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Synthesis of Energetic Material 4-Nitro-3,5-bis(trinitromethyl)-1*H*-pyrazole via [4 + 1] Cycloaddition

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Wentong Tu,† Tao Yu,† Linyuan Wen, Qiurong Li, Hongyao Xu,* and Yingzhe Liu*

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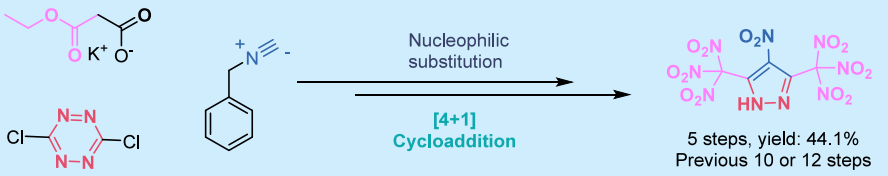

ABSTRACT: The synthesis of highly nitrated pyrazole derivatives, such as 4-nitro-3,5-bis(trinitromethyl)-1*H*-pyrazole, is challenging due to thermal instability and limited available ring sites. In this work, a novel, efficient synthetic route combining nucleophilic substitution and [4 + 1] cycloaddition skeletal editing was developed, achieving compound **1** in five steps with a 44.1% yield and its ammonium salt in four steps with a 56.5% yield. This strategy offers a promising approach for the efficient synthesis of poly-nitrated pyrazoles, marking the first use of skeletal editing of [4 + 1] cycloaddition in energetic material synthesis.

Energetic materials make up a class of substances that store significant chemical energy, which can be rapidly released through exothermic reactions. The primary research objectives in this field are to design and synthesize novel compounds that achieve a balance of high density, superior detonation performance, and low sensitivity. Current research efforts are focused on developing efficient and environmentally benign synthetic methodologies to tailor these properties for advanced applications in both the civilian and defense sectors. Over the past century, substantial progress has been made in synthesizing high-performance energetic materials, such as HMX, CL-20, TTTO, ONC, and poly-nitrated pyrazoles (Figure 1A).[1−3] In the field of pyrazole-based energetic materials, the challenge of incorporating an increasing number of nitro groups has become more pronounced. Consequently, there is a pressing need for innovative synthetic strategies, such as nucleophilic substitution and [4 + 1] cycloaddition reactions, to efficiently address this challenge.

Conventional methods for synthesizing energetic materials predominantly rely on oxidation, reduction, electrophilic addition, and nucleophilic addition. However, the application of radical reactions and [4 + 1] cycloadditions[4] in energetic material synthesis remains largely unexplored. Skeletal editing via [4 + 1] cycloaddition reactions[4c] offers distinct advantages over traditional methods, including high reaction efficiency, excellent atom economy, and mild reaction conditions. These advantages make [4 + 1] cycloaddition a promising strategy for the efficient synthesis of energetic materials, paving the way for novel pyrazole-based energetic compounds. This approach represents a significant optimization of the synthetic route, offering a more streamlined and environmentally friendly method compared to conventional multi-step, hazardous processes. As such, [4 + 1] cycloaddition holds great potential to revolutionize the development of energetic materials, opening up a new chapter in their synthesis.

Traditional synthetic routes for energetic materials often suffer from low atom economy and inefficiency.[5] Furthermore, reagents like hydrazine, commonly used in pyrazole ring synthesis, are not only hazardous to laboratory personnel but also environmentally unfriendly.[6] Hydrazine is not commercially available in several countries and poses a significant environmental risk. In contrast, skeletal editing of the tetrazine scaffold via [4 + 1] cycloaddition offers a more efficient and environmentally benign alternative, providing a direct route to 4-aminopyrazole frameworks. Several well-established methods for synthesizing tetrazine precursors, particularly those using cyano-containing compounds, make this approach highly viable.[7−9] Reactions typically employ metal Lewis acid catalysts, such as nickel triflate or zinc triflate, or non-metallic catalysts, like elemental sulfur or 3-mercaptopropionic acid (organocatalytic). These skeletal editing strategies not only enable the concise construction of target molecules but also

