Iridium-catalyzed synthesis of pyrazolone fused 1,4-dihydrocinnolin-3-one employing α-diazotized Meldrum’s acid

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Abstract

The [Ir]-catalysed carbenoid insertion and cyclization of N-arylpyrazolones has been carried out with α-diazotized Meldrum's acid to access tricyclic pyrazolone fused 1,4-dihydrocinnolin-3-one derivatives. Further, the selective reduction of these tricyclic derivatives has been studied under Birch reduction conditions.

Keywords: [Ir]-Catalysis, C-H activation, carbene Insertion, α-diazotized Meldrum's acid, N-arylpyrazolones, cinnoline derivatives
Introduction

Over the past three decades, directed C–H activation and functionalization of (hetero)aromatic rings has seen enormous progress with the deployment of various transition metal complexes and a wide range of electrophiles and directing groups being used.\textsuperscript{1-3} Amongst the various electrophiles employed, diazo compounds occupy a special place and evolved as a powerful cross-coupling partners in C–H functionalization reactions.\textsuperscript{4} Especially, the α-diazoated Meldrum’s acid introduced by Li and Yi groups as a two carbon coupling partner undergoes C–H carbenoid insertion and cyclization cascade that results in the direct construction of N-heterocycles.\textsuperscript{5-7} Following the original work from these groups, several interesting transformations have been reported by other groups employing α-diazoated Meldrum acid of which [Rh]-complexes occupy a prevalent position as catalysts.\textsuperscript{8-10} In this regard, we have reported earlier an Ir(III)-catalyzed C–H annulation of N-hydroxyoximes and benzamides with α-diazoated Meldrum’s leading to isoquinoline N-oxides and N-methoxyisoquinolinediones respectively.\textsuperscript{11} Importantly, these Ir(III)-catalysed C–H carbenoid functionalizations proceeded efficiently with high yield at room temperature over a broad range of substrates without requirement of any additional oxidants or base.

\begin{center}
\textbf{Scheme 1. Synthesis of pyrazolone fused 1,4-dihydrocinnolin-3-one derivatives.}
\end{center}

In continuation, we intended to explore this Ir(III)-catalysed C–H insertion and cyclization cascade with α-diazoated Meldrum acid employing 2-aryl-2,4-dihydro-3H-pyrazol-3-one as substrates. This possibility has been first explored by Yi and co-workers employing [Rh]-complexes that resulted in the synthesis of 1H-pyrazolo[1,2-\(a\)] cinnoline-1,5(6H)-diones. A successful outcome of this reaction warranted heating the reaction mixture at 100 °C in a seal tube and in THF as a solvent. In addition, the scope of the reaction has been limited mainly to the substrates having a 5-methyl substituent. The same group reported the [Ir]-catalysed version of this reaction, in methanol and at 100 °C and was limited to 3 entries. As such the reports on this particular transformation are limited and the synthetic utility and bioactivity of the resulting fused pyrazolone fused 1,4-dihydrocinnolin-3-one has never been explored. To overcome the limited substrate scope, the requirement of high temperature as well as to explore the synthetic potential of the resulting products, the Ir(III)-catalysed C–H insertion and cyclization cascade with α-diazoated Meldrum acid has been examined employing a wide range of 5-aryl/alkyl 2-aryl-2,4-dihydro-3H-pyrazol-3-one substrates.
Results and Discussion

To begin our studies, we chose 2,5-diphenyl-2,4-dihydro-3H-pyrazol-3-one (1a) and 5-diazo-2,2-dimethyl-1,3-dioxane-4,6-dione (α-diazotized Meldrum’s acid, 2) as model substrates for reaction optimization. Initial optimization to explore the reaction conditions have been carried out by employing 2.0 mol% of [IrCp*Cl2]2 and 8.0 mol % AgNTf2 in 1, 2-dichloroethane (1,2-DCE) at room temperature to furnish the desired compound 3a in 35% yield (Table 1, entry 1). Screening of different solvents has not guided us to any success in increasing the yield of 3a (Table 1. entries 2-4). Next, we altered various reaction parameters such as temperature, additives, and catalyst loading. To this end the yield of the cinnoline derivative 3a could be increased to 91% yield using 3.0 mol % of [IrCp*Cl2]2 and 8.0 mol % AgNTf2 in 1,2-DCE at 60 °C (Table 1. entries 5-7). Further screening of different additives concluded that the AgNTf2 is best the additive to offer compound 3a (Table 1. entries 9-10) in excellent yield. Finally, further optimization of reaction conditions led us to conclude that both the metal catalyst and silver additive are essential for the reaction (Table 1, entries 11−12) and 1,2-dichloroethane as the solvent of choice.

