Photochemical Strategies Enable the Synthesis of Tunable Azetidine-Based Energetic Materials

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ABSTRACT: Despite their favorable properties, azetidines are often overlooked as lead compounds across multiple industries. This is often attributed to the challenging synthesis of densely functionalized azetidines in an efficient manner. In this work, we report the scalable synthesis and characterization of seven azetidines with varying regio- and stereochemistry, and their application as novel azetidine-based energetic materials, enabled by the visible light-mediated aza Paternò-Büchi reaction. The performance and stark differences in physical properties of these new compounds make them excellent potential candidates as novel solid melt-castable explosive materials, as well as potential liquid propellant plasticizers. The nitroazetidine materials synthesized exhibit reasonable sensitivities, higher densities, better oxygen balances, increased detonation pressures and velocities, as well as improved specific impulses, compared to the state-of-the-art materials. This work highlights the scalability and utility of the visible-light aza Paternò-Büchi reaction and demonstrates the impact of stereochemical considerations on the physical properties of azetidine-based energetics. Considering the versatility and efficiency of the presented synthetic strategies, we expect that this work will guide the development of new azetidine-based materials in the energetics space as well as other industries, including pharmaceuticals and agrochemicals.

Azetidines are prominent structural scaffolds in a broad area of scientific disciplines.1–7 In recent years, azetidines have been widely recognized in the field of drug discovery8–12, such as Cobimetinib13 (1), for imparting favorable pharmacokinetic properties over 5- and 6-membered nitrogen heterocycles more commonly used.14 Azetidine-containing natural products including penazetidine A15–17 (3) have been long-standing targets in the field of total synthesis due to the challenges associated with their high strain of up to 104.6 kJ/mol (Fig 1A).6,18–20 As a direct consequence of this inherent strain, azetidines also represent promising scaffolds for energetic materials.21 However, no significant advances have been reported in azetidine-based energetic materials since the development of TNAZ (2, trinitroazetidine) in 1983 (Fig 1A).22–25 To date, TNAZ has remained the most prominent azetidine energetic discovered, which is classified as a melt-castable material. Because TNAZ significantly exceeds the performance of the state-of-the-art melt-castable explosive, TNT, it has been the subject of scalability efforts.26 Unfortunately, TNAZ suffers from a very high vapor pressure, which has led to its elimination as a melt-castable replacement for TNT.26

However, studies have shown that stereo- and regiochemistry both influence the physical properties and consequently the classification of energetic materials.27–31 It is thus expected that new and superior azetidine-based energetic materials could be developed as functionalized analogs of TNAZ. Despite this potential, the lack of scientific advances of new azetidine-based energetic materials is particularly surprising. Notably, this trend is also observed in other fields such as medicinal chemistry, where azetidines

Figure 1. A. Azetidines are useful scaffolds in a broad area of disciplines. B. Design principles for novel azetidine-based energetic materials. C. Synthetic strategies to access substituted azetidines: nucleophilic substitution and aza Paternò-Büchi.

[Diagram of azetidines as scaffolds for energetic materials, showing design principles and synthetic approaches]
find limited application in spite of favorable pharmacokinetic effects.14

These shortcomings across several scientific disciplines are a direct consequence of a lack of efficient synthetic strategies to access functionalized azetidines.3,4 Currently, the most common strategy to synthesize azetidines (4) remains an intramolecular substitution approach, which is often hampered by undesired side reactivity due to unfavorable conformational requirements for cyclization (Fig 1C). Among the most prominent limitations in the synthesis of functionalized azetidines are, 1) access to non-symmetric azetidines, 2) enabling substitution in the α-position of the azetidine nitrogen, 3) introduction of multiple substituents including stereocenters, and 4) incorporation of additional heteroatoms including O- and N-containing functionalities on the azetidine core (Fig 1B). Notably, overcoming these synthetic limitations is not only expected to propel efforts in drug discovery, but also provide an avenue to new and improved energetic materials compared to TNAZ.

