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

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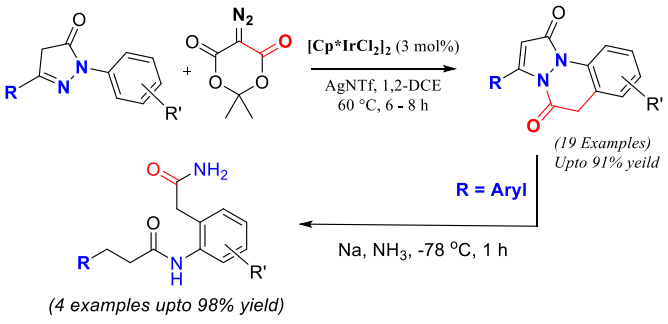
Dedicated to Professor Sambasivarao Kotha on the occasion of his 65th birthday

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Abstract

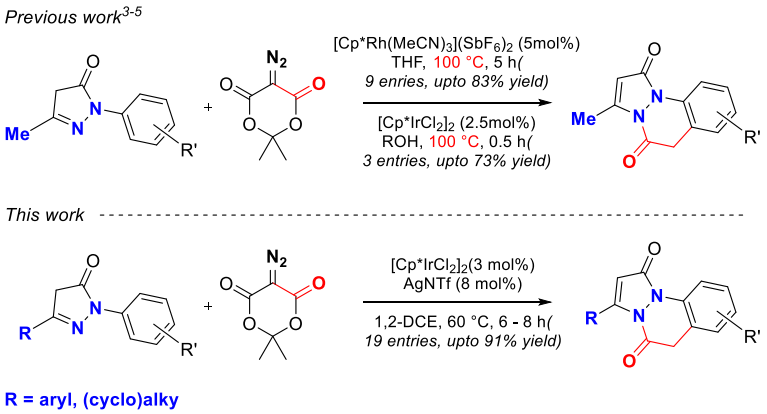
The [Ir]-catalysed carbenoid insertion and cyclization of N-arylpyrazolones has been carried out with α-diazotized Meldrum's acid to access tricyclic pyrazolone fused 1,4-dihydrocinnolin-3-one derivatives. Further, the selective reduction of these tricyclic derivatives has been studied under Birch reduction 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.[1] Amongst the various electrophiles employed, diazo compounds occupy a special place and evolved as a powerful cross-coupling partners in C–H functionalization reactions.[2] Especially, the α-diazotized 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.[3,4] Following the original work from these groups, several interesting transformations have been reported by other groups employing α-diazotized Meldrum acid of which [Rh]-complexes occupy a prevalent position as catalysts.[5] In this regard, we have reported earlier an Ir(III)-catalyzed C–H annulation of N-hydroxyoximes and of benzamides with *α*-diazotized Meldrum's leading to isoquinoline *N*-oxides and N-methoxyisoquinolinediones respectively.[6] 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.



Scheme 1. Synthesis of pyrazolone fused 1,4-dihydrocinnolin-3-one derivatives

In continuation, we intended to explore this Ir(III)-catalysed C–H insertion and cyclization cascade with α-diazotized Meldrum acid employing 2-aryl-2,4-dihydro-3*H*-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 1*H*-pyrazolo[1,2-*a*] cinnoline-1,5(6*H*)-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-diazotized Meldrum acid has been examined employing a wide range of 5-aryl/alkyl 2-aryl-2,4-dihydro-3*H*-pyrazol-3-one substrates.

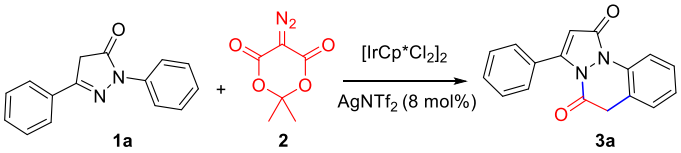
Results and Discussion

To begin our studies, we chose 2,5-diphenyl-2,4-dihydro-3*H*-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

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optimization. Initial optimization to explore the reaction conditions have been carried out by employing 2.0 mol% of $[IrCp^*Cl_2]_2$ and 8.0 mol % $AgNTf_2$ 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 $[IrCp^*Cl_2]_2$ and 8.0 mol % $AgNTf_2$ in 1, 2-dichloroethane (1,2-DCE) at 60 °C (Table 1. entries 5-7). Further screening of different additives concluded that the $AgNTf_2$ 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[a]



