185.9. Anal. Calcd. for C₁₃H₁₁N₃O₅: C, 53.98; H, 3.83; N, 14.53. Found: C, 54.16; H, 3.76; N, 14.39.

Ethyl 1-(3,4-dichlorophenyl)-4-formyl-1H-pyrazole-3-carboxylate (4l). Yield: 0.86 g (55%); mp 174°C. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ = 1.44 (t, *J* = 7.2 Hz, 3H, CH₃), 4.44 (q, *J* = 7.2 Hz, 2H, CH₂), 7.70 (d, *J* = 8.8 Hz, 1H, Ar-H), 8.03 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H, Ar-H), 8.30 (d, *J* = 2.4 Hz, 1H, Ar-H), 9.34 (s, 1H, CH_{pyr}), 10.31 (s, 1H, CHO); ¹³C-NMR (50 MHz, CDCl₃): δ = 14.3, 62.1, 119.0, 122.2, 126.0, 130.0, 131.3, 132.9, 134.1, 137.6, 144.7, 161.0, 186.2. Anal. Calcd. for C₁₃H₁₀Cl₂N₂O₃: C, 49.86; H, 3.22; N, 8.95. Found: C, 49.65; H, 3.08; N, 8.79.

Ethyl 1-(3,5-dichlorophenyl)-4-formyl-1H-pyrazole-3-carboxylate (4m). Yield: 1.50 g (96%); mp 233°C. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ = 1.44 (t, *J* = 7.2 Hz, 3H, CH₃), 4.44 (q, *J* = 7.2 Hz, 2H, CH₂), 7.51 (s, 1H, Ar-H), 8.03 (s, 2H, Ar-H), 9.41 (s, 1H, CH_{pyr}), 10.30 (s, 1H, CHO); ¹³C-NMR (CDCl₃, 50 MHz): δ = 14.3, 62.2, 118.8 (2C), 126.1, 128.7 (2C), 130.2, 136.3, 139.9, 144.8, 161.0, 186.1. Anal. Calcd. for C₁₃H₁₀Cl₂N₂O₃: C, 49.86; H, 3.22; N, 8.95. Found: C, 50.03; H, 3.12; N, 8.83.

General procedure for the synthesis of 1-aryl-4-formyl-1H-pyrazole-3-carboxylic acid (5a–c). To a solution of ethyl 1-aryl-4-formyl-1H-pyrazole-3-carboxylate (**4b,c** or **4l**) (1 mmol) in 6 mL ethanol was added a solution of 112 mg (2 mmol) KOH in 4 mL water and refluxed for 30 min. After cooling in ice, the reaction mixture was acidified with aqueous HCl (10%). The resulting precipitate was filtered off and recrystallized from ethanol.

4-Formyl-1-(4-methylphenyl)-1H-pyrazole-3-carboxylic acid (5a). Yield: 200 mg (87%); mp 230°C. ¹H-NMR (DMSO-*d*₆, 200 MHz) δ: 2.35 (s, 3H, CH₃), 7.34 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.83 (d, *J* = 8.4 Hz, 2H, Ar-H), 9.12 (s, 1H, CH_{pyr}), 10.31 (s, 1H, CHO), 13.69 (br s, 1H, CO₂H); ¹³C-NMR (DMSO-*d*₆, 50 MHz) δ: 20.6, 119.6 (2C), 124.9, 130.1 (2C), 131.0, 136.2, 138.0, 144.7, 162.5, 186.4. Anal. Calcd. for C₁₂H₁₀N₂O₃: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.39; H, 4.49; N, 12.02.

4-Formyl-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylic acid (5b). Yield: 202 mg (82%); mp 168°C. ¹H-NMR (DMSO-*d*₆,

200 MHz) δ: 3.80 (s, 3H, CH₃), 7.07 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.85 (d, *J* = 8.8 Hz, 2H, Ar-H), 9.05 (s, 1H, CH_{pyr}), 10.30 (s, 1H, CHO); ¹³C-NMR (DMSO-*d*₆, 50 MHz) δ: 55.6, 114.7 (2C), 121.4 (2C), 124.9, 130.9, 131.9, 144.6, 159.1, 162.6, 186.4. Anal. Calcd. for C₁₂H₁₀N₂O₄: C, 58.54; H, 4.09; N, 11.38. Found: C, 58.38; H, 4.21; N, 11.12.

