Synthesis of Spiro Pyrazolone-Oxindole and Bicyclic Pyrazolone Derivatives via Solvent-Dependent Regioselective Aza-1,4/1,6-Michael and Intramolecular Cycloaddition under Catalyst-Free Conditions

Kota Sathish
Sakkani Nagaraju
Dhurke Kashinath* 0000-0002-2509-0386

Department of Chemistry, National Institute of Technology, Warangal 506004, India
kashinath@nitw.ac.in

Abstract A solvent-dependent, highly regioselective [3+2]-cycloaddition reaction of isoxazole-styrenes and azomethine imines under catalyst-free conditions is reported, furnishing a library of pyrazolone–spirooxindole hybrids. Good regioselectivity for the isomeric structures was achieved by the reaction of isoxazole-styrene and azomethine imine in different solvents and temperatures. The developed method was extended for the synthesis of tri-substituted dinitrogen-fused pyrazolones by using a 1,6-Michael addition reaction. Furthermore, the isoxazole moiety was converted into a carboxylic acid as a model study via ring opening.

Key words spirooxindole-pyrazolone hybrids, bicyclic pyrazolones, isoxazole-styrenes, switchable 1,3-dipolar cycloaddition, solvent-dependent reactivity, catalyst-free conditions

Spirooxindoles are structurally complex molecules with a quaternary carbon at C-3 of the indole nucleus, joined by multiply substituted five-membered pyrrolidine rings with defined stereocenters. The spirooxindole skeleton is present in many natural products such as spirotryptostatins, rhynchophyllines, horsfiline, and (+)-elacomines, and members of this class show a wide range of biological properties. Due to their structural complexity and biological prominence, these compounds have attracted the attention of synthetic chemists. As a result, many methods have been developed over the years for their synthesis. The [3+2]-cycloaddition and tandem (one-pot), multicomponent reactions of isatin or its derivatives in the presence of metal-based and organocatalysis are some of the common methods employed. In many cases, the synthesized compounds were tested for biological activity and, as a result, this moiety has become a promising scaffold in drug discovery.

Pyrazolones (pyrazole–5–ones) represent another useful scaffold commonly found in many biologically active molecules. Derivatives of pyrazolones such as morazone, phenzone, phenylbutazone (NSAIDs), tartrazine (anticancer) phenidone, and BW357U (anorectic) are sold as commercial drugs. Acyl substituted pyrazolones can undergo isomerization (proton exchange) and keto–enol tautomerism. These features make them useful synths in organic chemistry for electrophilic and nucleophilic addition reactions. Reports on N,N'–fused bicyclic pyrazolones are rare. They have been reported as γ-lactam antibiotics, antibacterial agents, acyl-CoA carboxylase (ACC) inhibitors, sarcoplasmatic reticulum Ca2+-ATPase inhibitors, and anti-cancer agents, and they have also been used as herbicides and pesticides (Figure 1).

The development of a regioselective method to access these derivatives is highly desirable, particularly one that allows the generation of complex molecules with structural diversity. In this context, domino-cascade, cycloaddition and chelation controlled reactions have proven to be efficient in the presence of Lewis acids, organocatalysts, and metal catalysts and in various solvents.

Nitrones, N-imides and pyridinium ylides are useful intermediates for the synthesis of functionalized pyrrolidines, dihydrooxazoles, and isoxazoles via 1,3-dipolar cycloaddition reactions (Michael addition, followed by Mannich type cyclization). In particular, azomethine imines (acyclic and...
N,N′-cyclic) have been used as 1,3-dipoles for [3+2]-
cycloaddition reactions \(^{4,8}\) to give complex spirooxindole
derivatives. In this connection, spiro[pyrazolidin-3,3′-ox-
indo]es have been obtained by [3+2]-cycloaddition re-
action (β-regioselective 1,4-aza Michael addition and intra-
molecular cyclization) of azomethine imines and methyl-
eneindolinones in the presence of chiral bis-phosphoric
acid,\(^9\) as catalysts with high enantioselectivity. In a similar
approach, Yan and co-workers reported a catalyst-free method for generating
spiro[indole-3,3′-pyrazol][1,2-α]pyrazoles \(^{3,9}\) using 3-
phenacylicenoxindoles.\(^{3,9}\)