1a 2 3a

entry	catalyst (mol%)	temp (°C)	solvent	Yield of **3a**[b]
1	2 mol%	rt	1,2-DCE	35
2	2 mol%	rt	Toluene	10
3	2 mol%	rt	1,4 Dioxane	31
4	2 mol%	rt	THF	--
5	2 mol%	rt	MeOH	--
6	2 mol%	40	1,2-DCE	58
7	2 mol%	60	1,2-DCE	74
8	3 mol%	60	1,2-DCE	91
9	3 mol%	60	1,2-DCE	75[c]
10	3 mol%	60	1,2-DCE	49[d]
11	3 mol%	60	1,2-DCE	--[e]
12	--	60	1,2-DCE	--

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.22 mmol), $[IrCp^*Cl_2]_2$ (0.02 mmol), $AgNTf_2$ (0.08 mmol); 60 °C, 12 h, solvent (2 mL). [b]Isolated yields. [c]8mol% $AgSbF_6$, [d]8mol% AgOTf, [e]with out Ag additive.

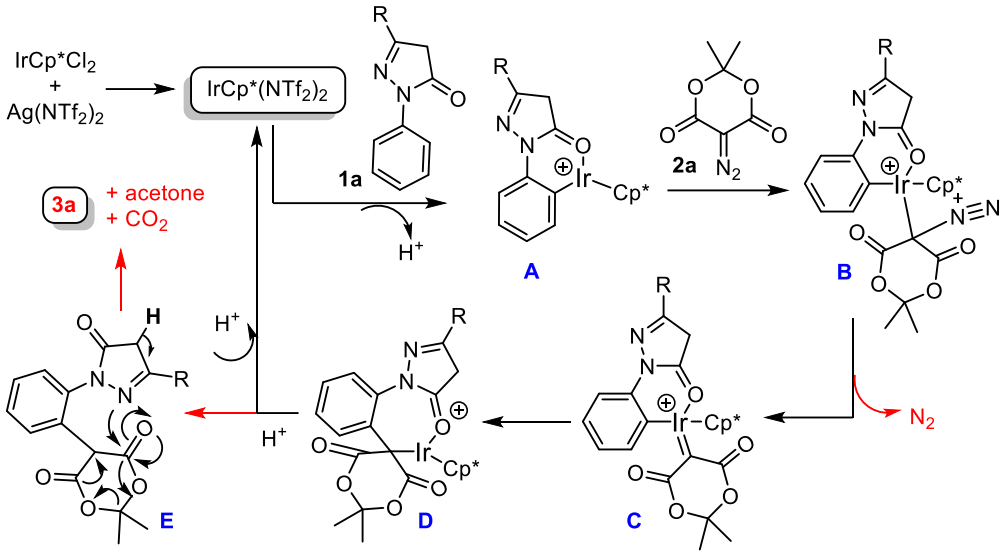
With the optimised reaction conditions in hand, we synthesised different 2-aryl-2,4-dihydro-3*H*-pyrazol-3-ones **1b**–**1j** with both electron donating and electron withdrawing groups being placed on phenyl rings and subjected for the current C-H functionalization with diazo compound **2**. Both EDG 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 (CF_3 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-3*H*-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).

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Scheme 2. Substrate scope.

Plausible Mechanism:-

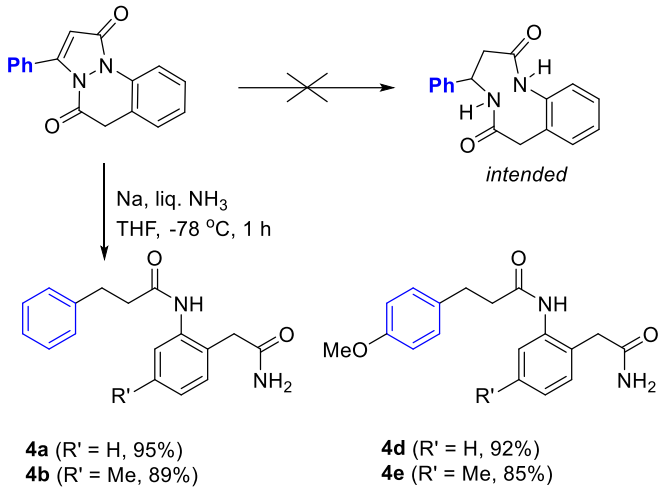


Scheme 3. Mechanism

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.[9]

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.[8] 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.[10-12] 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.[13] 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.[14] 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**.

