

Short Note

(5*R**,6*R**) 11-Benzoyl-4,10-dimethyl-2,8-diphenyl-2,3,8,9-tetraazadispiro [4.0.4⁶.1⁵]undeca-3,9-diene-1,7-dione

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Abstract

Cyclopropanes are important in drug discovery because their unique structure, including inherent three-dimensionality, can enhance a drug's properties, such as metabolic stability, target binding, and membrane permeability. In this communication, (5*R**,6*R**) 11-benzoyl-4,10-dimethyl-2,8-diphenyl-2,3,8,9-tetraazadispiro[4.0.4⁶.1⁵]undeca-3,9-diene-1,7-dione was prepared via a stereoselective one-pot reaction of phenylglyoxal hydrate with two equivalents of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one in EtOH in the presence of sodium acetate and *N*-bromosuccinimide. The structure of the newly synthesized compound was established by ¹H and ¹³C NMR, IR spectroscopy, high-resolution mass spectrometry, and elemental analysis.

Keywords: 2,3,8,9-tetraazadispiro[4.0.4.1]undeca-3,9-diene; phenylglyoxal; 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one; *N*-bromosuccinimide; sodium acetate; cyclization

1. Introduction

Cyclopropanes are important in drug discovery because their unique structure, including inherent three-dimensionality, can enhance a drug's properties, such as metabolic stability, target binding, and membrane permeability [1]. The strained ring system of cyclopropanes introduces significant bond angle distortion, which can lead to improved binding affinity and selectivity toward biological targets compared to less constrained analogs [2]. Additionally, the cyclopropyl group often acts as a bioisostere for alkenes, amides, or other functional groups, further expanding its utility in medicinal chemistry. Its ability to modulate lipophilicity and resist oxidative metabolism makes it a valuable motif in the design of protease inhibitors, kinase modulators, and CNS (central nervous system)-active drugs [3]. Recent studies have demonstrated that cyclopropane-containing compounds exhibit enhanced pharmacokinetic profiles, underscoring their importance in modern drug development [4].

Spiro compounds are biologically active organic compounds characterized by a unique structural motif where two rings share a single common atom, conferring three-dimensional rigidity and structural diversity [5]. This spirocyclic architecture enhances molecular stability, improves binding selectivity, and often increases metabolic resistance, making them valuable scaffolds in drug discovery [6]. Spiro compounds are found in numerous natural products and pharmaceuticals, exhibiting a wide range of biological activities, including antimicrobial, anticancer, and CNS modulation [7]. Their ability to occupy distinct spatial orientations allows for optimized interactions with biological targets, contributing to their



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prominence in medicinal chemistry [8]. Recent advances in synthetic methodologies have further expanded their application in the design of novel therapeutics.

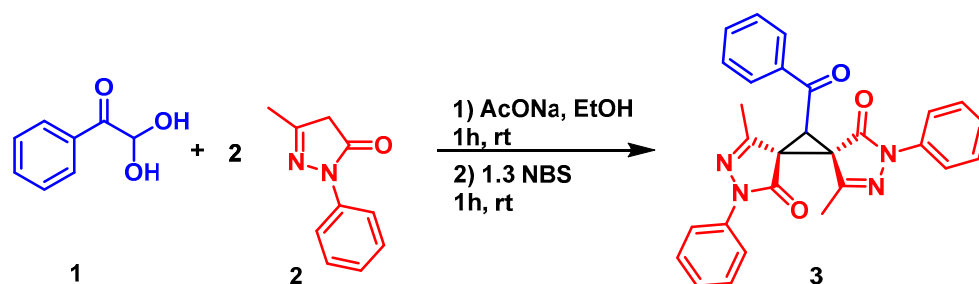
Thus, the synthesis of novel spiro compounds with cyclopropyl fragment is a prospective area of organic chemistry.

2. Results and Discussion

Various cyclization reactions have been achieved by action of *N*-bromosuccinimide (NBS) [9–12]. In these transformations, molecular bromine served as the source of the leaving group, either generated in situ during the reaction or introduced as an external reagent.

Earlier, our research group synthesized cyclopropanes from benzaldehydes and two equivalents of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one in the presence of sodium iodide as a mediator in methanol in an undivided cell (the stereoselective electrocatalytic direct transformation) [13].

In the present communication, we report the stereoselective efficient one-pot synthesis of the previously unknown (5*R**,6*R**) 11-benzoyl-4,10-dimethyl-2,8-diphenyl-2,3,8,9-tetraazadispiro[4.0.4⁶.1⁵]undeca-3,9-diene-1,7-dione **3** from phenylglyoxal hydrate **1** and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **2** in ethanol at room temperature in the presence of NBS and sodium acetate for 2 h, as shown in Scheme 1.