1-(3,4-Dichlorophenyl)-4-formyl-1H-pyrazole-3-carboxylic acid (5c). Yield: 231 mg (81%); mp 225°C. ¹H-NMR (DMSO-*d*₆, 200 MHz) δ: 7.80 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.96 (d, *J* = 8.4 Hz, 1H, Ar-H), 8.28 (s, 1H, Ar-H), 9.25 (s, 1H, CH_{pyr}), 10.34 (s, 1H, CHO); ¹³C-NMR (DMSO-*d*₆, 50 MHz) δ: 119.7, 121.4, 125.1, 130.4, 131.6, 131.6, 132.2, 138.1, 146.9, 162.6, 186.8. Anal. Calcd. for C₁₁H₆Cl₂N₂O₃: C, 46.34; H, 2.12; N, 9.83. Found: C, 46.11; H, 2.08; N, 10.00.

General procedure for the synthesis of 2-aryl-2,6-dihydro-7H-pyrazolo[3,4-d]pyridazin-7-ones (6a–d). Ethyl 1-aryl-4-formyl-1H-pyrazole-3-carboxylate (**4b,g,h**, or **l**) (1 mmol) and hydrazine monohydrate 100 mg (2 mmol) in ethanol (3 mL) refluxed for 4 h. After cooling, the mixture was diluted with water (5 mL). The precipitate was filtered off and recrystallized from DMF-ethanol.

2-(4-Methylphenyl)-2,6-dihydro-7H-pyrazolo[3,4-d]pyridazin-7-one (6a). Yield: 172 mg (76%); mp > 300°C. ¹H-NMR (DMSO-*d*₆, 200 MHz) δ: 2.38 (s, 3H, CH₃), 7.40 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.90 (d, *J* = 8.0 Hz, 2H, Ar-H), 8.35 (s, 1H, CH_{pyridazine}), 9.13 (s, 1H, CH_{pyrazole}), 12.40 (s, 1H, NH); ¹³C-NMR (DMSO-*d*₆, 50 MHz) δ: 20.6, 119.5, 120.4 (2C), 125.2, 130.2 (2C), 133.1, 136.8, 138.5, 142.7, 156.5. Anal. Calcd. for C₁₂H₁₀N₄O: C, 63.71; H, 4.46; N, 24.76. Found: C, 63.56; H, 4.53; N, 24.63.

2-(3-Chlorophenyl)-2,6-dihydro-7H-pyrazolo[3,4-d]pyridazin-7-one (6b). Yield: 170 mg (69%); mp > 300°C. ¹H-NMR (DMSO-*d*₆, 400 MHz) δ: 7.47 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.60 (t, *J* = 7.6 Hz, 1H, Ar-H), 8.04 (d, *J* = 7.6 Hz, 1H, Ar-H), 8.16 (s, 1H, Ar-H), 8.26 (s, 1H, CH_{pyridazine}), 9.21 (s, 1H, CH_{pyrazole}), 12.27 (s, 1H, NH); ¹³C-NMR (DMSO-*d*₆, 50 MHz) δ: 119.2, 119.6, 120.4, 126.0, 128.6, 131.6, 133.1, 134.2, 140.1, 143.1, 156.4. Anal. Calcd. for C₁₁H₇ClN₄O: C, 53.56; H, 2.86; N, 22.71. Found: C, 53.34; H, 2.67; N, 22.56.

2-(4-Bromophenyl)-2,6-dihydro-7H-pyrazolo[3,4-d]pyridazin-7-one (6c). Yield: 227 mg (78%); mp > 300°C. ¹H-NMR (DMSO-*d*₆, 200 MHz) δ: 7.80 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.99 (d, *J* = 8.0 Hz, 2H, Ar-H), 8.36 (s, 1H, CH_{pyridazine}), 9.21 (s, 1H, CH_{pyrazole}), 12.42 (s, 1H, NH); ¹³C-NMR (DMSO-*d*₆, 50 MHz) δ: 119.6, 121.6, 122.5 (2C), 125.7, 132.7 (2C), 133.1, 138.2, 143.1, 156.4. Anal. Calcd. for C₁₁H₇BrN₄O: C, 45.39; H, 2.42; N, 19.25. Found: C, 45.62; H, 2.25; N, 19.43.