3-Methyl-4-nitro-5-isatylidenyl-isoxazole (1)\(^{10}\) represents an excellent precursor for our studies, having two
reactive cites at the α- and β-positions to the unsaturated
double bond, as shown in Scheme 1. This feature has been
applied for use as a dipolarophile for the construction of
functionalized 3,3-disubstituted oxindoles and spirocyclic
oxindoles (via tandem Michael addition and aldol/Mannich
reactions)\(^{10,13,14}\) to give the desired products in good yields
with excellent regio- and/or stereoselectivity. In a similar
study, Liu and co-workers synthesized isoxazole-dispirobi-
soxindole and bispirecocyclic hexahydroxanthenes via β-regi-
oselective [3+2]-cycloaddition and domino Michael–Mi-
chael addition reactions using quinine and chiral thioareas
as organocatalysts.\(^11\) In a recent report, Chowhan and co-
workers demonstrated an unusual C-N-C [3+2]-cycloaddi-
tion of 3-methyl-4-nitro-5-styrylisoxazole and isatin N,N′-
cyclic azomethine imines with high diastereoselectivity.\(^12\)
All these methods have their own advantages in terms of
regioselectivity, stereoselectivity and product yields. How-
ever, a switchable regioselective reaction has never been re-
alyzed on 3-methyl-4-nitro-5-isatylidenyl-isoxazole (1).
Considering the importance of spiro- and bicyclic pyrazolo-
nes, we herein report the first example of a solvent-depen-
dent, regioselective-switchable reaction between N,N′-
cyclic azomethine imines and 3-methyl-4-nitro-5-isatylidenyloisoxazoles leading to complex dinitrogen-fused bicyclic and spirocyclic oxindoles in good yields.

Towards the synthesis of functionalized spirooxindole derivatives, we utilized 3-methyl-4-nitro-5-isatylidenyloisoxazole (1a) and azomethine imine (2) as model substrates in dichloromethane (DCM), both in the presence of organic bases (TEA and DABCO) and Lewis acids (Zn(OTf)3, AlCl3) at room temperature and heating (25–60 °C), but these conditions did not yield the expected products (Table 1; entries 1–5). The same reaction was then performed in 1,2-dichloroethane (DCE) at 80 °C for 12 h under catalyst-free conditions. To our satisfaction, the formation of products 3a and 4a was observed in 25 and 30% yield, respectively (Scheme 2 and Table 1, entry 6).

Encouraged by this result, the reaction was carried out in different solvents under catalyst-free conditions; the results are summarized in Table 1 (entries 7–26). It is important to note that the use of polar solvents (DMSO, DMF, MeCN, MeOH, EtOH and water) did not give the products even at elevated temperature. Even for the chlorinated solvents, the overall yield of products 3a and 4a could not be related to their boiling points and relative polarity [CH2Cl2 (no product), DCE (55%) and CHCl3 (60%)]. At this point, the use of other common solvents such as toluene, xylene, ethyl acetate, diethyl ether and tetrahydrofuran (from non-polar to moderately polar) were examined at temperatures between 40 and 80 °C (without the catalyst). Surprisingly, the reaction in toluene and xylene at 80 °C gave 3a in 84 and 70% yield, respectively, as major products, along with 4a in 5–10% yield as the minor regioisomer (Table 1, entries 14 and 15). On the other hand, reaction in tetrahydrofuran at 60 °C, gave a contrasting outcome, with 4a formed as the major product (75%) and 3a as the minor product (15%) for 4 h (Table 1, entry 21). Both the isomers were characterized by 1H and 13C NMR spectroscopic and mass spectrometric analyses. The 1H NMR spectrum of compound 3a in CDCl3 included two doublets at δ = 5.05 (d, J = 10.8 Hz) and 4.49 (d, J = 10.8 Hz) ppm, indicating that the phenyl and isoxazole ring protons are on adjacent carbons (Figure 1 in the Supporting Information); whereas for 4a the two characteristic protons appeared as singlets at δ = 5.97 and 4.12 ppm due to the phenyl and isoxazole rings being separated. The observed HRMS mass ion of 3a ([M+]+ 460.1614) of 4a ([M+]+ 460.1591) further confirmed the formation of the desired products.

At this juncture, we attempted to understand the solvent effect on the outcome of the reaction. Towards this, different combinations of toluene and tetrahydrofuran were studied (Table 1, entries 22–26). From these observations, we suggest that the polar chelating nature of the tetrahydrofuran helps to increase the electron density on the α-carbon of isoxazole-oxindole styrene, which facilitates attack of negatively charged nitrogen of the azomethine imine 2 to deliver product 4a as the major isomer.

**Table 1** Optimization of Reaction Conditions

<table>
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<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Cat. (20 mol%)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>3a</th>
<th>4a</th>
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<td>1</td>
<td>CH2Cl2</td>
<td>TEA</td>
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<tr>
<td>2</td>
<td>CH2Cl2</td>
<td>DABCO</td>
<td>rt</td>
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<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>CH2Cl2</td>
<td>Zn(OTf)3</td>
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<tr>
<td>4</td>
<td>CH2Cl2</td>
<td>AlCl3</td>
<td>rt</td>
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<td>ND</td>
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<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>CH2Cl2</td>
<td>–</td>
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</tr>
<tr>
<td>6</td>
<td>DCE</td>
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<tr>
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<tr>
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<td>THF</td>
<td>–</td>
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<td>23</td>
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<td>4</td>
<td>55</td>
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<tr>
<td>24</td>
<td>THF/Tol (1:3)</td>
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<td>4</td>
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<tr>
<td>25</td>
<td>THF/Tol (2:1)</td>
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<td>4</td>
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<tr>
<td>26</td>
<td>THF/Tol (3:1)</td>
<td>–</td>
<td>80</td>
<td>4</td>
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<td>55</td>
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*All reactions were performed with 1a (0.35 mmol) and 2 (0.35 mmol) in solvent (4 mL).

