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Synthetic Protocol toward Fused Pyrazolone Derivatives via a Michael Addition and Reductive Ring Closing Strategy

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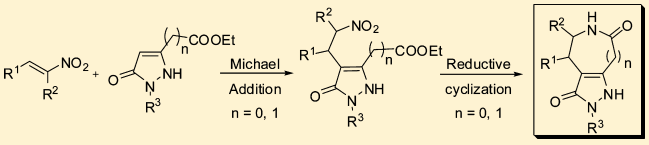
Supporting Information

ABSTRACT: A new class of pyrazolo[3,4-*c*]pyridine-3,7-dione and pyrazolo[3,4-*d*]azepine-3,7-dione scaffolds was synthesized via a Michael addition and reductive cyclization strategy. These fused heterocycles were accessed from simple starting materials such as nitroolefins and 3-ethoxycarbonyl-(methylene)pyrazoline-5-one. The pyrazolo-fused heterocycles were obtained in good overall yields.



The design and synthesis of novel N-heterocyclic moieties has always been an interesting and challenging task for organic chemists as these cores have found wide applications, most importantly in medicinal chemistry.[1] Heterocycles containing pyrazolone rings belong to a class of molecules that have been well-studied because of their diverse applications in drug molecules,[2a−c] agrochemicals,[2d,e] voltage-sensitive dyes,[2f,g] extraction, and separation of metal ions[2h] to name a few. Particularly, they are attractive targets in the field of medicinal chemistry and drug discovery.[3] A literature survey revealed the presence of a pyrazolone core in a number of promising pharmaceuticals that exhibit a broad range of biological properties such as antibacterial,[4a] antiviral,[4b] and anti-inflammatory[4c] activity. Some examples are edaravone (**1**), a potent drug used in the treatment of brain ischemia;[5] dipyrone (**2**), which possesses analgesic and antipyretic properties;[6] 2-arylpyrazolo[3,4-*c*]quinolin-4-ones (**3**), which function as adenosine receptor antagonists;[7] and pyrazolopyridinedione derivatives (**4**), which are effective for the treatment of idiopathic pulmonary fibrosis[8] (Figure 1).

Several reports have appeared on the reactivity of pyrazolone derivatives in Michael addition, 1,5-migration/Michael addition,[9a] condensation and substitution reactions,[9b] C−H activation,[9c] nucleophilic addition of conjugated azoalkenes and pyrazolinones,[9d] and palladium-catalyzed carbonylation.[9e] Only a few asymmetric transformations using pyrazolone derivatives as nucleophiles in Michael addition reactions have been reported.[10−13] Other reports on Michael addition of pyrazolones are reactions with maleimides,[14a] benzylidene malononitriles,[14b] and acyclic aliphatic α,β-unsaturated ketones,[14c] an organocatalytic amination of pyrazolone,[14d] and a one-pot sequential Michael addition/dearomative bromination.[14e]

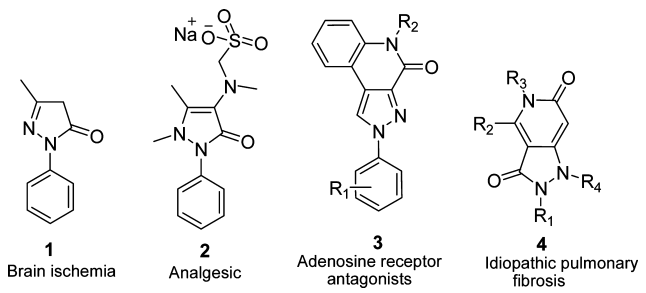


Figure 1. Bioactive molecules containing a pyrazolone unit.

It is a well-known fact that pyrazolin-5-ones can exist in various tautomeric forms.[15] Figure 2 shows the different tautomers of ethyl 5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate. The ^{1}H NMR spectrum revealed the presence of a mixture of tautomers in $CDCl_3$ and a single tautomer in DMSO.[16] To the best of our knowledge, the pyrazole-3-carboxylate has never been used as a nucleophile in Michael additions.

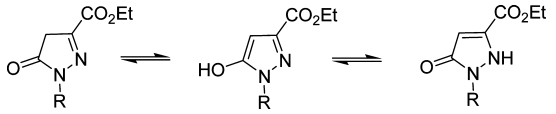


Figure 2. Possible tautomeric forms of ethyl 5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate.

A careful literature study showed that pyrazolones have been used for the Michael addition reaction, although further derivatization of the Michael adducts remains unexplored. We envisaged the use of substituted 5-hydroxy-*N*-phenyl-1*H*-pyrazole-3-carboxylate **2a** as a nucleophile for Michael addition to β-nitrostyrene. This Michael adduct could be then subjected

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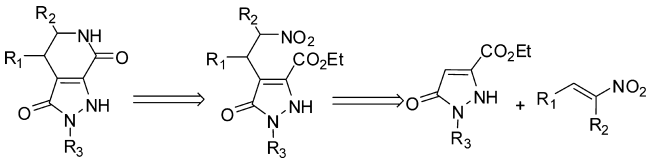
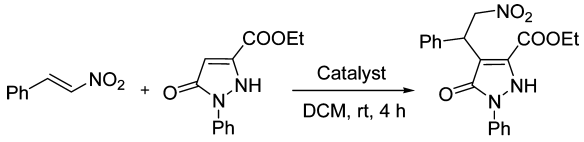
to a reductive cyclization strategy to furnish a novel class of heterocycles with a pyridone ring fused to pyrazolone. Herein we disclose our success in the design and synthesis of pyridone-fused pyrazolones via a Michael addition−reductive cyclization pathway (Scheme 1).

Scheme 1. Strategy toward Pyridone-Fused Pyrazolones



We initiated our studies of the Michael addition with the use of *β*-nitrostyrene (**1a**) and ethyl 4,5-dihydro-1-phenyl-1*H*-pyrazol-5-one-3-carboxylate (**2a**) using various bases, as summarized in Table 1. A model reaction was done using 1.0 equiv of both nitrostyrene **1a** and N-substituted pyrazolone **2a** in the presence of a catalytic amount of DMAP in dichloromethane at room temperature. The reaction was found to be incomplete even after 12 h, but the desired Michael adduct **3a** was isolated in 52% yield (Table 1, entry 1). When the base loading was increased to 1 equiv, the reaction time decreased to 4 h and the desired product was obtained in 64% isolated yield (Table 1, entry 2). It was also observed that the reaction failed to proceed in the absence of base (Table 1, entry 3). We were pleased to observe a clean reaction with 85% yield when pyridine was used as the base (Table 1, entry 4). A low yield (45%) was observed when triethylamine was used as the base (Table 1, entry 5). On the other hand, DABCO mediated the reaction in excellent yield (Table 1, entry 6). Lowering the base loading made the reaction sluggish (Table 1, entry 7), probably as a result of catalyst deactivation by nitronate formation with the product. Although comparable results were obtained using pyridine and DABCO, it was desirable to use less toxic, environmentally more friendly DABCO as the base to mediate the Michael reaction.