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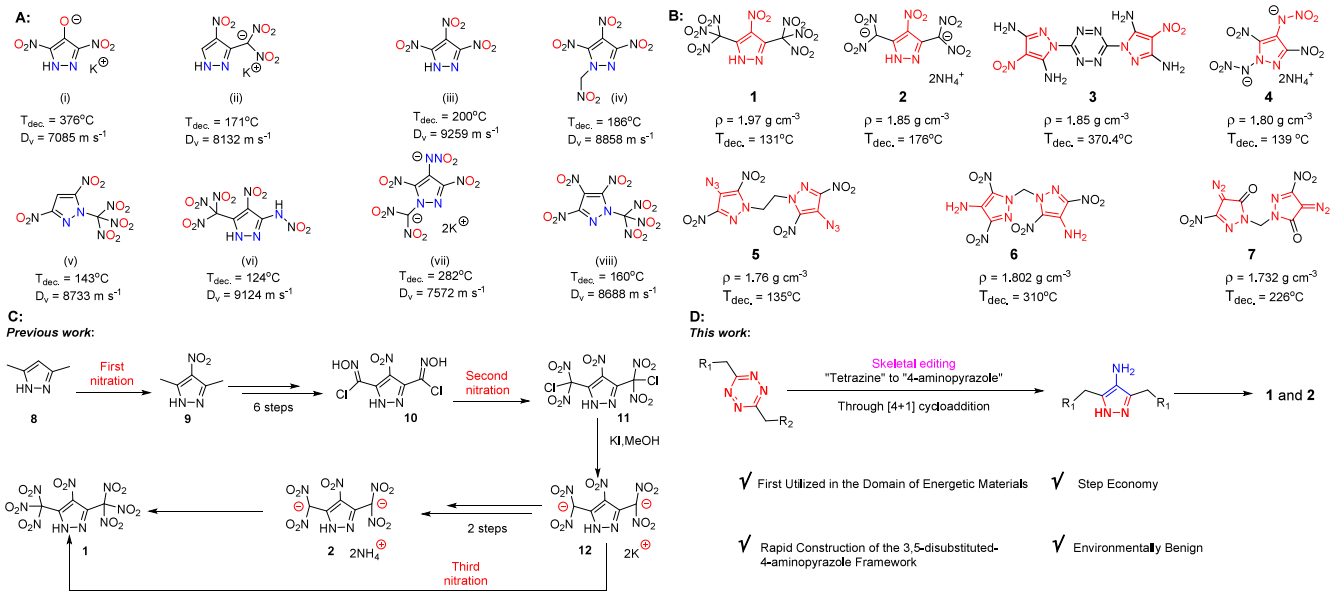

Figure 1. Conceptual design of 4-nitro-3,5-bis(trinitromethyl)-1*H*-pyrazole via [4 + 1] cycloaddition: (A) polynitro compounds based on pyrazole rings, (B) selected energetic pyrazole derivatives with various functional groups, (C) previous syntheses of compounds **1** and **2**, and (D) concise synthesis via [4 + 1] cycloaddition.

demonstrate significant promise in the field of energetic materials, an area that could benefit greatly from such innovative approaches.[10]

Pyrazole-based energetic materials play a crucial role in the energetic materials landscape, with compounds such as 4-nitropyrazole (**1**−**3**),[11] 4-nitraminopyrazole (**4**),[12] 4-azidopyrazole (**5**),[13] 4-aminopyrazole (**6**),[14a] and 4-diazopyrazole (**7**)[14] already synthesized (Figure 1B). Despite these advances, the development of efficient and environmentally friendly synthetic routes remains a significant challenge, as exemplified by the multi-step synthesis of high-nitrogen pyrazole derivatives (Figure 1C). In 2021, Professor Shreeve's group reported the synthesis of diammonium 3,5-bis(dinitromethyl)-4-nitro-1*H*-pyrazole (**2**), which required 11 steps, resulting in a low overall yield and impracticality for industrial applications.[11a]