* Isolated yields.
After identifying the two optimal reaction conditions, we turned our attention towards the substrate scope of the reactions. Accordingly, variously substituted isatins (substitution on aromatic ring and nitrogen) and azomethine imines (aromatic and heteroaromatic) were reacted under the optimized conditions (both in toluene and THF) to afford the corresponding cycloaddition products 3a–m (Scheme 3) and 4a–k (Scheme 4) in good yields 70–86% in 4–6 h. All newly synthesized compounds were characterized using $^1$H, $^{13}$C NMR spectroscopy and mass spectrometry. Furthermore, single-crystal X-ray crystallographic data were obtained for compounds 3b, 3d, 3i and 4c, clearly indicating that the isoxazole and phenyl groups are adjacent to each other in products in Scheme 3; whereas in the products in Scheme 4, the rings were assigned opposite each other.

Based on above results and on single-crystal data, a plausible mechanism can be proposed for the [3+2]-cycloaddition reaction (Scheme 5). Azomethine imine 2 reacts with 3-methyl-4-nitro-5-isatylidenyl-isoxazole 1 viaaza-1,6 Michael addition ($\beta$-regioselectivity) to give adduct 1. This adduct can undergo intramolecular cyclization to afford desired product 3; in contrast, in THF the same reaction proceeds through aza-1,4 Michael addition ($\beta$-regioselectivity) followed by intramolecular cyclization to deliver product 4.

Considering the biological importance of spirooxindoles, isoxazoles and pyrazolones (Figure 1), we extended our strategy to the synthesis of diphenyltetrahydropyrazolo pyrazolones (dinitrogen-fused heterocycles). To achieve this, isoxazole-styrenes 5 were treated with azomethine imines 2 under the optimized reaction conditions (in toluene and THF). To our surprise, the reaction was successful only in toluene, delivering isoxazole-based dinitrogen-fused compounds 6a–k in good yields 65–90% in 4–5 hours (Scheme 6). Similar to the above mechanism, in this case the desired compounds 6 were also formed by the reaction of isoxazole styrene 5 with azomethine imine 2 to afford adduct 6 via aza-1,6-Michael addition followed by.

Scheme 3 Substrate scope for the synthesis of functionalized dinitrogen-fused spirooxindoles 3a–m

Scheme 4 Substrate scope for the synthesis of functionalized dinitrogen-fused spirooxindoles 4a–k

Scheme 5 Proposed mechanism for the two cycloaddition pathways
intramolecular cyclization. The isoxazole moiety was also used as a masked ester to generate carboxylic acid via ring opening under basic-oxidative conditions.13 Finally the cycloaducts 3a and 6b were converted into carboxylic acids 7a and 8b in 78 and 85% yield, respectively, by treatment with aq. NaOH (Scheme 7 and Scheme 8). The carboxylic acid 8b was then further functionalized into ester 9b and amide 10b derivatives in 65 and 85% yield, respectively, under the standard conditions (Scheme 8).

![Scheme 6](image6.png)

**Scheme 6** Substrate scope for the synthesis of functionalized N,N'-fused bicyclic pyrazolones and possible mechanism for the reaction

![Scheme 7](image7.png)

**Scheme 7** Synthesis of spirooxindole-pyrazolone carboxylic acid derivative 7a

In summary, we have demonstrated a simple and catalyst-free [3+2]-cycloaddition reaction for the synthesis of dinitrogen-fused pyrazolone derivatives with moderate to good yields. The reaction proceeds via aza-1,4/1,6-Michael addition of azomethine imines onto a conjugated system followed by intramolecular cyclization. The generated dinitrogen-fused heterocyclic compounds 3a and 6b were converted into pyrazolone-based carboxylic acids by hydrolysis of the isoxazole ring. The carboxylic acid can be used as a starting point for the construction of hybrid molecules using esterification or amide bond formation, as shown in Scheme 8.

All the solvents and required chemicals were procured from SD-Fine, Sigma–Aldrich, and Spectrochem, and used without purification and distillation. 1H and 13C NMR spectra were recorded with Bruker Avance 400 or 500 MHz spectrometers using CDCl3 or DMSO-d6 as solvents and are reported in δ units (ppm). Mass spectra of all the compounds were recorded with an Agilent Technologies-6530 spectrometer.

![Scheme 8](image8.png)

**Scheme 8** Functionalization of pyrazolo pyrazolone 6b

![image9.png](image9.png)

**[3+2] Cycloaddition Reaction; General Procedure**

To a solution of isoxazole-styrene 1 or 5 (0.35 mmol, 1 equiv) in THF/toluene (4 mL) was added azomethine imine 2 (0.35 mmol, 1 equiv) and the contents were heated at reflux (Table 1) for 4–6 h. After completion of reaction (monitored by TLC) the mixture was cooled to r.t., solvent was evaporated, and the crude product was purified by silica gel chromatography. Elution of the column with hexane/EtOAc (40–50%) gave the desired products 3, 4, and 6.