Scheme 1. One-pot reaction of phenylglyoxal hydrate **1** and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **2**.

For this synthetic protocol, *N*-bromosuccinimide is recommended as the halogen source due to its advantageous properties [14]. As a widely employed reagent in organic synthesis, NBS offers high selectivity, operational simplicity, commercial availability, low cost, and reduced toxicity compared to molecular bromine.

Sodium acetate (NaOAc) serves as an effective and mild base catalyst in organic transformations, facilitating reactions such as condensations and nucleophilic substitutions while minimizing side reactions [15]. The use of NaOAc as a catalyst offers advantages including low cost, non-toxicity, moisture stability, and ease of removal from reaction mixtures by simple aqueous workup.

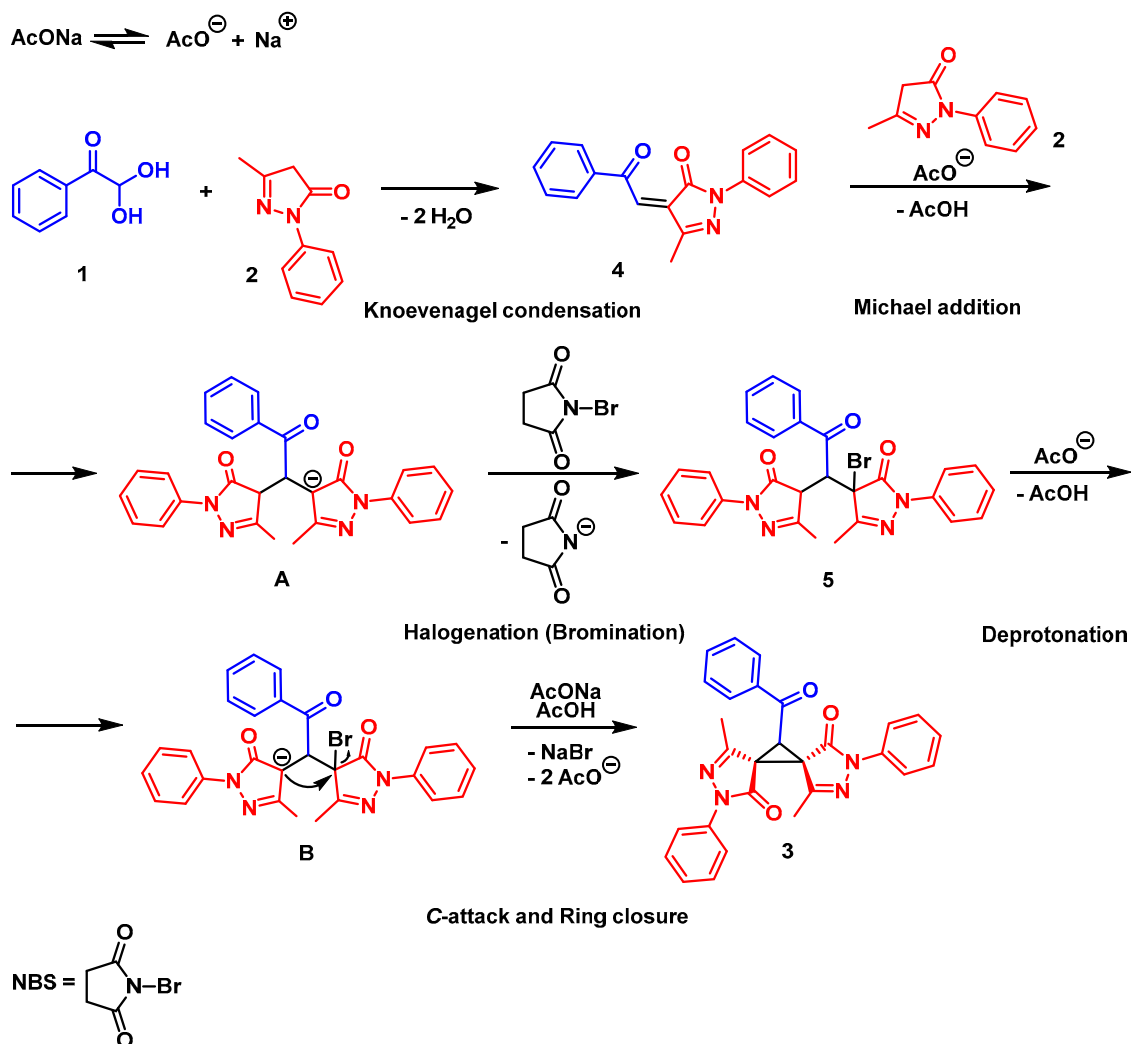
As the reaction progressed, 2,3,8,9-tetraazadispiro[4.0.4⁶.1⁵]undeca-3,9-diene (**3**) precipitated out of the solution. The reaction was deemed complete upon full discoloration of the mixture, transitioning from a yellow to a white suspension. The target compound **3** was isolated with a yield of 85%.