Table 1. Base Evaluation of Michael Addition Reaction[a]



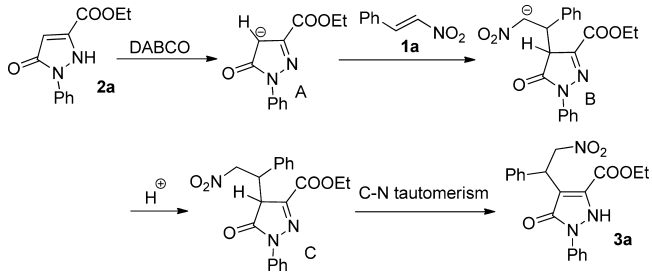
1a **2a** **3a**

entry	base	equiv	time (h)	yield (%)[b]
1	DMAP	0.1	12	52 (incomplete)
2	DMAP	1	4	64
3	–	–	12	no reaction
4	pyridine	1	4	85
5	TEA	1	12	45
6	**DABCO**	**1**	**4**	**92**
7	DABCO	0.1	12	62 (incomplete)

[a]Reaction conditions: **1a** (0.5 mmol) and **2a** (0.5 mmol) in DCM (2 mL) at 25 °C. [b]Isolated yields.

On the basis of these results, a plausible mechanism for the efficient formation of Michael adduct **3a** is illustrated in Scheme 2. In the first step, deprotonation of pyrazalone **2a** by the base leads to carbanion A, which then undergoes an intermolecular Michael addition to nitroolefin **1a** to afford intermediate B.

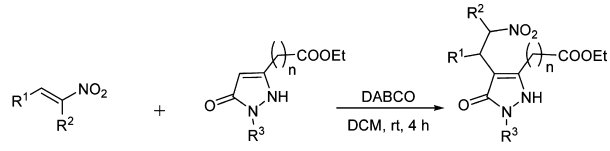
Scheme 2. Plausible Reaction Pathway for the Formation of 3a



Intermediate B subsequently abstracts a proton from the protonated base, after which a C−N tautomeric shift produces the desired Michael adduct **3a**.

Having the optimized protocol in hand (Table 1, entry 6) we examined the substrate generality with substituted nitroolefins **1a−g** and pyrazolones **2a−c** (Table 2). The electronic properties did not much influence the reaction rate, and the reactions of **1b** and **1c** with **2a** afforded the products **3b** and **3c** in excellent yields. Moreover, aliphatic and heteroaromatic nitroalkenes **1d** and **1e** gave the corresponding nitro adducts **3d** and **3e**. When *α*,*β*-disubstituted nitroalkene **1f** was used, ^{1}H NMR analysis of the crude reaction mixture showed the presence of diastereomers (1:0.9). After column purification we could only isolate a single diastereomer in a slightly lower yield (Table 2, entry 6). *N*-Methyl-substituted pyrazolone **2b** (Table 2, entry 7) also readily participated in the reaction, giving an 81% yield of **3g**. The insertion of one $-CH_2-$ unit in the pyrazolone (Table 2, entry 8) was also tolerated well in the reaction. The Michael additions with sterically hindered nitroalkene **1g** (Table 2, entries 9 and 10) showed very good diastereoselectivity (>99%), affording the adducts **3i** and **3j** in good yields.

Table 2. DABCO-Mediated Michael Addition of Nitroolefins 1a−g and Pyrazolones 2a−c[a]



1a; R^1 = Ph, R^2 = H
1b; R^1 = *p*-OMe-C_6H_4, R^2 = H
1c; R^1 = *p*-CO_2Me-C_6H_4, R^2 = H
1d; R^1 = *n*-Pr, R^2 = H
1e; R^1 = 2-Thienyl, R^2 = H
1f; R^1 = Ph, R^2 = Me
1g; R^1-R^2 = 1, 2-naptho

2a; R^3 = Ph, n = 0
2b; R^3 = Me, n = 0
2c; R^3 = Ph, n = 1

3a-3 j

entry	olefin **1**	pyrazolone **2**	product **3**	yield (%)[b]
1	**1a**	**2a**	**3a**	92
2	**1b**	**2a**	**3b**	81
3	**1c**	**2a**	**3c**	85
4	**1d**	**2a**	**3d**	80
5	**1e**	**2a**	**3e**	85
6	**1f**	**2a**	**3f**	74
7	**1a**	**2b**	**3g**	81
8	**1a**	**2c**	**3h**	90
9	**1g**	**2a**	**3i**	76
10	**1g**	**2c**	**3j**	77

[a]Reaction conditions: **1** (0.5 mmol) and **2** (0.5 mmol) in DCM (2 mL) at 25 °C. [b]Isolated yields.

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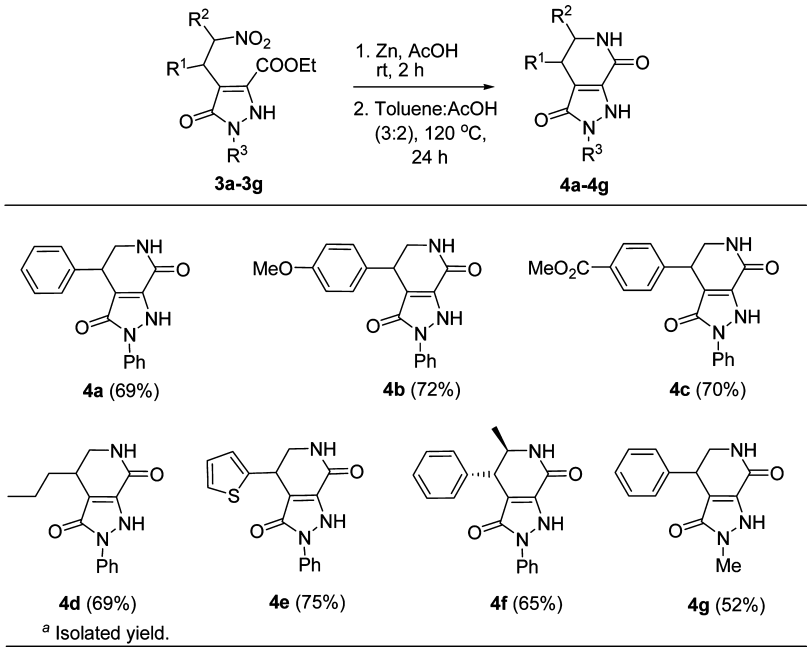
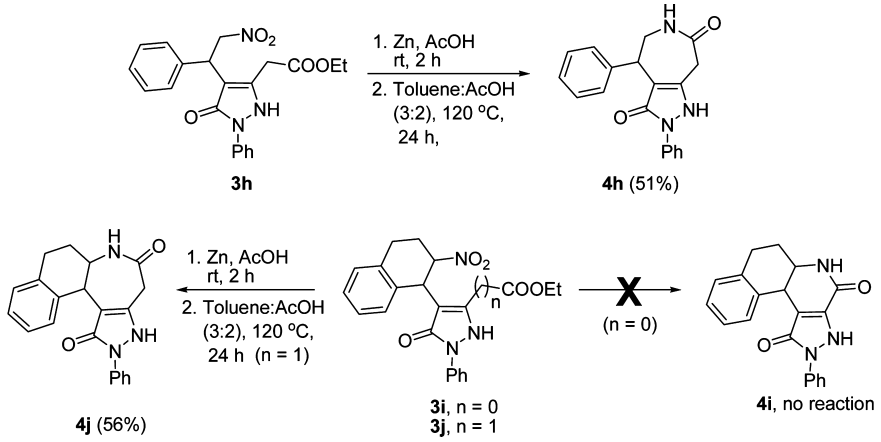
Table 3. Reductive Cyclization of Michael Adducts 3a−g[a]