![image10.png](image10.png)

**Synthesis of Pyrazolopyrazole Carboxylic Acids; General Procedure**

To a solution of cyclic adduct 3a or 6b (0.25 mmol, 1 equiv) in THF (2 mL) was added aq. NaOH [1.25 mmol, 5 equiv] and the resulting mixture was heated at reflux for 2 h. After completion of the reaction (monitored by TLC), the reaction was quenched with 2 M HCl at 0 °C. The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried using sodium sulfate, filtered, and evaporation of the solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography (hexane/EtOAc) to give the desired products 7a or 8b as white solids.

![image11.png](image11.png)

**Synthesis of Methyl 1-(Furan-2-yl)-5-oxo-3-phenylhexahydropyrazolo[1,2-a]pyrazole-2-carboxylate (9b)**

To a solution of carboxylic acid 8b (0.32 mmol, 1 equiv) MeCN (3 mL) was added DBU (0.32 mmol, 1 equiv) and Mel (0.38 mmol, 1.2 equiv). The reaction mixture was stirred at r.t. for 3 h, then the crude product was purified over silica gel by column chromatography to afford the desired product 9b.
Synthesis of 1-[(Furan-2-yl)-5-oxo-3-phenyl-N-(p-toly)]hexahydro-pyrazolo[1,2-a]pyrazole-2-carboxylic acid (10b)

To a solution of acid 8b (0.32 mmol, 1 equiv) in DMF (3 mL) was added DiPEA (0.96 mmol, 3 equiv). The mixture was cooled to 0 °C and treated with EDC·HCl (0.64 mmol, 2 equiv), HOBT (0.64 mmol, 2 equiv) and the amine (0.38 mmol, 1.2 equiv). The reaction mixture was then stirred at r.t. for 1 h. After completion, the mixture was diluted with H2O (15 mL) and extracted with EtOAc (15 mL). The organic layer was dried (Na2SO4), filtered, and concentrated under reduced pressure. The resulting material was purified by silica gel column chromatography to provide the final product 10b as a white solid.

1-Methyl-2′-(3-Methyl-4-nitroisoxazol-5-yl)-3′-phenyl-5′,6′-dihydro-2′H-spiro[indolino-3,1′-pyrazolo[1,2-a]pyrazole-2,7′(3′H)]dione (3d)

Yield: 134 mg (84%); yellow solid; mp 183–185 °C.

H NMR (400 MHz, CDCl3): δ = 7.59 (dd, J = 8.0, 1.6 Hz, 2 H), 7.34–7.27 (m, 3 H), 7.16 (dd, J = 8.0, 1.2 Hz, 1 H), 7.04 (dd, J = 7.2, 0.8 Hz, 1 H), 6.89–6.82 (m, 1 H), 6.69 (d, J = 8.0 Hz, 1 H), 5.05 (d, J = 10.8 Hz, 1 H), 4.49 (d, J = 10.8 Hz, 1 H), 3.55–3.48 (m, 1 H), 3.17 (s, 3 H), 2.99–2.80 (m, 2 H), 2.64–2.57 (m, 1 H), 2.20 (s, 3 H).

13C NMR (100 MHz, CDCl3): δ = 172.89, 167.35, 163.10, 155.70, 144.12, 133.83, 131.04, 130.76, 129.43, 129.18, 128.19, 124.08, 122.73, 122.01, 108.98, 70.96, 64.18, 59.54, 51.09, 36.15, 26.95, 11.17.

MS (ESI): m/z calc for C25H23N5O5: 473.1699; found: 474.1714 [M + 1].

1-Ethyl-2′-(3-Methyl-4-nitroisoxazol-5-yl)-3′-phenyl-5′,6′-dihydro-2′H-spiro[indolino-3,1′-pyrazolo[1,2-a]pyrazole-2,7′(3′H)]dione (3b)

Yield: 121 mg (75%); white solid; mp 168–170 °C.

H NMR (400 MHz, CDCl3): δ = 7.55 (d, J = 8.0 Hz, 2 H), 7.27–7.14 (m, 4 H), 7.15 (d, J = 7.4 Hz, 1 H), 6.94 (t, J = 7.6 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 1 H), 5.18 (d, J = 10.8 Hz, 1 H), 4.56 (d, J = 10.8 Hz, 1 H), 3.93–3.68 (m, 2 H), 3.58 (t, J = 8.0 Hz, 1 H), 2.97 (m, 2 H), 2.73–2.62 (m, 1 H), 2.35 (s, 3 H), 1.30 (t, J = 7.2 Hz, 3 H).