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Scheme 3. Birch reduction of selected cinnolinone derivatives

Conclusions

In summary, employing an iridium (III)-complex as a catalyst, the C–H carbenoid [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 N_2, CO_2, 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). ^{1}H 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 $CDCl_3$ (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). ^{13}C 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 $CDCl_3$ 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 Asear. All the pyrazol-3-ones[15] and Meldrum's acid diazo derivative[2] were prepared according to reported procedure.[16]

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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), $[IrCp^*Cl_2]_2$ (3.0 mol%, 10 mg), $AgNTf_2$ (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 CH_2Cl_2 (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 NH_4Cl 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 (Na_2SO_4) 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-1*H*-pyrazolo[1,2-*a*]cinnoline-1,5(6*H*)-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; **^{1}H NMR (400 MHz, $CDCl_3$):** 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); **^{13}C NMR (100 MHz, $CDCl_3$):** 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 $C_{17}H_{13}N_2O_2$ 277.0974: $[M + H]^+$: found: 277.0972.

8-Methyl-3-phenyl-1*H*-pyrazolo[1,2-*a*]cinnoline-1,5(6*H*)-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, **^{1}H NMR (400 MHz, $CDCl_3$):** δ = 8.46 (d, *J* 8.5 Hz, 1 H), 7.40-7.51 (m, 5 H), 7.19 (d, *J* 8.5 Hz, 1 H), 7.02 (s, 1 H), 5.9 (s, 1H), 3.84 (s, 2 H), 2.35 (s, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$):** 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 $C_{18}H_{15}N_2O_2$: 291.1128: $[M + H]^+$ found: 291.1131

3-Phenyl-8-(trifluoromethyl)-1*H*-pyrazolo[1,2-*a*]cinnoline-1,5(6*H*)-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: 174-176 ˚C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ= 8.8(d, *J* 8.7 Hz,1H),7.68(d, *J* 8.7 Hz,1H),7.46-7.52(m,6H),5.96(s,1H),3.98(s,2H);**^{13}C NMR (100 MHz, $CDCl_3$):** δ = 165.1 (s), 162.2 (s), 161.1 (s), 149.5 (s), 132,8 (s), 130.92 (d), 130.8 (d), 128.4 (s), 127.6 (d), 126.1 (d), 125.0 (s), 125.0 (s), 119.5 (s), 116.8 (d), 115.4 (d), 115.2 (d), 106.8(d), 36.7 (s);**HRMS (ESI+):** *m*/*z* calcd for $C_{18}H_{12}F_3N_2O_2$: 345.0845: $[M + H]^+$ 345.0844

3-(4-Methoxyphenyl)-1*H*-pyrazolo[1,2-*a*]cinnoline-1,5(6*H*)-dione (3d). Following the general procedure, compound **3d** was obtained in 90% yield (104 mg) as yellow solid; *Rf* 0.2 (30% ethyl acetate/pet. ether); mp: 195-197 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** 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); **^{13}C NMR (100 MHz, $CDCl_3$):**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 $C_{18}H_{15}N_2O_3$: 307.1077: $[M + H]^+$ found: 307.1073.

3-(4-Methoxyphenyl)-8-methyl-1*H*-pyrazolo[1,2-*a*]cinnoline-1,5(6*H*)-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

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acetate/pet. ether); mp: 206-208˚C; **^{1}H NMR (400 MHz, $CDCl_3$):** 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); **^{13}C NMR (125 MHz, $CDCl_3$):** 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 $C_{19}H_{17}N_2O_3$: 321.1234: $[M + H]^+$ found: 321.1222

3-(4-Methoxyphenyl)-8-(trifluoromethyl)-1*H*-pyrazolo[1,2-*a*]cinnoline-1,5(6*H*)-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; **^{1}H NMR (400MHz, $CDCl_3$):** 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); **^{13}C NMR (50 MHz, $CDCl_3$):** 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 $C_{19}H_{14}F_3N_2O_3$: 375.0951: $[M + H]^+$ found: 375.0950

3-(4-Fluorophenyl)-1*H*-pyrazolo[1,2-*a*]cinnoline-1,5(6*H*)-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;**^{1}H NMR (400 MHz, $CDCl_3$):** 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), 5.9(s, 1H), 3.89 (s, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** 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 (d), 36.7 (t); **HRMS (ESI+):** *m*/*z* calcd for $C_{17}H_{12}FN_2O_2$: 295.0877: $[M + H]^+$ found: 295.0880.