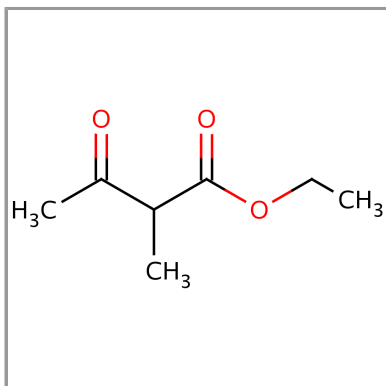
2-(3,4-Dichlorophenyl)-2,6-dihydro-7H-pyrazolo[3,4-d]pyridazin-7-one (6d). Yield: 202 mg (72%); mp > 300°C. ¹H-NMR (DMSO-*d*₆, 200 MHz) δ: 7.87 (d, *J* = 8.7 Hz, 1H, Ar-H), 8.05 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H, Ar-H), 8.35 (d, *J* = 2.4 Hz, 1H, Ar-H), 8.37 (s, 1H, CH_{pyridazine}), 9.27 (s, 1H, CH_{pyrazole}), 12.45 (s, 1H, NH); ¹³C-NMR (DMSO-*d*₆, 50 MHz) δ: 119.6, 120.6, 122.2, 126.1, 131.2, 131.7, 132.3, 133.1, 138.5, 143.2, 156.3. Anal. Calcd. for C₁₁H₆Cl₂N₄O: C, 47.00; H, 2.15; N, 19.93. Found: C, 47.16; H, 2.31; N, 19.79.

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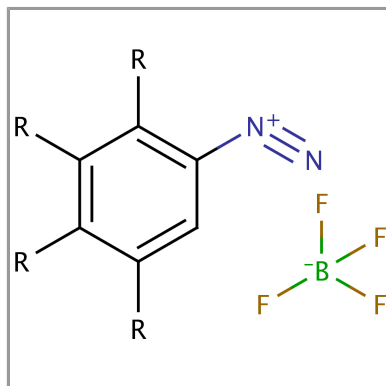
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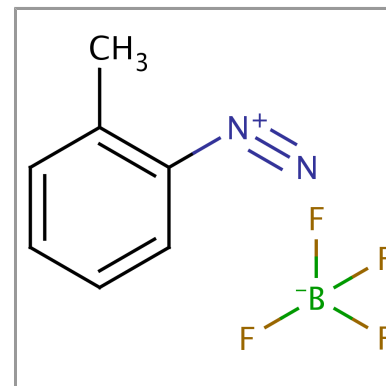
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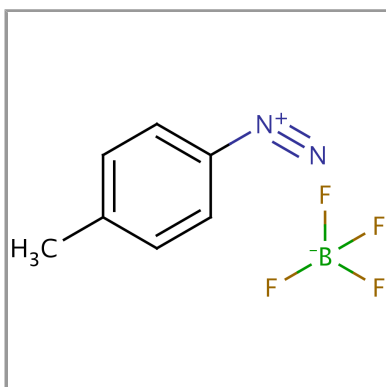
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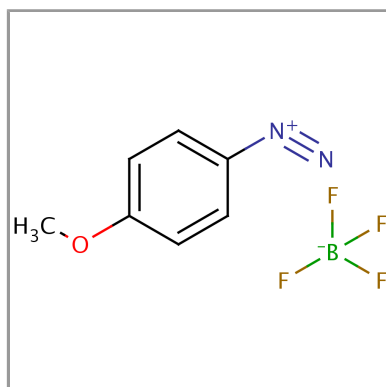
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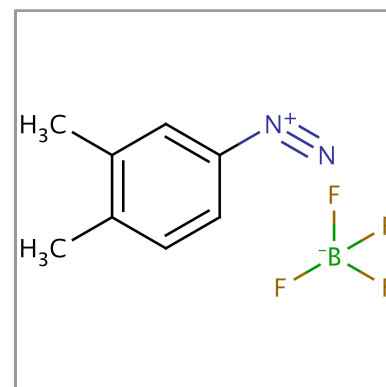
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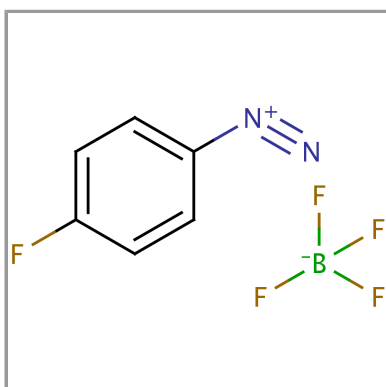
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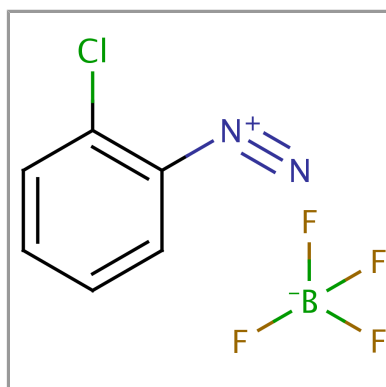
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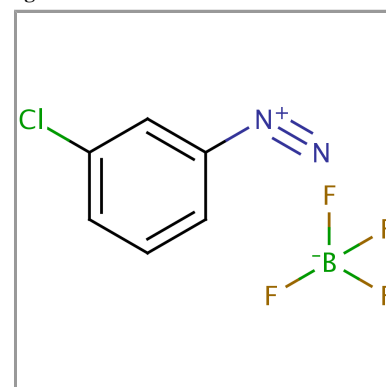
1f