13C NMR (100 MHz, CDCl3): δ = 172.03, 166.93, 163.18, 155.75, 142.05, 133.57, 131.12, 130.70, 129.51, 129.23, 128.12, 127.96, 124.85, 123.98, 109.97, 70.88, 63.94, 59.06, 51.09, 36.13, 35.74, 12.01, 11.23.

MS (ESI): m/z calc for C25H23N5O5: 473.1699; found: 474.1714 [M + 1].

2′-(3-Methyl-4-nitroisoxazol-5-yl)-3′-phenyl-1-propyl-5′,6′-dihydro-2′H-spiro[indolino-3,1′-pyrazolo[1,2-a]pyrazole-2,7′(3′H)]dione (3c)

Yield: 114 mg (70%); white solid; mp 194–196 °C.

H NMR (400 MHz, CDCl3): δ = 7.55 (d, J = 8.0 Hz, 2 H), 7.26–7.18 (m, 3 H), 7.15 (d, J = 7.2 Hz, 1 H), 6.94 (t, J = 7.6 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 1 H), 5.18 (d, J = 10.8 Hz, 1 H), 4.56 (d, J = 10.8 Hz, 1 H), 3.93–3.68 (m, 2 H), 3.58 (t, J = 8.0 Hz, 1 H), 3.10–2.84 (m, 2 H), 2.73–2.62 (m, 1 H), 2.35 (s, 3 H), 2.30 (s, 3 H), 1.30 (t, J = 7.2 Hz, 3 H).

13C NMR (100 MHz, CDCl3): δ = 172.43, 167.42, 163.04, 155.70, 143.43, 133.90, 131.00, 130.72, 129.41, 129.18, 128.17, 124.37, 122.50, 122.27, 109.05, 71.00, 64.26, 59.13, 51.08, 36.19, 35.58, 12.08, 11.21.

MS (ESI): m/z calc for C25H23N5O5: 473.1699; found: 474.2758 [M + 1].

1-Benzyl-2′-(3-methyl-4-nitroisoxazol-5-yl)-3′-phenyl-5′,6′-dihydro-2′H-spiro[indolino-3,1′-pyrazolo[1,2-a]pyrazole-2,7′(3′H)]dione (3g)

Yield: 109 mg (70%); yellow solid; mp 175–177 °C.

H NMR (400 MHz, CDCl3): δ = 7.51 (d, J = 8.6 Hz, 2 H), 7.25 (m, 5 H), 7.10 (d, J = 7.4 Hz, 1 H), 7.02 (t, J = 7.5 Hz, 1 H), 6.83 (t, J = 6.7 Hz, 3 H), 6.47 (d, J = 7.8 Hz, 1 H), 5.22 (d, J = 16.1 Hz, 1 H), 5.14 (d, J = 10.8 Hz, 1 H), 4.50 (d, J = 10.7 Hz, 1 H), 3.50 (t, J = 8.1 Hz, 1 H), 4.57 (s, 3 H), 3.40 (s, 3 H), 3.02–2.81 (m, 2 H), 2.61 (dd, J = 15.4, 7.1 Hz, 1 H), 2.21 (s, 3 H).
1H NMR (400 MHz, CDCl3): δ = 7.57 (dd, J = 7.6, 1.6 Hz, 2 H), 7.34–7.27 (m, 3 H), 7.15 (dd, J = 8.4, 2.0 Hz, 1 H), 7.04 (d, J = 2.0 Hz, 1 H), 6.64 (d, J = 8.4 Hz, 1 H), 5.09 (d, J = 10.4 Hz, 1 H), 4.48 (d, J = 10.4 Hz, 1 H), 3.81–3.70 (m, 1 H), 3.70–3.58 (m, 1 H), 3.53–3.46 (m, 1 H), 2.99–2.80 (m, 2 H), 2.64–2.56 (m, 1 H), 2.25 (s, 3 H), 1.20 (d, J = 7.2 Hz, 3 H).

13C NMR (100 MHz, CDCl3): δ = 173.54, 167.82, 164.29, 156.16, 144.28, 130.12, 129.09, 128.30, 128.07, 127.59, 127.32, 123.01, 122.87, 122.48, 108.69, 77.28, 67.59, 54.07, 52.27, 36.63, 26.19, 11.31.

MS (ESI): m/z calcd for C13H11NO4: 459.1543; found: 460.1591 [M + 1].
1-Ethyl-3-(3-methyl-4-nitroisoxazol-5-yl)-1′-phenyl-6′,7′-dihydro-1′H-spiro[indoline-3′,2′-pyrazolo[1,2-a]pyrazole]-2,5′(3′H)-dione (4b)
Yield: 128 mg (81%); white solid; mp 156–158 °C.