Herein, we report viable solutions that overcome these challenges and enable access to desirable azetidines bearing distinct substitution patterns (Fig 2). Our innovative approach complements existing nucleophilic substitution reactions and combines visible-light-mediated inter- and intramolecular aza Paternò-Büchi reactions to access functionalized azetidines in a stereodivergent manner to explore their potential as energetic materials and feasible alternatives to TNAZ.22,33 Importantly, our synthetic strategies have generated the first nitroazetidine energetic materials that incorporate stereochemical considerations, which further enhances tuning of the physical properties. Consequently, the new azetidine materials described represent more powerful energetics that exhibit higher densities, better oxygen balance, greater detonation pressures and velocities, and improved specific impulses than previously disclosed cyclobutane-based materials.37 Ultimately, our studies have resulted in the rational design of propellant plasticizers and standalone melt-castable energetic materials. These materials possess optimal physical properties and performances when compared to state-of-the-art materials (Fig 3A and Fig 3B).

Two desirable categories for energetic materials exist, including standalone solid melt-castable compounds21,34,35 and liquid propellant plasticizers36-38. TNT is currently viewed as the state-of-the-art material that constitutes the benchmark in the development of a new, standalone melt-
Standalone melt-castable energetic materials typically have the following physical requirements: A high melting point (70–90 °C), low vapor pressure, and a sufficient charge separation between melting and the onset of decomposition (T_{dec} > T_{melt}) (Fig 3A). In addition to solid melt-castable explosives, the generation of liquid energetic materials can result in propellant plasticizers. While many plasticizers employed in propellants are inert (i.e. acetate-, phthalate-, and adipate-based), an energetic plasticizer can enhance performance properties. For example, TMETN (trimethyloltrane trihydrate) is an energetic plasticizer found in propellants today (Fig 3A). State-of-the-art energetic plasticizers aim to further increase energy, maintain desirable mechanical properties, and improve combustion as well as burning rates. It is expected that designing energetic compounds incorporating additional strain, while improving density and oxygen balance can advance the performance of both categories of energetic materials due to their inherent increased heat of formation (Fig 3B). A known example building on this design principle includes cyclobutyl tetranitric esters. These cyclobutane-based materials were found to be potential melt-castable explosives, or low freezing point liquids, while also having an elevated decomposition temperature.27

We hypothesized that synthesizing a series of stereochemical nitroazetidine polymeric nitrates could be used to provide a significant increase in explosive and propellant performance. Specifically, the use of azetidines would result in more favorable heat of formation, oxygen balance, density, detonation pressure and velocity and specific impulse. Yet, despite the potential of azetidines as promising energetic materials, TNAZ remains one of the few examples known to date incorporating this nitrogen-heterocycle (Fig 3B). This is due in large part to the historic difficulties in synthesizing functionalized azetidine scaffolds and nitration precursors. To investigate the potential of novel azetidine-scaffolds as energetic materials we aimed to systematically vary the substitution and stereochemistry at the carbons about the azetidine (Fig 2).

Our initial studies commenced with the goal of synthesizing a symmetric 2,3,4-trisubstituted azetidine, with the potential of accessing two stereoisomers in the azetidine forming step. It was envisioned that simply switching from the cis-alkene to the trans-alkene diol, would enable the synthesis of other stereoisomers (Fig 3C). cis-Diol 5 was converted to epoxide 6 in 86% yield over two steps. Epoxide 6 could then be opened with benzylamine and subsequent N-alkylation to furnish amino alcohol 7. Chlorination of the alcohol to the secondary halide (8) proceeded in 96% yield. Unfortunately, even after extensive optimization, the desired azetidine could only be isolated in small amounts. The major isomer being the all-cis azetidine (10) in 28% yield and the minor diastereomer (9) in only 5% yield. Notable by-products in the reaction included elimination of the chloride to the 1,2-disubstituted alkene (13) and the Grob fragmentation product (14) (Fig 3D). Considering 5 g of the final azetidine was needed for subsequent nitration and sensitivity characterization studies, only the major stereoisomer could be carried forward. Azetidine 10 was reduced and deprotected to afford HCl salt 11. Overall, 183 mmol of 5 was needed to access the required amount of azetidine 11 in eight steps and 15% overall yield. Importantly, while previous work on nitrocyclobutane energetics utilized concentrated nitric acid, this strategy is not amenable to azetidines due to the presence of the amine functionality. Thus, aprotic nitration conditions were developed with acetyl nitrate to access 12. Azetidine 12 could be classified as a potential standalone melt-castable energetic with a detonation pressure 42% higher than TNT. These initial promising results

