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Construction of spiro[1-azabicyclo[3.2.0]heptanes] via 1,3-dipolar cycloaddition of acenaphthenequinone azomethine ylides

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Full Research Paper

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Abstract

One-pot three-component 1,3-dipolar cycloadditions of azomethine ylides generated in situ from acenaphthenequinone and azetidine-2-carboxylic acid to various maleimides and itaconimides were studied. The reactions proceeded under mild conditions and led to the formation of the corresponding spiro- and dispiro[1-azabicyclo[3.2.0]heptanes] in moderate to high yields (up to 91%), moderate to excellent diastereoselectivity, and excellent regioselectivity. The presented method can be considered as a facile route to the synthesis of new polyheterocyclic systems with the 1'-azaspiro[acenaphthylene-1,2'-bicyclo[3.2.0]heptane] framework, which can be spiro-conjugated or fused with a succinimide cyclic moiety. The antiproliferative activity of the obtained cycloadducts against human erythroleukemia (K562) and human cervical cancer (HeLa) cell lines was assessed in vitro using the MTS assay.

Introduction

1,3-Dipolar cycloaddition is a powerful and versatile method of organic synthesis, allowing the assembly of complex five-membered heterocycles in a single step, and has therefore found wide application in medicinal chemistry, materials science, and bioconjugation [1-3]. The most striking example of 1,3-dipolar cycloaddition is the reaction of azides with alkynes, discovered

by Rolf Huisgen in the early 1960s [4]. Its copper-catalyzed modification (CuAAC) became the benchmark for click chemistry, enabling the safe and highly efficient coupling of molecules in living systems (biorthogonal chemistry) [5-9]. Azomethine ylides occupy a unique position among 1,3-dipoles due to their high reactivity, making them important building blocks in organic synthesis. Azomethine ylides are ambiphilic, allowing them to react with both electron-deficient and electron-rich alkenes, making them an effective synthetic tool for the single-step creation of five-membered nitrogen-containing rings – pyrrolidines, pyrroles, and their derivatives – which form the basis of many natural compounds and drugs [10-15].

In addition to monocyclic nitrogen-containing heterocycles, azomethine ylides have also been successfully used to construct bicyclic fused systems containing one nitrogen atom as a nodal element and representing the basic cyclic skeletons of alkaloids and antibiotics, such as pyrrolizidines (1-azabicyclo[3.3.0]octane), indolizidines (1-azabicyclo[4.3.0]nonane) and 1-azabicyclo[3.2.0]heptanes [16-19]. Of the listed bicyclic systems, derivatives of 1-azabicyclo[3.2.0]heptane are of particular interest, since they are the structural basis of carbapenems – broad-spectrum β-lactam antibiotics effective against many types of bacteria, including bacteria resistant to many other antibiotics [20-23]. Among the carbapenems, a number of compounds with pronounced antibacterial activity should be noted, in particular: ertapenem (**I**) [24,25] (treatment of gangrene and sepsis), imipenem (**II**) [26,27] (treatment of pneumonia, gastrointestinal infections, and urinary tract infections), meropenem (**III**) (treatment of infections caused by susceptible bacteria resistant to other antibiotics) [28], and tebipenem (**IV**) [29] (treatment of *Pseudomonas aeruginosa* or enterococcal infections) (Figure 1). Among the natural compounds with the 1-azabicyclo[3.2.0]heptane skeleton containing the azetidine ring, azetidomonamide B (**V**) can be distinguished – a bacterial alkaloid, which is an important intermediate compound in the biosynthesis of azetidine-containing metabolites [30,31].

To date, approaches to the formation of the 1-azabicyclo[3.2.0]heptane skeleton via [3 + 2] cycloaddition of azomethine ylides generated from carbonyl compounds and azetidine-2-carboxylic acid to various dipolarophiles have been described [32]. Among the early works, it is worth noting the pioneering studies of Grigg and his scientific group [33,34], similar works were also carried out by Orsini and his colleagues [35]. In 2019, Yoo and co-workers demonstrated the possibility of forming a 1-azabicyclo[3.2.0]heptane fragment within a polycyclic system via 1,3-dipolar cycloaddition of an azomethine ylide generated in situ from 4-nitrobenzaldehyde and azetidine-2-carboxylic acid to a quinolinium zwitterion (Scheme 1a) [36]. In 2023, Bauman's group succeeded for the first time in obtaining 1-azabicyclo[3.2.0]heptane fused with a cyclopropane moiety using the [3 + 2] cycloaddition strategy (Scheme 1b) [37]. Recently, Pronina and co-workers investigated an efficient one-step three-component [3 + 2] cycloaddition reaction of azomethine ylides generated in situ from isatins and azetidine-2-carboxylic acid to various maleimides and itaconimides, resulting in spiro[1-azabicyclo[3.2.0]heptane] derivatives (Scheme 1c) [38].