1H NMR (400 MHz, CDCl3): δ = 7.24 (t, J = 7.6 Hz, 2 H), 7.16 (t, J = 7.2 Hz, 2 H), 7.00 (d, J = 7.6 Hz, 2 H), 6.90 (t, J = 7.6 Hz, 1 H), 6.60 (d, J = 8.0 Hz, 1 H), 6.50 (d, J = 7.6 Hz, 1 H), 5.99 (s, 1 H), 4.15 (s, 1 H), 3.73 (t, J = 8.4 Hz, 1 H), 3.67–3.55 (m, 1 H), 3.34–3.19 (m, 2 H), 3.09–2.96 (m, 1 H), 2.92–2.82 (m, 1 H), 2.51 (s, 3 H), 0.68 (t, J = 7.2 Hz, 3 H).

13C NMR (100 MHz, CDCl3): δ = 173.07, 167.83, 164.22, 156.10, 143.43, 130.40, 129.27, 129.02, 128.28, 127.24, 123.23, 123.13, 122.24, 108.73, 77.42, 67.46, 53.91, 52.50, 36.67, 34.53, 11.61, 11.31.

MS (ESI): m/z calcd for C26H23N5O5: 473.1699; found: 474.1714 [M + 1].

1-Benzyl-3′-(3-methyl-4-nitroisoxazol-5-yl)-1′-phenyl-6′,7′-dihydro-1′H-spiro[indoline-3′,2′-pyrazolo[1,2-a]pyrazole]-2,5′(3′H)-dione (4c)
Yield: 125 mg (85%); light-yellow solid; mp 160–162 °C.

1H NMR (400 MHz, CDCl3): δ = 7.36 (t, J = 7.2 Hz, 1 H), 7.22 (t, J = 7.6 Hz, 2 H), 7.19–7.14 (m, 1 H), 7.14–7.06 (m, 5 H), 6.87 (s, J = 7.6 Hz, 1 H), 6.65 (d, J = 7.6 Hz, 1 H), 6.44 (d, J = 7.6 Hz, 2 H), 3.67 (d, J = 8.0 Hz, 1 H), 1.06 (s, 3 H), 0.50 (d, J = 16.4 Hz, 1 H), 4.33 (d, J = 7.6 Hz, 1 H), 4.26 (s, 1 H), 3.76 (t, J = 8.4 Hz, 1 H), 3.35–3.22 (m, 1 H), 3.08–2.98 (m, 1 H), 2.89 (dd, J = 16.0, 7.6 Hz, 1 H), 2.51 (s, 3 H).

13C NMR (100 MHz, CDCl3): δ = 137.75, 167.69, 164.29, 156.10, 143.84, 143.53, 134.55, 130.58, 130.33, 129.17, 128.71, 128.63, 127.70, 127.24, 126.29, 123.09, 122.81, 122.46, 110.03, 77.24, 67.54, 54.59, 52.29, 43.91, 36.66, 11.29.

MS (ESI): m/z calcd for C26H25N5O5: 536.1856; found: 536.1940 [M + 1].

3′-(3-Methyl-4-nitroisoxazol-5-yl)-1′-phenyl-1-propyl-6′,7′-dihydro-1′H-spiro[indoline-3′,2′-pyrazolo[1,2-a]pyrazole]-2,5′(3′H)-dione (4d)
Yield: 132 mg (85%); yellow solid; mp 155–157 °C.

1H NMR (400 MHz, CDCl3): δ = 7.24–7.18 (m, 2 H), 7.14 (t, J = 7.6 Hz, 2 H), 7.00 (d, J = 7.2 Hz, 2 H), 6.86 (t, J = 7.6 Hz, 1 H), 6.58 (d, J = 8.0 Hz, 1 H), 6.48 (d, J = 7.6 Hz, 1 H), 5.96 (d, J = 8.4 Hz, 1 H), 3.55–3.46 (m, 1 H), 3.31–3.13 (m, 2 H), 3.03–2.92 (m, 1 H), 2.85 (m, 1 H), 2.49 (s, 1 H), 1.22–1.07 (m, 2 H), 0.58 (t, J = 7.6 Hz, 3 H).

13C NMR (125 MHz, CDCl3): δ = 173.40, 167.82, 164.23, 156.10, 144.06, 130.46, 129.26, 129.05, 128.34, 128.16, 127.41, 123.16, 122.96, 122.15, 108.93, 77.22, 67.37, 54.13, 52.28, 41.67, 36.65, 20.20, 11.31, 11.00.

MS (ESI): m/z calcd for C26H24N5O5: 487.1856; found: 488.1971 [M + 1].

1-Allyl-3′-(3-methyl-4-nitroisoxazol-5-yl)-1′-phenyl-6′,7′-dihydro-1′H-spiro[indoline-3′,2′-pyrazolo[1,2-a]pyrazole]-2,5′(3′H)-dione (4e)
Yield: 134 mg (86%); white solid; mp 162–164 °C.