**Figure 4.** A. General synthetic route for accessing azetidines via intermolecular aza Paternò-Büchi reaction. B. Synthesis of liquid energetics 25 and 26. C. Synthesis of azetidine 31 and partial nitration to 32.
further motivated the synthesis of azetidines with differing regio- and stereochemistry.

However, this initial synthetic pathway was lengthy and most importantly proved challenging to conduct on scale and was impractical to access other stereoisomers. Attempts to convert chloride 15 to the azetidine almost exclusively resulted in Grob fragmentation (16) as the major product (Fig 3E). Additionally, efforts were undertaken to epimerize azetidine 10 with little success (Fig 3E). This inspired us to consider how azetidine 12, these both were liquid materials with very promising physical properties, such as low freezing points and high decomposition temperatures. Due to the aforementioned physical properties, azetidines 25 and 26 can be classified as potential liquid propellant plasticizers.

In order to study the substitution pattern about the azetidine, we envisioned an intermolecularaza Paternò–Büchi reaction with a 1,1-disubstituted alkene (28) resulting in distinct substitution in the 4-position. The 2+2-cycloaddition proceeded in 87% yield and good regioselectivity. The azetidine 29 was efficiently reduced to mono-alcohol 30 and converted to the monocylic deprotected azetidine 31. Various nitration conditions were evaluated, but ultimately the steric hindrance about the azetidine nitrogen prevented full nitration from occurring (Fig 4C). Regardless, an efficient synthesis of this 2,2,4,4-tetrasubstituted azetidine alcohol (31) demonstrates the power of this synthetic methodology in accessing novel azetidine substitution patterns.

In subsequent efforts, we recognized that substitution across from the nitrogen could not easily be achieved via the

**Figure 5.** General scheme of intramolecular aza Paternò–Büchi reaction. B. Crystal structures of nitrate ester azetidines. C. Synthesis of azetidine energetics 40 and 41. D. Synthesis of azetidine energetic 46.
intermolecular [2+2]-cycloaddition. We envisioned that an intramolecular aza Paternò-Büchi reaction held enormous potential to control both the regio- and stereoselectivity. By tethering the oxime and alkene components together, only one regiosomer was possible and the formation of a lactone would aid in the stereoselectivity giving rise to new substitution patterns (Fig 5A). Oxime 33 was accessed in one step via a coupling between the oxime carboxylic acid and substituted alcohol. Initial studies mimicking the intermolecular conditions resulted in a low combined yield of 34 and 35 with significant amounts of undesired intermolecular cycloaddition by-products. While substantially lowering the reaction concentration suppressed this undesired reactivity, a more scalable solution was found by slow addition of substrate 33 to a solution of catalyst. Consequently, a combined yield of 70% on a multi-gram scale could now be achieved at five times the concentration, resulting in a 1:1 mixture of 34 and 35 (Fig 5C). After separation of the tricyclic azetidines, reduction of the lactones with RED-Al, followed by hydrogenolysis, the monocyclic azetidine HCl salts 38 and 39 were isolated. Our aprotic global nitration conditions installed five nitro groups in one step to access nitro-azetidines 40 and 41 in 75% and 84% yields respectively. Interestingly, azetidine 41 immediately solidified and was classified as a standalone melt-castable material with an optimal melting point (89 °C). Azetidine 40 initially presented as a liquid and was stored in temperatures < -40 °C for six months. During this time the material solidified resulting in a low-melting solid (56 °C) (Fig 5C). These results further demonstrate the importance of stereochemistry in the design of novel energetic materials as one stereocenter can have drastic impact on the physical properties of these compounds and therefore downstream applications.