8-Methyl-3-(*p*-tolyl)-1*H*-pyrazolo[1,2-*a*]cinnoline-1,5(6*H*)-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 ;**^{1}H NMR (500 MHz, $CDCl_3$):** 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); **^{13}C NMR (125 MHz, $CDCl_3$):** 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 $C_{18}H_{14}FN_2O_2$ 309.1034: $[M + H]^+$ found: 309.1027.

3-(4-Fluorophenyl)-8-(trifluoromethyl)-1*H*-pyrazolo[1,2-*a*]cinnoline-1,5(6*H*)-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: 208-210 ˚C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 8.75 (d, *J* 8.4 Hz, 1 H), 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); **^{13}C NMR (125 MHz, $CDCl_3$):** 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 $C_{18}H_{11}F_4N_2O_2$: 363.0751: [M + H] + found: 363.0745

3-(4-Chlorophenyl)-1*H*-pyrazolo[1,2-*a*]cinnoline-1,5(6*H*)-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; **^{1}H NMR (500 MHz, $CDCl_3$):** 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); **^{13}C NMR (50 MHz, $CDCl_3$):** 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 $C_{17}H_{12}ClN_2O_2$311.0582: $[M + H]^+$ found: 311.0576.

3-Methyl-1*H*-pyrazolo[1,2-*a*]cinnoline-1,5(6*H*)-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; **^{1}H NMR (500 MHZ, $CDCl_3$):** δ = 8.71 (d, *J* 8.4 Hz, 1H), 7.41 (ddd, *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); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 161.8 (s), 161.6 (s), 148.2 (s), 132.7 (s), 128.3 (d),

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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 $C_{12}H_{10}N_2O_2Na$: 237.0634: $[M + Na]^+$ found: 237.0656

3,8-Dimethyl-1*H*-pyrazolo[1,2-*a*]cinnoline-1,5(6*H*)-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; **^{1}H NMR (500 MHZ, $CDCl_3$):** 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); **^{13}C NMR (125 MHz, $CDCl_3$):** 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 $C_{13}H_{13}N_2O_2$: 229.0972: $[M + H]^+$found: 229.0975

10-Ethyl-3-methyl-1*H*-pyrazolo[1,2-*a*]cinnoline-1,5(6*H*)-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); **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 8.82 (d, *J* 8.8 Hz, 1 H), 7.63 (dd, *J* 1.9, 8.8 Hz, 1 H), 7.49 (s, 1 H), 5.66 (s, 1 H), 3.92 (s, 2 H), 2.64 (s, 3 H); **^{13}C NMR (125 MHz, $CDCl_3$):** 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 $C_{14}H_{15}N_2O_2$ 243.1128: $[M + H]^+$ found: 243.1133

8-Chloro-3-methyl-1*H*-pyrazolo[1,2-*a*]cinnoline-1,5(6*H*)-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; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 8.62 (d, *J* 8.8 Hz, 1 H), 7.30 (dd, *J* 2.3, 8.7 Hz, 1 H), 7.17 (d, *J* 2.3 Hz, 1 H), 5.64 (s, 1 H), 3.86 (s, 2 H), 2.61 (s, 3 H); **^{13}C NMR (125 MHz, $CDCl_3$):** 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 $C_{12}H_{10}ClN_2O_2$ 249.0425: $[M + H]^+$ found: 249.0430

3-Methyl-8-(trifluoromethyl)-1*H*-pyrazolo[1,2-*a*]cinnoline-1,5(6*H*)-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;**^{1}H NMR (400 MHz, $CDCl_3$):** δ = 8.82 (d, *J* 8.7 Hz, 1 H), 7.61 (d, J 8.7 Hz, 1 H), 7.46 (s, 1 H), 5.68 (s, 1 H), 3.95 (s, 2 H), 2.65 (s, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$):** 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 $C_{13}H_{10}F_3N_2O_2$: 283.0689: $[M + H]^+$ found: 283.0694

8,10-Difluoro-3-methyl-1*H*-pyrazolo[1,2-*a*]cinnoline-1,5(6*H*)-dione (3p). Following the general procedure, compound **3p** was obtained in 79% yield (95 mg) as brown solid; *Rf* 0.3 (30% ethyl acetate/pet. ether); mp: 166-168°C ;**^{1}H NMR (500 MHz, $CDCl_3$):** δ = 8.34 (d, *J* 10.3 Hz, 1 H), 6.66 (td, *J* 2.3, 9.1 Hz, 1 H), 7.17 (d, *J* 2.3 Hz, 1 H), 5.60 (s, 1 H), 3.80 (s, 2 H), 2.60 (s, 3 H); **^{13}C NMR (125 MHz, $CDCl_3$):** 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 $C_{12}H_9F_2N_2O_2$: 251.0627$[M + H]^+$ found: 251.0631