1H NMR (400 MHz, CDCl3): δ = 7.27–7.12 (m, 4 H), 7.00 (d, J = 7.2 Hz, 2 H), 6.93–6.87 (m, 1 H), 6.33 (dd, J = 27.2, 7.6 Hz, 2 H), 5.97 (s, 1 H), 5.24–5.16 (m, 1 H), 4.83 (d, J = 10.4 Hz, 1 H), 4.32 (dd, J = 60.4, 17.6 Hz, 2 H), 4.16 (s, 1 H), 3.82 (dd, J = 16.4, 4.0 Hz, 1 H), 3.70 (t, J = 8.4 Hz, 1 H), 3.30–3.17 (m, 1 H), 3.07–2.82 (m, 1 H), 2.49 (s, 3 H).

MS (ESI): m/z calcd for C26H24N5O5: 485.1699; found: 486.1767 [M + 1].
5-Chloro-1-ethyl-3′-(3-methyl-4-nitroisoxazol-5-yl)-1′-phenyl-6,7′-dihydro-1′H-spiro[indoline-3,2′-pyrazolo][1,2-a]pyrazole-2,5′(3′H)-dione (4j)

Yield: 123 mg (81%); light-yellow solid; mp 164–166 °C.

1H NMR (400 MHz, CDCl3): δ = 7.25 (d, J = 7.2 Hz, 1 H), 7.24–7.16 (m, 3 H), 7.05 (d, J = 7.2 Hz, 2 H), 6.53 (d, J = 8.4 Hz, 1 H), 6.41 (s, 1 H), 5.96 (s, 1 H), 4.10 (s, 1 H), 3.72 (t, J = 4.8 Hz, 1 H), 3.65–3.54 (m, 1 H), 3.30–3.21 (m, 2 H), 3.04–2.94 (m, 1 H), 2.92–2.83 (m, 1 H), 2.53 (s, 3 H), 0.66 (t, J = 7.2 Hz, 3 H).

13C NMR (100 MHz, CDCl3): δ = 172.63, 167.52, 164.25, 156.23, 141.98, 131.07, 130.22, 130.03, 129.26, 128.44, 128.34, 127.91, 127.86, 124.82, 123.67, 109.59, 77.19, 67.55, 53.80, 52.16, 36.63, 34.71, 11.53, 11.15.

MS (ESI): m/z calcd for C26H21ClN5O2: 515.1815; found: 516.1817 [M + 1].

6-(3-Methyl-4-nitrosoazol-5-yl)-7-(4-nitrophenyl)-5-phenyl-tetrahydropyrazolopyrazol-1,2-a[pyrazol-1(5H)]-one (6c)

Yield: 133 mg (82%); white solid; mp 182–184 °C.

1H NMR (400 MHz, CDCl3): δ = 8.29 (d, J = 8.8 Hz, 2 H), 7.66 (d, J = 8.8 Hz, 2 H), 7.28 (m, 3 H), 7.12 (d, J = 7.6 Hz, 2 H), 5.76 (d, J = 4.0 Hz, 1 H), 4.97–4.90 (m, 1 H), 4.66 (d, J = 6.8 Hz, 1 H), 3.41 (t, J = 11.2 Hz, 1 H), 3.22 (dd, J = 20.0, 10.0 Hz, 1 H), 2.76–2.63 (m, 2 H), 2.38 (3 H, J = 8.4 Hz, 1 H).

13C NMR (125 MHz, CDCl3): δ = 168.90, 155.89, 148.02, 144.92, 132.07, 130.65, 129.36, 128.98, 128.07, 128.70, 127.52, 124.53, 70.45, 57.03, 56.75, 47.61, 35.12, 11.37.

MS (ESI): m/z calcd for C29H22N5O5: 499.1335; found: 490.1403 [M + 1].

6-(3-Methyl-4-nitrosoazol-5-yl)-7-(4-nitrophenyl)-5-(p-tolyl)tetrahydropyrazolopyrazol-1,2-a[pyrazol-1(5H)]-one (6d)

Yield: 117 mg (70%); white solid; mp 179–181 °C.

1H NMR (400 MHz, CDCl3): δ = 8.27 (d, J = 8.8 Hz, 2 H), 7.64 (d, J = 8.8 Hz, 2 H), 7.05 (d, J = 8.0 Hz, 2 H), 6.97 (d, J = 8.0 Hz, 2 H), 5.79 (d, J = 4.4 Hz, 1 H), 4.91–4.84 (m, 1 H), 4.66 (d, J = 6.8 Hz, 1 H), 3.33 (t, J = 10.4 Hz, 1 H), 2.33 (dd, J = 19.2, 9.6 Hz, 1 H), 2.61 (m, 2 H), 2.38 (3 H, J = 8.4 Hz, 1 H), 2.28 (3 H, J = 3.3 Hz).

13C NMR (125 MHz, CDCl3): δ = 168.97, 155.97, 147.99, 139.40, 130.66, 129.71, 128.97, 128.15, 127.45, 124.52, 124.42, 114.91, 70.15, 57.10, 56.64, 34.70, 29.71, 21.12, 11.43.

MS (ESI): m/z calcd for C29H22N5O5: 463.1492; found: 464.1566 [M + 1].