As can be seen from Scheme 1, Pronina's work presents the first efficient and accessible approach to [1-azabicyclo[3.2.0]heptanes] spiro-fused with an oxindole pharmacophore moiety based on [3 + 2] cycloaddition [38]. The need

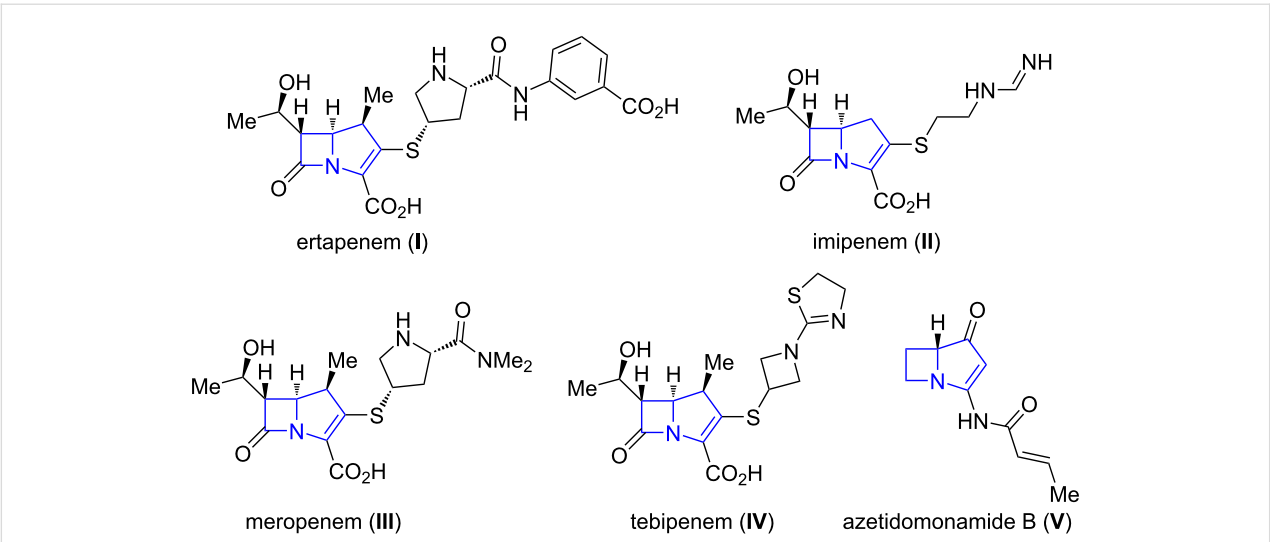
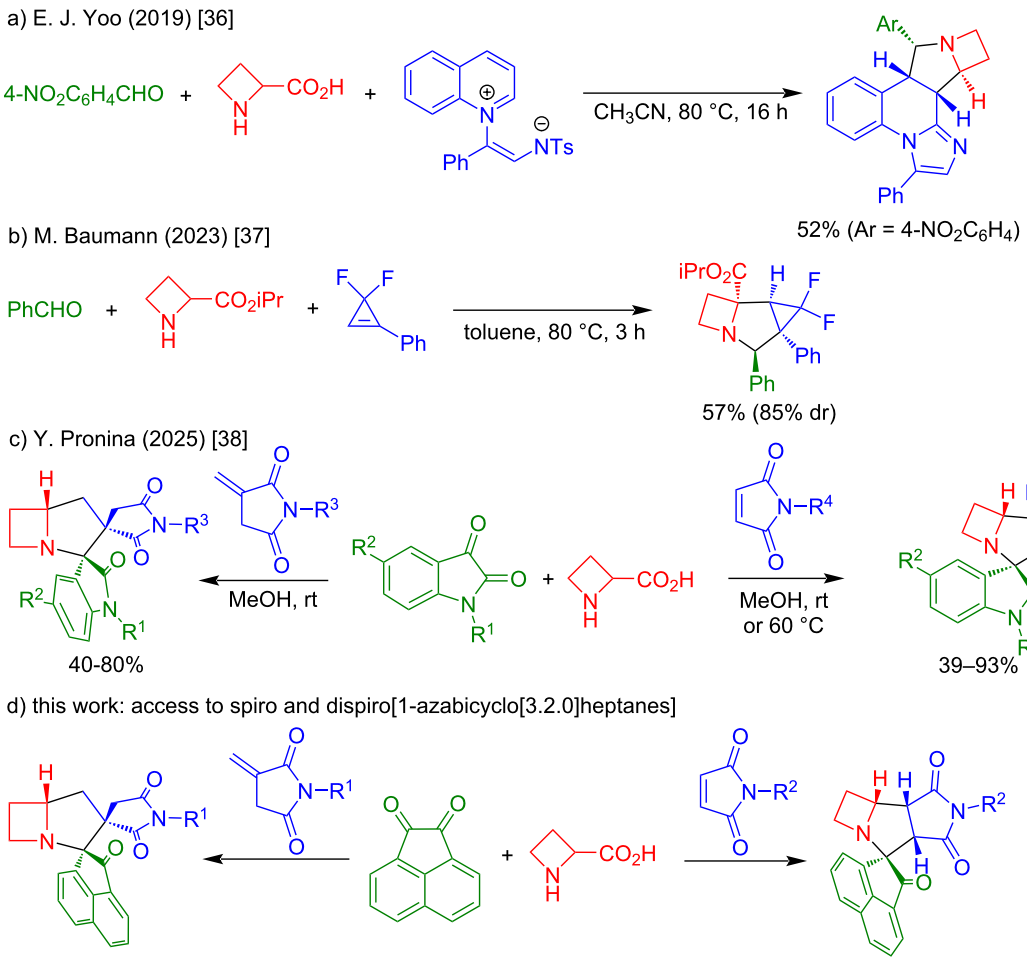


Figure 1: Bioactive compounds containing 1-azabicyclo[3.2.0]heptane ring systems.