In 2023, building on previous work, they reported the synthesis of compound **1**, which required 10−12 steps and three separate nitration steps, creating safety concerns due to the complexity of the process.[11b]

In contrast, the synthetic route presented in this study significantly optimizes the process by employing nucleophilic substitution to form the key intermediate of aliphatic 1,2,4,5-tetrazines[15] and skeletal editing of [4 + 1] cycloaddition to form the key intermediate of aliphatic 4-aminopyrazole. The subsequent first nitration step provides the target compound **2**, and the second nitration step affords final compound **1** (Figure 1D). This efficient five-step process not only improves the overall yield but also reduces the number of steps and safety concerns associated with traditional methods. The adoption of skeletal editing and [4 + 1] cycloaddition offers a safer, more sustainable, and highly efficient synthetic route for poly-nitrated pyrazoles, representing a significant advancement in the field of energetic materials.

From previous reports, the synthesis of compound **2** starts from commercially available 3,5-dimethylpyrazole (**8**), through the classical nitration (first nitration) of 3,5-dimethyl-1*H*-pyrazole at the 4 position to form 3,5-dimethyl-4-nitro-1*H*-pyrazole (**9**). A six-step transformation afforded dichloroxime derivative **10**. Dipotassium 3,5-bis(dinitromethyl)-4-nitro-1*H*-pyrazole (**12**), which has five nitro groups, was obtained by the reaction of a chloroxime derivative **10** with trifluoroacetic anhydride (TFAA)/HNO_3 (second nitration) to afford **11**, followed by the reaction with KI in methanol. Diammonium 3,5-bis(dinitromethyl)-4-nitro-1*H*-pyrazole (**2**) is obtained from **12** by reaction with $AgNO_3$ and NH_4Cl, respectively.[11a] Either compound **2** or **12** is converted to **1** by the reaction with mixed acid, H_2SO_4 (98%) and HNO_3 (100%) (third nitration), in a 1:2 ratio. At 0 °C, a white solid (**1**) precipitated from the reaction mixture. It is removed by filtration and washed with trifluoracetic acid (TFA).

In other words, the current syntheses for compounds **1** and **2** are inefficient and impractical. Compound **2** requires an 11-step sequence, while compound **1** necessitates 10−12 steps. These lengthy routes result in low overall yields, poor efficiency, high reagent consumption, increased cost, elevated safety risks, and a significant environmental impact. Consequently, this makes scaling up the process for practical or industrial applications exceedingly difficult. To address these challenges, the development of a green and sustainable synthetic strategy is imperative. Such a route must enable the efficient and high-yielding production of both compounds **1** and **2**. Herein, we report a concise, combined strategy of nucleophilic substitution and [4 + 1] cycloaddition reaction, with the ultimate synthesis of compounds **1** and **2** in excellent yields and with high efficiency.

In this work, we present an improved synthetic route for the preparation of poly-nitrated pyrazoles, focusing on the synthesis of the key intermediate compound **18**, which is derived from commercially available 3,6-dichloro-1,2,4,5-tetrazine (**13**) (Scheme 1). The synthesis begins with a nucleophilic substitution reaction, where compound **13** reacts with potassium ethoxide (**14**) in the presence of magnesium chloride ($MgCl_2$) as a catalyst, leading to the formation of intermediate compound **15** in an excellent yield of 84%. This reaction proceeds smoothly, offering a robust method for accessing this crucial intermediate. Next, compound **15** is