Table 1. Optimization of reaction conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (mol%)</th>
<th>temp (°C)</th>
<th>solvent</th>
<th>Yield of 3a&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>1</td>
<td>2 mol %</td>
<td>rt</td>
<td>1,2-DCE</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>2 mol %</td>
<td>rt</td>
<td>Toluene</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>2 mol %</td>
<td>rt</td>
<td>1,4 Dioxane</td>
<td>31</td>
</tr>
<tr>
<td>4</td>
<td>2 mol %</td>
<td>rt</td>
<td>THF</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>2 mol %</td>
<td>rt</td>
<td>MeOH</td>
<td>--</td>
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<tr>
<td>6</td>
<td>2 mol %</td>
<td>40</td>
<td>1,2-DCE</td>
<td>58</td>
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<td>7</td>
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<td>8</td>
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<td>91</td>
</tr>
<tr>
<td>9</td>
<td>3 mol %</td>
<td>60</td>
<td>1,2-DCE</td>
<td>75&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>3 mol %</td>
<td>60</td>
<td>1,2-DCE</td>
<td>49&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>3 mol %</td>
<td>60</td>
<td>1,2-DCE</td>
<td>--&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>--</td>
<td>60</td>
<td>1,2-DCE</td>
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</tr>
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</table>

<sup>a</sup>Reaction conditions: 1a (0.2 mmol), 2 (0.22 mmol), [IrCp*Cl2]2 (0.02 mmol), AgNTf2 (0.08 mmol); 60 °C, 12 h, solvent (2 mL).<sup>b</sup>Isolated yields. <sup>c</sup>8mol % AgSbF6, <sup>d</sup>8mol % AgOTf, <sup>e</sup>with out Ag additive.

With the optimised reaction conditions in hand, we synthesised different 2-aryl-2,4-dihydro-3H-pyrazol-3-ones 1b–1j with both electron donating and electron withdrawing groups being placed on phenyl rings and subjected for the current C-H functionalization with diazo compound 2. Both EDG and EWG on aryl ring are tolerated under reaction conditions and furnished the cinnoline derivatives with good to excellent
yields. However, when electron withdrawing groups are present on the N-aryl ring (CF₃ on 3c and 3f) the reactions gave slightly higher yields than those with electron donating groups (H and Me) of 3b and 3h (Scheme 1).

Next, the [Ir]-catalysed C-H functionalization with various 2-(cyclo)alkyl-2,4-dihydro-3H-pyrazol-3-ones 1k–1s has been carried out under optimised conditions. In general, the reactions proceeded smoothly and afforded the desired compounds 3k–3s in very good yields (Scheme 2).

Scheme 2. Substrate scope.
Plausible Mechanism:

Based upon the previous reports, a plausible mechanism for the current reaction is proposed in Scheme 3. The initial exchange of the Cl\(^-\) from [Cp*IrCl\(_2\)]\(_2\) with –Ntf\(_2\) to generate the active Ir(III) catalyst which upon coordination with carbonyl of imidazolone and subsequent insertion across the ortho C–H of the N-aryl ring results in the intermediate A. Next, coordination of diazo compound with 2a and nitrogen elimination from the resulting intermediate B gave α-oxo[Ir]-carbene intermediate C. Subsequent carbene insertion leads to a seven membered intermediate D which upon protonation of the Ir–O and Ir–C bonds results in intermediate E together with the regeneration of the active catalyst. Intermediate E could undergo intramolecular nucleophilic attack by nitrogen on carbonyl which leads to formation of product 3a along with acetone and carbon dioxide.\(^{15}\)

To demonstrate the synthetic utility of these products obtained, we looked at the possible reduction of the N-N bond of the pyrazole ring that will result in the ring expansion to a 9-membered ring derivative.\(^{13,14}\) Our initial attempts with compound 3a to carry this transformation by hydrogenation employing different catalysts like H\(_2\)/Ra-Ni, H\(_2\)/Pd-C and PMHS/PdCl\(_2\) turned to be unsuccessful and some cases partial hydrogenation of double bond of the pyrazole ring has been noticed.\(^{16-18}\) Next, the single electron reduction of the N-N bond using SmI\(_2\) in THF has been also explored with compound 3a as a substrate and it resulted in a complex reaction mixture.\(^{19-21}\) Interestingly when compound 3a was subjected to Birch reduction employing excess Na in liq. NH\(_3\) at −78 °C, an open chain amide 5a was formed in 98% yield.\(^{22-24}\) However, in the case of the 2-methyl derivative 3k, the reaction led to a mixture of compounds and their structural assignment was found to be a difficult task. With these results in hand, the scope of Birch reduction by employing 2-aryl derivatives 3b, 3d, and 3e.
Scheme 3. Birch reduction of selected cinnolinone derivatives.