[a] Isolated yield.

Scheme 3. Synthesis of a Seven-Membered Fused Heterocycle and a Tetracyclic Fused System



It is important to note that for all of the Michael adducts shown in Table 2, distinct line broadening in the ^{1}H NMR spectrum was typically observed for benzylic and methylene protons. This most likely is due to the simultaneous presence of several tautomers that are in dynamic equilibrium on the time scale of the NMR experiment (intermediate exchange regime). The ^{1}H NMR spectrum in the presence of DABCO proved to be simpler because of an increase in the rates of these dynamic processes (fast exchange). In all of the structural formulas, for simplicity we have written only the −NH tautomer.

Starting from Michael adducts **3a**, we proceeded with the reduction of the nitro group to an amine followed by intramolecular cyclization. A few reduction methods to give the corresponding amines were tried, including $NaBH_4/NiCl_2$, Raney Ni/H_2, zinc/acetic acid, and Pd/H_2. In practice, isolation of the amine was difficult because of low solubility during the $NaBH_4/NiCl_2$ procedure, which uses MeOH as the solvent. By using either Raney Ni/H_2 or zinc/acetic acid we were able to reduce the nitro compound to an amine effectively. The prepared amine was then subjected to cyclization without further purification. Further optimization in 3:2 toluene/AcOH solvent at reflux temperature afforded the corresponding product **4a** in 69% isolated yield (Table 3). However, the one-pot reductive cyclization strategy using zinc/acetic acid gave a low yield of product **4a**, which was difficult to separate from excess zinc. Therefore, the scope of Michael adducts was studied using the optimized protocol as shown in Table 3. By this procedure, we successfully prepared fused pyrazolo[3,4-*c*]pyridine-3,7-diones **4a−g** from Michael adducts **3a−g** in satisfactory overall yields (Table 3). Surprisingly, a single diastereomer **4f** was obtained in 65% isolated yield starting from the Michael adduct **3f**. This presumably arises through deprotonation of **3f**, giving a nitronate that upon reduction gives a single diastereomeric amine. From the NMR experiments we were able to confirm the product **4f** to have the trans geometry (see the Supporting Information).

Seven-membered heterocycles form an important framework in many biologically active drugs.[17] Key examples that belong to this class include diazepam, dibenzazepine, and oxcarbazepine. The present methodology provides an interesting access toward fused seven-membered heterocycles (Scheme 3). We started from the above-synthesized Michael adduct **3h**, which

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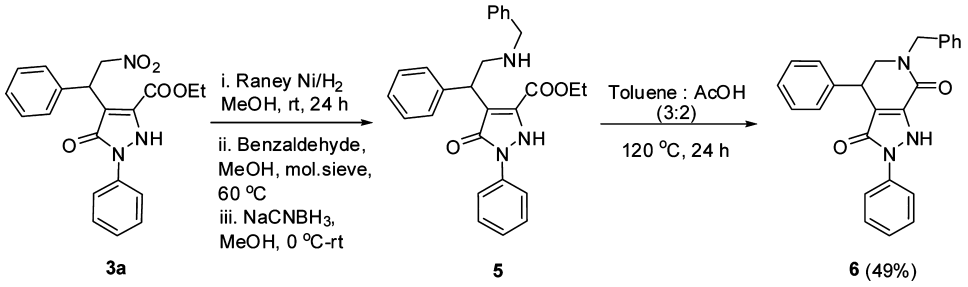
Scheme 4. Synthetic Utility of Michael Adduct 3a



underwent reductive cyclization to form substituted pyrazolo[4,3-*d*]azepine-3,7-dione heterocycle **4h** in 51% isolated yield.

Michael adduct **3i** could easily undergo reduction to the corresponding amine, but the formation of the targeted compound **4i** failed (Scheme 3). In order to force the cyclization we tried using the more acidic CF_3COOH instead of CH_3COOH as well as using a high-boiling solvent such as xylene. Unfortunately, these attempts also did not furnish the cyclized product. A possible explanation could be that the conformation of the molecule is such that the ester and the amine functionalities are too far away from each other to allow cyclization. It was thought that Michael adduct **3j** in which a methylene group is inserted between the ester and pyrazolone unit would bring some flexibility so as to facilitate cyclization. We were indeed able to synthesize the tetracyclic fused pyrazolone compound **4j** in satisfactory yield.

We decided to investigate the further utility of these Michael adducts by introducing an additional point of diversity. The primary amine from **3a** was transformed into secondary amine **5** using standard conditions via imine formation followed by reduction. Secondary amine **5** without any purification was subjected to cyclization in toluene/AcOH to give the desired fused six-membered pyrazolopyridinone **6** in 49% overall yield (Scheme 4) with increased solubility in organic solvents.

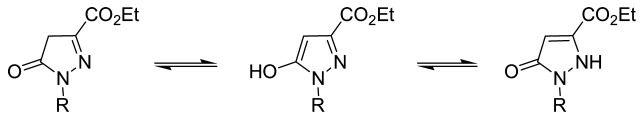
In conclusion, we have developed a facile methodology for the synthesis of novel fused pyrazolo[3,4-*c*]pyridine-3,7-diones via Michael addition followed by reductive cyclization starting from pyrazolones and nitroalkenes. In the case where two stereocenters are present, the reaction occurs in a diastereoselective manner. Interestingly, we were also successful in building pyrazolo[3,4-*d*]azepine-3,7(4*H*,8*H*)-dione and rigid tetracyclic substituted pyrazolone derivatives and in introducing an additional point of diversity by reductive amination prior to cyclization.