3-Methyl-1,5-dioxo-5,6-dihydro-1*H*-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; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 8.82 (d, *J* 8.8 Hz, 1 H), 7.63 (dd, *J* 1.9, 8.8 Hz, 1 H), 7.49 (s, 1 H), 5.66 (s, 1 H), 3.92 (s, 2 H), 2.64 (s, 3 H); **^{13}C NMR (125 MHz, $CDCl_3$):** 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 $C_{13}H_{10}N_3O_2$: 240.0768: $[M + H]^+$ found: 240.0771

3-Cyclopropyl-1*H*-pyrazolo[1,2-*a*]cinnoline-1,5(6*H*)-dione (3r). Following the general procedure, compound **3r** was obtained in 83% yield (100 mg) as yellow solid; *Rf* 0.3 (30% ethyl acetate/pet. ether); mp: 182-186 ˚C; **^{1}H NMR (500 MHz, $CDCl_3$):** δ = 8.82 (d, *J* 8.8 Hz, 1 H), 7.63 (dd, *J* 1.9, 8.8 Hz, 1 H), 7.49 (s, 1 H), 5.66 (s, 1 H), 3.92 (s, 2 H), 2.64 (s, 3 H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ = 162.66 (s), 162.03 (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 $C_{14}H_{13}N_3O_2$: 241.0972 [$M + H]^+$found: 241.0969

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3-Cyclopentyl-1*H*-pyrazolo[1,2-*a*]cinnoline-1,5(6*H*)-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; **^{1}H NMR (400 MHz, $CDCl_3$):** 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); **^{13}C NMR (125 MHz, $CDCl_3$):** 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 (s, 2C), 25.0 (s), 20.8 (s); **HRMS (ESI+):** *m*/*z* calcd for $C_{16}H_{16}N_2O_2$: 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; **^{1}H 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); **^{13}C NMR (125 MHz, DMSO-d6):** δ = 173.5 (s), 170.1 (s), 141.0 (s), 137.0 (s), 130.2 (d), 129.7 (d 2C), 128.3 (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 $C_{17}H_{18}N_2O_2$: 305.1260: $[M + Na]^+$ found: 305.1264.nnn

***N*-(2-(2-Amino-2-oxoethyl)-4-methylphenyl)-3-phenylpropanamide (4b).** Following the general procedure, compound **4b** was obtained in 89% yield (87 mg) colourless solid; *Rf* 0.2 (90% ethyl acetate/pet. ether); mp: 200-204 ˚C; **^{1}H 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); **^{13}C 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 $C_{18}H_{20}N_2O_2$: 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; **^{1}H 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); **^{13}C 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 $C_{18}H_{20}N_2O_3$: 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; **^{1}H 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); **^{13}C 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 $C_{19}H_{22}N_2O_3$: 349.1523: [$M + Na]^+$ found: 349.1526

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References

1. (a) Carvalho, R. L.; de Miranda, A. S.; Nunes, M. P.; Gomes, R. S.; Jardim, G. A. M.; da Silva Jr, E. N. *Beilstein J. Org. Chem.* **2021,** *17,* 1849.

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https://doi.org/10.3762/bjoc.17.126
(b) Rogge, T.; Kaplaneris, N.; Chatani, N.; Kim J.; Chang, S.; Punji, B.; Schafer, L.; Musaev,D.; Wencel-Delord, J.; Roberts, C.; Sarpong, R.; Wilson, Z.; Brimble, M.; Johansson, M.; Ackermann, L. *Nat. Rev. Methods Primers* **2021**, *1***,** 43.
https://doi.org/10.1038/s43586-021-00041-2
(c) Yuan, H. ; Zilong, H. ; Kaikai, W.; Juan, M.; Yong-Gui, Z.; Zhengkun, Y. *Chem. Soc. Rev.* **2022**, *51*, 2759.
https://doi.org/10.1039/D1CS00895A