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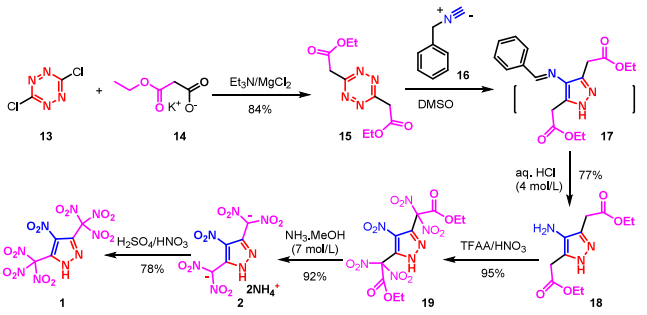
Scheme 1. Four-Step Synthesis of Compound 2 and Five-Step Synthesis of Compound 1



dissolved in DMSO and treated with benzyl isocyanide ($PhCH_2NC$, **16**) at room temperature for 24 h, allowing the [4 + 1] cycloaddition to take place. Upon completion of the reaction, water is added to precipitate intermediate compound **17**. In the following step, the hydrolysis of intermediate **17** is conducted under acidic conditions, resulting in the formation of 4-aminopyrazole advanced intermediate **18**, with a yield of 77%. This step is critical for setting the stage for subsequent nitration and functionalization processes.

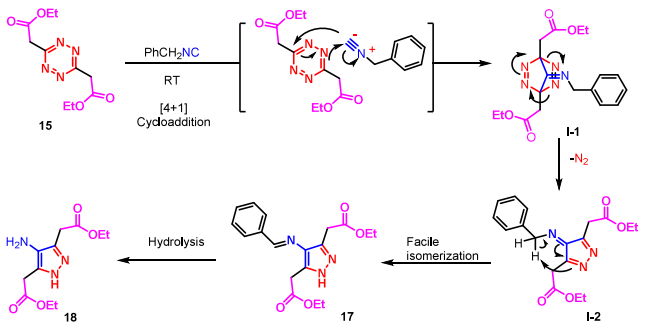
The nitration of compound **18** is then carried out under mixed acid conditions, using trifluoroacetic anhydride (TFAA) and concentrated nitric acid (HNO_3) in a 2:1 ratio, which provides stable nitrated compound **19**. This intermediate is crucial for achieving the high nitro substitution on the pyrazole ring, which is characteristic of energetic materials. Subsequently, ammonolysis of compound **19** is performed by stirring the compound in a methanolic ammonia solution (7.0 mol/L) at room temperature for 12 h. The reaction mixture is then concentrated to approximately one-third of its original volume under reduced pressure. Filtration of the resulting mixture yielded the energetic ammonium salt compound **2** with a high yield of 92%. This compound exhibits favorable physicochemical properties, making it a promising candidate for further development as an energetic material.

Finally, compound **2** is subjected to a nitration reaction with mixed acid (H_2SO_4 and HNO_3 in a 2:1 ratio), yielding the target compound **1** with a yield of 78%. This step completes the synthesis of the highly nitrated pyrazole derivative compound **1**, which exhibits exceptional properties, such as a high oxygen balance and an excellent density, making it a promising candidate for use in energetic materials. The entire synthetic route is notable for its efficiency, requiring only five steps for the preparation of compound **1** and four steps for the preparation of corresponding ammonium salt **2**. This streamlined process, combining nucleophilic substitution, [4 + 1] cycloaddition, hydrolysis, nitration, and ammonolysis, represents a significant improvement over traditional synthetic routes, offering higher atom economy, reduced waste, and better overall yields.

In this study, we introduce an innovative application of the [4 + 1] cycloaddition reaction for the synthesis of highly nitrated energetic pyrazole compounds, including the pivotal compound **1**, which contains seven nitro groups. Although [4 + 1] cycloaddition reactions are well-established in bioorthogonal chemistry,[16] their application in energetic material synthesis has not been reported. This work marks the first use of this strategy in the field of energetic materials, providing a novel and efficient method for constructing poly-nitrated pyrazole frameworks. Our approach lays the foundation for the development of pyrazole-based energetic materials and opens new avenues for high-performance compound design and synthesis.