Conclusions

In summary, employing an iridium (III)-complex as a catalyst, the C−H carbeneoid [using diazotized Meldrum’s acid] functionalization of N-arylpyrazole-3-ones has been carried out. The method has mild reaction conditions, broad substrate scope, and afforded the corresponding cinnoline derivatives in good yields and releases easily removable N₂, CO₂, and acetone as by products. Further the synthetic utility of these C−H functionalised derivatives has been carried out by reducing both the substrate and we witnessed the substituent dependent ring opening (R = Ar) using Birch conditions, and that of R = alkyl group which decomposed in all the conditions used for reduction.

Experimental Section

General. Unless otherwise stated, all commercial reagents and solvents were used without additional purification. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F254 plates. Visualization on TLC was achieved using UV light (254 nm). Column chromatography was carried out by using spectrochem silica gel (60–120, 100–200, 230–400 mesh). ¹H NMR spectra were recorded on Bruker AC 200 MHz, Bruker DRX 400/500 MHz spectrometers. TMS was used as an internal standard and the chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm) or CDCl₃ (7.27 ppm) or DMSO-d₆ (2.50 ppm). In case of the peak, patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, J are reported in Hertz (Hz). ¹³C NMR spectra were obtained by, Bruker DRX (125 MHz), and Bruker DRX (100 MHz) spectrometers and referenced to the internal solvent signals (central peak is 77.0 ppm in CDCl₃ or 39.5ppm in DMSO-d₆) For carbon appearing as doublet, peak at higher value was mentioned along with coupling constant in Hz. High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. Dichloro(η⁵-pentamethylcyclopentadienyl) iridium(III) dimer (99%) was purchased from Alfa Aesar, and all the silver salts were purchased from Aldrich Chemicals and Alfa Aesar. All the pyrazol-3-ones and Meldrum’s acid diazo derivative were prepared according to reported procedure.²⁶
General procedure for the C-H insertion and cyclization. All reactions were carried out employing 100 mg of pyrazole derivative. To a screw capped vial with a spinvane triangular-shaped Teflon stir bar were added pyrazole 1a (100 mg, 0.42 mmol), diazocompound (86.40 mg, 0.50 mmol), [IrCp*Cl]2 (3.0 mol%, 10 mg), AgNTf2 (8.0 mol%, 2 mg), and solvent (1.0 mL) under air. The reaction mixture was stirred at 60 °C for 10 h. The reaction mixture was filtered through a pad of celite and then washed with CH2Cl2 (5 mL x 3). Solvents were removed under reduced pressure and the residue was purified by column chromatography (Ethylacetate/petether) to obtain the pure product.

General procedure for the N-N bond cleavage. At −78 °C, to a solution of sodium (200 mg) in ammonia (10 mL) was added compound 3a (100 mg, mmol) dissolved in THF (2 ml) and stirring was continued at the same temperature for 2 h. After complete consumption of starting material, the reaction mixture was quenched adding a saturated solution of NH4Cl drop wise and the reaction mixture was allowed to attain room temperature. The contents were partitioned between EtOAc (20 ml) and water (20 ml). Organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10 ml). Combined organic layer was dried (Na2SO4) and concentrated under reduced pressure and the residue was purified by column chromatography (Ethyl acetate/petether) to obtain the product 4a as a colorless solid.

3-Phenyl-1H-pyrazolo[1,2-a]cinnoline-1,5(6H)-dione (3a). Following the general procedure, compound 3a was obtained in 91% yield (107 mg) as White solid; RF 0.3 (30% ethyl acetate/pet ether); mp: 192-194°C; 1H NMR (400 MHz, CDCl3): δ = 8.61 (d, J 7.9 Hz, 1H), 7.43 -7.52 (m, 6H), 7.25 (t, J 4.4 Hz, 2H), 5.94 (s, 1H), 3.91 (s, 2H); 13C NMR (100 MHz, CDCl3): δ = 162.0 (s), 161.4 (s), 150.6 (s), 132.9 (s), 130.5 (d), 129.0 (s), 128.7 (d, 2 C), 128.5 (d), 128.1 (d, 2 C), 127.6 (d), 126.0 (d), 119.5 (s), 116.8 (d), 106.8 (d), 36.7 (t); HRMS (ESI+): m/z calcd for C17H13N2O2 277.0974: (M + H)+; found: 277.0972.

8-Methyl-3-phenyl-1H-pyrazolo[1,2-a]cinnoline-1,5(6H)-dione (3b). Following the general procedure, compound 3b was obtained in 75% yield (87 mg) as White solid; RF 0.3 (30% ethyl acetate/pet ether); mp: 188-190 °C; Off white solid, 1H NMR (400 MHz, CDCl3): δ = 8.46 (d, J 8.5 Hz, 1H), 7.40-7.51 (m, 5 H), 7.19 (d, J 8.5 Hz, 1H), 7.02 (s, 1 H), 5.9 (s, 1H), 3.84 (s, 2 H), 2.35 (s, 3 H); 13C NMR (100 MHz, CDCl3): δ = 162.1 (s), 161.1(s), 150.2 (s), 135.8 (s), 130.5 (s), 130.3 (d), 129.1 (s), 129.0 (d), 128.7 (d, 2 C), 128.0 (d, 2 C), 127.9 (d), 119.3 (s), 116.6 (d), 106.8 (d), 36.6 (t), 20.9 (q); HRMS (ESI+): m/z calcd for C18H15N2O2: 291.1128: (M + H)+; found: 291.1131.