6-(3-Methyl-4-nitrosoazol-5-yl)-7-(4-nitrophenyl)tetrahydropyrazolopyrazol-1,2-a[pyrazol-1(5H)]-one (6e)

Yield: 135 mg (85%); light-yellow solid; mp 175–177 °C.

1H NMR (400 MHz, CDCl3): δ = 8.15 (d, J = 8.8 Hz, 2 H), 7.60 (d, J = 4.8 Hz, 2 H), 7.34 (s, 1 H), 6.25 (m, 2 H), 6.11 (d, J = 4.8 Hz, 1 H), 5.01 (d, J = 6.8 Hz, 1 H), 4.71–4.65 (m, 1 H), 3.59 (dd, J = 22.0, 9.6 Hz, 1 H), 3.20–3.10 (m, 1 H), 2.41 (s, 3 H), 2.38–2.32 (m, 1 H), 1.64 (m, 1 H).

13C NMR (125 MHz, CDCl3): δ = 168.97, 155.97, 147.99, 139.40, 130.66, 129.71, 128.97, 128.15, 127.45, 124.52, 124.42, 114.91, 70.15, 57.10, 56.64, 34.70, 29.71, 21.12, 11.43.

MS (ESI): m/z calcd for C29H22N5O5: 439.1128; found: 440.1188 [M + 1].

5-(Furan-2-yl)-6-(3-methyl-4-nitrosoazol-5-yl)-7-(4-nitrophenyl)tetrahydropyrazolopyrazol-1,2-a[pyrazol-1(5H)]-one (6f)

Yield: 119 mg (70%); white solid; mp 164–166 °C.

1H NMR (400 MHz, CDCl3): δ = 7.33 (d, J = 7.6 Hz, 2 H), 7.22 (m, 5 H), 7.14–7.09 (m, 2 H), 5.53 (d, J = 4.0 Hz, 1 H), 4.88 (dd, J = 6.8, 4.8 Hz, 1 H), 4.51 (d, J = 6.8 Hz, 1 H), 3.32 (t, J = 10.4 Hz, 1 H), 3.05 (dd, J = 20.0, 10.0 Hz, 1 H), 2.72–2.58 (m, 2 H), 2.28 (s, 3 H).

13C NMR (125 MHz, CDCl3): δ = 167.32, 155.89, 148.02, 144.92, 132.07, 130.65, 129.36, 128.98, 128.07, 128.70, 127.52, 124.53, 70.45, 57.03, 56.75, 49.65, 35.12, 10.59.

MS (ESI): m/z calcd for C28H20N5O5: 404.1485; found: 405.1558 [M + 1].
1H NMR (400 MHz, CDCl3): δ = 7.39 (s, 4 H), 7.22 (m, 3 H), 7.13–7.08 (m, 2 H), 5.57 (d, J = 4.0 Hz, 1 H), 4.91 (dd, J = 7.2, 4.8 Hz, 1 H), 4.56 (d, J = 7.2 Hz, 1 H), 3.39 (m, 1 H), 3.11 (q, J = 10.0 Hz, 1 H), 2.70 (m, 2 H), 2.35 (s, 3 H).

13C NMR (100 MHz, CDCl3): δ = 169.29, 164.87, 155.50, 151.21, 147.30, 141.14, 137.22, 130.64, 130.36, 129.57, 129.35, 128.89, 128.59, 127.73, 126.46, 126.43, 124.71, 123.22, 63.57, 58.53, 55.60, 49.52, 36.41, 11.37.

MS (ESI): m/z calcd for C22H23N3O3: 402.1785; found: 402.1783 [M].

Methyl 1-{Furan-2-yl}-5-oxo-3-phenylhexahydropyrazolo[1,2-α]pyrazole-2-carboxylate (9b)

Yield: 67 mg (65%); light-yellow liquid.

1H NMR (400 MHz, DMSO-d6): δ = 7.69 (d, J = 1.2 Hz, 2 H), 7.44 (d, J = 4.8 Hz, 1 H), 7.37 (t, J = 4.6 Hz, 1 H), 7.12 (m, 5 H), 5.24 (d, J = 3.2 Hz, 1 H), 5.14 (dd, J = 7.2, 3.6 Hz, 1 H), 4.63 (d, J = 7.2 Hz, 1 H), 3.43 (m, 1 H), 2.98–2.86 (m, 2 H), 2.73 (m, 1 H), 2.27 (s, 3 H).

13C NMR (125 MHz, CDCl3): δ = 175.42, 169.82, 164.87, 155.34, 154.17, 153.22, 133.22, 131.71, 129.30, 127.78, 127.48, 126.45, 122.75, 118.23, 117.24, 69.84, 52.71, 52.31, 48.24, 35.34, 10.37.

MS (ESI): m/z calcd for C22H22N3O3: 347.1383; found: 347.1453 [M].

1-(Furan-2-yl)-5-oxo-3-phenylhexahydropyrazolo[1,2-α]pyrazole-2-carboxamide (10b)

Yield: 109 mg (85%); white solid; mp 222–224 °C.
Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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References