The proposed mechanism for the formation of 4-aminopyrazole compound **18** from tetrazine compound **15** (Scheme 2) involves a sequence of key steps.[4c,16e] The reaction begins

Scheme 2. Proposed Mechanism for the Synthesis of 18 from 15



with a [4 + 1] cycloaddition between compound **15** and (isocyanomethyl)benzene: electron density from the electron-rich moiety in compound **15** transfers toward the electron-deficient carbon center of the isocyano group in (isocyanomethyl)benzene, driving the formation of a cyclic transition state and thus yielding intermediate **I-1**; subsequently, this intermediate undergoes a retro-Diels–Alder reaction, where electron redistribution occurs around the N–N bond in **I-1**, with electron pairs on the nitrogen atoms shifting toward the bond interface to facilitate N–N linkage cleavage, thereby eliminating nitrogen gas (N_2) while accompanying intramolecular electron transfer to form intermediate **I-2**, which then undergoes facile isomerization via intramolecular electron rearrangement within its heterocyclic skeleton, adjusting bond connectivity to produce intermediate **17**; finally, complete hydrolysis of **17** under acidic conditions yields 4-aminopyrazole product **18**, and this sequence showcases the power of skeletal editing, offering a streamlined, efficient route to functionalized pyrazoles, while this novel strategy not only enhances the synthesis of energetic materials but also holds promise for broader applications in the field.

In this study, we successfully concisely synthesized excellent properties of energetic compounds (**1** and **2**) featuring 4-nitropyrazole frameworks. All compounds were comprehensively characterized using HRMS, NMR, EA, IR, and DSC techniques. The incorporation of nucleophilic substitution and skeletal editing of the [4 + 1] cycloaddition reaction strategy into the synthetic route significantly shortens the number of steps, paving the way for industrial production. The synthesis of compound **2** was streamlined from the previous 11 steps to just 4 steps (nucleophilic substitution/[4 + 1] cycloaddition/nitration/ammonolysis), achieving an overall yield of 56.5%. Likewise, the synthesis of compound **1** was shortened from 10 or 12 steps to 5 steps, with an overall yield of 44.1%; meanwhile, the number of nitration steps was reduced from three to two. In other words, we have accomplished an efficient and concise synthesis of compounds **1** and **2**, owing to the key strategies of nucleophilic substitution and skeletal editing of [4 + 1] cycloaddition reactions. We anticipate that this approach

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will pave the way for the future development of pyrazole-based energetic materials.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c05140.

Synthesis of compounds **1**, **2**, **15**, and **17**−**19**, HRMS, DSC, IR, and NMR (^{1}H, ^{13}C, and ^{13}DEPT) spectroscopy, and elemental analysis data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Hongyao Xu − *School of Materials and Chemical Engineering, Fuyang University of Technology, Fuyang, Anhui 236000, P. R. China;* orcid.org/0000-0002-6290-4780; Email: hongyaoxu@dhu.edu.cn

Yingzhe Liu − *Xi'an Modern Chemistry Research Institute, Xi'an 710065, P. R. China;* orcid.org/0000-0003-4150-1111; Email: liuyz_204@163.com

Authors

Wentong Tu − *School of Materials and Chemical Engineering, Fuyang University of Technology, Fuyang, Anhui 236000, P. R. China*

Tao Yu − *Xi'an Modern Chemistry Research Institute, Xi'an 710065, P. R. China;* orcid.org/0000-0001-6768-8266

Linyuan Wen − *Xi'an Modern Chemistry Research Institute, Xi'an 710065, P. R. China;* orcid.org/0000-0002-2603-0078

Qiurong Li − *School of Materials and Chemical Engineering, Fuyang University of Technology, Fuyang, Anhui 236000, P. R. China;* orcid.org/0000-0002-4744-1044

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.5c05140

Author Contributions

†Wentong Tu and Tao Yu contributed equally to this work.

Notes

The authors declare no competing financial interest.

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