3-Phenyl-8-(trifluoromethyl)-1H-pyrazolo[1,2-a]cinnoline-1,5(6H)-dione (3c). Following the general procedure, compound 3c was obtained in 82% yield (93 mg) as light pale yellow solid; RF 0.3 (30% ethyl acetate/pet ether); mp: 195-197 °C; 1H NMR (400 MHz, CDCl3): δ = 8.56 (d, J 8.2 Hz, 1H), 7.47 (d, J 8.7 Hz, 2 H), 7.37-7.44 (m, 1 H), 7.23-7.27 (m, 2 H), 6.95 (d, J 8.8 Hz, 2H), 5.88 (s, 1H), 3.90 (s, 2H), 3.87 (s, 3H); 13C NMR (100 MHz, CDCl3): δ =162.4 (s), 161.4 (s), 150.9 (s), 144.0 (s), 133.1 (s), 130.5 (d, 2 C), 128.4 (d), 127.6 (d), 126.0 (d), 119.8 (s), 119.8 (d), 116.9 (d), 113.5 (d, 2 C), 105.8 (d), 55.4 (q), 36.9 (t); HRMS (ESI+): m/z calcd for C18H15N2O3: 307.1077: [M + H]+; found: 307.1073.

3-(4-Methoxyphenyl)-8-methyl-1H-pyrazolo[1,2-a]cinnoline-1,5(6H)-dione (3e). Following the general procedure, compound 3e was obtained in 85% yield (98 mg) as light pale yellow solid; RF 0.3 (30% ethyl
acetoxy/pet. ether); mp: 206-208°C; 1H NMR (400 MHz, CDCl3): δ = 8.41 (d, J 8.5 Hz, 1 H), 7.45 (d, J 9 Hz, 2 H), 7.20 (d, J 8.5 Hz, 1 H), 7.03 (s, 1H), 6.93 (d, J 9 Hz, 2 H), 5.86 (s, 1H), 3.86 (s, 2 H), 3.85 (s, 3 H), 2.36 (s, 3 H); 13C NMR (125 MHz, CDCl3): δ = 161.6 (s), 161.3 (s), 151.5 (s), 143.5 (s), 139.1 (s), 130.4 (d), 129.6 (d, 2C), 126.3 (d, 2C), 120.1 (s), 117 (d, 2C), 113.6 (d, 2C), 105.51 (s), 55.3 (q), 36.5 (t), 21.4 (t); HRMS (ESI+): m/z calcd for C19H17N2O3: 321.1234: (M + H)+ found: 321.1222

3-(4-Methoxyphenyl)-8-(trifluoromethyl)-1H-pyrazolo[1,2-α]cinnoline-1,5(6H)-dione (3f). Following the general procedure, compound 3b was obtained in 81% yield (91 mg) as light brown solid; Rf 0.3 (30% ethyl acetate/pet. ether); mp: 178-180°C; 1H NMR (400MHz, CDCl3): δ = 8.73 (d, J 8.72 Hz, 1H), 7.65 (d, J 8.21 Hz, 1H), 7.43-7.5 (m, 3H), 6.95 (d, J 8.8Hz, 2H), 5.88 (s, 1H), 3.94 (s, 1H), 3.86 (s, 3H); 13C NMR (50 MHz, CDCl3): δ = 161.6 (s), 161.25(s), 151.6 (s), 145.3 (s), 135.6 (s), 130.4 (d, 2 C), 128.1 (s), 127.5 (d), 125.7 (d), 124.9 (d), 120.7 (d), 120.1 (d), 117.1 (d), 113.6 (d, 2C), 105.6 (d), 55.4 (q), 36.6 (t); HRMS (ESI+): m/z calcd for C19H13F3N2O3: 375.0951: (M + H)+ found: 375.0950

3-(4-Fluorophenyl)-1H-pyrazolo[1,2-α]cinnoline-1,5(6H)-dione (3g). Following the general procedure, compound 3g was obtained in 79% yield (92 mg) as light brown solid; Rf 0.3 (30% ethyl acetate/pet. ether); mp: 185-187°C; 1H NMR (400 MHz, CDCl3): δ = 8.57 (d, J 7.9 Hz, 1H), (dd, J 5.5, 7.9 Hz, 2H), 7.38-7.43 (m, 1H), 7.23 (d, J 4.3 Hz, 2H), 7.12 (t, J 8.5 Hz, 2H), 5.93 (s, 1H), 3.89 (s, 2H); 13C NMR (100 MHz, CDCl3): δ = 162.7 (s), 161.2 (s), 149.6 (s), 132.8 (s), 130.8 (s), 130.9 (d, 2 C), 128.5 (d), 127.6 (d), 126.1 (d), 125.0 (d), 119.5 (s), 116.8 (d), 115.2(d, 2 C), 106.8 (s), 36.7 (t); HRMS (ESI+): m/z calcd for C17H12F2N2O: 295.0877: (M + H)+ found: 295.0880.