[Compound Details](#)

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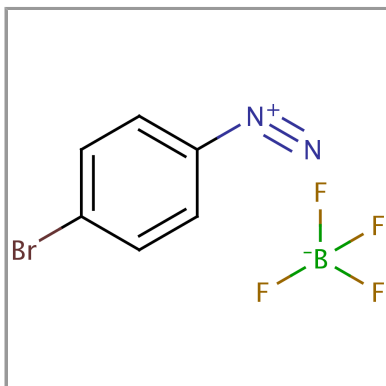
1g



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[Structure Search](#)

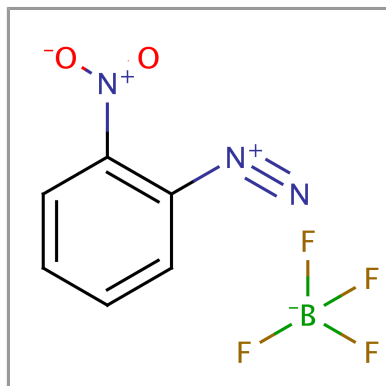
1h



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[Structure Search](#)

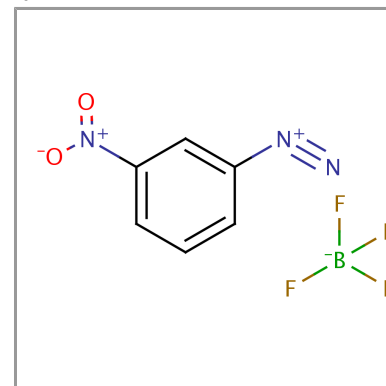
1i



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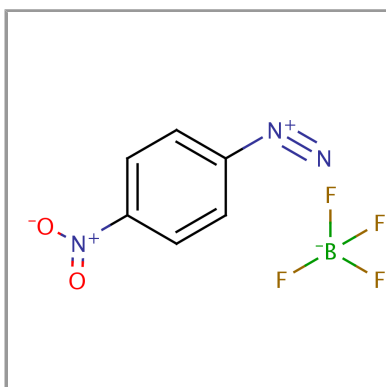
1j



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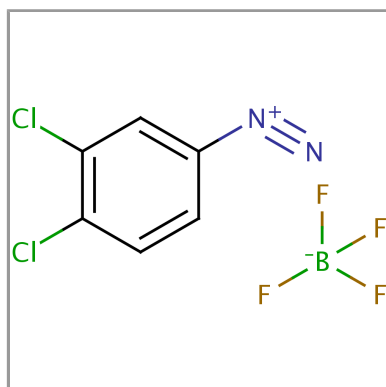
1k



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[Structure Search](#)

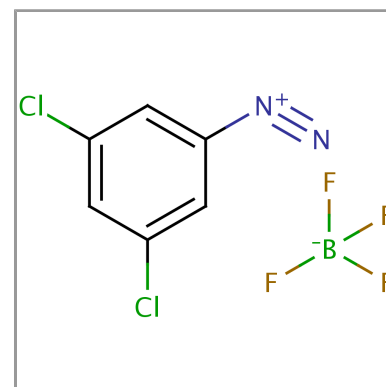
1l



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[Structure Search](#)

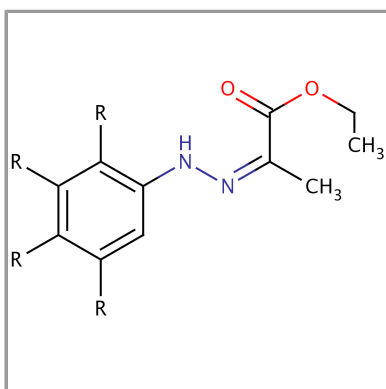
1m



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[Structure Search](#)

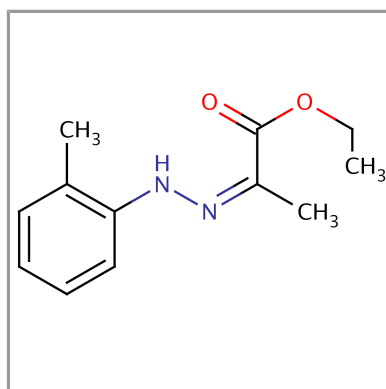
3



[Compound Details](#)