We next turned our attention to terminal alkene 42, which was expected to be a challenging substrate as terminal alkenes react substantially slower due to the intermediate primary radical, leading to competing intermolecular side-reactivity. Using the knowledge gained from our previous multi-gram intramolecular aza Paternò-Büchi reaction, slow addition of substrate 42 to a photocatalyst solution resulted in formation of the tricyclic azetidine 43 in 60% yield. Rel-AI reduction to diol 44 proceeded in 68% yield and N-O bond cleavage and HCl salt formation gave quantitative formation of azetidine 45 (Fig 5D). Notably, this strategy provides access to substitution patterns that are complementary, but inaccessible with the intermolecular [2+2]-cycloaddition reaction. The nitration smoothly provided 46 in 82% yield. Interestingly, this material immediately solid-
ified and had a low-melting point (65 °C), between the previous two materials. Seeing that both the degree and placement of substitution about the azetidine drastically affects the physical properties and ultimately the energetic applications, demonstrates the vast tunability of these azetidine materials.

With six nitroazetidine polynitric esters in hand, the physical properties were evaluated and theoretical energetic values were calculated with the results summarized in Table 1.39–43 Comparing the synthesized nitroazetidine materials to existing materials showed vastly improved energetic properties including: higher densities, better oxygen balances, higher detonation pressures (Pd) and detonation velocities (Vd) in addition to improved specific impulses. More specifically, out of the solid materials isolated (12, 40, 41, 46) two are categorized as standalone melt-castable energetic. Nitroazetidines 12 and 41 stood out as extremely promising scaffolds for modern energetic materials due to their optimal melting points and decomposition temperatures for melt-casting. When comparing to the state-of-the-art standalone melt-castable energetic, TNT, notable advancements are present. Both azetidines 12 and 41 have significantly higher detonation pressures and velocities than TNT, the most important parameters for gauging the energetic activity. Interestingly, the diastereomer of 40, differing by one stereocenter, has a much lower melting point (56 °C). Together with 46, these azetidines are considered low-melting solids and therefore are not classified as melt-castable energetics. These minor structural changes demonstrate the tunability of these materials (Fig 6).

Two novel liquid energetic materials were also characterized. Azetidines 25 and 26 both have freezing points less than −40 °C classifying them as potential energetic propel-lant plasticizers. The low freezing points are especially impressive when being compared to the state-of-the-art energetic propellant plasticizer, TMETN44, which has a relatively high freezing point of −3 °C. Furthermore, the impact, friction, and electrostatic discharge sensitivities were measured. The specific impulses of the liquid energetics 25 and 26 (250 s) exceeds that of TMETN (243 s). Additionally, all nitroazetidines synthesized show equal or lower sensitivity to friction and electrostatic discharge as compared to TNT. Impact sensitivities for all newly synthesized nitroazetidines were found to be in between PETN and RDX, both of which are commonly manufactured and handled secondary explosive materials.

In summary, we have developed a unified approach towards accessing unique azetidine scaffolds and the generation of highly energetic materials (Fig 6). The development of both inter- and intramolecular azza Paternò-Büchi reactions proved necessary for achieving a scalable, efficient, and regio- and stereodivergent synthetic approach. Exceptional energetic properties were observed ranging from standalone melt-castable energetics to propellant plasticizers. While this work signifies the first application of azza Paternò-Büchi reactions in the development of novel materials, we anticipate our effective synthesis of unique azetidine scaffolds will be impactful beyond energetic materials as azetidines continue to permeate a broad area of disciplines.


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Notes

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REFERENCES