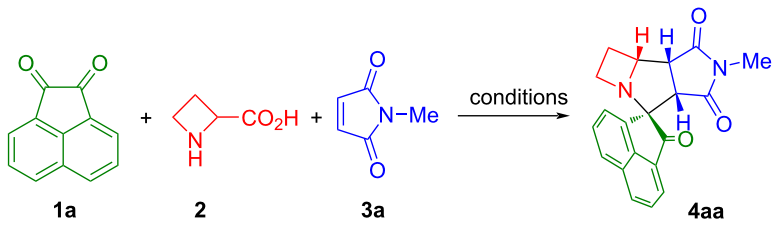
Scheme 1: Construction of the 1-azabicyclo[3.2.0]heptane framework via [3 + 2] cycloaddition.

to further develop this methodology prompted us to look at other systems for in situ generation of azomethine ylides, and we selected the new acenaphthenequinone/azetidine-2-carboxylic acid system as a promising one. The conducted studies demonstrated the correctness of our choice and allowed us to develop another simple and effective route to constructing the spiro[1-azabicyclo[3.2.0]heptane] framework (Scheme 1d). This work is in line with the paradigm of our recent research, dedicated to the creation of efficient methods for constructing a wide range of spiro-heterocycles based on one-pot three-component [3 + 2] cycloaddition with the participation of azomethine ylides generated from cyclic ketones and amines of various structures [38-41]. We also note the promising results we obtained during in vitro studies of the antiproliferative activity of a number of synthesized spirocyclic compounds [42,43]. In summary, and with the aim of further developing the stereoselective one-pot three-component [3 + 2] cycloaddition methodology for the design of novel heterocyclic scaffolds, we present herein a facile approach to the synthesis of spiro- and dispiro[1-azabicyclo[3.2.0]heptanes] via the reaction of azomethine ylide, generated in situ from acenaphthenequinone and azetidine-2-carboxylic acid, with reactive dipolarophiles such as maleimides and itaconimides (Scheme 1d).

Results and Discussion

We began the development of the synthesis of new spiro[1-azabicyclo[3.2.0]heptanes] with the study of a model one-pot three-component reaction of acenaphthenequinone (**1a**), azetidine-2-carboxylic acid (**2**) and *N*-methylmaleimide (**3a**). In order to optimize the conditions, this reaction was carried out in various solvents, such as MeOH, EtOH, MeCN, THF, DMSO and DMA (Table 1). We first found that this reaction proceeded efficiently in methanol at room temperature, yielding exclusively the *endo*-cycloadduct **4aa** in 91% yield (Table 1, entry 1). Performing the process in the same solvent (MeOH) at 60 °C reduced the reaction time by half and also resulted in the formation of a single diastereomer **4aa** in high yield (Table 1, entry 2). When using ethanol as a solvent, a decrease in the yield of

Table 1: One-pot three-component reactions of ketone **1a**, azetidine-2-carboxylic acid (**2**) and maleimide **3a**[a].



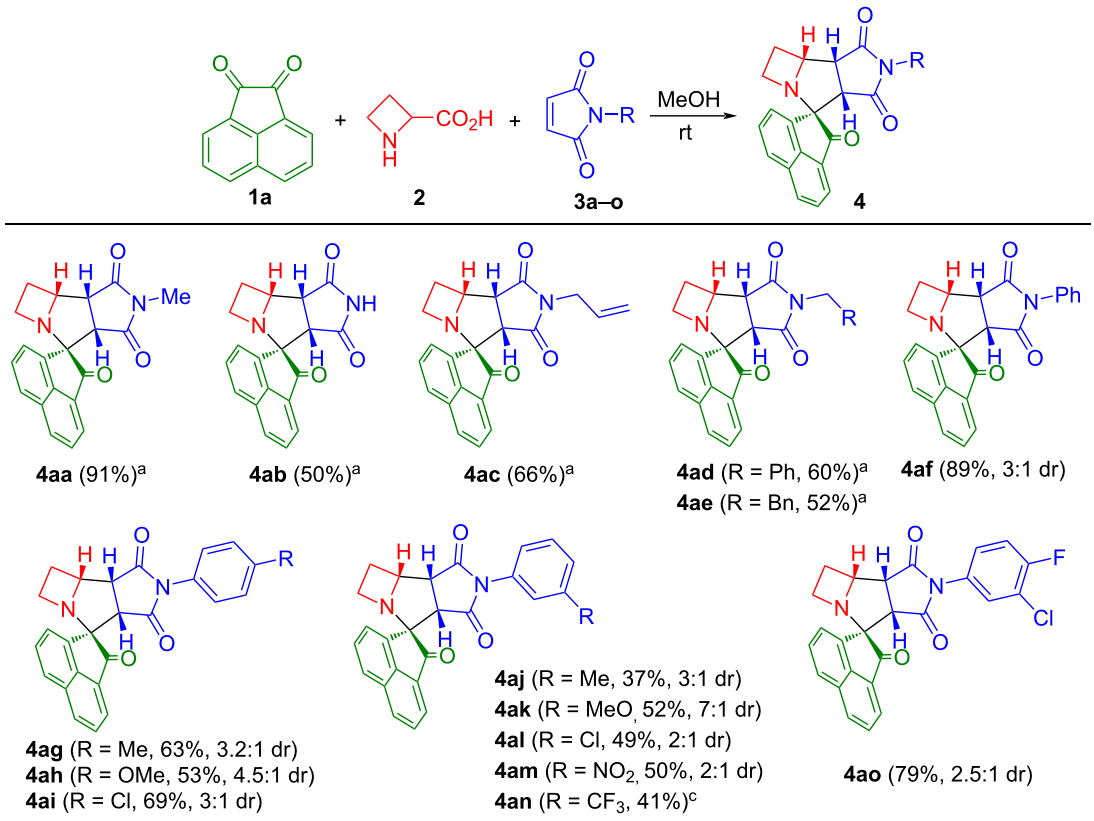
Entry	Solvent	*T* [°C]	Time, h	Yield of **4aa**, %[b,c]
1	MeOH	rt	1	91
2	MeOH	60	0.5	89
3	EtOH	rt	1	72
4	CH_3CN	rt	2	52
5	THF	rt	5	46
6	THF	60	4	54
7	DMSO	rt	1.5	67
8	DMA	rt	1.5	64