[Structure Search](#)

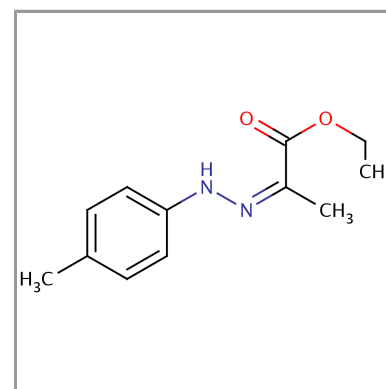
3a



[Compound Details](#)

[Structure Search](#)

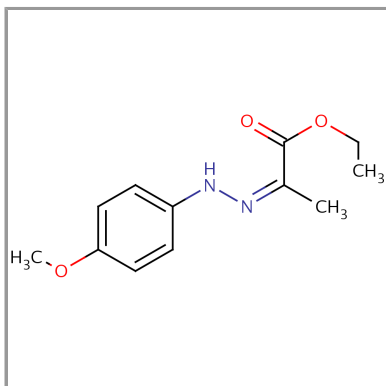
3b



[Compound Details](#)

[Structure Search](#)

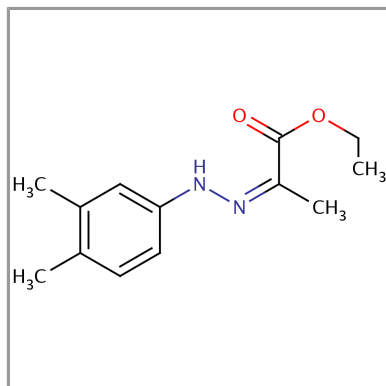
3c



[Compound Details](#)

[Structure Search](#)

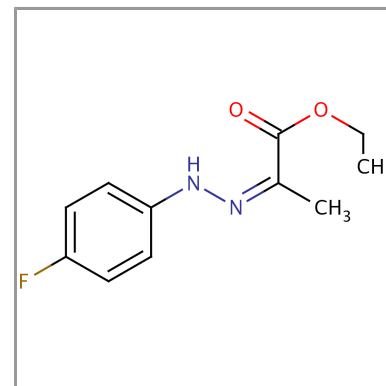
3d



[Compound Details](#)

[Structure Search](#)

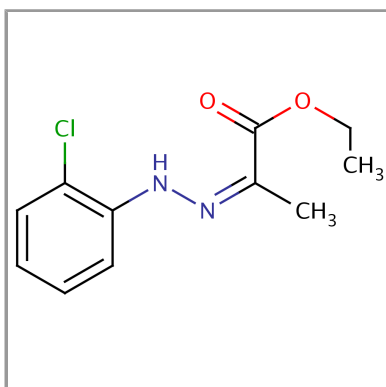
3e



[Compound Details](#)

[Structure Search](#)

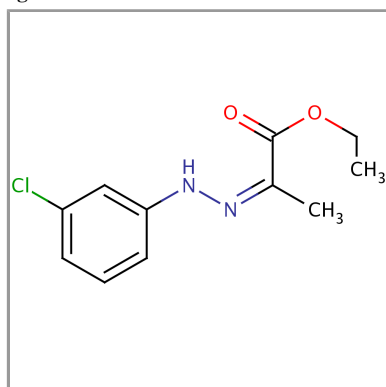
3f



[Compound Details](#)

[Structure Search](#)

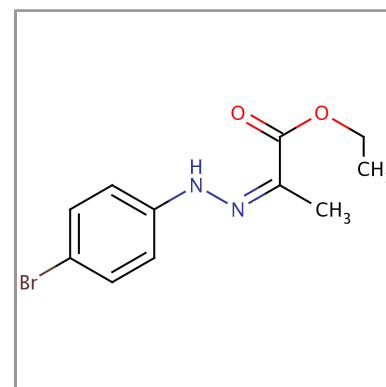
3g



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[Structure Search](#)

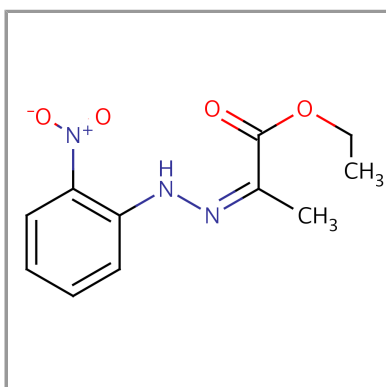
3h



[Compound Details](#)

[Structure Search](#)