8-Methyl-3-(p-tolyl)-1H-pyrazolo[1,2-α]cinnoline-1,5(6H)-dione (3h). Following the general procedure, compound 3h was obtained in 73% yield (84 mg) as light yellow solid; Rf 0.3 (30% ethyl acetate/pet. ether); mp: 200-202°C; 1H NMR (500 MHz, CDCl3): δ = 8.44 (d, J 8.4 Hz, 1H), 7.48 (dd, J 5.3, 8.77 Hz, 2H), 7.20 (d, J 8.4 Hz, 1H), 7.11(t, J 8.5 Hz, 2H), 7.03 (s, 1H), 5.89 (s, 1H), 3.84 (s, 2 H), 2.36 (s, 3H); 13C NMR (125 MHz, CDCl3): δ = 164.9 (d), 162.3 (s), 161.0 (s), 149.3 (s), 130.8 (d 2C), 136.0 (s), 130.5 (s), 129.1 (d), 127.9 (d), 125.1 (d), 119.3 (s), 116. (d), 115.2 (d 2C), 106.9 (d), 36.7 (t), 20.9 (q); HRMS (ESI+): m/z calcd for C18H14FN2O: 309.1034: (M + H)+ found: 309.1027.

3-(4-Fluorophenyl)-8-(trifluoromethyl)-1H-pyrazolo[1,2-α]cinnoline-1,5(6H)-dione (3i). Following the general procedure, compound 3i was obtained in 77% yield (87 mg) as light brown solid; Rf 0.3 (30% ethyl acetate/pet. ether); mp: 178-180°C; 1H NMR (500 MHz, CDCl3): δ = 8.75 (d, J 8.7 Hz, 1H), 7.66 (d, J 8.4 Hz, 1H), 7.51 (s, 1H), 7.49 (dd, J 5.3, 8.8 Hz, 2 H), 7.14 (d, J 8.8 Hz, 2 H), 5.93 (s, 1H), 3.96 (s, 2H); 13C NMR (125 MHz, CDCl3): δ = 165.3 (s), 161.2 (s), 161.0 (s), 150. (s), 135.3 (d), 130.9 (d, 2C), 130.8(d, 2C), 125.7 (t), 124.9 (s), 117 (d), 115.6(d, 2C), 115.3(d), 106.6 (d), 36.3 (t) 29.7 (q); HRMS (ESI+): m/z calcd for C18H14FN2O: 363.0751: (M + H)+ found: 363.0745.

3-(4-Chlorophenyl)-1H-pyrazolo[1,2-α]cinnoline-1,5(6H)-dione (3j). Following the general procedure, compound 3j was obtained in 67% yield (77 mg) as white solid; Rf 0.4 (30% ethyl acetate/pet. ether); mp: 201-203°C; 1H NMR (500 MHz, CDCl3): δ = 8.6 (d, J 8.0 Hz, 1 H), 7.42-7.47 (m, 5 H), 7.23 (d, J 4.6 Hz, 2 H), 5.95 (s, 1 H), 3.92 (s, 2 H); 13C NMR (50 MHz, CDCl3): δ = 162.1 (s), 161.1 (s), 149.4 (s), 136.7 (s), 132.8 (s), 130.1 (d, 2 C), 128.5 (s), 128.5 (d, 2 C), 127.7 (d), 127.4 (s), 126.2 (d), 119.4 (s), 116.9 (d), 107.1 (d), 36.7 (t); HRMS (ESI+): m/z calcd for C17H12ClN2O2: 311.0582: (M + H)+ found: 311.0576.

3-Methyl-1H-pyrazolo[1,2-α]cinnoline-1,5(6H)-dione (3k). Following the general procedure, compound 3k was obtained in 83% yield (96 mg) as yellow solid; Rf 0.3 (30% ethyl acetate/pet. ether); mp: 157-158°C; 1H NMR (500 MHZ, CDCl3): δ = 8.71 (d, J 8.4 Hz, 1H), 7.41 (dd, J 3.2, 5.4, 9.2 Hz, 1H), 7.24-7.25 (m, 2H), 5.72 (s, 1H), 3.95 (s, 2H), 2.69 (s, 3H); 13C NMR (125 MHz, CDCl3): δ = 161.8 (s), 161.6 (s), 148.2 (s), 132.7 (s), 128.3 (d),
127.6 (d), 125.5 (d), 118.6 (s), 115.8 (s), 104.9 (d), 36.4 (t), 15.8 (q); HRMS (ESI+): m/z calcd for C_{12}H_{10}N_{2}O_{2}Na: 237.0634; (M + Na)^+ found: 237.0656