The structure of (5*R**,6*R**) 2,3,8,9-tetraazadispiro[4.0.4⁶.1⁵]undeca-3,9-diene **3** was unambiguously confirmed by ¹H and ¹³C NMR spectroscopy, IR spectroscopy, mass spectrometry, and elemental analysis. Both ¹H and ¹³C NMR spectra displayed a single set of signals, indicating high purity and the absence of isomeric or polymeric byproducts.

Bispyrazolone cyclopropane **3** exists as a pair of diastereoisomers with an (*R**,*R**) or (*R**,*S**) relative disposition of pyrazolone fragments. The ¹H and ¹³C NMR spectra clearly indicated that the methyl groups of pyrazolone rings occupy different sides relative to the cyclopropane cycle. In the ¹H NMR spectrum of **3**, protons of the CH₃ groups appeared as

two different singlets at 2.28 and 2.52 ppm (this signal is superimposed on the signal from DMSO- d_5). Thus, NMR data clearly support the (R^*,R^*) configuration of bispyrazolone cyclopropanes **3**, with the methyl groups of pyrazolone rings lying on different sides of the cyclopropane plane. Please, see also Supplementary Materials.

In light of our previous studies [9–13], a possible mechanism for the stereoselective synthesis of compound **3** was suggested (Scheme 2).



Scheme 2. Mechanism of the one-pot transformation.

The process begins with the condensation of phenylglyoxal hydrate (**1**) and 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (**2**) resulting in the formation of the Knoevenagel adduct **4**. The following Michael addition of the second equivalent of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one **2** affords the formation of anion **A**. Compound **5** is then produced by halogenating the anion **A** using NBS as an electrophilic halogen source. In the presence of a base, compound **5** undergoes deprotonation, leading to the formation of intermediate **B**. Intramolecular C-attack results in ($5R^*,6R^*$) 11-benzoyl-4,10-dimethyl-2,8-diphenyl-2,3,8,9-tetraazadispiro[4.0.4⁶.1⁵]undeca-3,9-diene-1,7-dione **3**. The steric hindrance between the two methyl groups of the pyrazolin-5-one ring appears to be the primary factor influencing the stereoselectivity of the cyclization, resulting in the preferred bis[spiro-2,4-dihydro-3H-pyrazol-3-one]cyclopropane **3** with (R^*,R^*) configuration.

3. Materials and Methods

3.1. General Methods

The solvents and reagents were purchased from commercial suppliers (Sigma-Aldrich, St. Louis, MO, USA) and were used without any purification.

The melting point was determined using a Gallenkamp melting-point apparatus (Gallenkamp & Co., Ltd., London, UK). ^1H and ^{13}C NMR spectra were recorded with a Bruker AM300 spectrometer (Bruker Corporation, Billerica, MA, USA) in $\text{DMSO}-d_6$ at ambient temperature (Me_4Si as internal standard). The IR spectrum was registered with a Bruker ALPHA-T FT-IR spectrometer (Bruker Corporation, Billerica, MA, USA) in KBr pellets. The high-resolution mass spectral analysis was performed on a Bruker MicrOTOF-Q II spectrometer (Bruker Daltonik GmbH, Bremen, Germany) in electrospray ionization (ESI) mode and processed with Bruker Compass DataAnalysis 4.0 software (Bruker Daltonics GmbH & Co. KG, Bremen, Germany). Elemental analysis was carried out using a 2400 Elemental Analyzer (Perkin Elmer Inc., Waltham, MA, USA).

3.2. Synthesis of (5*R**,6*R**) 11-Benzoyl-4,10-dimethyl-2,8-diphenyl-2,3,8,9-tetraazadispiro[4.0.4⁶.1⁵]undeca-3,9-diene-1,7-dione (3)

A solution of phenylglyoxal monohydrate (1) (0.152 g, 1 mmol), 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2) (0.348 g, 2 mmol), and sodium acetate (0.082 g, 1 mmol) was stirred at room temperature in 5 mL of ethanol for 1 h. Then, *N*-bromosuccinimide (0.231 g, 1.3 mmol) was added, and the reaction mixture was stirred at room temperature for 1 h. After completion of the reaction, the formed precipitate was separated by filtration, washed with cold ethanol (2×3 mL), and dried, isolating (5*R**,6*R**) 11-benzoyl-4,10-dimethyl-2,8-diphenyl-2,3,8,9-tetraazadispiro[4.0.4⁶.1⁵]undeca-3,9-diene-1,7-dione (3).