EXPERIMENTAL SECTION

General Experimental Methods. NMR spectra were acquired on commercial instruments (300 and 400 MHz), and chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane (^{1}H) or the internal (NMR) solvent signal (^{13}C). Mass spectra (EI, 70 eV ionization energy) were acquired. Exact mass measurements were performed in the EI mode at a resolution of 10 000 and also on a quadrupole orthogonal acceleration time-of-flight mass spectrometer. Samples were infused at 3 μL/min, and spectra were obtained in positive (or negative) ionization mode with a resolution of 15 000 (fwhm) using leucine enkephalin to lock the mass. Melting points (not corrected) were determined using a Reichert Thermovar apparatus. For column chromatography, 70@230 mesh silica 60 (E. M. Merck) was used as the stationary phase. Chemicals received from commercial sources were used without further purification. Solvents used in reactions were used as received.

Important Notes.

1. The compound ethyl 5-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (**2a**) can exist in several tautomeric forms (**A**–**C**) in solution. NMR spectra for **2a** in DMSO-d_6, $CDCl_3$, and $CDCl_3$ with DABCO were recorded.



2. In DMSO-d_6, it exist in one tautomeric form i.e either **B** or **C**; in $CDCl_3$, mixture of two tautomer i.e **A** and **B**/**C**; in $CDCl_3$-DABCO its **B**/**C**.
3. The ^{1}H NMR and ^{13}C NMR spectra for compound **2a** in $CDCl_3$, DMSO-d_6, and $CDCl_3$ with DABCO are below.
4. For convenience, we present the −NH tautomeric form (structure **C**) for all of the compounds.

Synthetic Procedures and Characterization Data. *Syntheses of 1 and 2.* The nitroalkenes[18] (**1a**–**g**) and pyrazolone derivatives[19] (**2a**–**c**) were prepared according to literature methods.

*General Procedure for the Synthesis of Michael Adducts (**3a**–**j**).* Pyrazolone **2** (1 mmol), nitroalkene **1** (1 mmol), and DABCO (1 mmol) were stirred in dry DCM (5 mL) under N_2 at room temperature for 4 h. The reaction progress was monitored by TLC. When the reaction was complete, the DCM was evaporated off. The crude sample was purified by column chromatography on silica gel (with petroleum ether/ethyl acetate as the eluent) to afford the corresponding Michael adduct **3**.[20]

*Ethyl 4-(2-Nitro-1-phenylethyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrazole-3-carboxylate (**3a**).* ((*E*)-2-Nitrovinyl)benzene (**1a**) (100 mg, 0.67 mmol), ethyl 2,5-dihydro-5-oxo-1-phenyl-1*H*-pyrazole-3-carboxylate (**2a**) (156 mg, 0.67 mmol), DABCO (75 mg, 0.67 mmol), and DCM (5 mL) were used. The product was obtained as a light-yellow solid (242 mg) in 92% yield. Mp 41–43 °C; R_f 0.30 (hexane/ethyl acetate = 6:4); MS (EI) *m*/*z* 381 (M^+); HRMS (EI) calcd for $C_{20}H_{19}N_3O_5$ 381.1324, found *m*/*z* 381.1325; ^{1}H NMR (400 MHz, $CDCl_3$ with DABCO) δ 9.3 (bs, 1H), 7.74 (d, 2H, *J* = 8.0 Hz), 7.47 (d, 2H, *J* = 7.6 Hz), 7.40–7.36 (m, 2H), 7.28–7.17 (m, 4H), 5.55–5.52 (m, 1H), 5.46–5.44 (m, 1H), 5.0 (dd, 1H, *J* = 12.1, 6.3 Hz), 4.35 (q, 2H, *J* = 7.0 Hz), 1.35 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$ with DABCO) δ 163.6, 157.5, 141.2, 140.2, 139.2, 132.1, 129.4, 129.1, 128.8, 128.4, 127.9, 126.6, 126.4, 123.8, 100.8, 77.8, 60.6, 39.2, 14.3.

*Ethyl 4-(1-(4-Methoxyphenyl)-2-nitroethyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrazole-3-carboxylate (**3b**).* 1-Methoxy-4-((*E*)-2-nitrovinyl)benzene (**1b**) (100 mg, 0.56 mmol), ethyl 2,5-dihydro-5-oxo-1-phenyl-1*H*-pyrazole-3-carboxylate (**2a**) (129 mg, 0.56 mmol), DABCO (62 mg, 0.56 mmol), and DCM (5 mL) were used. The product was obtained as a green solid (184 mg) in 81% yield. Mp 48–50 °C; R_f 0.23 (hexane/ethyl acetate = 6:4); MS (EI) *m*/*z* 411 (M^+); HRMS (EI) calcd for $C_{21}H_{21}N_3O_6$ 411.1453, found *m*/*z* 411.1449; ^{1}H NMR (300 MHz, $CDCl_3$ with DABCO) δ 8.42 (bs, 1H), 7.82–7.78 (m, 2H), 7.43–7.38 (m, 4H), 7.27–7.23 (m, 1H), 6.82 (d, 2H, *J* = 8.6 Hz), 5.64–5.57 (m, 1H), 5.42–5.36 (m, 1H), 4.92 (dd, 1H, *J* = 12.1, 6.2 Hz), 4.40–4.32 (m, 2H), 3.76 (s, 3H), 1.37 (t, 3H, *J* = 7.0 Hz);

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^{13}C NMR (75 MHz, $CDCl_3$ with DABCO) δ 163.8, 158.3, 158.3, 140.4, 139.5, 133.6, 129.0, 128.9, 126.3, 123.9, 113.8, 100.6, 78.1, 60.6, 55.3, 38.9, 14.5.

*Ethyl 4-(1-(4-(Methoxycarbonyl)phenyl)-2-nitroethyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrazole-3-carboxylate (**3c**).* Methyl 4-((*E*)-2-nitrovinyl)benzoate (**1c**) (53 mg, 0.25 mmol), ethyl 2,5-dihydro-5-oxo-1-phenyl-1*H*-pyrazole-3-carboxylate (**2a**) (60 mg, 0.25 mmol), DABCO (29 mg, 0.25 mmol), and DCM (5 mL) were used. The product was obtained as a yellow semisolid (96 mg) in 85% yield. R_f 0.24 (hexane/ethyl acetate = 6:4); MS (EI) *m*/*z* 439 (M^+); HRMS (EI) calcd for $C_{22}H_{21}N_3O_7$ 439.1379, found *m*/*z* 439.1377; ^{1}H NMR (300 MHz, $CDCl_3$ with DABCO) δ 9.1 (bs, 1H), 7.96−7.93 (m, 2H), 7.77 (d, 2H, *J* = 8.1 Hz), 7.56 (d, 2H, *J* = 8.2 Hz) 7.41 (t, 2H, *J* = 7.5 Hz), 7.27−7.22 (m, 1H), 5.65−5.58 (m, 1H), 5.51−5.46 (m, 1H), 4.99 (dd, 1H, *J* = 11.8, 5.9 Hz), 4.38−4.31 (m, 2H), 3.88 (s, 3H), 1.35 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$ with DABCO) δ 167.0, 163.7, 158.6, 146.8, 140.3, 139.5, 129.8, 128.9, 128.5, 128.0, 126.5, 124.0, 99.4, 77.3, 60.7, 52.1, 39.5, 14.5.