3,8-Dimethyl-1H-pyrazolo[1,2-a]cinnoline-1,5(6H)-dione (3l). Following the general procedure, compound 3l was obtained in 68% yield (83 mg) as pale yellow solid; Rf 0.4 (30% ethyl acetate/pet. ether); mp: 170-172 °C; ^1H NMR (500 MHz, CDCl3): δ = 8.49 (d, J 8.4 Hz, 1H), 7.11 (d, J 8.4 Hz, 1H), 6.94 (s, 1H), 5.60 (s, 1H), 3.81 (s, 2H), 2.58 (s, 3H), 2.30 (s, 3H); ^13C NMR (125 MHz, CDCl3): δ = 161.7 (s), 161.6 (s), 147.8 (s), 135.3 (s), 130.4 (s), 128.9 (d), 127.9 (d), 118.5 (s), 115.7 (s), 105.0 (d), 36.4 (t), 20.8 (q), 15.8 (q); HRMS (ESI+): m/z calcd for C_{13}H_{13}N_{2}O_{2}: 229.0972; (M + H)^+ found: 229.0975

10-Ethyl-3-methyl-1H-pyrazolo[1,2-a]cinnoline-1,5(6H)-dione (3m). Following the general procedure, compound 3m was obtained in 58% yield (70 mg) gummy solid; Rf 0.3 (30% ethyl acetate/pet. ether); ^1H NMR (500 MHz, CDCl3): δ = 8.82 (d, J 8.8 Hz, 1H), 7.63 (dd, J 1.9 Hz, 8.8 Hz, 1H), 7.49 (s, 1H), 5.66 (s, 1H), 3.92 (s, 2H), 2.64 (s, 3H); ^13C NMR (125 MHz, CDCl3): δ = 161.8 (s), 160.0 (s), 149.6 (s), 135.7 (s), 132.5 (d), 131.6 (s), 119.4 (s), 117.9 (s), 116.4 (d), 108.8 (s), 104.8 (d), 35.7 (t), 16.0 (q); HRMS (ESI+): m/z calcd for C_{14}H_{15}N_{2}O_{2} 243.1128: (M + H)^+ found: 243.1133

8-Chloro-3-methyl-1H-pyrazolo[1,2-a]cinnoline-1,5(6H)-dione (3n). Following the general procedure, compound 3n was obtained in 76% yield (91 mg) as light brown solid; Rf 0.3 (30% ethyl acetate/pet. ether); mp: 145-147 °C; ^1H NMR (500 MHz, CDCl3): δ = 8.62 (d, J 8.8 Hz, 1H), 7.30 (dd, J 2.3 Hz, 8.7 Hz, 1H), 7.17 (d, J 2.3 Hz, 1H), 5.64 (s, 1H), 3.86 (s, 2H), 2.61 (s, 3H); ^13C NMR (125 MHz, CDCl3): δ = 161.7 (s), 160.8 (s), 148.6 (s), 131.3 (s), 130.6 (s), 128.5 (d), 127.5 (d), 120.4 (s), 117.3 (d), 105.1 (d), 36.1 (t), 15.9 (q); HRMS (ESI+): m/z calcd for C_{13}H_{12}ClN_{2}O_{2} 254.0492: (M + H)^+ found: 249.0430

3-Methyl-8-(trifluoromethyl)-1H-pyrazolo[1,2-a]cinnoline-1,5(6H)-dione (3o). Following the general procedure, compound 3o was obtained in 85% yield (100 mg) as light yellow solid; Rf 0.3 (30% ethyl acetate/pet. ether); mp: 162-164 °C; ^1H NMR (400 MHz, CDCl3): δ = 8.82 (d, J 8.7 Hz, 1H), 7.61 (d, J 8.7 Hz, 1H), 7.46 (s, 1H), 5.68 (s, 1H), 3.95 (s, 2H), 2.65 (s, 3H); ^13C NMR (100 MHz, CDCl3): δ = 161.9 (s), 160.5 (s), 149.2 (s), 135.2 (s), 128.0 (q), 125.7 (d), 124.9 (d), 122.2 (s), 119.0 (s), 116.1 (d), 104.9 (d), 36.1 (t), 16.0 (q); HRMS (ESI+): m/z calcd for C_{13}H_{10}F_{3}N_{2}O_{2} 283.0689: (M + H)^+ found: 283.0694