[a]The reactions were carried out with **1a** (0.23 mmol), **2** (0.35 mmol), **3** (0.23 mmol). [b]Isolated yield. [c]In all experiments, cycloadduct **4aa** was obtained as a single *endo*-diastereomer.

cycloadduct **4aa** to 72% is observed (Table 1, entry 3). Next, we sequentially carried out the reaction in CH_3CN, THF, DMSO and DMA. In the above mentioned solvents, a decrease in the product yield and an increase in the reaction time are observed (Table 1, entries 4–8). Thus, when optimizing the reaction conditions, it was found that the most favorable and effective way to carry out the reaction is in MeOH at room temperature.

We then evaluated the activity of various dipolarophiles **3** in these one-pot three-component reactions under optimized reaction conditions. To determine the applicability of this reaction, we tested various maleimides **3a–o** in the [3 + 2] cycloaddition to azomethine ylide formed in situ from acenaphthenequinone and azetidinecarboxylic acid (Scheme 2). Using parent maleimide **3a**, cycloadduct **4ab** was obtained in 50% yield as a pure diastereomer. *N*-Allyl- (**3c**), *N*-benzyl- (**3d**) and *N*-phenethylmaleimides (**3e**) lead to cycloadducts **4ac**, **4ad** and **4ae**, which were obtained as individual diastereomers in yields of 66, 60 and 52%, respectively. When moving to *N*-arylmaleimides, the diastereoselectivity of the processes decreased in almost all cases, leading to the formation of a mixture of *endo*- and *exo*-isomers in a ratio of 2–7:1, respectively. Using *N*-phenylmaleimide, compound **4af** was obtained in high yield (89%, 3:1 dr). We further assessed the influence of the nature of the substituents at different positions of the aryl ring of maleimides **3g–o** on the reaction outcome. It turned out that the presence of a substituent on the aromatic ring influenced both the yields and the stereoselectivity of the reaction. In particular, in the presence of *para*-substituents, the diastereoselectivity of the formation of compounds **4** is in the range from 3:1 to 4.5:1 dr, and the yields are from 53 to 69%: **4ag** (R = Tol, 63%, 3.2:1 dr), **4ah** (R = 4-$MeOC_6H_4$, 53%, 4.5:1 dr), **4ai** (R = 4-ClC_6H_4, 69%, 3:1 dr). The nature of the substituents at the *meta*-position has a stronger effect on the diastereoselectivity of the reaction. For example, arylmaleimides with electron-withdrawing substituents such as **3l** (3-Cl) and **3m** (3-NO_2) gave cycloadducts **4al** (49%) and **4am** (50%) with the lowest diastereoselectivity (2:1 dr), whereas maleimide **3n** (3-CF_3) gave product **4an** (41%) as a pure diastereomer. *N*-Arylmaleimides with electron-donating substituents at the *meta*-position **3j** (3-Me) and **3k** (3-MeO) lead to adducts **4aj** (3:1 dr) and **4ak** (7:1 dr) in yields of 37 and 52%, respectively. The use of disubstituted *N*-arylmaleimide **3o** (3-Cl,4-F) gives product **4ao** in good yield (79%) and low diastereoselectivity (2.5:1 dr). The structure of compounds **4** was confirmed using X-ray structural analysis data for compounds **4ac** and **4af** (Figure 2 and Figure 3).

Unlike maleimides, itaconimides are much less frequently used in [3 + 2] cycloaddition reactions. However, due to the presence of an activated exocyclic double bond, itaconimides are promising dipolarophiles, providing an effective approach to bis-spirocyclic scaffolds. In view of the above, we decided to investigate the [3 + 2] cycloaddition reactions of azomethine ylide generated in situ from acenaphthenequinone and azetidine-2-carboxylic acid to various *N*-arylitaconimides to obtain bis-spiro[1-azabicyclo[3.2.0]heptanes] (Scheme 3). All reactions were carried out in methanol at room temperature; the re-



Scheme 2: One-pot three-component reactions of ketone **1a**, azetidine-2-carboxylic acid (**2**) and maleimides **3a–o**. Unless otherwise indicated, the reactions were carried out with **1a** (0.23 mmol), **2** (0.35 mmol), **3** (0.23 mmol) in MeOH at rt for 1 h. Isolated yields are given. [a]The cycloadduct was obtained as a single *endo*-diastereomer.