*Ethyl 2,5-Dihydro-4-(1-nitropentan-2-yl)-5-oxo-1-phenyl-1H-pyrazole-3-carboxylate (**3d**).* (*E*)-1-nitropent-1-ene (**1d**) (25 mg, 1.74 mmol), ethyl 2,5-dihydro-5-oxo-1-phenyl-1*H*-pyrazole-3-carboxylate (**2a**) (50 mg, 1.74 mmol), DABCO (24 mg, 1.74 mmol), and DCM (4 mL) were used. The product was obtained as a yellow viscous oil (59 mg) in 80% yield. R_f 0.34 (hexane/ethyl acetate = 6:4); MS (EI) *m*/*z* 347 (M^+); HRMS (EI) calcd for $C_{17}H_{21}N_3O_5$ 347.1481, found *m*/*z* 347.1485; ^{1}H NMR (300 MHz, $CDCl_3$ with DABCO) δ 9.6 (bs, 1H), 7.73−7.70 (m, 2H), 7.41−7.35 (m, 2H), 7.26- 7.22 (m, 1H), 5.11−5.03 (m, 1H), 4.61 (dd, 1H, *J* = 11.4, 5.6 Hz), 4.37 (q, 2H, *J* = 7.1 Hz), 3.90−3.85 (m, 1H), 1.89−1.82 (m, 1H), 1.64−1.57 (m, 1H), 1.39 (t, 3H, *J* = 7.0 Hz), 1.33−1.25 (m, 2H), 0.87 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$ with DABCO) δ 164.1, 158.1, 140.5, 139.6, 128.8, 126.3, 123.7, 101.3, 79.3, 60.6, 34.9, 34.1, 20.9, 14.5, 14.1.

*Ethyl 2,5-Dihydro-4-(2-nitro-1-(thiophen-2-yl)ethyl)-5-oxo-1-phenyl-1H-pyrazole-3-carboxylate (**3e**).* 2-((*E*)-2-nitrovinyl)thiophene (**1e**) (33 mg, 0.22 mmol), ethyl 2,5-dihydro-5-oxo-1-phenyl-1*H*-pyrazole-3-carboxylate (**2a**) (50 mg, 0.22 mmol), DABCO (24 mg, 0.22 mmol), and DCM (5 mL) were used. The product was obtained as a yellow viscous oil (70 mg) in 85% yield. R_f 0.31 (hexane/ethyl acetate = 6:4); MS (EI) *m*/*z* 387 (M^+); HRMS (EI) calcd for $C_{18}H_{17}N_3O_5S$ 387.0888, found *m*/*z* 387.0880; ^{1}H NMR (300 MHz, $CDCl_3$ with DABCO) δ 9.76 (bs, 1H), 7.68 (bs, 2H), 7.35−7.33 (m, 2H), 7.27−7.21 (m, 1H), 7.10−7.09 (m, 1H), 6.94−6.87 (m, 2H), 5.60−5.59 (bm, 1H), 5.44−5.40 (bm, 1H), 5.07 (dd, 1H, *J* = 12.2, 6.6 Hz), 4.34 (q, 2H, *J* = 7.1 Hz), 1.36−1.32 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ with DABCO) δ 163.4, 156.8, 144.5, 140.01, 138.9, 134.7, 132.2, 131.7, 128.8, 126.8, 124.5, 124.0, 123.6, 101.3, 78.2, 60.8, 34.8, 14.4.

*Ethyl 4-(2-Nitro-1-phenylpropyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrazole-3-carboxylate (**3f**).* ((*E*)-2-nitroprop-1-enyl)benzene (**1f**) (100 mg, 0.61 mmol), ethyl 2,5-dihydro-5-oxo-1-phenyl-1*H*-pyrazole-3-carboxylate (**2a**) (142 mg, 0.61 mmol), DABCO (68 mg, 0.61 mmol), and DCM (5 mL) were used. The product was obtained as an off-white solid (179 mg) in 74% yield as a single diastereomer. Mp 151−153 °C; R_f 0.33 (hexane/ethyl acetate = 6:4); MS (EI) *m*/*z* 395 (M^+); HRMS (EI) calcd for $C_{21}H_{21}N_3O_5$ 395.1481, found *m*/*z* 395.1487; ^{1}H NMR (300 MHz, $CDCl_3$ with DABCO) δ 7.72−7.66 (m, 4H), 7.43−7.30 (m, 2H), 7.27−7.17 (m, 4H), 6.20−6.14 (m, 1H), 5.09 (d, 1H, *J* = 11.4 Hz), 4.42−4.36 (m, 2H), 1.43−1.38 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$ with DABCO) δ 163.9, 157.9, 141.8, 140.3, 139.6, 128.9, 128.6, 128.2, 128.1, 126.8, 126.4, 126.3, 124.4, 123.7, 101.8, 84.8, 60.5, 19.8, 14.5.

*Ethyl 2,5-Dihydro-1-methyl-4-(2-nitro-1-phenylethyl)-5-oxo-1H-pyrazole-3-carboxylate (**3g**).* ((*E*)-2-Nitrovinyl)benzene (**1a**) (43 mg, 0.29 mmol), ethyl 2,5-dihydro-1-methyl-5-oxo-1*H*-pyrazole-3-carboxylate (**2b**) (50 mg, 0.29 mmol), DABCO (33 mg, 0.29 mmol), and DCM (6 mL) were used. The product was obtained as a greenish-yellow solid (76 mg) in 81% yield. Mp 54−56 °C; R_f 0.29 (hexane/ethyl acetate = 1:9); MS (EI) *m*/*z* 319 (M^+); HRMS (EI) calcd for $C_{15}H_{17}N_3O_5$ 319.1168, found *m*/*z* 319.1164; ^{1}H NMR (300 MHz, $CDCl_3$ with DABCO) δ 9.57 (bs, 1H), 7.36−7.28 (m, 2H), 7.22−7.13 (m, 3H), 5.37−5.26 (m, 2H), 5.03 (dd, 1H, *J* = 9.1, 3.7 Hz), 4.32−4.25 (m, 2H), 3.55 (s, 3H), 1.31 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$ with DABCO) δ 163.3, 155.8, 140.7, 137.9, 128.4, 127.8, 126.8, 101.9, 78.1, 60.7, 39.2, 33.7, 14.4.