8,10-Difluoro-3-methyl-1H-pyrazolo[1,2-a]cinnoline-1,5(6H)-dione (3p). Following the general procedure, compound 3p was obtained in 95% yield (90 mg) as brown solid; Rf 0.3 (30% ethyl acetate/pet. ether); mp: 166-168 °C; ^1H NMR (500 MHz, CDCl3): δ = 8.34 (d, J 10.3 Hz, 1H), 6.66 (td, J 2.3 Hz, 9.1 Hz, 1H), 7.17 (d, J 2.3 Hz, 1H), 5.60 (s, 1H), 3.80 (s, 2H), 2.60 (s, 3H); ^13C NMR (125 MHz, CDCl3): δ = 163.7 (d), 161.4 (s), 159.8 (s), 158 (s), 149.0 (s), 133.4 (d), 104.8 (d), 102.2 (d), 100.3 (t), 99.3 (d), 29.3 (t), 16.1 (q); HRMS (ESI+): m/z calcd for C_{12}H_{9}F_{2}N_{2}O_{2} 251.0627: (M + H)^+ found: 251.0631

3-Methyl-1,5-dioxo-5,6-dihydro-1H-pyrazolo[1,2-a]cinnoline-8-carbonitrile (3q). Following the general procedure, compound 3q was obtained in 83% yield (100 mg) as gummy solid; Rf 0.3 (30% ethyl acetate/pet. ether); mp: 174-176 °C; ^1H NMR (500 MHz, CDCl3): δ = 8.82 (d, J 8.8 Hz, 1H), 7.63 (dd, J 1.9 Hz, 8.8 Hz, 1H), 7.49 (s, 1H), 5.66 (s, 1H), 3.92 (s, 2H), 2.64 (s, 3H); ^13C NMR (125 MHz, CDCl3): δ = 162.66 (s), 160.32 (s), 155.72 (s), 133.20 (s), 128.69 (s), 127.88 (s), 125.93 (s), 119.18 (s), 116.33 (s), 100.12 (s), 37.20 (s), 29.96 (s), 9.91 (d), 9.78 (d); HRMS (ESI+): m/z calcd for C_{14}H_{13}N_{2}O_{2} 241.0972: (M + H)^+ found: 241.0969
3-Cyclopentyl-1H-pyrazolo[1,2-α]cinnoline-1,5(6H)-dione (3s). Following the general procedure, compound 3s was obtained in 83% yield (98 mg) as reddish brown solid; RF 0.3 (30% ethyl acetate/pet. ether); mp: 188-190 °C; 1H NMR (400 MHz, CDCl3): δ = 8.48 (d, J 8.4 Hz, 1 H), 7.08 - 7.22 (m, 1 H), 7.00 (s, 1 H), 5.71 (d, J 1.1 Hz, 1 H), 3.84 (s, 2 H), 3.74 (t, J 8.0 Hz, 1 H), 2.34 (s, 4 H), 2.08 - 2.19 (m, 2 H), 1.64 - 1.84 (m, 5 H), 1.47 - 1.64 (m, 2 H); 13C NMR (125 MHz, CDCl3): δ = 162.2 (s) 161.5 (s), 156.9 (s), 135.5 (s), 130.6 (s), 128.9 (s), 127.8 (s), 118.9 (s), 116.0 (s), 101.9 (s), 38.5 (s), 37.0 (s), 32.0 (2 C), 25.0 (s), 20.8 (s); HRMS (ESI+): m/z calcd for C16H16N2O2: 269.1285: (M + H)+ found: 269.1396.

N-(2-(2-Amino-2-oxoethyl)phenyl)-3-phenylpropanamide (4a). Following the general procedure, compound 4a was obtained in 95% yield (98 mg) as white solid; RF 0.2 (90% ethyl acetate/pet. ether); mp: 200-201 °C; 1H NMR (500 MHz, DMSO-d6): δ = 10.1 (s, 1 H), 7.7 (bs, 1 H), 7.61 (d, J 8.0 Hz, 1 H), 7.25-7.31 (m, 4 H), 7.21 (dd, J 7.2, 8.6 Hz, 3 H), 7.07 (dd, J 6.6, 8.8 Hz, 1 H), 3.34 (s, 2 H), 2.94 (t, J 8.0 Hz, 2 H), 2.64 (t, J 8.0 Hz, 2 H); 13C NMR (125 MHz, DMSO-d6): δ = 173.5 (s), 170.1 (s), 141.0 (s), 134.3 (s), 130.2 (d), 129.7 (d 2 C), 128.3 (d, 2 C), 126.0 (d), 124.5 (d), 124.0 (d), 39.0 (t), 38.1 (t), 31.0 (t); HRMS (ESI+): m/z calcd for C17H18N2O2: 305.1260: (M + Na)+ found: 305.1264.