3.3. (5*R**,6*R**) 11-Benzoyl-4,10-dimethyl-2,8-diphenyl-2,3,8,9-tetraazadispiro[4.0.4⁶.1⁵]undeca-3,9-diene-1,7-dione (3)

Yellow solid; yield 85% (0.393 g); mp = 173–174 °C (from EtOH); FTIR (KBr) cm^{-1} : 3062 (C-H Ar), 1711 (C=O), 1683 (C=O), 1594 (C-C Ar), 1493 (C-C Ar), 1290 (C-N), 1226 (C-O), 1129 (C-O). ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 2.28 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 4.98 (s, 1H, CH), 7.19 (t, $^3J = 7.7$ Hz, 1H, C(4)H Ph), 7.28 (t, $^3J = 7.3$ Hz, 1H, C(4)H Ph), 7.38 (t, $^3J = 7.7$ Hz, 2H, C(3)H and C(5)H Ph), 7.45–7.70 (m, 7H, C(2)H, 2 C(3)H, C(4)H, 2 C(5)H, C(6)H Ph), 7.80 (d, $^3J = 7.7$ Hz, 2H, C(2)H and C(6)H Ph), 7.88 (d, $^3J = 8.2$ Hz, 2H, C(2)H and C(6)H Ph) ppm; ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ 18.1 (CH_3), 19.8 (CH_3), 44.8 (CH), 47.9 (C(5)), 50.3 (C(6)), 118.7 (4C, 2 C(2)H, 2 C(6)H Ph), 125.3 (C(4)H Ph), 125.4 (C(4)H Ph), 128.0 (2C, C(2)H, C(6) Ph), 128.9 (2C, C(3)H, C(5)H Ph), 129.0 (4C, 2 C(3)H, 2 C(5)H Ph), 134.2 (C(4) Ph), 135.2 (C(1) Ph), 137.1 (C(1) Ph), 137.5 (C(1) Ph), 155.1 ($\text{C}-\text{CH}_3$), 155.7 ($\text{C}-\text{CH}_3$), 165.1 (C(1)=O), 166.7 (C(7)=O), 188.5 (C=O benzoyl) ppm; HRMS (ESI): m/z : $[\text{M} + \text{H}]^+$, calcd for $\text{C}_{28}\text{H}_{23}\text{N}_4\text{O}_3$ 463.1765, found 463.1763; Anal. calcd. for $\text{C}_{28}\text{H}_{22}\text{N}_4\text{O}_3$: C, 72.71; H, 4.79; N, 12.11%; found: C, 72.79; H, 4.85; N, 11.99%.

4. Conclusions

In summary, a convenient stereoselective one-pot process, pseudo-three-component reaction with subsequent NBS-induced cyclization, for the synthesis of previously unknown (5*R**,6*R**) 11-benzoyl-4,10-dimethyl-2,8-diphenyl-2,3,8,9-tetraazadispiro[4.0.4⁶.1⁵]undeca-3,9-diene-1,7-dione was elaborated. The advantages of this Knoevenagel–Michael transformation with cyclization are the application of readily available starting compounds, atom economy, and easy work-up procedures, which can avoid chromatographic purification. The structure of the synthesized compound was confirmed via ^1H and ^{13}C NMR, IR spectroscopy, high-resolution mass spectrometry, and elemental analysis.

Supplementary Materials: Compound 3 spectra: ^1H NMR (Figure S1), ^{13}C NMR (Figure S2), HRMS (Figure S3), IR (Figure S4).