*Ethyl 2-(2,5-Dihydro-4-(2-nitro-1-phenylethyl)-5-oxo-1-phenyl-1H-pyrazol-3-yl)acetate (**3h**).* ((*E*)-2-Nitrovinyl)benzene (**1a**) (200 mg, 1.34 mmol), ethyl 2-(2,5-dihydro-5-oxo-1-phenyl-1*H*-pyrazol-3-yl)acetate (**2c**) (330 mg, 1.34 mmol), DABCO (150 mg, 1.34 mmol), and DCM (10 mL) were used. The product was obtained as a yellow solid (420 mg) in 90% yield. Mp 100−102 °C; R_f 0.26 (hexane/ethyl acetate = 6:4); MS (EI) *m*/*z* 395 (M^+); HRMS (EI) calcd for $C_{21}H_{21}N_3O_5$ 395.1481, found *m*/*z* 395.1476; ^{1}H NMR (600 MHz, $CDCl_3$ with DABCO) δ 8.6 (bs, 1H); 7.73 (d, 2H, *J* = 8.1 Hz), 7.42−7.36 (m, 4H), 7.28 (t, 2H, *J* = 8.1 Hz), 7.20−7.15 (m, 2H), 5.35 (dd, 1H, *J* = 12.4, 8.8 Hz), 4.99−4.96 (m, 1H), 4.74−4.72 (m, 1H), 4.04−4.02 (m, 2H), 3.5 (s, 2H), 1.58 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$ with DABCO) δ 170.9, 156.8, 144.6, 140.8, 139.7, 132.2, 129.4, 129.2, 128.8, 128.5, 127.9, 126.7, 125.3, 122.8, 77.8, 60.9, 39.9, 34.6, 14.1.

*Ethyl 2,5-Dihydro-4-(1,2,3,4-tetrahydro-2-nitronaphthalen-1-yl)-5-oxo-1-phenyl-1H-pyrazole-3-carboxylate (**3i**).* 1,2-Dihydro-3-nitronaphthalene (**1g**) (46 mg, 0.26 mmol), ethyl 2,5-dihydro-5-oxo-1-phenyl-1*H*-pyrazole-3-carboxylate (**2a**) (61 mg, 0.26 mmol), DABCO (29 mg, 0.26 mmol), and DCM (3 mL) were used. The product was obtained as a light-yellow solid (81 mg) in 76% yield. Mp 80−82 °C; R_f 0.35 (hexane/ethyl acetate = 6:4); MS (EI) *m*/*z* 407 (M^+); HRMS (EI) calcd for $C_{22}H_{21}N_3O_5$ 407.1481, found *m*/*z* 407.1476; ^{1}H NMR (600 MHz, $CDCl_3$ with DABCO) δ 7.86 (d, 2H, *J* = 7.5 Hz) 7.40 (t, 2H, *J* = 7.8 Hz), 7.27−7.22 (m, 1H), 7.09−7.04 (m, 4H), 6.36 (bs, 1H), 5.71 (ddd (observed as dt), 1H, *J* = 11.1, 11.2, 3.4 Hz), 5.14−5.12 (m, 1H), 4.25 (q, 2H, *J* = 6.8 Hz), 3.15−3.00 (m, 2H), 2.54−2.44 (m, 2H), 1.24 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$ with DABCO) δ 163.6, 158.9, 140.8, 139.6, 138.3, 134.5, 128.9, 128.8, 128.7, 128.3, 127.8, 126.3, 126.1, 125.6, 123.5, 101.6, 87.1, 60.5, 39.7, 29.3, 28.4, 14.3.

*Ethyl 2-(2,5-Dihydro-4-(1,2,3,4-tetrahydro-2-nitronaphthalen-1-yl)-5-oxo-1-phenyl-1H-pyrazol-3-yl)acetate (**3j**).* 1,2-Dihydro-3-nitronaphthalene (**1g**) (50 mg, 0.28 mmol), ethyl 2-(2,5-dihydro-5-oxo-1-phenyl-1*H*-pyrazol-3-yl)acetate (**2c**) (70 mg, 0.28 mmol), DABCO (32 mg, 0.28 mmol), and DCM (2 mL) were used. The product was obtained as a yellow solid (92 mg) in 77% yield. Mp 41−43 °C; R_f 0.31 (hexane/ethyl acetate = 6:4); MS (EI) *m*/*z* 421 (M^+); HRMS (EI) calcd for $C_{23}H_{23}N_3O_5$ 421.1637, found *m*/*z* 421.1640; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, 2H, *J* = 7.9 Hz), 7.36 (t, 2H, *J* = 7.9 Hz), 7.26−6.99 (m, 5H), 5.41 (bs, 1H), 4.61−4.58 (bs, 1H), 4.21 (q, 2H, *J* = 7.1 Hz), 3.61 (bs, 2H), 3.12−2.94 (m, 2H), 2.58−2.30 (m, 2H), 1.30 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$ with DABCO) δ 171.2, 156.7, 144.9, 139.9, 137.7, 134.7, 129.6, 128.7, 128.1, 126.4, 125.9, 125.1, 122.4, 99.4, 87.1, 60.9, 39.4, 34.5, 29.2, 28.3, 14.2.

*General Procedure for Reductive Cyclization (**4a**−**h** and **4j**).* To a stirred solution of Michael adduct **3** (1 mmol) in acetic acid (5 mL) was added zinc dust (10 mmol). The reaction mixture was stirred for 2 h at room temperature. After completion of the reaction, the reaction mixture was filtered through Celite. The filtrate was concentrated and subjected to cyclization by addition of 3:2 toluene/acetic acid and refluxing at 120 °C for 24 h. The reaction mixture was concentrated, and the residue was quenched with saturated $NaHCO_3$ solution and further washed with organic solvents such as DCM and Et_2O. The residue was concentrated to afford the pure product (**4a**−**g**) or purification was done by column chromatography using 95:5 EtOAc/MeOH as the eluent (**4h** and **4j**).[21]

*2,4-Diphenyl-5,6-dihydro-1H-pyrazolo[3,4-c]pyridine-3,7(2H,4H)-dione (**4a**).* Michael adduct **3a** (54 mg) was used. The product was obtained as a white solid (32 mg) in 69% overall yield (two steps). Mp >250 °C (compound decomposes above 250 °C); MS (EI) *m*/*z* 305 (M^+); HRMS (EI) calcd for $C_{18}H_{15}N_3O_2$ 305.1164, found *m*/*z* 305.1166; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.14 (bs, 1H), 7.78 (d, 2H, *J* = 7.7 Hz), 7.48 (t, 3H, *J* = 7.5 Hz), 7.33−7.26 (m, 3H), 7.22−7.14 (m, 3H), 4.19 (s, 1H), 3.79 (dd, 1H, *J* = 12.8, 4.7 Hz), one proton

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overlapped with the solvent peak; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 157.6, 143.9, 141.8, 140.9, 128.2, 127.6, 127.5, 125.7, 123.8, 123.0, 102.6, 48.3, 34.5.