N-(2-(2-Amino-2-oxoethyl)-4-methylphenyl)-3-phenylpropanamide (4b). Following the general procedure, compound 4b was obtained in 89% yield (87 mg) as white solid; RF 0.2 (90% ethyl acetate/pet. ether); mp: 200-204 °C; 1H NMR (400 MHz, DMSO-d6): δ = 9.92 (s, 1 H), 7.62 (bs, 1 H), 7.43 (d, J 7.3 Hz, 1 H), 7.19-7.30 (m, 5 H), 7.0-7.11 (m, 3 H), 3.27 (s, 2 H), 2.92 (t, J 7.6 Hz, 2 H), 2.62 (t, J 7.6 Hz, 2 H), 2.2 (s 3 H); 13C NMR (100 MHz, DMSO-d6): δ = 173.4 (s), 170.1 (s), 141.0 (s), 134.8 (s), 134.5 (s), 131.0 (d), 129.3 (s), 128.9 (s), 128.3 (d, 2 C), 128.3 (d), 127.4 (d), 126.0 (d), 124.1 (d), 38.8 (t), 38.0 (t), 30.1 (t), 20.4 (q): HRMS (ESI+): m/z calcd for C18H20N2O2: 319.1417: (M + Na)+ found: 319.1421.

N-(2-(2-Amino-2-oxoethyl)phenyl)-3-(4-methoxyphenyl)propanamide (4d). Following the general procedure, compound 4d was obtained in 92% yield (85 mg) as light solid; RF 0.2 (90% ethyl acetate/pet. ether); mp: 204-206 °C; 1H NMR (500 MHz, DMSO-d6): δ = 10.06 (s, 1 H), 7.69 (bs, 1 H), 7.60 (d, J 8.0 Hz, 1 H), 7.15-7.22 (m, 5 H), 7.07 (t, J 7.2 Hz, 1 H), 6.85 (d, J 8.4 Hz, 2 H), 3.71 (s, 3 H), 3.30 (s, 2 H), 2.87 (t, J 7.6 Hz, 2 H), 2.59 (t, J 7.6 Hz, 2 H); 13C NMR (125 MHz, DMSO-d6): δ = 173.5 (s), 170.2 (s), 157.6 (s), 137.0 (s), 132.8 (s), 130.2 (s), 129.2 (d, 2 C), 129.8 (s), 126.9 (d), 124.5 (d), 123.9 (d), 113.7 (d, 2 C), 55.0 (q), 38.9 (t), 38.4 (t), 30.1 (t); HRMS (ESI+): m/z calcd for C18H18N2O2: 335.1366: (M + Na)+ found: 335.1369.

N-(2-(2-Amino-2-oxoethyl)-4-methylphenyl)-3-(4-methoxyphenyl)propanamide (4e). Following the general procedure, compound 4e was obtained in 85% yield (75 mg) as colourless solid; RF 0.2 (90% ethyl acetate/pet. ether); mp: 198-200 °C; 1H NMR (400 MHz, DMSO-d6): δ = 9.91 (s, 1 H), 7.64 (bs, 1 H), 7.42 (d, J 7.9 Hz, 1 H), 7.16 (d, J 8.5 Hz, 2 H), 7.0-7.11 (m, 3 H), 6.84 (d, J 8.5 Hz, 2 H), 3.71 (s, 3 H), 3.26 (s, 2 H), 2.85 (t, J 7.3 Hz, 2 H), 2.56 (t, J 7.3 Hz, 2 H), 2.24 (s 3 H); 13C NMR (100 MHz, DMSO-d6): δ = 173.5 (s), 170.2 (s), 157.6 (s), 134.4 (s), 133.6 (s), 132.9 (s), 130.6 (d), 129.2 (d, 2 C), 128.9 (s), 127.4 (d), 124.2 (d), 113.7 (d, 2 C), 55.0 (q), 38.8 (t), 38.4 (t), 30.2 (t), 20.5 (q); HRMS (ESI+): m/z calcd for C19H22N3O3: 349.1523: (M + Na)+ found: 349.1526.

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References

   https://doi.org/10.3762/bjoc.17.126

   https://doi.org/10.1038/s43586-021-00041-2

   https://doi.org/10.1039/D1CS00895A

   https://doi.org/10.1002/adsc.201800960

   https://doi.org/10.1039/C4CC08407A

   https://doi.org/10.1002/ejoc.201601212

   https://doi.org/10.1039/C8OB03214A

   https://doi.org/10.1016/j.jorganchem.2021.122009

   https://doi.org/10.1021/acs.orglett.5b01052

    https://doi.org/10.1039/C9OB01301F

    https://doi.org/10.1021/acs.orglett.5b03462

    https://doi.org/10.1179/13510003225001520

    https://doi.org/10.1002/cber.19580910933

    https://doi.org/10.1016/S0040-4039(00)88382-3

    https://pubs.acs.org/doi/full/10.1021/acs.joc.8b02582

    https://doi.org/10.1021/ol061303m


    https://doi.org/10.1016/j.tetlet.2015.12.116

    https://doi.org/10.1021/ol036480r

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