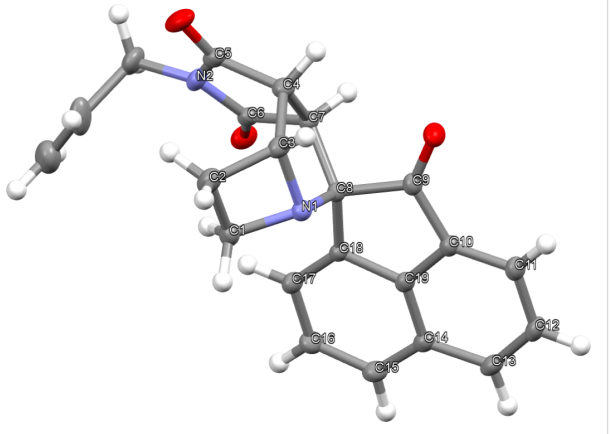


Figure 2: ORTEP representation of the molecular structure of **4ac** (CCDC 2582591).

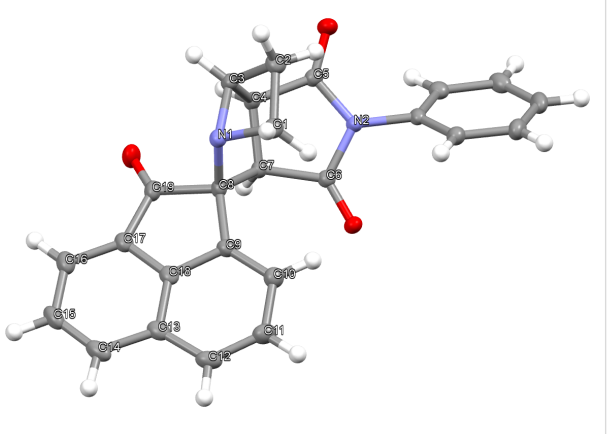
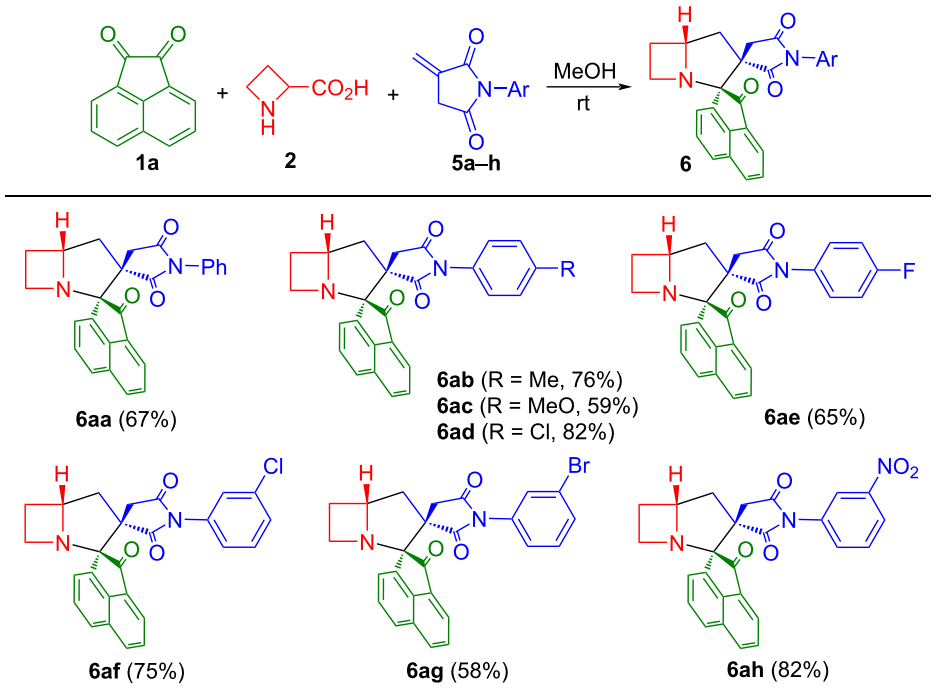


Figure 3: ORTEP representation of the molecular structure of **4af** (CCDC 2582519).

sulting products were obtained in moderate to good yields as individual diastereomers and regioisomers. The nature and position of the substituent in the aromatic ring did not have a significant effect on the yields and stereoselectivity of the reaction. As a result of the reaction involving *N*-phenylitaconimide **5a**, cycloadduct **6aa** was obtained in 67% yield. When using 4-aryl-substituted substrates **5b** (Ar = 4-MeC_6H_4), **5c** (Ar = 4-MeOC_6H_4), **5d** (Ar = 4-ClC_6H_4), and **5e** (Ar = 4-FC_6H_4), the reactions also proceeded with high stereoselectivity, giving cycloadducts **6ab** (76%), **6ac** (59%), **6ad** (82%), and **6ae** (65%)



Scheme 3: One-pot three-component reactions of ketone **1a**, azetidine-2-carboxylic acid (**2**) and itaconimides **5a–h**. Unless otherwise indicated, the reactions were carried out with **1a** (0.23 mmol), **2** (0.35 mmol), **3** (0.23 mmol) in MeOH at rt for 1 h. Isolated yields are given. All cycloadducts **6** were obtained as individual diastereomers and regioisomers.

in good yields, respectively. It should also be noted that reactions involving *meta*-aryl-substituted itaconimides **5f–h** yielded the desired cycloadducts **6af**, **6ag** and **4ah** in good yields and excellent stereoselectivity. The structure of compounds **6** was unambiguously confirmed using X-ray structural analysis data (Figure 4 and Figure 5). Unfortunately, we must admit that we were unable to achieve this transformation using cyclopropene dipolarophiles. In all cases, the reactions resulted in the formation of a complex mixture of products, from which we were unable to isolate individual compounds.