*4-(4-Methoxyphenyl)-2-phenyl-5,6-dihydro-1H-pyrazolo[3,4-c]-pyridine-3,7(2H,4H)-dione (**4b**).* Michael adduct **3b** (60 mg) was used. The product was obtained as a gray solid (35 mg) in 72% overall yield (two steps). Mp >260 °C (compound decomposes above 260 °C); MS (ESI) m/z 358 ([M + Na]$^+$); HRMS (ESI) calcd for $C_{19}H_{17}N_3O_3$ 358.1167 ([M + Na]$^+$), found m/z 358.1162; ^{1}H NMR (400 MHz, MeOD) δ 7.92 (d, 2H, J = 7.6 Hz); 7.39−7.16 (m, 5H), 6.79 (d, 2H, J = 8.5 Hz), 4.08−4.07 (m, 1H), 3.88 (dd, 1H, J = 12.3, 5.0 Hz), 3.73 (s, 3H), 3.46 (dd, 1H, J = 12.3, 2.2 Hz); ^{13}C NMR (100 MHz, MeOD) δ 166.9, 161.4, 161.0, 159.7, 142.8, 141.9, 136.6, 129.8, 129.4, 126.1, 123.4, 114.5, 101.9, 55.6, 50.9, 36.2.

*Methyl 4-(3,7-Dioxo-2-phenyl-2,3,4,5,6,7-hexahydro-1H-pyrazolo[3,4-c]pyridin-4-yl)benzoate (**4c**).* Michael adduct **3c** (50 mg) was used. The product was obtained as an brown solid (29 mg) in 70% overall yield (two steps). Mp >250 °C (compound decomposes above 250 °C); MS (ESI) m/z 386 ([M + Na]$^+$); HRMS (ESI) calcd for $C_{20}H_{17}N_3O_4$ 386.1116 ([M + Na]$^+$), found m/z 386.1110; ^{1}H NMR (300 MHz, MeOD) δ 8.20 (d, 2H, J = 7.7 Hz), 7.82 (d, 2H, J = 8.2 Hz), 7.39 (d, 2H, J = 8.2 Hz), 7.27 (t, 2H, J = 7.5 Hz), 7.16−7.14 (m, 1H), 6.98 (t, 1H, J = 7.1 Hz), 3.9 (bs, 1H), 3.82 (s, 3H), 3.71 (dd, 1H, J = 12.4, 5.1 Hz), 3.34−3.29 (m, 1H); ^{13}C NMR (75 MHz, MeOD) δ 166.3, 164.1, 161.2, 150.7, 142.2, 141.6, 128.6, 128.1, 128.0, 127.9, 127.1, 122.2, 118.4, 96.4, 51.9, 48.1, 35.5.

*2-Phenyl-4-propyl-5,6-dihydro-1H-pyrazolo[3,4-c]pyridine-3,7-(2H,4H)-dione (**4d**).* Michael adduct **3d** (50 mg) was used. The product was obtained as an off-white solid (26 mg) in 69% overall yield (two steps). Mp >270 °C (compound decomposes above 270 °C); MS (EI) m/z 271 (M$^+$); HRMS (EI) calcd for $C_{15}H_{17}N_3O_2$ 271.1320, found m/z 271.1316; ^{1}H NMR (400 MHz, MeOD) δ 7.55 (d, 2H, J = 7.8 Hz), 7.38 (t, 2H, J = 7.8 Hz), 7.28 (d, 1H, J = 7.6 Hz), 3.57 (dd, 1H, J = 12.8, 5.0 Hz), 3.35 (dd, 1H, J = 12.8, 3.3 Hz), 2.85 (bs, 1H), 1.68−1.65 (m, 1H), 1.50−1.42 (m, 3H), 0.94 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, MeOD) δ 165.8, 156.8, 141.1, 139.6, 129.6, 127.8, 124.8, 95.5, 47.3, 36.3, 31.5, 21.4, 14.5.

*2-Phenyl-4-(thiophen-2-yl)-5,6-dihydro-1H-pyrazolo[3,4-c]-pyridine-3,7(2H,4H)-dione (**4e**).* Michael adduct **3e** (50 mg) was used. The product was obtained as a white solid (31 mg) in 75% overall yield (two steps). Mp >280 °C (compound decomposes above 280 °C); MS (EI) m/z 311 (M$^+$); HRMS (EI) calcd for $C_{16}H_{13}N_3O_2S$ 311.0728, found m/z 311.0725; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.47 (bs, 1H), 7.79 (d, 2H, J = 7.7 Hz), 7.63 (bs, 1H), 7.46 (t, 2H, J = 7.7 Hz), 7.30−7.29 (m, 2H), 6.92 (bs, 1H), 6.82 (bs, 1H) 4.44 (s, 1H), 3.77−3.78 (m, 1H), 1H merged in the DMSO-d_6 water peak; ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.7, 157.4, 148.5, 140.9, 140.5, 128.3, 126.4, 124.3, 124.1, 123.4, 120.6, 101.6, 48.9, 30.4.

*(4S,5R)-5-Methyl-2,4-diphenyl-5,6-dihydro-1H-pyrazolo[3,4-c]-pyridine-3,7(2H,4H)-dione (**4f**).* Michael adduct **3f** (60 mg) was used. The product was obtained as a white solid (31 mg) in 65% overall yield as single diastereomer (two steps). Mp >280 °C (compound decomposes above 280 °C); MS (EI) m/z 319 (M$^+$); HRMS (EI) calcd for $C_{19}H_{17}N_3O_2$ 319.1320, found m/z 319.1321; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.44 (bs, 1H), 7.77 (d, 2H, J = 8.5 Hz), 7.66 (bs, 1H), 7.49 (t, 2H, J = 7.6 Hz), 7.35−7.28 (m, 3H), 7.23−7.16 (m, 3H), 4.04 (s, 1H), 3.66−3.63 (m, 1H), 1.27 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.6, 149.5, 142.8, 141.6, 138.6, 128.9, 128.2, 127.5, 126.5, 126.4, 121.9, 100.9, 55.4, 40.9, 22.9. Assignment of stereochemistry: From the NOESY experiment we concluded that the methyl protons are correlated with the benzylic proton (see the NOESY spectrum on p S23 in the Supporting Information).

*2-Methyl-4-phenyl-5,6-dihydro-1H-pyrazolo[3,4-c]pyridine-3,7-(2H,4H)-dione (**4g**).* Michael adduct **3g** (50 mg) was used. The product was obtained as a white solid (19 mg) in 52% overall yield (two steps). Mp >250 °C (compound decomposes above 250 °C); MS (EI) m/z 243 (M$^+$); HRMS (EI) calcd for $C_{13}H_{13}N_3O_2$ 243.1007, found m/z 243.1001; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.99 (bs, 1H), 7.32 (bs, 1H), 7.27 (t, 2H, J = 7.4 Hz), 7.19 (t, 1H, J = 7.4 Hz), 7.10 (d, 2H, J = 7.4 Hz), 4.10 (bs, 1H), 3.72 (dd, 1H, J = 12.4, 4.7 Hz), 3.59 (s, 3H), 3.29 (m, 1H, merged in the H_2O peak); ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.8, 148.6, 142.4, 140.1, 128.0, 127.5, 126.3, 101.1, 54.9, 48.6, 34.6.