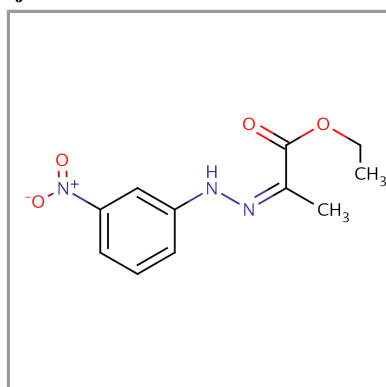
3i



[Compound Details](#)

[Structure Search](#)

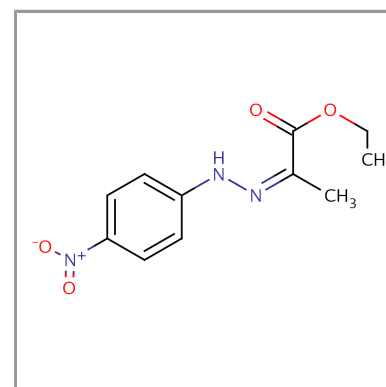
3j



[Compound Details](#)

[Structure Search](#)

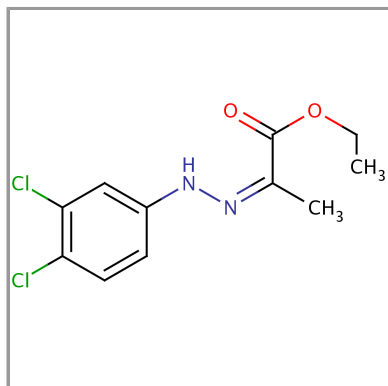
3k



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[Structure Search](#)

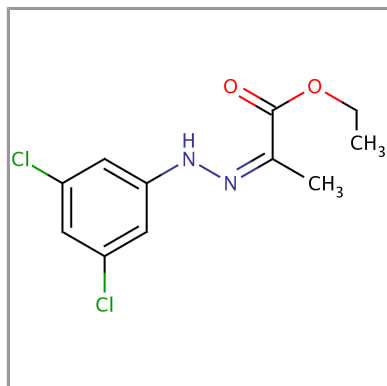
3l



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[Structure Search](#)

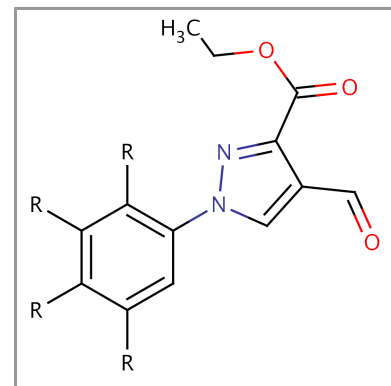
3m



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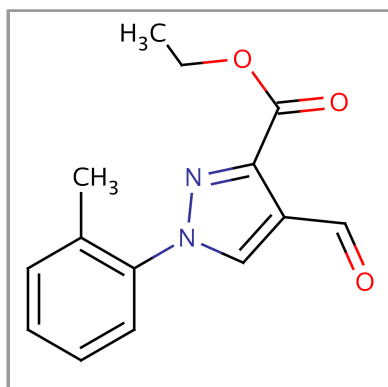
4



[Compound Details](#)

[Structure Search](#)

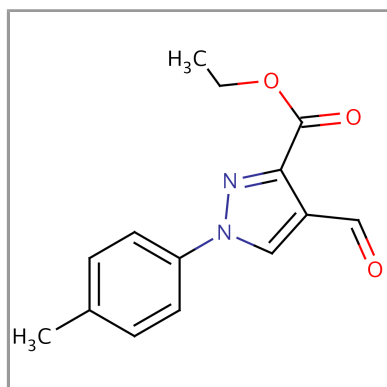
4a



[Compound Details](#)

[Structure Search](#)

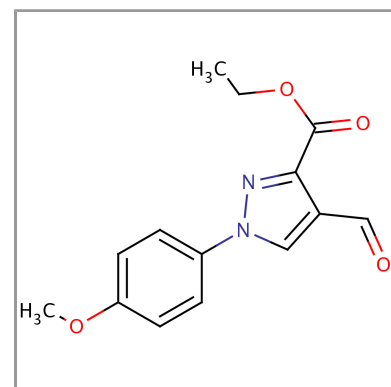
4b



[Compound Details](#)

[Structure Search](#)

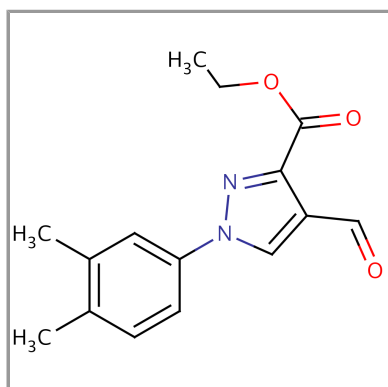
4c



[Compound Details](#)