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References

1. Li, D. The roles of fused-cyclopropanes in medicinal chemistry: Insights from the past decade. *Eur. J. Med. Chem.* **2025**, *297*, 117951. [CrossRef] [PubMed]
2. Talele, T.T. The “Cyclopropyl Fragment” is a Versatile Player that Frequently Appears in Preclinical/Clinical Drug Molecules. *J. Med. Chem.* **2016**, *59*, 8712–8756. [CrossRef] [PubMed]
3. Uthumange, S.S.; Liew, A.J.H.; Chee, X.W.; Yeong, K.Y. Ringing medicinal chemistry: The importance of 3-membered rings in drug discovery. *Bioorg. Med. Chem.* **2024**, *116*, 117980. [CrossRef] [PubMed]
4. Luckhurst, C.A.; Breccia, P.; Stott, A.J.; Aziz, O.; Birch, H.L.; Bürl, R.W.; Hughes, S.J.; Jarvis, R.E.; Lamers, M.; Leonard, P.M.; et al. Potent, Selective, and CNS-Penetrant Tetrasubstituted Cyclopropane Class IIa Histone Deacetylase (HDAC) Inhibitors. *ACS Med. Chem. Lett.* **2015**, *7*, 34–39. [CrossRef] [PubMed]
5. Basavaraja, D.; Siddalingeswar, V.D.; Athira, C.S.; Siby, A.; Sreelakshmi, V.; Ancy, A.; Sasidhar, B.S. Spiro-Heterocycles: Recent Advances in Biological Applications and Synthetic Strategies. *Tetrahedron* **2025**, *173*, 134468. [CrossRef]
6. Varela, M.T.; Dias, G.G.; de Oliveira, L.F.N.; de Oliveira, R.G.; Aguiar, F.D.; Nogueira, J.P.; Cruz, L.R.; Dias, L.C. Spirocyclic compounds as innovative tools in drug discovery for medicinal chemists. *Eur. J. Med. Chem.* **2025**, *287*, 117368. [CrossRef]
7. Chupakhin, E.; Babich, O.; Prosekov, A.; Asyakina, L.; Krasavin, M. Spirocyclic Motifs in Natural Products. *Molecules* **2019**, *24*, 4165. [CrossRef]
8. Habibi, D.; Beiranvand, M. *Nomenclature, Synthesis and Applications of Spirocyclic Compounds*; Cambridge Scholars Publishing: Newcastle upon Tyne, UK, 2023; ISBN 978-1-5275-3941-9. Available online: <https://books.google.ru/books?id=ZdriEAAQBAJ&printsec=frontcover&hl=ru#v=onepage&q&f=false> (accessed on 13 October 2025).
9. Kale, S.B.; Jori, P.K.; Thatikonda, T.; Gonnade, R.G.; Das, U. 1,6-Conjugate-addition-induced [2+1] annulation of para-quinone methides and pyrazolones: Synthesis of bis-spirocompounds with contiguous quaternary spiro-centers. *Org. Lett.* **2019**, *21*, 7736–7740. [CrossRef] [PubMed]
10. Liu, S.; Shao, P.; Li, Y.; Wang, D.; Hou, D.; Qu, C.; Yan, X. Regioselective synthesis of spirobarbiturate-dihydrofurans and dihydrofuro [2,3-d]pyrimidines via one-pot cascade reaction of barbiturate-based olefins and ethyl acetoacetate. *Tetrahedron* **2021**, *79*, 131859. [CrossRef]
11. Nakamura, A.; Rao, F.; Ukiya, K.; Matsunaga, R.; Ohiraa, S.; Maegawa, T. A concise synthesis of thioaurones via NBS-induced cyclization of MOM-protected 2'-mercaptochalcones. *Org. Biomol. Chem.* **2023**, *21*, 1134–1137. [CrossRef] [PubMed]
12. Mandal, D.; Ravikanth, M. NBS-Enabled rapid cyclization of 5,6-diaryl dipyrroethenes to access meso-tetraaryl porphycenes. *Org. Lett.* **2025**, *27*, 8679–8684. [CrossRef] [PubMed]
13. Elinson, M.N.; Dorofeeva, E.O.; Vereshchagin, A.N.; Nasybullin, R.F.; Egorov, M.P. Electrocatalytic stereoselective transformation of aldehydes and two molecules of pyrazolin-5-one into (R^* , R^*)-bis(spiro-2,4-dihydro-3H-pyrazol-3-one)cyclopropanes. *Catal. Sci. Technol.* **2015**, *5*, 2384–2387. [CrossRef]
14. Grjol, B.; Jereb, M. Reactivity of substrates with multiple competitive reactive sites toward NBS under neat reaction conditions promoted by visible light. *Chem. Pap.* **2021**, *75*, 5235–5248. [CrossRef]
15. Elinson, M.N.; Nasybullin, R.F.; Nikishin, G.I. Sodium acetate catalyzed tandem Knoevenagel–Michael multicomponent reaction of aldehydes, 2-pyrazolin-5-ones, and cyano-functionalized C–H acids: Facile and efficient way to 3-(5-hydroxypyrazol-4-yl)-3-aryl-propionitriles. *Comptes Rendus Chim.* **2013**, *16*, 789–794. [CrossRef]

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