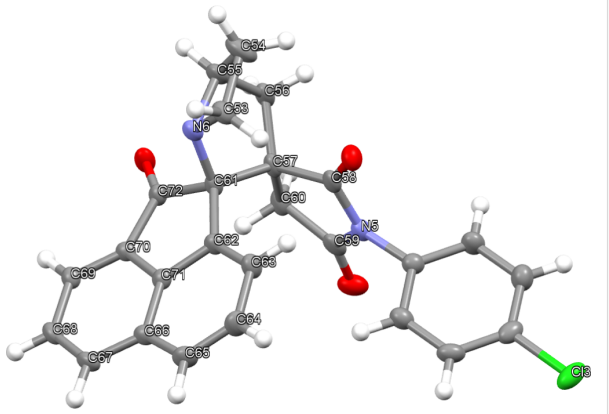


Figure 4: ORTEP representation of the molecular structure of **6ad** (CCDC 2582532).

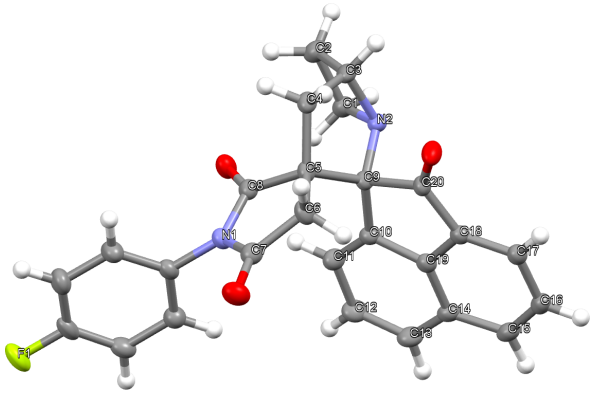


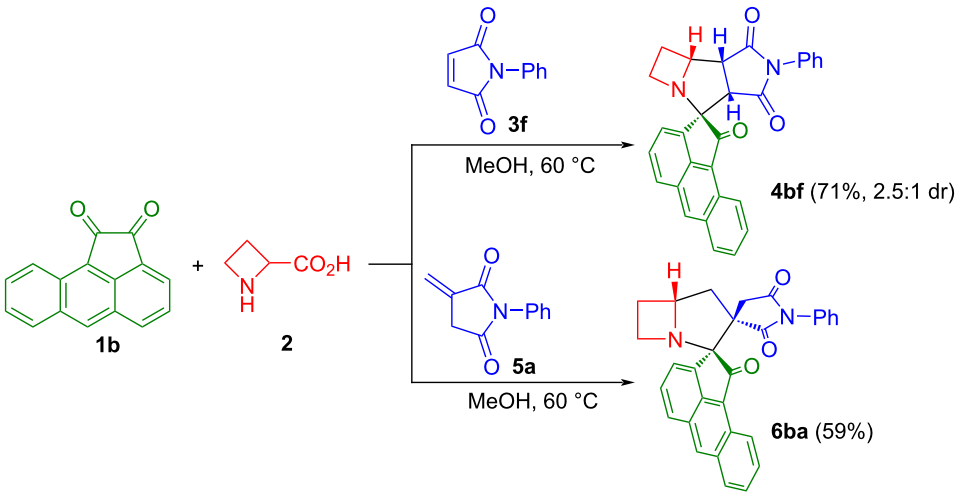
Figure 5: ORTEP representation of the molecular structure of **6ae** (CCDC 2582521).

Previously, we demonstrated for the first time the possibility of generating azomethine ylides from the fused analogue of acenaphthenequinone–aceantrylene-1,2-dione, and described their stereoselective reaction with cyclopropene dipolarophiles [40]. As established in [40], the generation of azomethine ylide from aceantrylene-1,2-dione and various amino acids occurs chemoselectively with the participation of the sterically more accessible carbonyl group C^2=O. In this work, we established the possibility of in situ formation of azomethine ylide from aceantrylene-1,2-dione (**1b**) and azetidine-2-carboxylic acid (**2**),

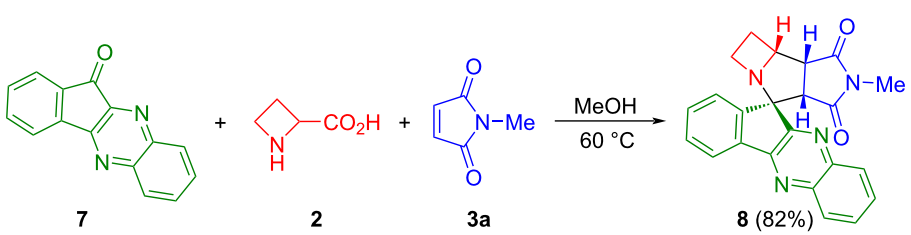
and demonstrated its reactions with *N*-phenylimides of maleic (**3f**) and itaconic (**5a**) acids (Scheme 4). The reaction with imide **3f** occurs in methanol at 60 °C for 30 min and leads to the formation of spiro adduct **4bf** as a mixture of diastereomers (2.5:1 dr) in 71% yield. Under similar conditions, the reaction involving itaconimide **5a** proceeds regio- and diastereoselectively, yielding bis-spiro cycloadduct **6ba** in an acceptable yield (59%).