[Structure Search](#)

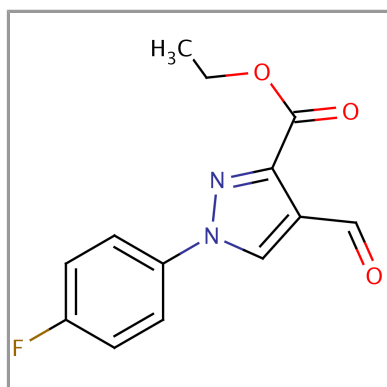
4d



[Compound Details](#)

[Structure Search](#)

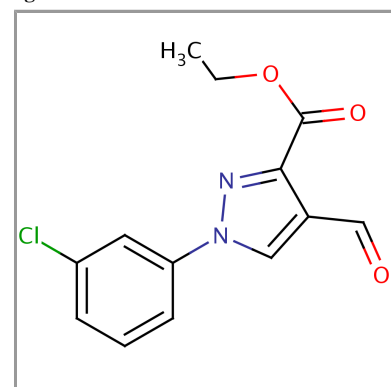
4e



[Compound Details](#)

[Structure Search](#)

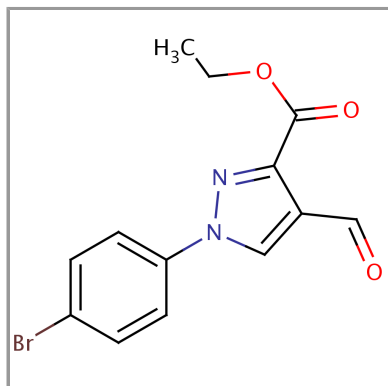
4g



[Compound Details](#)

[Structure Search](#)

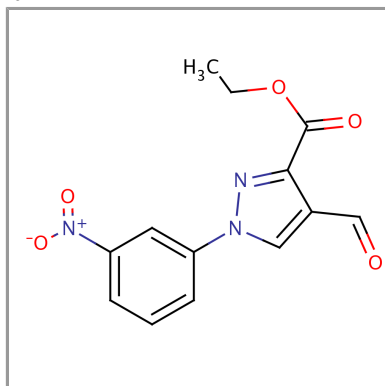
4h



[Compound Details](#)

[Structure Search](#)

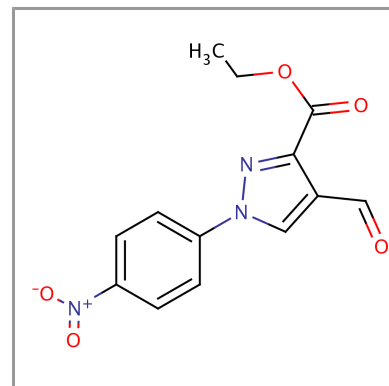
4j



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[Structure Search](#)

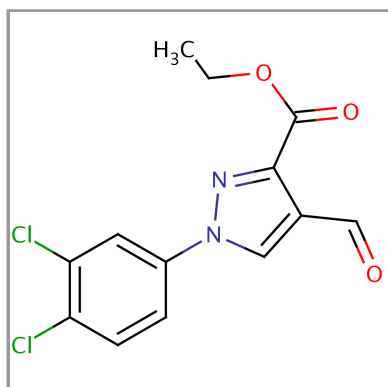
4k



[Compound Details](#)

[Structure Search](#)

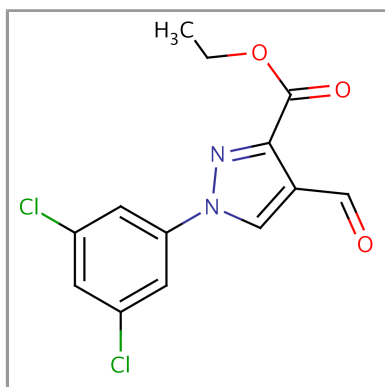
4l



[Compound Details](#)

[Structure Search](#)

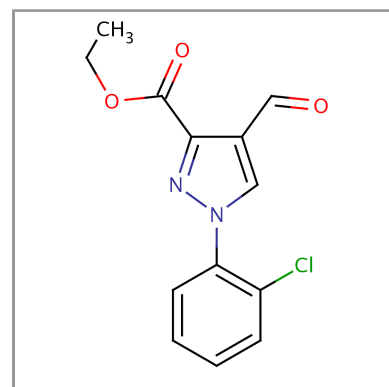
4m



[Compound Details](#)