2. Xiang Y.; Wang C.; Ding Q.; Peng Y.; *Adv. Synth. Catal.* **2019**, *361*, 919.
https://doi.org/10.1002/adsc.201800960
3. Shi, J. ; Zhou, J.; Yan, Y.; Jia, J. ; Liu, X. ; Song, H. ; Xu, H. ; Yi, W. ; *Chem. Commun.* **2015**, *51*, 668.
https://doi.org/10.1039/C4CC08407A
4. (a) Lv, H.; Xu, W.; Lin, K.; Shi, J.; Yi, W. *Eur. J. Org. Chem.* **2016**, 5637.
https://doi.org/10.1002/ejoc.201601212
(b) Borah, G.; Patel, P. *Org. Biomol. Chem.* **2019**, *17*, 2554.
https://doi.org/10.1039/C8OB03214A
5. (a) Yuan, C.; Chen, D.; Pan, C.; Yu, J.-T. *J. Organomet. Chem.* **2021,** *951*,122009.
https://doi.org/10.1016/j.jorganchem.2021.122009
(b) Son, J.-Y; Kim, S.; W.; Lee, P. *Org. Lett.* **2015**, *17*, 2518.
https://doi.org/10.1021/acs.orglett.5b01052
(c) Golubev, A.; Smetanin, I.; Agafonova, A.; Rostovskii, N.; Khlebnikov, A.; Starova, G.; Novikov, M. *Org. Biomol. Chem***. 2019**, *17*, 6821.
10.1039/C9OB01301F
6. Phatake, R.; Patel, P.; Ramana, C. *Org. Lett.* **2016**, *18*, 292.
https://doi.org/10.1021/acs.orglett.5b03462
7. Watanabe, K.; Morinaka, Y.; Katsuhiko, I.; Watanabe, T.; Yuki, S.; Nish, H. *Redox Report* **2003**, 8, 151.
https://doi.org/10.1179/135100003225001520
8. (a) Stetter, H.; Spangenberger, H.; *Chem. Ber.* **1958**, *91*, 1982.
https://doi.org/10.1002/cber.19580910933
(b) Alder, R.; Eastment, P.; Moss, R.; Sessions, R.; Stringfellow, M.; *Tetrahedron Lett.* **1982**, *23*, 4181.
https://doi.org/10.1016/S0040-4039(00)88382-3
9. Liu, C.-F.; Liu, M.; Dong, L. *J. Org. Chem.* **2019**, *84*, 409.
https://pubs.acs.org/doi/full/10.1021/acs.joc.8b02582
10. Sinha, P.; Kofink, C.; Knochel, P.; *Org. Lett*. **2006**, *8*, 3741.
https://doi.org/10.1021/ol061303m
11. Nagarajan, R.; Emmanuvel, L. *Asian J. Chem.* **2019***,* 31,1057.
https://www.asianpubs.org/index.php/ajchem/article/view/240
12. Dey, S.; Gadakh, S.; Ahuja, B.; Kamble, S.; Sudalai, A.; *Tetrahedron Lett.* **2016,** *57*,684.
https://doi.org/10.1016/j.tetlet.2015.12.116
13. (a)Ding, H.; Freistad, G. *Org. Lett.* **2004**, *6*, 637.
https://doi.org/10.1021/ol036480r
(b)Enders, D.; Funabiki, K. *Org. Lett.* **2001**, *3*, 1575.
https://doi.org/10.1021/ol015869g
(c) Friestad, G.; Ding, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4491.

 ©AUTHOR(S)

https://doi.org/10.1002/1521-3773(20011203)40:23
14. (a)Jacobi, P.; Martinelli, M.; Polanc, S. *J. Am. Chem. Soc*. **1984**, *106*, 5594. https://doi.org/10.1021/ja00331a032
(b)Wasserman, H.; Matsuyama, H. *J. Am. Chem. Soc*. **1981**, *103*, 461. https://pubs.acs.org/doi/pdf/10.1021/ja00392a036
(c) Feuer, H.; Brown, F. *J. Org. Chem*. **1970**, *35*, 1468. https://pubs.acs.org/doi/pdf/10.1021/jo00830a045
15. Watanabe, K.; Morinaka, Y.; Iseki ,K.; Watanabe, T.; Yuki, S.; Nishi, H. *Redox Report* **2003**, 8, 15. https://doi.org/10.1179/135100003225001520
16. Koskinen, A.; Muñoz, L. *J. Chem. Soc., Chem. Commun.* **1990**, 652. https://doi.org/10.1039/C39900000652

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