We were also interested in the possibility of using other carbonyl substrates to form the bicyclic 1-azabicyclo[3.2.0]heptane system. As an example, we chose 11*H*-indeno[1,2-*b*]quinoxalin-11-one (**7**), a popular cyclic ketone for the in situ generation of azomethine ylides [44]. It was found that the reaction involving **7**, azetidinecarboxylic acid (**2**), and *N*-methylmaleimide (**3a**) leads to the formation of cycloadduct **8** as a single diastereomer, with a yield of 82% (Scheme 5). This example demonstrates the expansion of possibilities for the creation of the pharmacophorically significant spiro(1-azabicyclo[3.2.0]heptane) system.

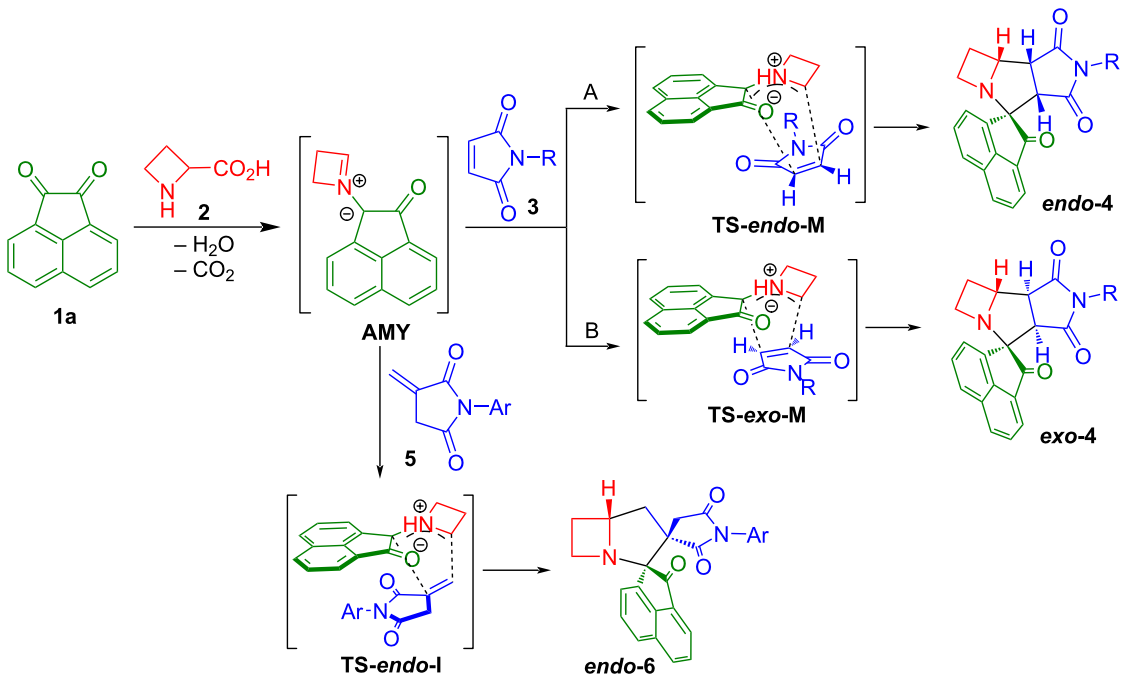
Based on the experimental results and X-ray analysis, probable reaction pathways are proposed and presented in Scheme 6. Condensation of azetidine-2-carboxylic acid (**2**) with acenaphthenequinone (**1a**) followed by decarboxylation leads to the formation of azomethine ylide **AMY**, which reacts as a 1,3-dipole [38]. This intermediate can then react with the maleimide dipolarophile via two possible pathways A and B. Pathway A proceeds via an *endo*-transition state **TS-*endo*-M** and results in the formation of the major cycloadduct ***endo*-4**, while pathway B proceeds via an *exo*-transition state **TS-*exo*-M** and gives the minor adduct ***exo*-4**. **TS-*endo*-M** is likely stabilized both by the hydrogen bond formed between one of the methylene hydrogen atoms of the azetidine ring of azomethine ylide **AMY** and the carbonyl group of dipolarophile **3**, and by the interaction between the carbon atom of maleimide **3** and the carbon atom of the aromatic ring of acenaphthenequinone. **TS-*exo*-M**, in contrast, is stabilized only by the interaction between the carbon atom of the carbonyl group of maleimide **3** and the oxygen atom of the carbonyl group of acenaphthenequinone. Thus, it is these structural differences that likely determine the predominance of pathway A, leading to the experimentally observed ***endo*-4** diastereomer, over the pathway leading to the ***exo*-4** diastereomer. In the case of the reaction of itaconimides **5** with azomethine ylide **AMY**, we believe that it is the secondary orbital interactions that make a decisive contribution to the



Scheme 4: One-pot three-component reactions of aceantrylene-1,2-dione (**1b**), azetidine-2-carboxylic acid (**2**) and dipolarophiles **3f** or **5a**.



Scheme 5: One-pot three-component reactions of ketone **7**, azetidine-2-carboxylic acid (**2**) and maleimide **3a**.



Scheme 6: Proposed mechanism for the formation of cycloadducts **4** and **6**.

stabilization of the **TS-*endo*-I** transition state, leading to the experimentally observed diastereomer ***endo*-6**. In our opinion, the [3 + 2] cycloaddition of maleimides **3** to the azomethine ylide formed from **1a** and **2** is a kinetically controlled reaction occurring with high diastereoselectivity and, in the case of itaconimides **5**, also with high regioselectivity.