[Structure Search](#)

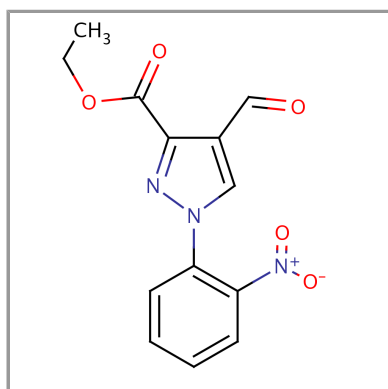
4f



[Compound Details](#)

[Structure Search](#)

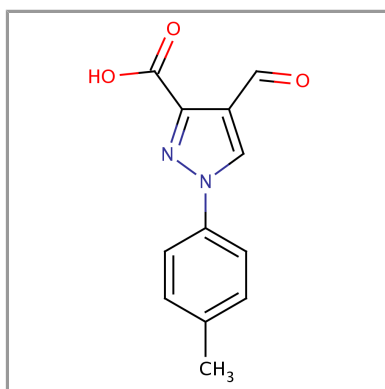
4i



[Compound Details](#)

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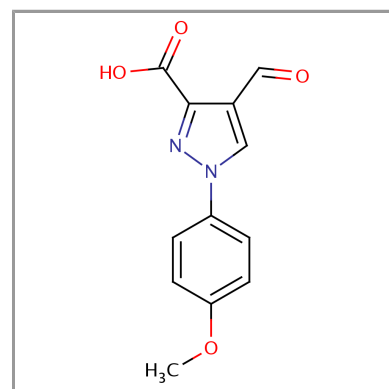
5a



[Compound Details](#)

[Structure Search](#)

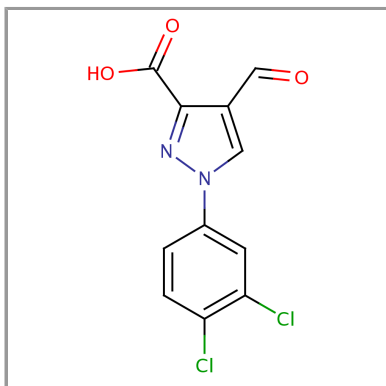
5b



[Compound Details](#)

[Structure Search](#)

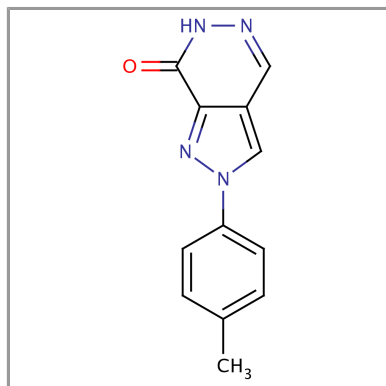
5c



[Compound Details](#)

[Structure Search](#)

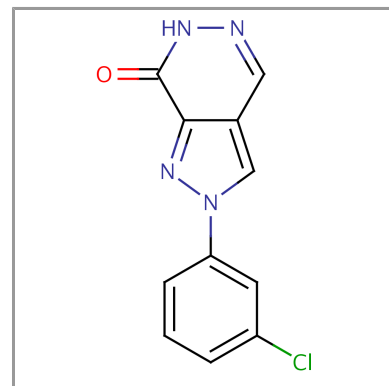
6a



[Compound Details](#)

[Structure Search](#)

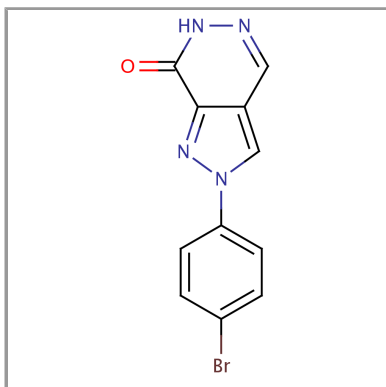
6b



[Compound Details](#)

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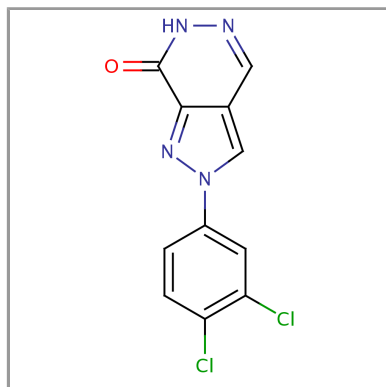
6c



[Compound Details](#)

[Structure Search](#)

6d



[Compound Details](#)

[Structure Search](#)