*2,4-Diphenyl-1,2,4,5,6,8-hexahydropyrazolo[3,4-d]azepine-3,7-dione (**4h**).* Michael adduct **3h** (65 mg) was used. The product was obtained as a white solid (26 mg) in 51% overall yield (two steps). Mp >280 °C (compound decomposes above 280 °C); MS (EI) m/z 319 (M$^+$); HRMS (EI) calcd for $C_{19}H_{17}N_3O_2$ 319.1320, found m/z 319.1323; ^{1}H NMR (600 MHz, MeOD) δ 7.61 (d, 2H, J = 7.5 Hz), 7.44 (t, 2H, J = 7.5 Hz), 7.31−7.27 (m, 3H), 7.22−7.19 (m, 3H), 4.06 (bs, 1H), 3.92−3.77 (m, 3H), 3.56−3.52 (m, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.1, 162.3, 144.8, 142.5, 141.5, 128.1, 127.9, 127.8, 127.4, 125.2, 121.2, 117.6, 47.3, 41.6, 37.5.

*2-Phenyl-2,3,4,6,6a,7,8,12b-octahydronaphtho[2,1-b]pyrazolo-[4,3-d]azepine-1,5-dione (**4j**).* Michael adduct **3j** (70 mg) was used. The product was obtained as a light-brown solid (32 mg) in 56% overall yield (two steps). Mp >250 °C (compound decomposes above 250 °C); MS (EI) m/z 345 (M$^+$); HRMS (EI) calcd for $C_{21}H_{19}N_3O_2$ 345.1477, found m/z 345.1478; ^{1}H NMR (300 MHz, MeOD) δ 7.73−7.72 (m, 2H), 7.48−7.50 (m, 2H), 7.35−7.33 (m, 1H), 7.16−7.13 (m, 4H), 4.18 (d, 1H, J = 7.1 Hz), 3.87−3.86 (m, 2H), 3.20 (d, 1H, J = 7.3 Hz), 3.10−3.01 (m, 2H), 2.34−2.31 (m, 1H), 2.07−2.04 (m, 1H); ^{13}C NMR (75 MHz, MeOD) δ 175.2, 159.9, 131.9, 130.2, 129.8, 128.8, 127.7, 127.6, 127.0, 126.8, 126.5, 120.1, 53.9, 52.9, 42.6, 29.2, 28.2.

*Synthesis of 6-Benzyl-2,4-diphenyl-5,6-dihydro-1H-pyrazolo[3,4-c]pyridine-3,7(2H,4H)-dione (**6**).* To a stirred solution of nitro adduct **3a** (50 mg) in methanol (10 mL) was cautiously added a 50% (w/w) aqueous slurry of Raney nickel (100 mg). The reaction mixture was stirred under a H_2 balloon at rt for 24 h. The reaction mixture was filtered through a pad of Celite, and the pad was rinsed with MeOH (10 mL). The filtrate was concentrated under reduced pressure to give a quantitative yield of the amine as a white solid.

To the stirred solution of the amine (42 mg, 0.12 mmol, 1 equiv) in methanol (5 mL) were added benzaldehyde (14 mg, 0.13 mmol, 1.1 equiv) and molecular sieves (nos. 5−6) at room temperature. The reaction mixture was heated at 60 °C for 6 h. After completion of the reaction, the reaction mass was cooled to room temperature, and to it was added sodium cyanoborohydride (38 mg, 0.60 mmol, 5 equiv). Further, the reaction mass was stirred for 24 h at rt. The reaction was quenched by addition of water, and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated. Without any further purification, it was subjected to cyclization in 3:2 toluene/acetic acid by refluxing for 24 h. The reaction mixture was concentrated and washed with a saturated solution of $NaHCO_3$. The pure compound was precipitated in petroleum ether. The product was obtained as a light-brown solid (24 mg) in 49% overall yield (three steps). Mp >140 °C (compound decomposes above 140 °C); MS (EI) m/z 395 (M$^+$); HRMS (EI) calcd for $C_{25}H_{21}N_3O_2$ 395.1633, found m/z 395.1634; ^{1}H NMR (300 MHz, MeOD) δ 7.79 (d, 2H, J = 6.6 Hz), 7.43−7.27 (m, 6H), 7.16−6.99 (m, 7H), 4.74 (d, 1H, J = 14.7 Hz), 4.38 (d, 1H, J = 14.5 Hz), 4.16 (s, 2H), 3.94 (d, 1H, J = 10.1 Hz), 3.47 (d, 1H, J = 12.1 Hz); ^{13}C NMR (75 MHz, MeOD) δ 163.9, 159.8, 143.1, 143.0, 140.3, 137.8, 136.3, 132.5, 131.0, 130.5, 130.2, 129.8, 129.4, 129.3, 128.8, 128.6, 128.2, 127.7, 123.9, 102.5, 56.6, 50.5, 36.4.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of the novel precursors. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) (a) The Michael adducts **3a–j** can exist in several tautomeric forms in solution. Because of this, broadening of peaks in the ^{1}H NMR spectra and disappearance of some carbon signals in the ^{13}C NMR spectra were observed for some of the compounds. (b) The ^{1}H NMR and ^{13}C NMR spectra for compound **3d** in $CDCl_3$ without DABCO are shown on p S5 in the Supporting Information). (c) Compound **3h** after column purification showed a complex ^{1}H NMR spectrum, but when the exact ratio of DABCO was added to the same NMR tube, the spectrum was simplified and was easy to interpret. The ^{1}H NMR spectrum without DABCO is shown on p S13 in the Supporting Information. (d) The spectra for the Michael adducts **3a–j** recorded in $CDCl_3$ in the presence of DABCO (the peaks at 2.6 ppm in the ^{1}H NMR spectrum and δ 45–46 ppm in the ^{13}C NMR spectrum correspond to DABCO) showed good splitting in ^{1}H NMR spectrum and distinct ^{13}C signals.

(21) (a) Compounds **4a–j** had very low solubility in DCM and EtOAc, so their spectra were recorded in either DMSO-d_6 or MeOD. (b) Tautomerism is also possible in the fused heterocycles (**4a–h**, **4j**, **6**). It is difficult to interpret the existence of a particular tautomer from NMR spectroscopic studies. (c) In some cases it was seen that in the ^{1}H NMR spectrum the benzylic proton appeared as broad singlet and one −C*H* peak of the methylene protons was merged into the DMSO-d_6 water peak. (d) Exchangeable protons were sometimes seen when spectra were recorded in DMSO-d_6 and MeOD. (e) In the ^{13}C NMR spectrum, overlapping of signals was observed and quaternary carbons were just seen.