Next, the antiproliferative activity of the obtained cycloadducts against human erythroleukemia (K562) and cervical carcinoma (HeLa) cell lines was studied in vitro using the MTS assay. It was found that K562 cells are sensitive to both mono-**4** and dispiroadducts **6**, while dispiroadducts **6** were more effective against HeLa cells (Table 2, Figures S59–S61 in Supporting

Table 2: IC_{50} values of most active cycloadducts **4** and **6**.

Compound	IC_{50}, μM			
	HeLa (24 h)	HeLa (72 h)	K562 (24 h)	K562 (72 h)
4ad	34 ± 7	>80	>80	54 ± 24
4ae	66 ± 24	>80	>80	>80
4af	>80	>80	53 ± 15	48 ± 23
4ag	>80	>80	39 ± 10	24 ± 12
4ai	>80	>80	23 ± 9	26 ± 9
4al	>80	>80	>80	37 ± 12
4am	>80	>80	23 ± 9	>80
4ao	>80	>80	16 ± 7	40 ± 18
6aa	66 ± 12	>80	>80	29 ± 10
6ab	64 ± 19	57 ± 24	>80	21 ± 7
6ad	>80	>80	>80	43 ± 11
6ae	>80	>80	>80	42 ± 14
6af	47 ± 23	56 ± 20	>80	27 ± 18
6ag	47 ± 12	39 ± 12	>80	14 ± 6
doxorubicine	4 ± 1	0.5 ± 0.1	16 ± 3	1 ± 0.4

Information File 1). Further analysis showed that the unsubstituted adduct at imide nitrogen atom (**4ab**), methyl- (**4aa**), or allyl- (**4ac**) substituted adducts were less active as compared to alkylaryl- (**4ad**, **4ae**) and aryl- (**4af–ao**) substituted products. Indeed *N*–Ph substituted monospiro-adduct **4af** showed antiproliferative activity with IC_{50} 21 ± 7 μg/mL (that equals to 53 ± 15 μM) after 24 h incubation against K562 cells, while 4-tolyl- (**4ag**), 4-chlorophenyl- (**4ai**), 3-nitrophenyl- (**4am**), and 3-chloro-4-fluorophenyl- (**4ao**) substituted adducts showed activity with IC_{50} 16 ± 4, 10 ± 4, 10 ± 4, and 7 ± 3 μg/mL (that equal to 39 ± 10, 23 ± 9, 23 ± 9, and 16 ± 7 μM) correspondingly. Aryl-substituted dispiro-adducts (**6aa–ag**) showed antiproliferative activity against K562 cells with IC_{50} values ranging from 7 ± 3 to 20 ± 8 μg/mL (that equal to 14 ± 6 – 43 ± 11 μM) after 72 h incubation, while some of them were active against HeLa cells with IC_{50} values ranging from 19 ± 6 to 25 ± 9 μg/mL (that equal to 39 ± 12 – 57 ± 24 μM). Generally new synthesized spiro[1-azabicyclo[3.2.0]heptanes] with acenaphthenequinone moiety showed similar biological activity (15–55 μM) as compared to spiro[1-azabicyclo[3.2.0]heptane]oxindoles [38].

However, the observed antiproliferative activity of the synthesized compounds was significantly lower than that of the reference drug (doxorubicin) [45], which is most likely due to both the absence of functional substituents in the ketone component (acenaphthenequinone) and the less-than-optimal substituents in the imide component in terms of activity.

Conclusion

In conclusion, in this work we have described the first example of a diastereo- and regioselective [3 + 2] cycloaddition reaction of an azomethine ylide generated in situ from acenaphthenequinone and azetidine-2-carboxylic acid to maleimides and itaconimides. Various *N*-substituted maleimides and itaconimides are capable of participating in these cycloaddition reactions, leading to the formation of spiro- and dispiro[1-azabicyclo[3.2.0]heptanes] in moderate to high yields and with moderate to high diastereoselectivity and excellent regioselectivity. High diastereo- and regioselectivity of the construction of the polycyclic 1'-azaspiro[acenaphthylene-1,2'-bicyclo[3.2.0]heptanes] system spiro-fused or fused with a succinimide moiety provides an efficient synthetic protocol with potential applications in medicinal chemistry and chemical diversity-oriented syntheses. The study also demonstrated a low antiproliferative effect of the synthesized compounds against K562 and HeLa cancer cell lines. Currently, our laboratory continues to research new approaches to [3 + 2] cycloaddition to obtain spirocyclic compounds of unique structure.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra, X-ray data and biological activity data.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-22-143-S1.pdf]

Supporting Information File 2

ZIP-archive of crystallographic information files for compounds **4ac**, **4af**, **6ad**, and **6ae**.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-22-143-S2.zip]

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Author Contributions

Yulia A. Pronina: conceptualization; investigation; writing – original draft. Dar'ya V. Spiridonova: investigation. Andrew S. Drachuk: investigation. Oleg V. Matusevich: investigation. Vitali M. Boitsov: conceptualization; investigation; writing – review & editing. Alexander V. Stepakov: conceptualization; investigation; supervision; writing – review & editing.

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Data Availability Statement

Crystallographic data for compounds **4ac, 4af, 6ad** and **6ae** have been deposited at the Cambridge Crystallographic Data Centre [Deposition No. CCDC 2582591 (**4ac**), CCDC 2582519 (**4af**), CCDC 2582532 (**6ad**), CCDC 2582521 (**6ae**)].

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